Adventures with Highly Reactive Enediamines and Enetetramines

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Signed: Date:

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Semper laetare.

Contents

Abbreviations

AcOH	acetic acid
AIBN	azobisisobutyronitrile
aq.	aqueous
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
Bn	benzyl
°C	degree Celsius
CI	chemical ionisation
CV	cyclic voltammetry
d	doublet
ds	diastereoselective
DDTF	diazadithiafulvalenes
DIT	di-tethered imidazole-derived tetraazafulvalene
DTBB	1,4-di-*tert*-butylbiphenyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DCM or CH_2Cl_2	dichloromethane
DFT	density functional theory
DMA	*N*,*N*-dimethylacetamide
DMAP	4-*N*,*N*-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
$E_{1/2}$	half-wave potential
$E°$	standard potential
e.g.	*exempli gratia*
EDG	electron-donating group
EI	electron impact, now known as electron ionisation
EPHP	1-ethylpiperidine hypophosphite

eq. or equiv.	equivalents
ESI	electrospray ionisation
ET	electron transfer
EWG	electron-withdrawing group
g	grams
GC	gas chromatography
h	hour(s)
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
Hz	hertz
i.e.	*id est*
ir	irreversible
IR	infrared
J	joule (s)
J	coupling constant
KHMDS	potassium hexamethyldisilazide
LiNp	lithium naphthalide
Lit.	literature
LUMO	lowest unoccupied molecular orbital
M	molarity *or* generic metal
m	multiplet
Med	mediator
m	*meta*
Me	methyl
Mes	mesityl (2,4,6-trimethylphenyl)
min(s)	minute(s)
mol	mole
mp	melting point
Ms	methanesulfonyl
mV	millivolts
m/z	mass-to-charge ratio
Na/Hg	sodium amalgam
NHC	*N*-heterocyclic carbene
NHE	normal hydrogen electrode

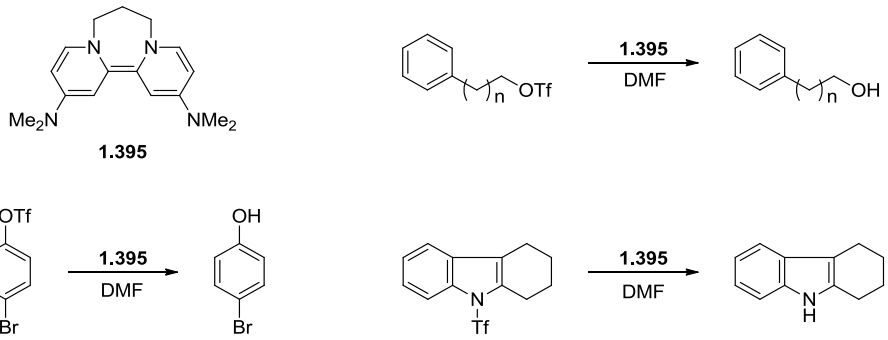
NMP	*N*-methylpyrrolidinone
NMR	nuclear magnetic resonance
o	*ortho*
p	*para*
PET	Photo-induced electron transfer
Ph	phenyl
ppm	parts per million
pyr.	pyridine
q	quartet
R	alkyl group
rpm	rotations per minute
rt	room temperature
s	singlet
sat.	saturated
SCE	saturated calomel electrode ($E°$ = –0.242 V vs. NHE)
SED	super-electron-donor
SET	single electron transfer
S_N1	unimolecular nucleophilic substitution
S_N2	bimolecular nucleophilic substitution
soln	solution
SOMO	singly occupied molecular orbital
t	triplet
TBAHFP	*tetra*-*n*-butylammonium hexafluorophosphate
TBATFB	*tetra*-butylammonium tetrafluoroborate
TBDPS	*tert*-butyldiphenylsilyl
*t*Bu	*tert*-butyl
*t*BuOH	*tert*-butyl alcohol
TDAE	*tetrakis*(dimethylamino)ethylene
Tf or triflyl	trifluoromethylsulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMAHFP	*tetra*-methylammonium hexafluorophosphate
TMATFB	*tetra*-methylammonium tetrafluoroborate
TMP	2,2,6,6-tetramethylpiperidide

TMPPD	*N*,*N*,*N'*,*N'*-Tetramethyl-*p*-phenylenediamine
TON	turnover numbers
Ts	tosyl (*p*-toluenesulfonyl)
TTF	tetrathiafulvalene
TTMSS	tristrimethylsilylsilane
UV	ultra-violet
vs.	versus

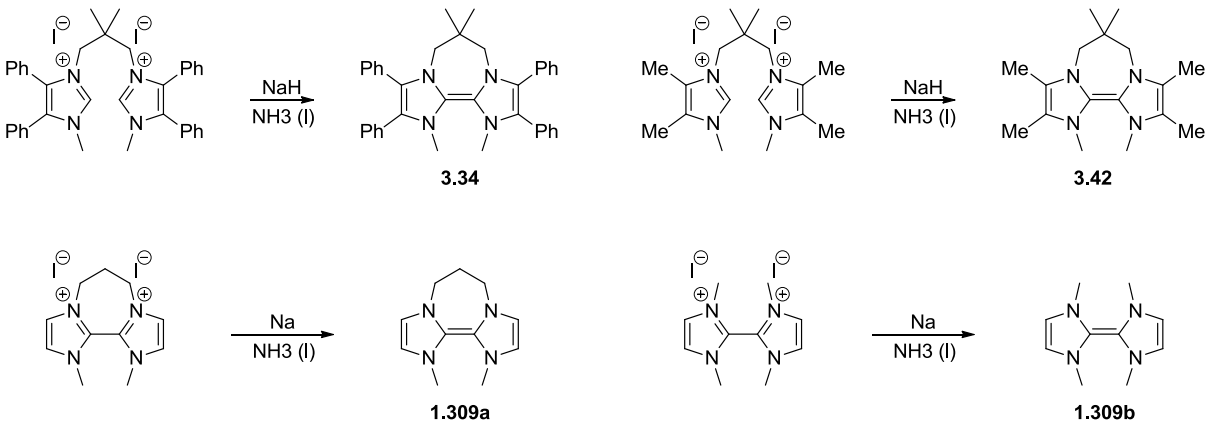
Abstract

This thesis makes a contribution to three discrete projects in organic electron transfer chemistry.

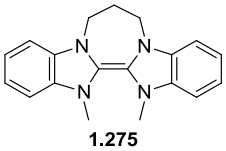
Chapter 2 investigates the new reactivity of *bis*-pyridinylidene **1.395**. It successfully demonstrates the novel conversion of triflate esters and triflamides to the corresponding alcohols and amines and explores the reaction mechanism,[1] and concludes that alkyl triflates are deprotected by a reductive mechanism. Aryl triflates are also deprotected by this reagent, but it is not yet clear whether these reactions are effected by electron transfer or by nucleophile-electrophile chemistry.



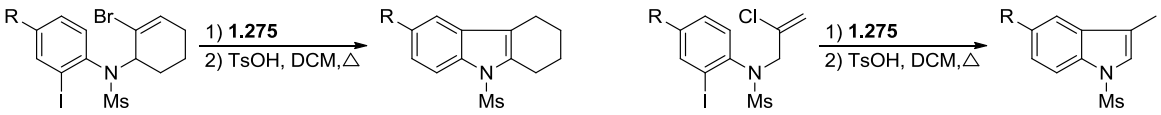
Chapter 3 showcases the development of two new *mono*-tethered super-electron-donors **3.34** and **3.42**.[2] The isolation of these highly reactive tetraazafulvalenes was followed by efforts to prepare the most unstable *mono*- and non-tethered tetraazafulvalenes **1.309a** and **1.309b**, respectively *via* a deprotonation route; this showed NMR evidence of tetraazafulvalene-like molecules, and analysis of these is discussed. In turn, this inspired the successful synthesis and isolation of these compounds within our group by Birch reduction.[2] Until now it was believed that *mono*- and non-tethered imidazole-derived tetraazafulvalenes were too unstable to exist.[3,4]



Chapter 4 Finally the reactivity of a benzimidazole-derived tetraazafulvalene, **1.275** is reported. This molecule generates aryl radicals from iodoarenes by single electron transfer. The novel reactivity of this benzimidazole-derived super-electron-donor is demonstrated in its application to indole synthesis.



1.275



1 Reductive Electron Transfer Reagents – A Review

Synthetic chemists have found many applications for electron transfer based chemistry. Reactive intermediates, namely radical and organometallic species, can be formed by the reduction of organic substrates *via* electron transfer from an electron donor. Traditionally and in many cases metals in low oxidation states have been used as electron donors. Alternative methods include electrochemical reduction at a (usually metal) cathode,[5,6,7] reduction by solvated electrons,[8-12] reduction by lithium naphthalide[13] or related radical anions of organic molecules,[14-16] or photochemically assisted electron transfer.[17,18] However, each of these processes has its limitations; harsh reaction conditions, environmentally hazardous waste or poor applicability. Circumventing these issues is a current focus within our laboratories where we seek to develop neutral ground-state organic molecules as powerful reducing electron transfer reagents and apply them in organic synthesis. The use of such reagents, so called super-electron-donors (SED) is attractive as it would allow reductions to be mediated (i) under mild conditions due to their neutrality (ii) without metal ions and the environmental issues resulting from certain metal residues and (iii) with wider applicability than currently seen for photochemically assisted reactions.

This introduction is intended to give the reader a brief overview of some previous methods employed for electron transfer. However, it is not an exhaustive review but should highlight the fact that generation of reactive intermediates such as radicals is almost as diverse and dynamic a subject as the subsequent chemistry they perform.

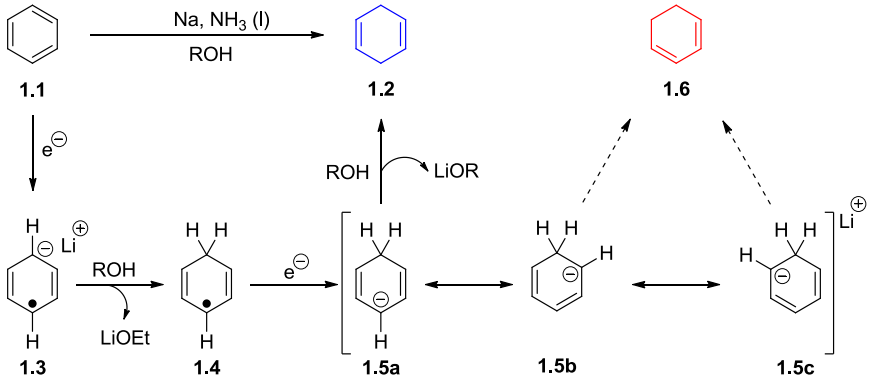
1.1 Metals as Electron Transfer reagents:

1.1.1 Alkali Metals

Alkali metals such as lithium, sodium or potassium can become strong reducing agents when dissolved in suitable solvents like ammonia, amines or ethanol. The single electron liberated from their outer-shell easily reduces a range of functionalities to their radical anions, including aromatics, alkynes and carbonyl compounds. In fact, alkali metals will reduce any functional group that has a low–energy π^* or σ^* orbital to accommodate the unpaired electron.[19]

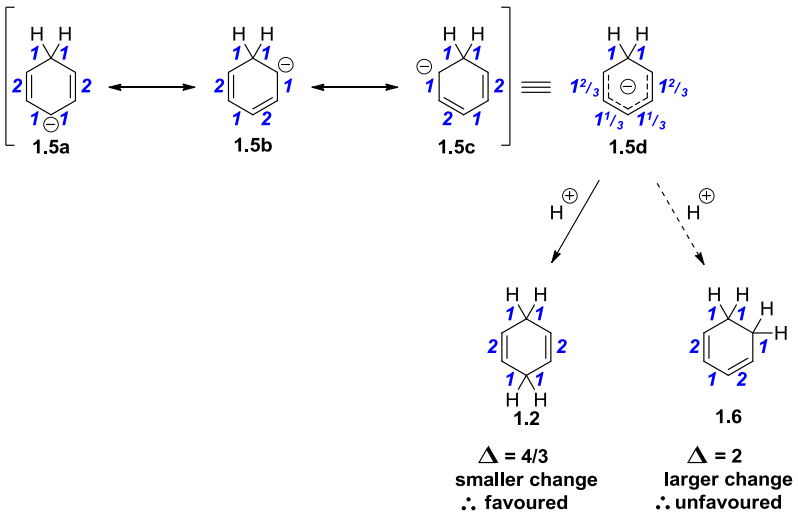
The Birch reduction[8-10,12] employs lithium, sodium or potassium and is possibly the most well known reaction involving alkali metals. The metal, lithium in **Scheme 1.1**, is dissolved in liquid ammonia forming a blue solution of free solvated electrons which are then transferred to the LUMO of the benzene forming radical anion **1.3**. In reality there are actually three species solvated, free solvated electrons, metal anions or alkalides (*e.g.* $Na^{\bullet-}$) and electrides (a complexed alkali metal cation with trapped electron *e.g.* $[Na(NH_3)_6]^+e$).[20] Radical anion **1.3** is protonated forming radical **1.4** which is reduced to anion **1.5** by a further electron transfer. The anion **1.5** is stabilised by delocalisation and so it is somewhat surprising that the final protonation occurs preferentially at the *para* position to the original protonation affording the 1,4-diene **1.2**,[21] a thermodynamically less stable product than the alternative conjugated 1,3-diene **1.6**, that would result from protonation of either **1.5b** or **1.5c**.

Scheme 1.1 The Birch reduction of Benzene.



The principles of least motion,[22] which favour products resulting from reaction paths that involve the least change in atomic position and electronic configuration help to account for the formation of 1,4-diene **1.2**. If in each of the 3 resonance structures (**Scheme 1.2**) a single bonds is assigned a value of 1 and double-bonds a value of 2, then the average is represented by **1.5d**. Thus on protonation the smallest overall change occurs going from **1.5d** to 1,4-diene **1.2** (Δ = 4/3) as opposed to **1.5d** to 1,3-diene **1.6** (Δ = 2). If the conjugated 1,3-diene is desired it can be obtained by tautomerisation of the 1,4-diene with acid.[19]

Scheme 1.2 Favourable 1,4-diene **1.2** formation governed by principles of least motion.



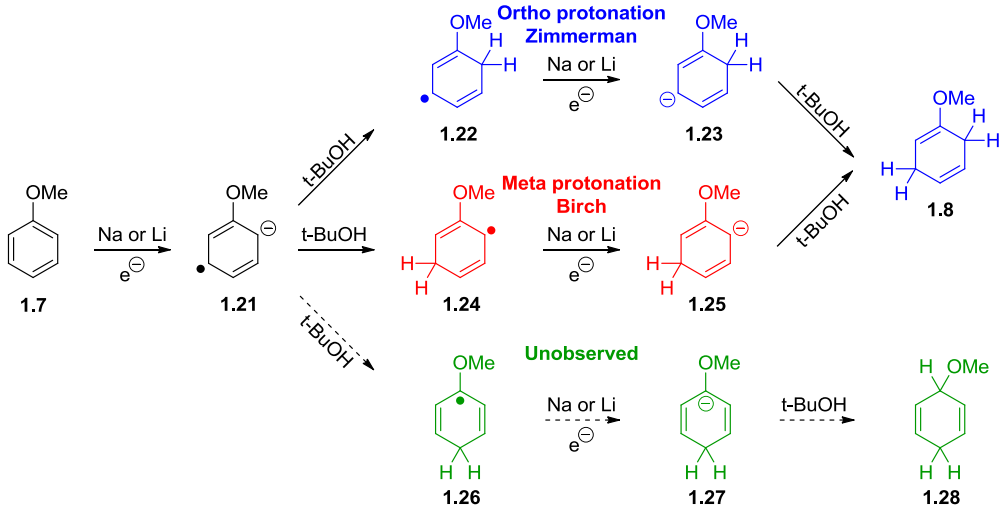
Again the principles of least motion favour the formation of 1,4-dienes **1.8** and **1.20**, with the regiochemistry of the product being decided by the electronic nature of the substituent, as illustrated below.

Scheme 1.3 The Birch reduction with electron-donating and -withdrawing substituents.

A recent review by Zimmerman,[12] a key contributor in the clarification of the reaction mechanism operating in the Birch reductions, recounts the developments and debate on course to our current understanding. The reduction of electron-rich anisole **1.7** affords 1,4-diene **1.8** without formation of 1,4-diene **1.28**, therefore protonation at the *para* position leading to intermediates **1.26** and **1.27** can be discounted immediately. Similarly *ipso* protonation which would also afford **1.28** with intermediates analogous to **1.26** and **1.27** can also be discounted. Thus initial protonation must occur at either the *ortho* or the *meta* positions. In either case the same final product is ultimately afforded so the question of where protonation first occurs is an esoteric one, however it has ignited debate. In his original publications, Birch[8-10] favoured initial *meta* protonation (shown in red **Scheme 1.4**) while Zimmerman, supported by Hückel computational calculations[23] (showing the highest electron

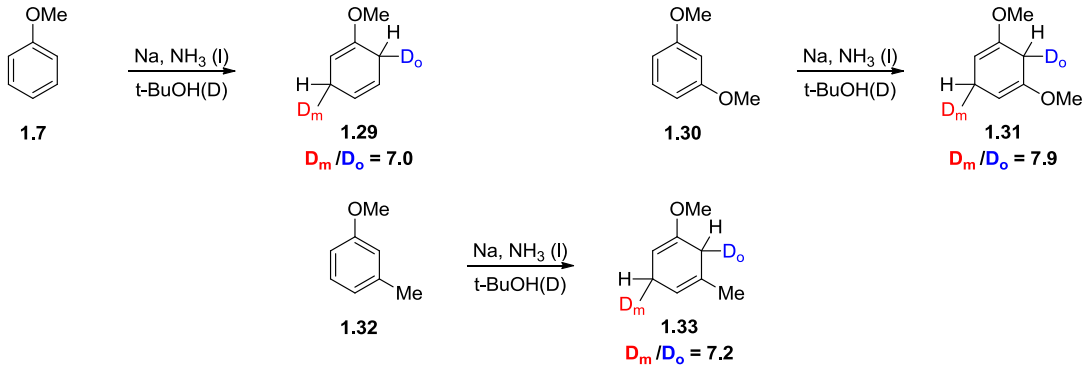
density in radical anion to reside at the *ortho* position) suggested protonation occurred first at the *ortho* position (shown in blue **Scheme 1.4**).

Scheme 1.4 Conflicting opinions, Birch favours initial *meta* protonation while Zimmerman suggested that *ortho* protonation predominates (the product is shown in blue as reaction does indeed proceed by *ortho* protonation, *vide infra*).



Over the decades the question of mechanism was controversial with Birch continuing to support *meta* protonation until in the early 1990's, over 50 years after its inception, Zimmerman and Wang[24,25] devised an experiment that demonstrated the *ortho* protonation mechanism predominated in the reduction of anisole. Understanding that radical anions such as **1.21** are less basic than carbanions[26] *i.e.* **1.23** and **1.25**, Zimmerman and Wang reasoned that the radical anion would act as a more selective base.[27] Thus when running a competition reaction in the presence of some deuterated and non-deuterated alcohol, less deuterium should be incorporated into the more selective radical anion, and conversely more deuteration would be expected in more reactive carbanions. In short, the site of least deuteration in the final product corresponds to the site of initial protonation and predominant reaction mechanism. When Zimmerman and Wang ran the Birch reduction with anisole **1.7** at -78 ºC, with sodium in liquid ammonia and *tert*-butyl alcohol (*ca*. 2% deuterated) they discovered that most deuterium was incorporated in the *meta* position of the 1,4-diene product **1.29**, in a 7:1 ratio *meta* to *ortho*, thus identifying the *ortho* position as the site of the initial, more selective protonation and confirming Zimmerman's proposed *ortho* mechanism as the correct one.

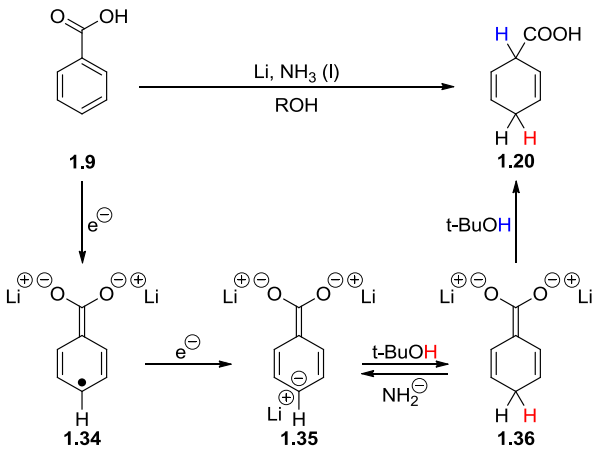
Scheme 1.5 *ortho*/*meta* deuteration competition reactions by Zimmerman and Wang.[24,25]



The reductions of **1.30** and **1.32** affording the anticipated greater *meta* deuteration in products **1.31** and **1.33** respectively further supported Zimmerman's *ortho* mechanism.

The Birch reduction of benzenoid systems bearing electron-withdrawing substituents again affords unconjugated 1,4-diene but in the 2 and 5 positions relative to the EWG.[11,12] When the substituent is a carbonyl group as in carboxylic acid **1.9**, electron transfer first affords a radical anion intermediate that is stabilised by delocalisation of negative charge on carboxyl group forming an enolate equivalent, in this case the radical dianion **1.34** (ester, ketone or amide substituents afford corresponding singly charged 'radical enolate' equivalents *i.e.* **1.46**). A further electron transfer produces the aryl anion **1.35** and it is at this juncture that protonation occurs. Protonation first occurs at the *para* position affording **1.36**, followed by protonation of enolate at the *ipso* position and then finally carboxylate anion (not shown) to yield **1.20**.

Scheme 1.6 The Birch reduction of benzoic acid.[12,27]

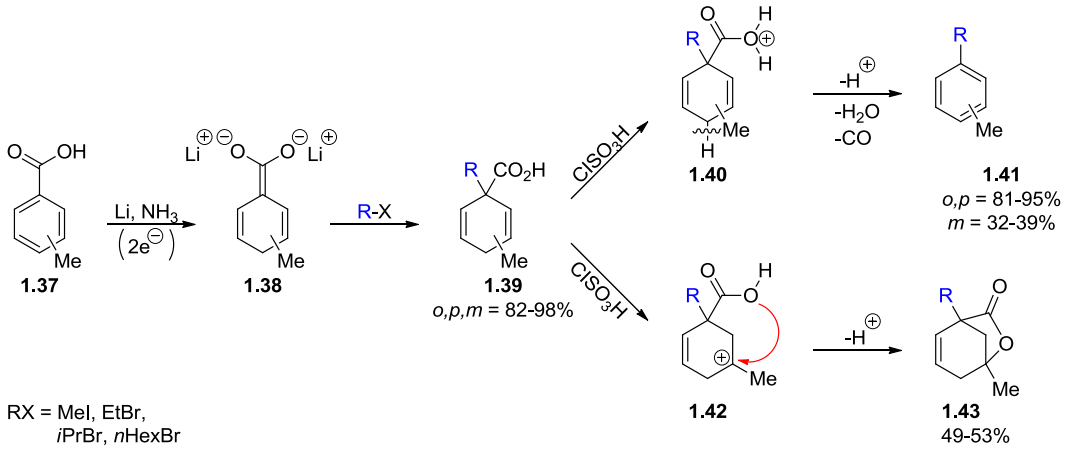


As mentioned above the basicity of anions like **1.35** (pK_a ~ 34) is such that protonation at the *para* position will take place in absence of alcohol by the deprotonation of the ammonium (formed by protonation of ammonia by carboxylic acid) or by the deprotonation of ammonia[27] (when an aromatic substrate that is not acidic is reduced). This sequence of electron transfer, intermediate formation and protonation is clearly demonstrated in work by Linker *et al.*,[28] in which the carboxylate group was successfully substituted for an electrophile at the *ipso* position (**Scheme 1.7**). Reduction of **1.37** affords an anion intermediate analogous to **1.35**. *Para* protonation proceeds to **1.38**, which undergoes *ipso* alkylation by reaction of enolate with electrophiles furnishing **1.39**. Alkylated cyclohexadienes **1.39** were afforded in excellent yield regardless of *ortho*, *meta* or *para* methyl substituent. The *ortho* and *para* analogues **1.39** can be rearomatised in good yields by protonation and decarboxylation to aromatics **1.41** while *meta* analogues afford mixtures of aromatic and cyclic lactone products, **1.41** and **1.43**, respectively.

Features of note:

- alkylation occurs selectively at the *ipso* position, therefore initial protonation must occur at *para* position otherwise the alternative *para* alkylated products would be observed
- the regiochemistry is dictated by electron-withdrawing carboxylate

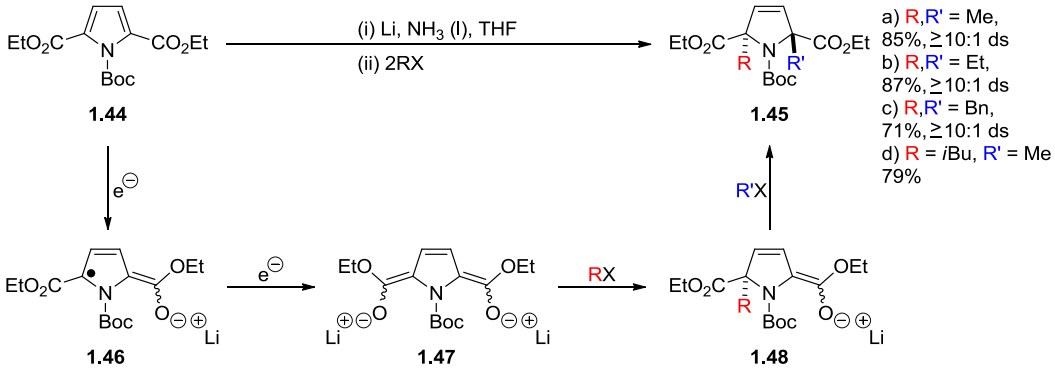
Scheme 1.7 Alkylation at *ipso* position after initial *para* protonation.[28]



Donohoe *et al.*[29] successfully employed the Birch reduction in the stereoselective reductive alkylation of activated 2,5-disubstituted pyrroles. Two sequential electron transfers form *bis*-enolate **1.47** which nucleophilically attacks alkyl halides. The stereochemistry in **1.45** is

determined by the second alkylation, that of *mono*-enolate **1.48**. Attack occurs from the less hindered face, *syn* to the ester substituent. Sequential alkylation with a different alkyl halide is also possible, *e.g.* in the formation of **1.45d**.

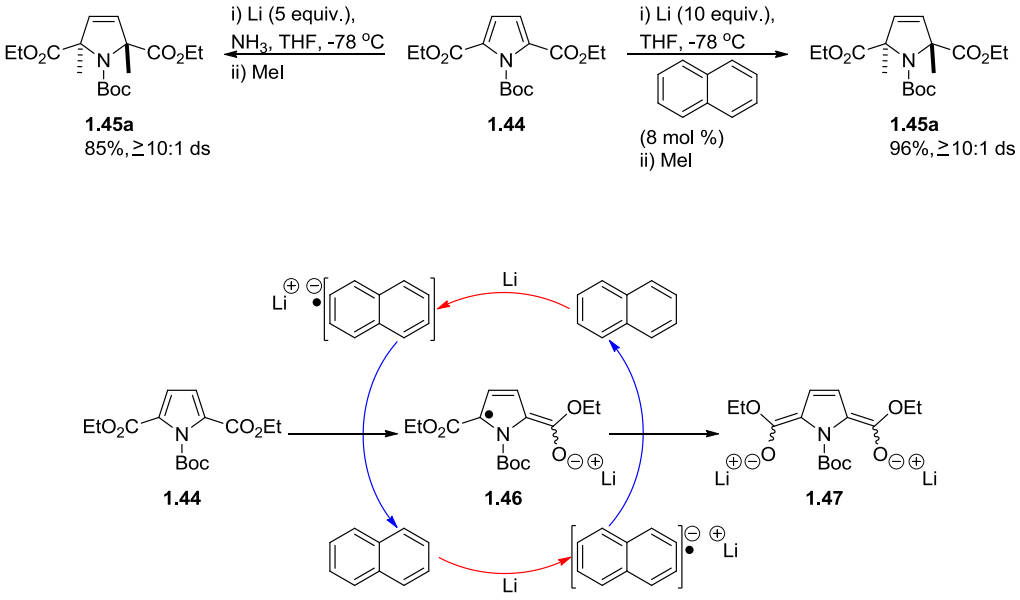
Scheme 1.8 Stereoselective Birch reduction of activated 2,5-disubstituted pyrroles.



Donohoe *et al*.[29] noted that deprotonation of ammonia was not necessary in the generation of the reactive *bis*-enolate **1.47**, suitable for alkylation. Thus, investigations into ammonia-free reductive alkylations that might be more practical on a large scale and compatible with electrophiles that would otherwise react with ammonia (only alkyl halides or non-enolisable aldehydes are compatible) were initiated. It was found lithium naphthalide (LiNp) in THF at -78 ºC was a suitable reducing agent for effective reductive alkylation of *N*-protected pyrrole. Indeed, for some substrates naphthalene can be used catalytically as an electron shuttle undergoing multiple electron uptakes from lithium powder and electron donations to pyrrole **1.44** and radical anion **1.46**.

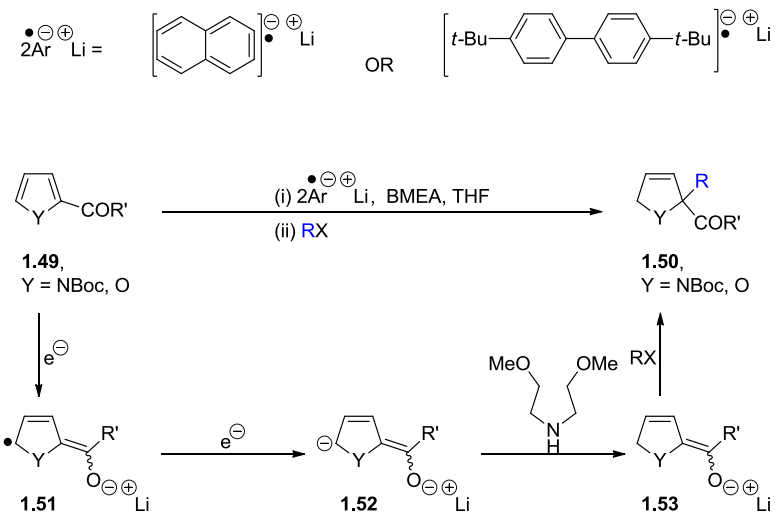
Donohoe *et al*. were able to extend the reduction capability of lithium naphthalide to nitrogen and oxygen heterocycles bearing only one activating EWG, as well as introducing acid chlorides as compatible electrophiles.[15,29] The success of this reductive process relies on the use of *bis*(methoxyethyl)amine (BMEA) which crucially is acidic enough to protonate dianion **1.52** but does not quench the desired resultant reactive intermediate, enolate **1.53**. Lithium di-*tert*-butylbiphenyl (LiDTBB) was also disclosed in the 2002 publication,[15] as a more efficient reagent for the mediation of ammonia-free Birch reductions (**Scheme 1.9** and **1.10**).

Scheme 1.9 Ammonia-free Birch reduction with Lithium Naphthalide.[29]

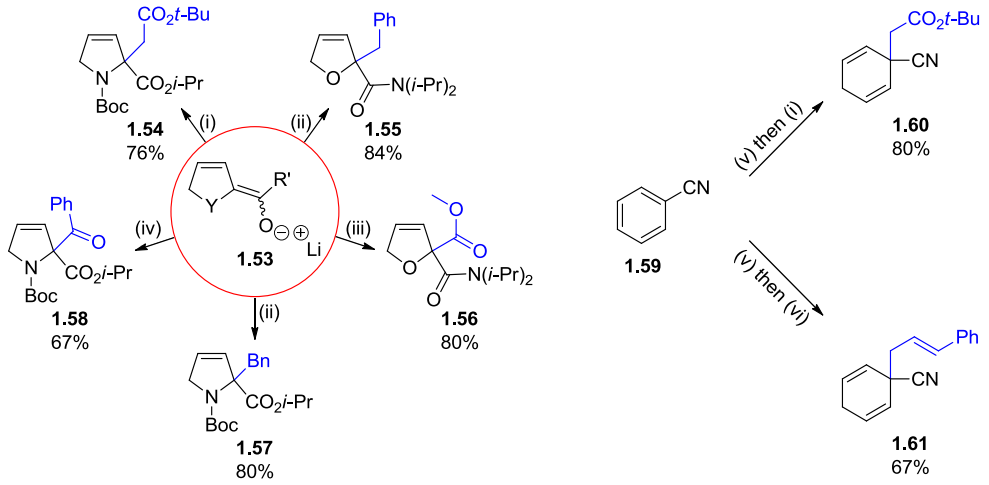


The higher yields observed with lithium di-*tert*-butylbiphenyl were attributed to its increased steric bulk disfavouring radical coupling with partially reduced species **1.51**, as well as its greater redox potential compared to lithium naphthalide. The increased reducing power of lithium di-*tert*-butylbiphenyl allowed the ammonia-free reductive-alkylation of activated benzenoids *e.g.* cyanobenzene **1.59** (**Scheme 1.11**).

Scheme 1.10 Ammonia-free Birch reduction with lithium naphthalide and lithium di-*tert*-butylbiphenyl (LiDTBB).



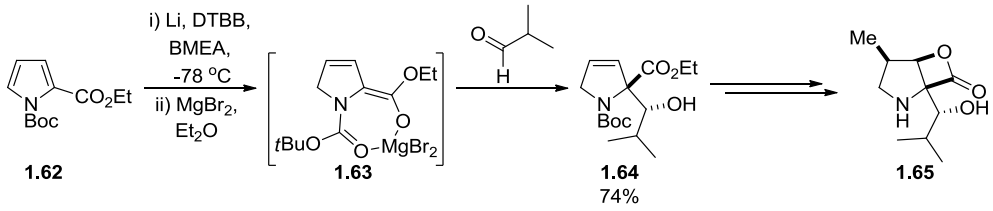
Scheme 1.11 Reductive alkylation of aromatics with LiDTBB and a various electrophiles.



Reaction conditions; (i) $BrCH_2CO_2t$-Bu; (ii) BnBr; (iii) MeOCOCl; (iv) PhCOCl; (v) Li, DTBB, THF, -78 ºC; (vi) (*E*)-PhCH=CHCH$_2$Br

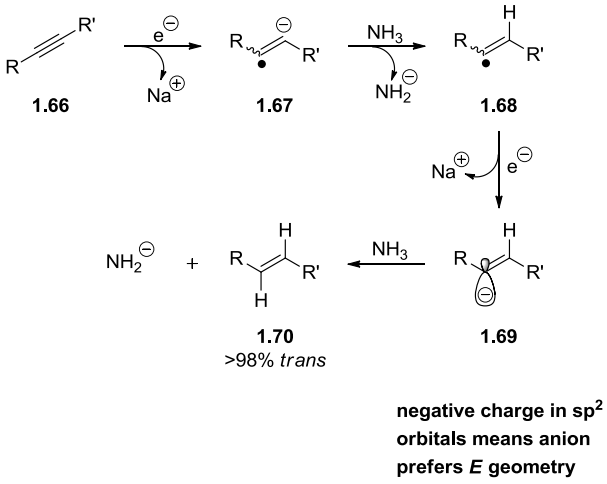
Donohoe *et al*. were able to apply the ammonia-free Birch reduction to the total synthesis of Lactacystin *β*-lactone **1.65**.[30] Transmetallation with $MgBr_2.Et_2O$ proved crucial for a high yield and diastereoselective outcome.

Scheme 1.12 Ammonia-free total synthesis of Lactacystin *β*-lactone.



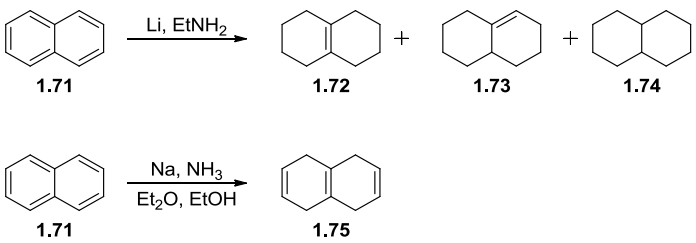
The Birch reduction of alkynes in ammonia affords *trans*-alkenes.[9] The *trans*- geometry is adopted in vinyl radical anion **1.67** due to electron repulsion between the radical and carbanion; **1.67** is protonated by ammonia to give *trans*-vinyl radical **1.68** which again is reduced to a vinyl carbanion **1.69** with bulky R groups on opposing faces of the double-bond. The final protonation by ammonia typically affords >98% *trans*-alkene **1.70**. No additional proton source is required as the vinyl anions are basic enough to deprotonate ammonia.

Scheme 1.13 The Birch reduction of alkynes.



The solvent in which the alkali metal is dissolved and thus which by the electron is 'solvated' can have a profound effect on the reduction capacity of the system. The Benkeser reaction employs low molecular weight amines in place of liquid ammonia. From a purely practical perspective the alkyl amines are advantageous due to being liquid at ambient temperature. Benkeser[31] reported the "absorption of large quantities of lithium by various compounds" when using ethylamine in place of ammonia. The Benkeser reaction conditions are significantly more reducing than Birch conditions, with reduction to *mono*-olefins occurring readily for the former. In a Benkeser reduction, the initial 1,4-diene generated is tautomerised by deprotonation to a 1,3-diene which undergoes further reduction more readily. Thus, the reduction of naphthalene by lithium in ethylamine afforded $\Delta^{9,10}$- **1.72** and $\Delta^{1,9}$-octaline **1.73** (50:1) and small quantities of decalin; by contrast Birch conditions afford 1,4,5,8-tetrahydronaphthalene **1.75**.[32,33]

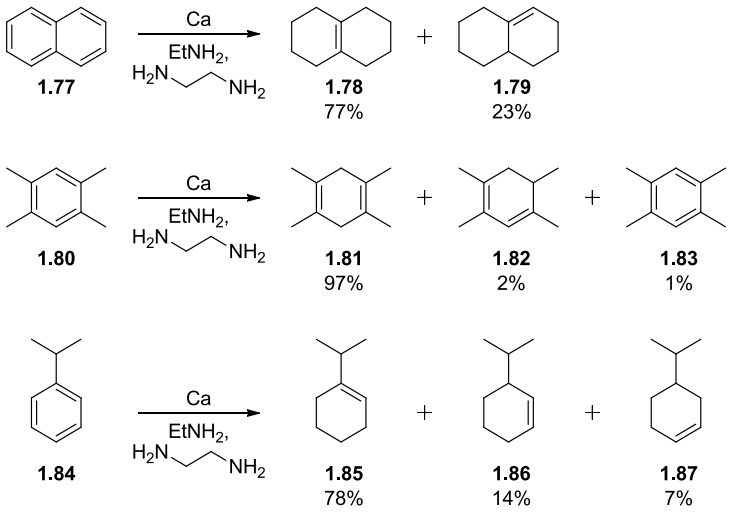
Scheme 1.14 Naphthalene reduction under Birch and Benkeser reaction conditions.



Using calcium in place of lithium (**Scheme 1.15**), Benkeser demonstrated the effective reduction of aromatic compounds to *mono*-and di-alkenes in methylamine-ethylenediamine

(1:1).[34] However, a disadvantage of the Benkeser reaction can be its lack of selectivity with products of differing reduction level and different regiochemistry being produced.

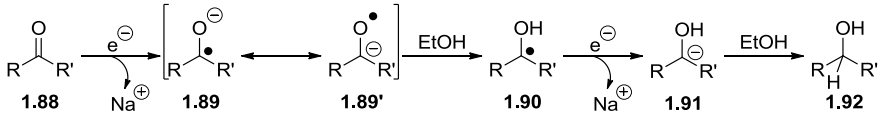
Scheme 1.15 Benkeser reduction with calcium in methylamine-ethylenediamine.



Solvent also has a large effect on the outcome of alkali metal reactions with carbonyl functionalities. In protic solvent like ethanol, carbonyl compounds are reduced to their corresponding alcohols in the Bouveault-Blanc reaction.[35-38] Aldehydes and esters are both reduced to primary alcohols while ketones afford secondary alcohols (**Scheme 1.16**).

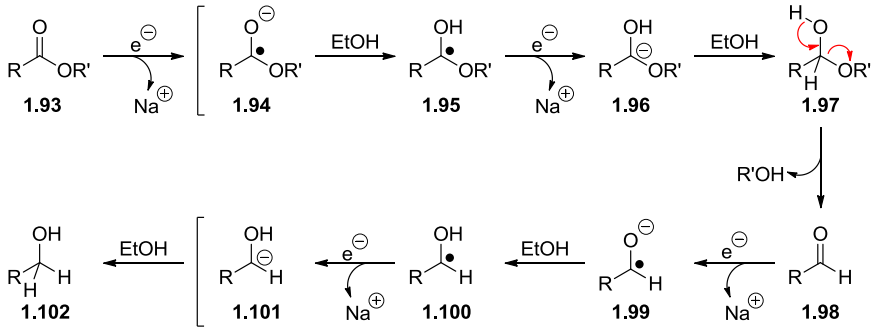
An electron is transferred from sodium to the low-lying π*-orbital of the C=O bond, forming ketyl radical anion **1.89**. In aldehydes and ketones, **1.89** is sequentially protonated by ethanol giving radical **1.90** and then reduced by metal once more. Protonation of the subsequent carbanion **1.91** affords alcohol **1.92**.

Scheme 1.16 The Bouveault-Blanc reduction of an aldehyde or ketone.



Esters are converted to alcohols in a similar fashion but reach a hemi-acetal intermediate **1.97**. Elimination yields aldehyde **1.98** that proceeds to primary alcohol **1.102** *via* the reduction and protonation sequence described above (**Scheme 1.17**).

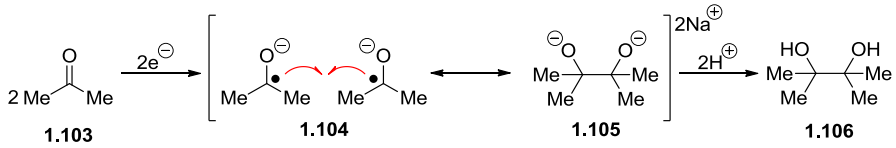
Scheme 1.17 The Bouveault-Blanc reduction of an ester.



In aprotic solvents such as benzene, tetrahydrofuran or ether, alkali metals can mediate pinacol couplings of ketones (**Scheme 1.18**).[19,38] As no protons are available, ketyl radical ions **1.104** dimerise to form dianion **1.105**, protonation of which now affords diol. In the case of acetone **1.36**, the product is 2,3-dimethylbutane-2,3-diol **1.39**, also known as pinacol.

However, in order for the reaction to proceed smoothly the ketyl radical anions must overcome anionic repulsion. Increased yields can be achieved if the reaction is mediated by a metal that can easily form dications such as magnesium and aluminium.

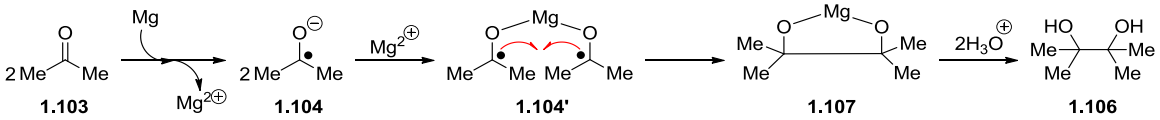
Scheme 1.18 Pinacol reaction of acetone.



1.1.2 Alkaline Earth Metals

When the pinacol reaction is carried out with magnesium, improved yields are achieved as the dication formed from oxidation of magnesium can covalently bond to the oxygens carrying the negative charge of the two ketyl radical anions **1.104'**.[39] Formation of diradical species **1.104** brings the two radical centres into close proximity and therefore dimerisation is more favourable. Hydrolysis of the five-membered ring **1.107** affords pinacol **1.106**.

Scheme 1.19 Pinacol reduction of ketones with magnesium.



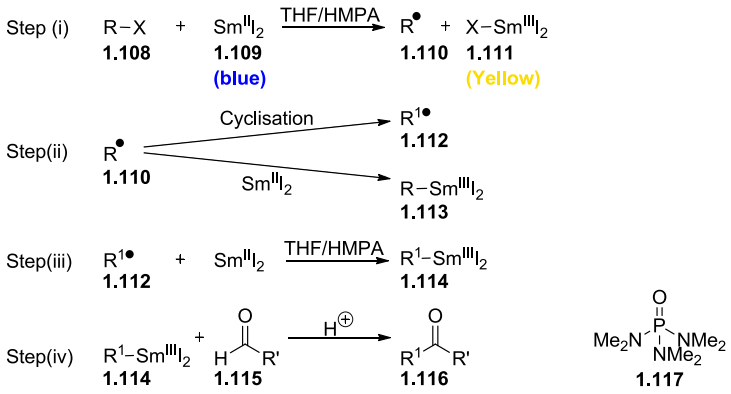
1.2 Lanthanides as Electron Transfer Reagents

Of the lanthanides, samarium and its salt samarium(II) iodide, have proved to be the most versatile as electron donors. These compounds have the ability to transform functional groups *via* selective reductions as well as being able to form new C-C bonds.[40,41]

The samarium(II) iodide is typically prepared by reacting metallic samarium with 1,2-diiodoethane under an inert atmosphere in dry THF. Co-solvent hexamethylphosphoramide **1.117** (HMPA) can be utilised (up to a maximum of 4 equivalents) to increase the redox potential of samarium(II). This affords increased rates of reduction and allows more than just primary iodide and bromide reductions.

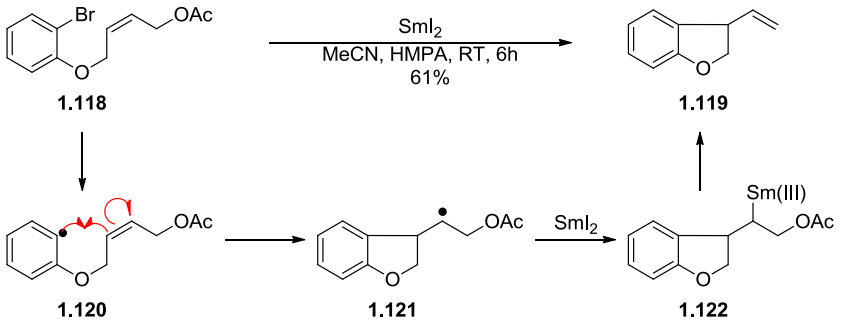
As such, samarium(II) iodide has proved an effective reagent for generating radicals by single electron transfer (SET) reductions of organic halides. In the generalised reaction **Scheme 1.20**, the reaction is initiated by the reduction of organic halide **1.108** to radical species **1.110** with Sm^{II} **1.109** metal being oxidised to Sm^{III} **1.111**. The oxidation of samarium(II) corresponds to a colour change in THF solution from blue to yellow. The radical **1.110** can now be reduced by a further equivalent of samarium(II) iodide to form organosamarium compound **1.113** or react to form new radical species **1.112**. This new radical species is itself reduced to an organosamarium compound **1.114** before the final coupling. It is therefore vitally important that the desired radical reaction (**1.110** to **1.112**) takes place before the second reduction by the second equivalent of samarium(II) iodide.

Scheme 1.20 Radical generation from an alkyl halide with samarium(II) iodide.



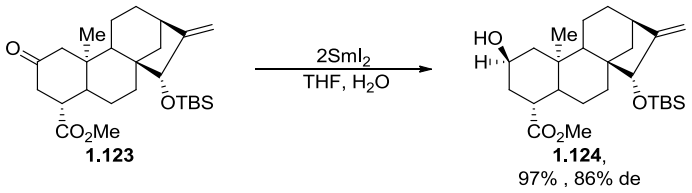
Samarium(II) iodide has proved particularly useful for radical cyclisations, as demonstrated by 5-*exo-trig* cyclisation in the synthesis of the benzodihydrofuran **1.119**, below.[42] However the alkyl radical obtained after cyclisation can be trapped with SmI_2 forming organosamarium (III) intermediate which may lead to other reactions.

Scheme 1.21 Reductive cyclisation of aryl halide.



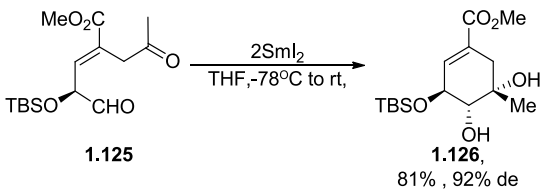
Aldehydes and ketones are also easily reduced by samarium(II) iodide. In the presence of a proton source, such as water or alcohol, samarium(II) iodide reduces carbonyl compounds *e.g.* **1.123** to corresponding alcohols **1.124** as illustrated by Corey *et al*. in their advances towards (±)-Atractyligenin.[43]

Scheme 1.22 Corey *et al*. reduction of ketone group to alcohol using samarium(II) iodide.



As with alkali metals, pinacol type coupling can be carried out with samarium(II) iodide when the electron transfer is carried out in an aprotic solvent, in the absence of protons. Hanessian *et al*.[44] **Scheme 1.23** demonstrated an intramolecular coupling of the highly stereoselective reduction of dicarbonyl compound **1.125** to afford *cis*-diol **1.126** in good yield.

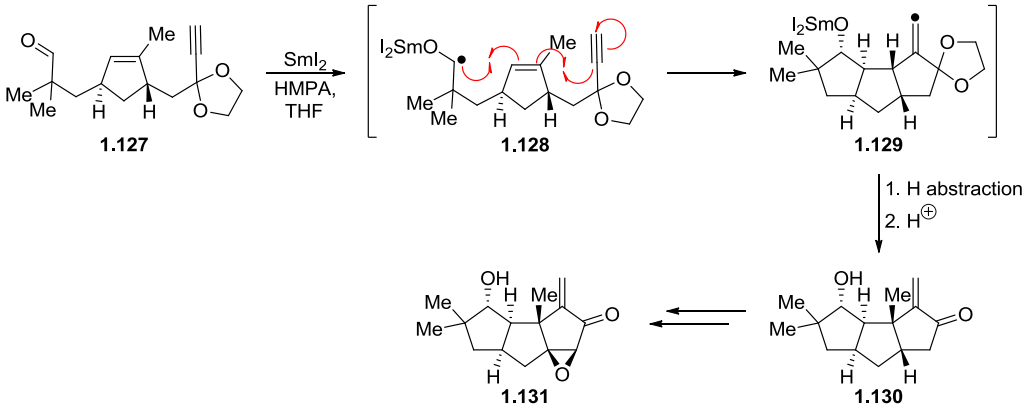
Scheme 1.23 Pinacol reaction with samarium(II) iodide.



A beautiful example of samarium(II) iodide's potential for radical chemistry was demonstrated by Curran *et al*. (**Scheme 1.24**) when they utilised carbonyl reduction and tandem radical cyclisation in their synthesis of the terpene hypnophilin **1.131**.[45]
Although a versatile electron transfer reagent the frequent requirement for reactions to be carried out in presence of carcinogenic HMPA has led to alternatives to samarium(II) iodide being sought.

A more negative redox potential for samarium(II) iodide can be achieved when it is complexed with water (SmI_2-H_2O up to -1.9 V *vs.* Ag/$AgNO_3$ in THF; SmI_2 = -1.33 V *vs.* Ag/$AgNO_3$ in THF).[46] Recently the reduction of unactivated esters to alcohols by samarium(II) iodide was reported for the first time by Procter *et al.*, employing SmI_2-H_2O-amine system.[47] A current review highlights recent advances in the reductive chemistry of samarium(II) iodide, as well as other lanthanides.[48]

Scheme 1.24 The use of samarium(II) iodide in tandem radical cyclisation.



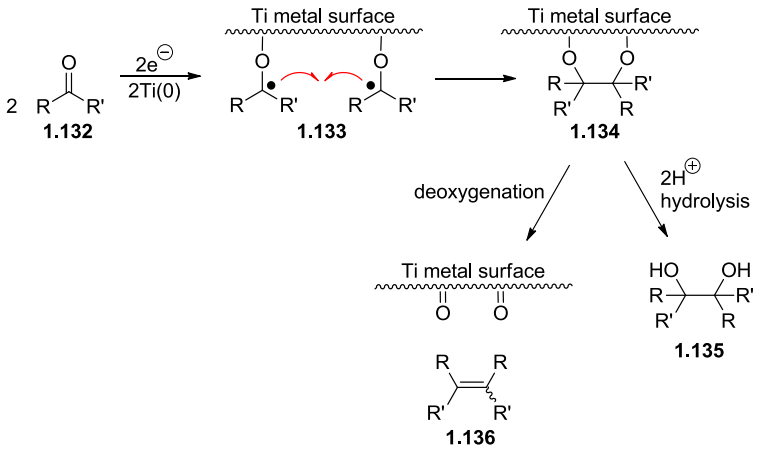
1.3 Transition Metals as Electron Donors, Titanium

Many transition metals such as Sc, Ti, V, Cr, Mn, Fe, Co, Ni, Cu, Zn and their compounds exhibit electron transfer chemistry but are beyond the scope of this review. Only titanium is presented here.

The McMurry reaction is the reductive coupling of two carbonyl compounds using low-valent titanium to afford alkenes.[19,49] Ti(0) is the source of electrons, formed by the reduction of a Ti(III) salt, usually $TiCl_3$ with $LiAlH_4$ or Zn/Cu. The reaction cannot be carried out with powdered titanium metal. In the first step of the McMurry reaction a pinacol radical-radical coupling takes place on the surface of the metal, **1.134**. At low temperature (typically

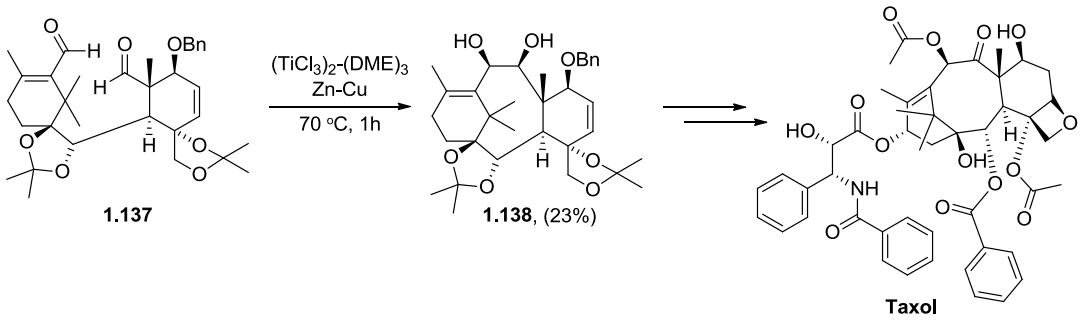
< 0 °C) **1.134** can be hydrolysed to afford diol **1.135**, or else deoxygenation yields alkene **1.136**. The mechanism is not fully understood.

Scheme 1.25 The McMurry Reaction.



One of the best examples of the McMurry reaction was its application by Nicolaou *et al*. in an intermolecular pinacol coupling of two carbonyl groups affording the central 8-membered ring of taxol® intermediate **1.38**.[50,51]

Scheme 1.26 McMurry reaction utilised in advances towards taxol®.

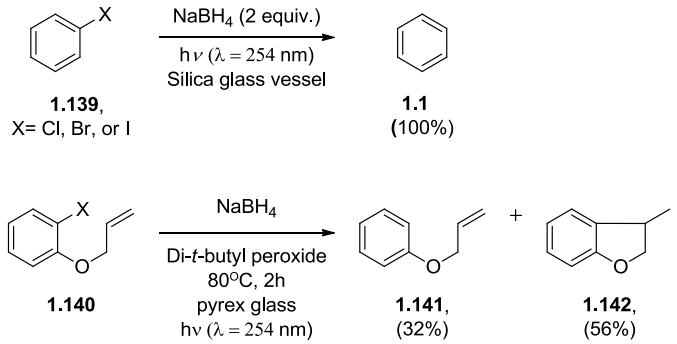


1.4 Photo-induced Electron Transfer Process

Photo-induced electron transfer (PET) reactions have great potential for environmentally-friendly organic synthesis. As such PET reactions have been widely utilised. However, this review will only consider reductions of organic halides.

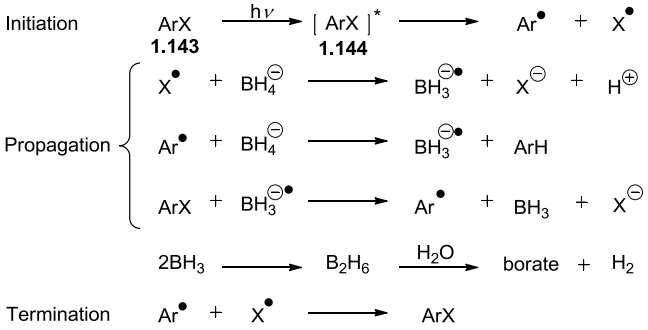
Barltrop and co-workers[52] used UV radiation to reduce iodo-benzene **1.139** in a solution of sodium borohydride in aqueous acetonitrile to afford quantitative yields of benzene **1.1** (**Scheme 1.27**).

Scheme 1.27 PET reductions of aryl halides.[52,53]



A general mechanism for the reaction is given in **Scheme 1.28**, and involves the excitation of neutral organic molecule **1.143** by UV radiation. The energy from UV radiation is absorbed by an electron, promoting it from the molecule's HOMO to its LUMO, generating an excited state molecule **1.144** that subsequently undergoes homolytic dehalogenation.

Scheme 1.28 The reaction mechanism for PET reductions of aryl halides.



A UV photo-stimulation reduction process was employed by Abeywickrema and Beckwith[53] to generate aryl radicals in the cyclisation of *o*-allyloxyiodobenzene **1.140** in the presence of sodium borohydride and di-*tert*-butyl peroxide as the initiator (**Scheme 1.27**).

Curran[54] used photolysis to initiate an intermolecular addition of **1.148** to phenyl isocyanide, supervened by two intramolecular cyclisations in his elegant core tetracycle synthesis of camptothecin **1.153** (**Scheme 1.29**). Irradiation of hexamethylditin **1.145** generates trimethyltin radical **1.146** which yields new radical species **1.148** by the abstraction of bromine from **1.147**. Intermolecular addition to the carbon of phenyl isonitrile yields imidoyl radical intermediate **1.149** which undergoes intramolecular 5-*exo*-*dig* cyclisation with an

alkyne generating vinyl radical **1.150**. Subsequent 6-*exo-trig* cyclisation and rearomatisation affords core tetracycle **1.153**, in 45% yield.

Scheme 1.29 Synthesis of Camptothecin.

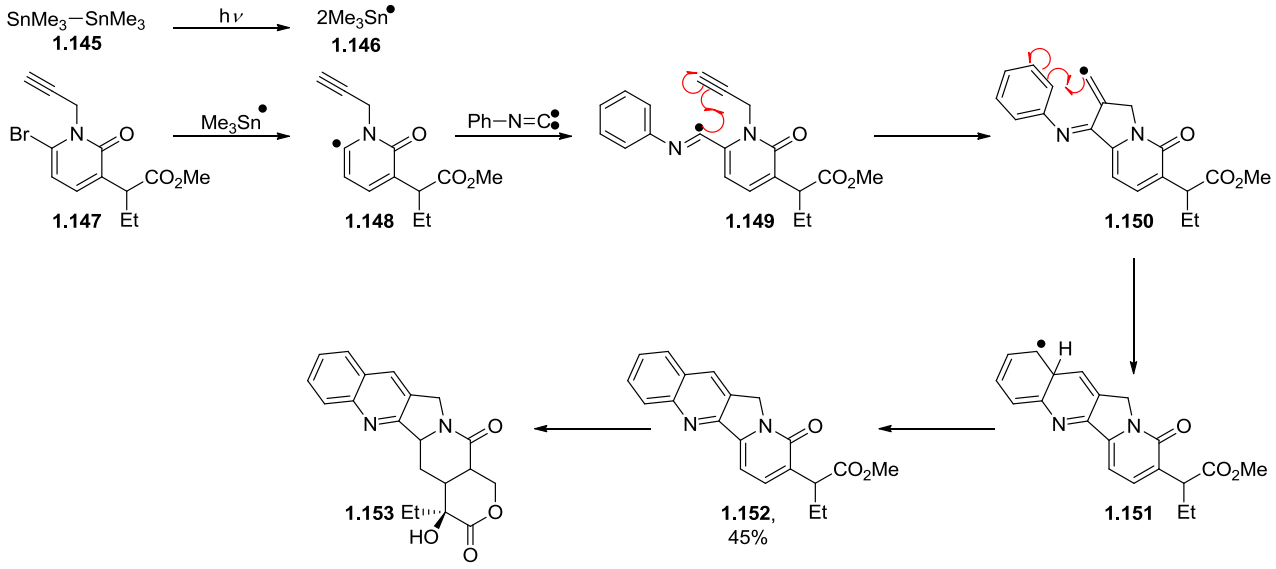
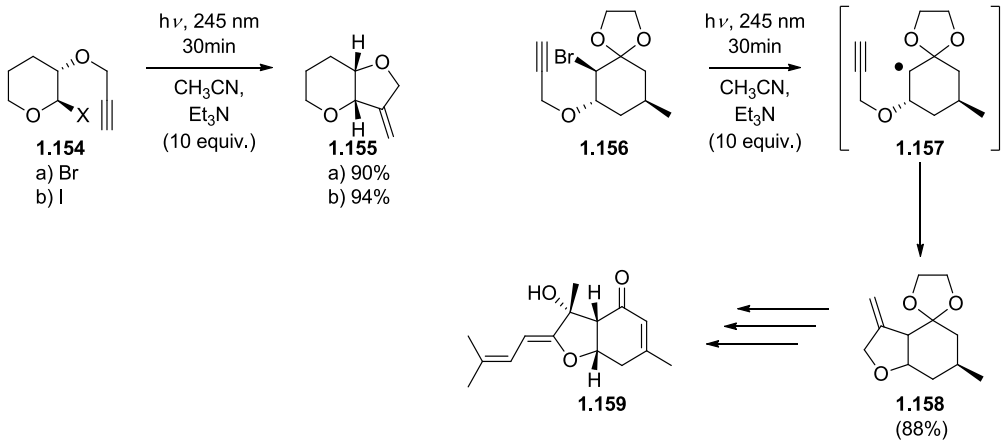


Photo-induced electron transfer can also be useful for cyclisations of aliphatic organic halide compounds. 5-*Exo-dig* cyclisation afforded heterocycle **1.155** in 90 and 94%, respectively from bromo and iodo precursor compounds, **1.154a** and **1.154b** when they were irradiated at 254 nm in acetonitrile in the presence of triethylamine for 30 minutes. This photo-reductive cyclisation was then used to generate **1.158**, an intermediate in the natural product synthesis (±)-bisabolangelone **1.159**[55] (**Scheme 1.30**).

Scheme 1.30 Synthesis of (±)-bisabolangelone.

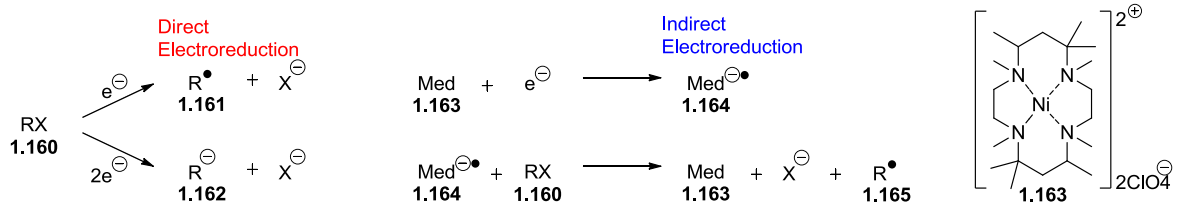


1.5 Electro-reductive Cyclisation Processes

Electrochemistry can provide a very clean, catalytic and environmentally friendly alternative route to reactive intermediate generation *via* electron transfer. In some instances addition of further reagents can be avoided, thus circumventing associated hazards and purification issues. Electrochemistry can be particularly useful for the formation of new intramolecular C-C bonds,[56] as well as the transformation of electron-poor functional groups, like cyano-, nitro- and carbonyl- groups by cathodic reduction to their corresponding nucleophiles.

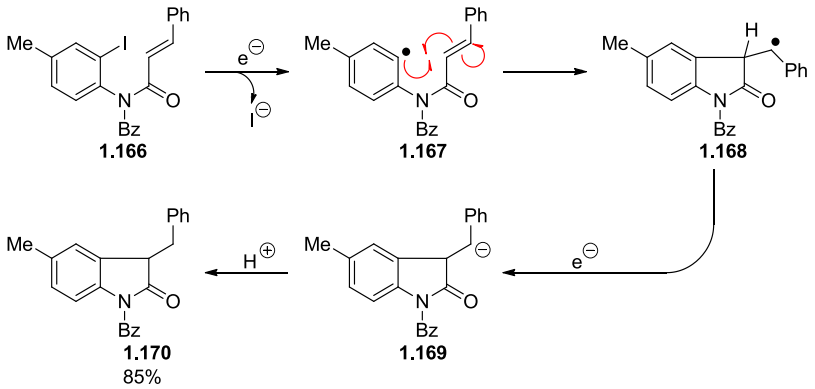
The electrochemical reduction of organic halides is well studied and can be conducted either by direct electrochemical reduction of substrates at the surface of an electrode or indirect electrochemical reduction in which a catalyst or mediator, (Med) *e.g.* $Ni(Me_6\text{-cyclam})(ClO_4)_2$ the complex **1.163** is reduced *in situ* at the electrode; reactive mediator **1.164** then transfers an electron to organic halide regenerating **1.163**.[56] The use of a catalyst can be beneficial for radical chemistry, preventing generation of anions by second electron transfer (**1.162**) often observed with direct electrochemical reduction.

Scheme 1.31 Direct and indirect electrochemical reduction.



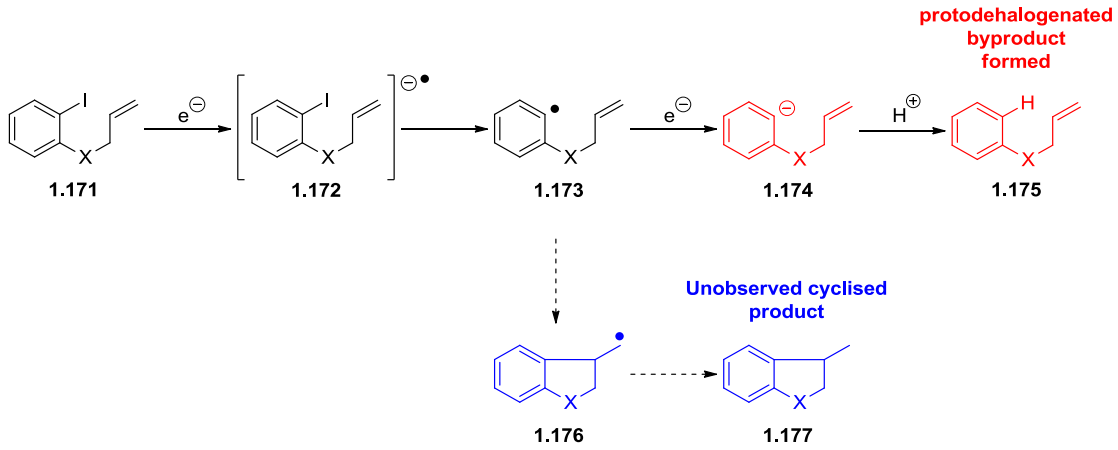
Munusamy *et al.*[57] were able to perform an elegant radical cyclisation by cathodic electrochemical reduction of iodophenyl alkylcinnamides **1.166** (**Scheme 1.32**).

Scheme 1.32 Aryl radical cyclisation *via* the electrochemical reduction of aryl iodide **1.166**.



However, as mentioned above, the direct electrochemical method can lead to further reduction of desired radicals like **1.173** to undesired anions **1.174**, when the kinetics of radical cyclisation are less favourable. Duñach *et al.*[58] observed the formation of protodehalogenated byproducts **1.175** as opposed to desired cyclised products **1.177**. This is perhaps not surprising, the potential for reduction of phenyl radical to phenyl anion is only E^0 = +0.05 V.[59]

Scheme 1.33 The electrochemical reduction of aryl halides.

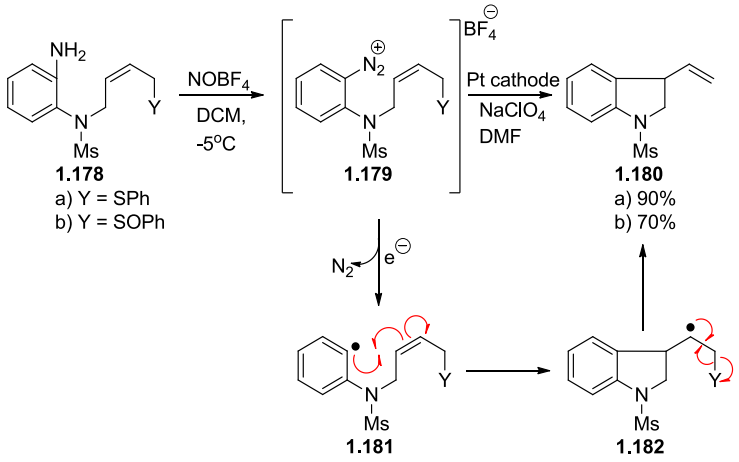


Although the alternative indirect *in situ* electrochemical reduction of metal complexes can be employed to generate radicals, both the indirect and direct electrochemical reductions of aryl halides tend to be carried out at more negative potentials, -1.5 to -2.5 V versus SCE, particularly harsh conditions to use on substrates bearing sensitive functionalities.

The report of very mild electrochemical reduction of diazonium salts at 0 V *vs*. SCE[60] encouraged Murphy *et al.*[61] to explore their application in synthesis. In contrast to aryl halides, arenediazonium salts were excellent electron acceptors and selectively converted to aryl radicals under milder conditions. This direct controlled electro-reduction of arenediazonium salts afforded indoles and indolines from appropriate substrates.

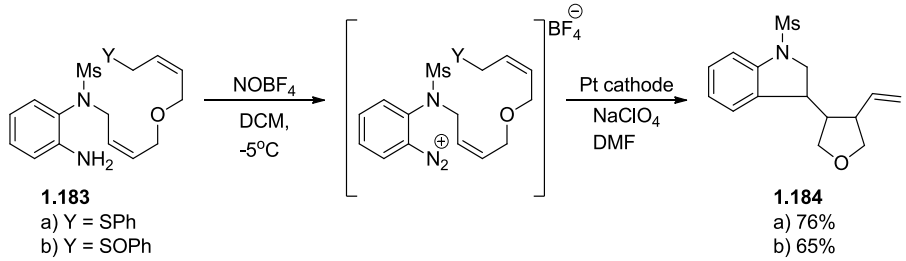
Indoline **1.180** was first synthesised employing sulfide and sulfoxide as leaving groups (**Scheme 1.34**). Compounds **1.178a** and **b** were converted to diazonium tetrafluoroborates **1.179** *in situ*. Electro-reduction at a platinum cathode promoted the loss of nitrogen and formation of aryl radical **1.181**; 5-*exo-trig* cyclisation generated radical intermediate **1.182** which eliminated thiyl or sulfinyl radical to afford vinylindoline **1.180** in good to excellent yield.

Scheme 1.34 Cathodic reduction of arene diazoniums salts affording indoline.



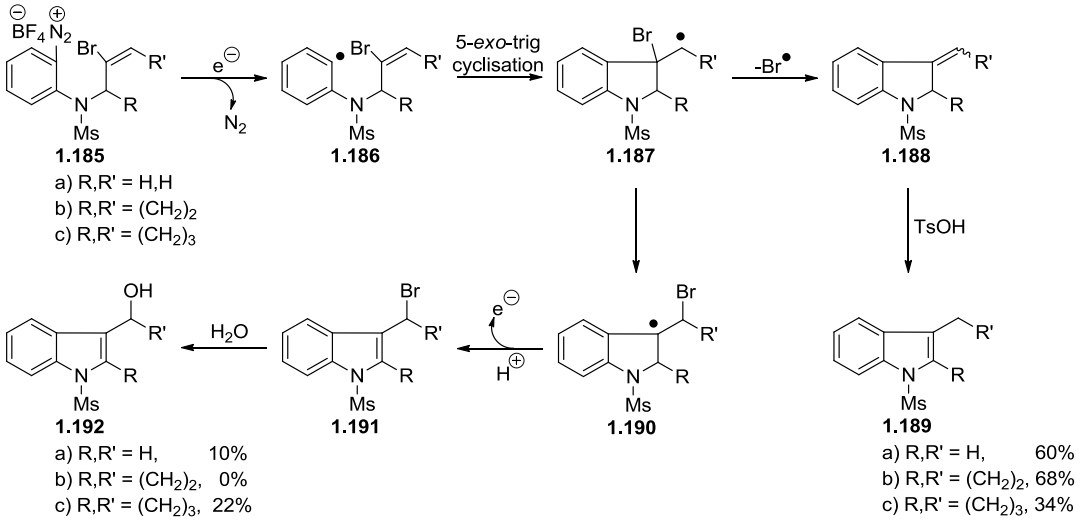
This methodology was then applied to more complex substrates **1.183a**,**b** which successfully underwent two intramolecular 5-*exo*-*trig* cyclisations to produce vinyltetrahydrofuran **1.184** in good yield.

Scheme 1.35 The electro-reductive cyclisation to vinyltetrahydrofuran **1.184**.



Finally advances were made towards indoles (**Scheme 1.36**). Electro-reduction of **1.185** generated aryl radical **1.186** which underwent rapid cyclisation and elimination *via* **1.187** to afford *exo*-cyclic alkene, indolenine **1.188**. The indolenines can be easily tautomerised to indoles **1.189** in the presence of acid. Intriguingly however, a second unexpected product was isolated from these reactions, namely alcohols **1.192a**,**c**, the result of a 1,2-bromine shift[62] from **1.187** to **1.190**. It is possible that an oxidation of this benzylic radical occurs by transfer of an electron to a diazonium cation, a proton loss would now form bromoalkyl indole **1.191** which could easily undergo hydrolysis to alcohol **1.192a**,**c**.

Scheme 1.36 The electro-reductive indole synthesis.

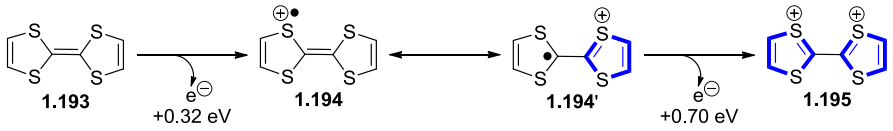


1.6 Neutral Organic Electron Donors:

1.6.1 Tetrathiafulvalene, TTF

Tetrathiafulvalene (TTF), is a neutral, air-stable organic compound capable of electron transfer to easily reduced organic substrates. The driving force for electron transfer from TTF **1.193** is associated with the gain in aromatic stabilisation energy upon oxidation to radical cation **1.194** and dication **1.195** (illustrated in blue **Scheme 1.37**).

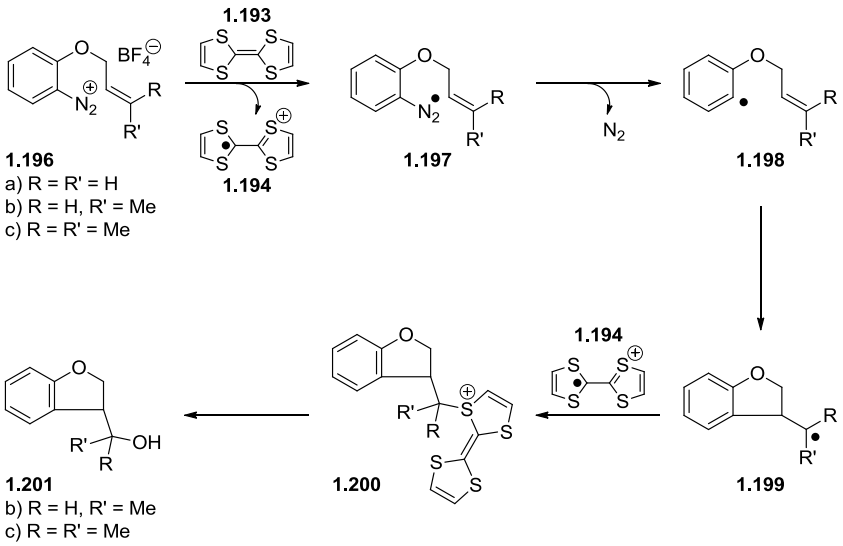
Scheme 1.37 Gain in aromaticity upon oxidation of TTF.



The redox potential for donation of the first electron is $E_{1/2}$ = +0.32 V *vs.* SCE in MeCN for TTF → $TTF^{\bullet+}$ (**1.193** → **1.194**), while the second is weaker $E_{1/2}$ = +0.70 V *vs.* SCE for $TTF^{\bullet+}$ → TTF^{2+} (**1.194** → **1.195**).[63] The lone pairs of electrons on the four sulfur atoms donate electron density making TTF a moderate electron-donor, with the capability of reducing arenediazonium salts. [64-69] Previous work in our laboratories focused on the fate of the diazonium substrate using TTF to develop useful synthetic applications under neutral reaction conditions. The most important reaction to take place between TTF and arenediazonium salts is radical polar cross-over,[64-69] where radical and ionic (polar) reactions

occur consecutively in a single chemical process. This is unusual as most organic reactions usually proceed by only a radical or ionic path.

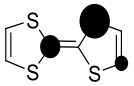
Scheme 1.38 The reaction mechanism for radical-polar cross-over.



The reaction is initiated by donation of an electron from the HOMO of TTF **1.193** to the LUMO of arenediazonium salt **1.196** forming radical species **1.197** and $TTF^{\bullet+}$ radical cation **1.194**. Decomposition of **1.197** with evolution of nitrogen gas generates a new radical species **1.198**; this rapidly undergoes 5-*exo-trig* cyclisation and the cyclised radical **1.199** is trapped by $TTF^{\bullet+}$ radical cation **1.194** affording sulfonium salt **1.200**. It is at this stage that the process makes the transition from a radical to a polar mechanism with solvolysis of **1.200** yielding alcohol products **1.201b** and **c**.

The original experiments were carried out on three substrates **1.196a-c**, in undried acetone at room temperature. Intriguingly, no alcohol was isolated from the reaction of **1.196a**. Instead tetrathiafulvalenium salt **1.200a** was isolated as a mixture of diastereoisomers. This established that recombination had taken place and also indicated that sulfur must have tetrahedral geometry, thus a C-S rather than C-C bond was formed during radical trapping. Indeed, the computational results of Zahradnik *et al.*[70] showed the greatest spin density of TTF radical cation associated with sulfur atoms of TTF and therefore the most likely site for radical trapping.

Figure 1.1 Spin density on radical cation $TTF^{\bullet+}$.[70]

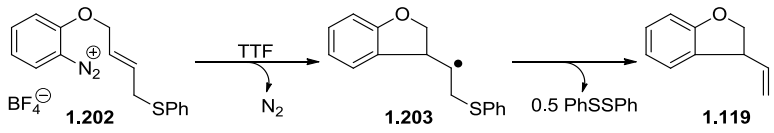


As **1.196b** and **c** both yielded alcohol but **1.196a** did not, then at least one terminal alkyl group needed to be alkyl for solvolysis to take place. As the primary salt resists solvolysis by S_N2 it was suggested that the reaction proceeded *via* an S_N1 mechanism.

Nucleophiles other than water were shown to be able to participate in the termination step. Reactions carried out with methanol afforded methyl ethers and reactions with acetonitrile afforded nitrilium salts that could be further hydrolysed to amides.

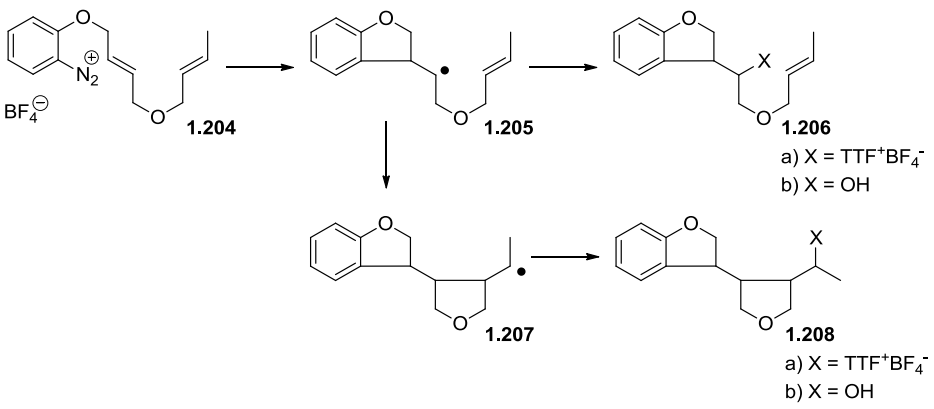
The reaction of **1.202** with TTF afforded alkene product **1.119** and diphenyl disulfide by rapid elimination phenylsulfanyl radical, clearly demonstrating that cyclisation proceeded by a radical mechanism *via* electron transfer from TTF.

Scheme 1.39 Synthesis of 3-vinyl-2,3-dihydrobenzofuran.



Tandem radical cyclisation of **1.204** mediated by TTF afforded a mixture of *mono*-cyclised **1.206** and bi-cyclised **1.208** products, showing that cyclisation of intermediate radical **1.205** and recombination with $TTF^{\bullet+}$ occurred at comparable rates.

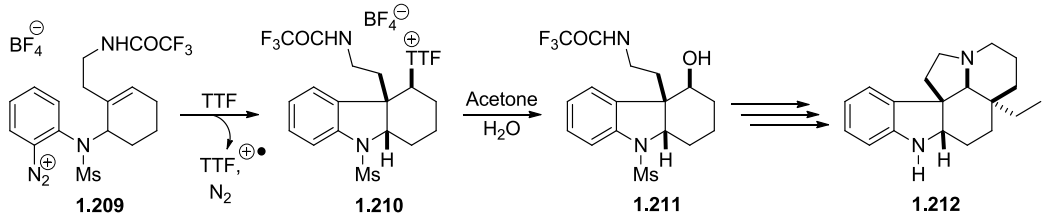
Scheme 1.40 The tandem radical cyclisation to dihydrofuran **1.208**.



Based on the success of these early studies the chemistry was now directed towards the synthesis of indoles and the Murphy group were successful in the total synthesis of (±)-aspidospermidine **1.212**,[68,71] a compound closely related to potent anti-cancer drugs vinblastine and vincristine (**Scheme 1.41**).

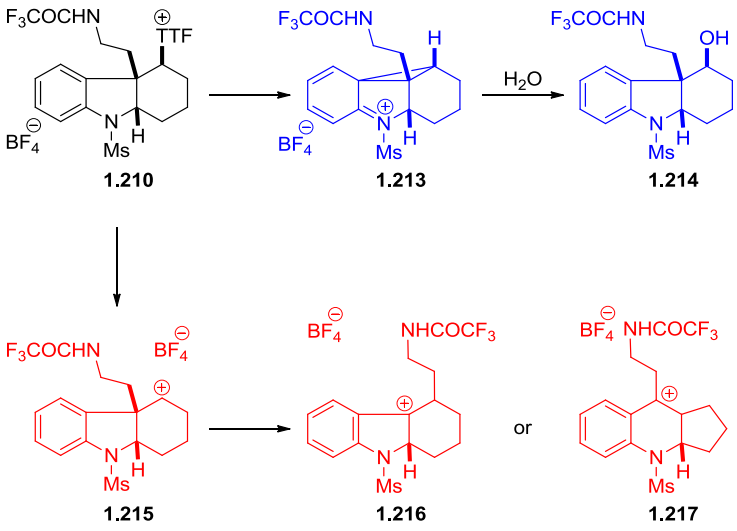
Fundamentally important to the success of this synthesis was the formation of the *cis*- ring junction in **1.210**, and the isolation of alcohol **1.211** as a single diastereoiomer, suggesting that $TTF^{\bullet+}$ trapped the radical formed after cyclisation in a stereoselective manner and that water trapped a subsequent cation selectively.

Scheme 1.41 Synthesis of (±)-Aspidospermidine **1.212**.



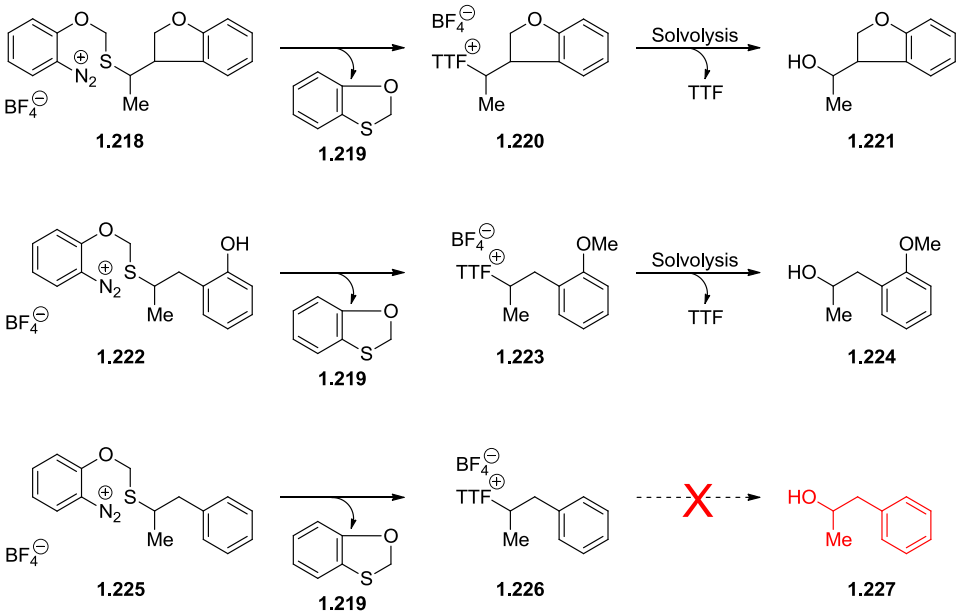
Considering the intermediate tetrathiafulvalenium salt **1.210** (**Scheme 1.42**), this should lead to carbocation **1.215** which, in turn, should undergo rearrangement to potentially more stable carbocations **1.216** or **1.217**. However, this was not observed which led Murphy *et al*. to conclude that **1.215** was not formed but, instead the more stable delocalised carbocation **1.213** involving the aromatic ring and heteroatom.

Scheme 1.42 Cation intermediates.



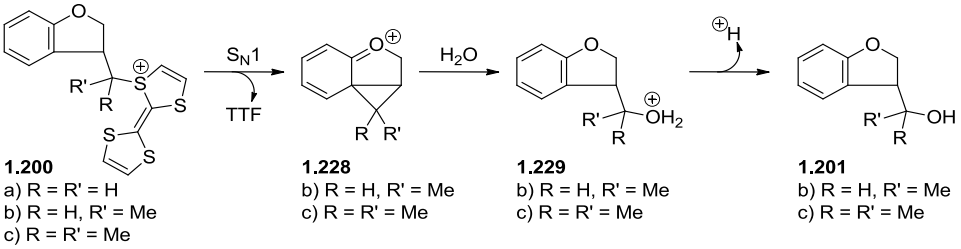
Further investigations revealed the importance of the aromatic ring in assisting solvolysis and the need for one extra electron-donating group, for 'neighbouring group participation' (**Scheme 1.43**).[65] Thus, tetrathiafulvalenium salts **1.218** and **1.222** bearing the electron-donating oxygen in the *ortho* position undergo solvolysis to alcohols **1.221** and **1.224**, respectively unlike **1.225**, without a neighbouring electron-donating group.

Scheme 1.43 Neighbouring group participation.[65]



It was also noted that primary tetrathiafulvalenium salts required greater electron donation through neighbouring group participation than secondary tetrathiafulvalenium salts. Reconsidering **Scheme 1.38**, solvolysis of secondary (**1.200b**) and tertiary (**1.200c**) tetrathiafulvalenium salts (**Scheme 1.44**) is assisted by neighbouring group participation of oxygen through the aryl ring thus forming cyclopropanes in cationic intermediates **1.228b** and **c** respectively.

Scheme 1.44 Solvolysis observed in secondary and tertiary tetrathiafulvalenium salts.



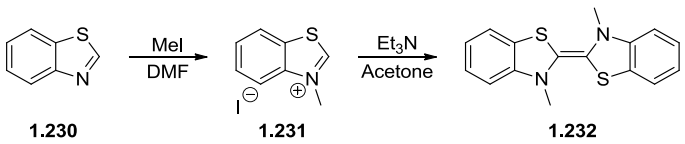
Importantly, this helps to explain why rearrangement is not observed in **1.210** (to **1.198**). Solvolysis is assisted by electron donation through neighbouring group participation of the nitrogen and the aryl ring, forming delocalised carbocation **1.213**, which may prevent rearrangement and also serve to protect one face of the cyclohexyl ring from attack. In relation to the synthesis of (±)-aspidospermidine, this may explain why alcohol **1.214** was isolated as a single diastereoisomer.

Although TTF had been successfully applied in synthesis, its redox potential of $E_{1/2}$(MeCN) = +0.32 and +0.71 V *vs.* SCE would restrict its chemistry to the reductions of arenediazonium salts. More readily available bromobenzenes and iodobenzenes have redox potentials of E^0 = -2.43 V (*vs.* SCE in DMF) and E^0 = -1.91 V (*vs.* SCE in DMF)[72] respectively, much too challenging for TTF. As the reduction of aryl bromides and iodides as useful intermediates was desirable, alternative more powerful electron donors TTF would be required.

1.6.2 Diazadithiafulvalenes, DDTF

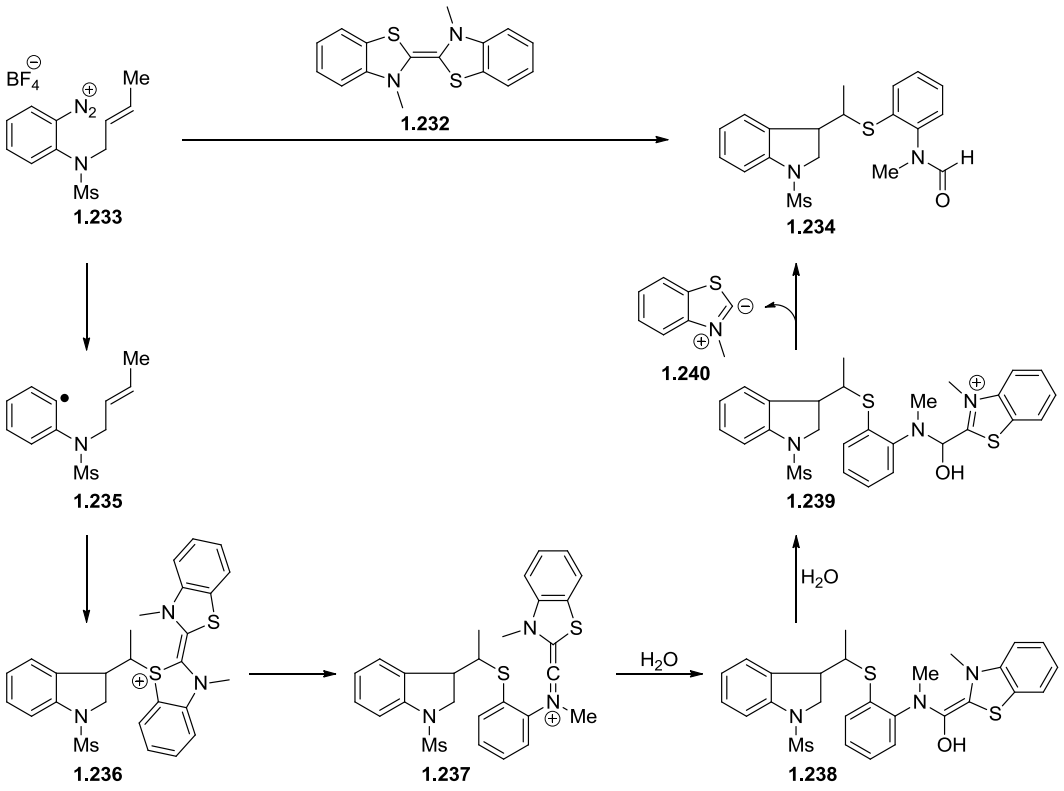
One of the earliest reports relating to the synthesis of DDFT-like molecules was that of benzannelated derivative **1.232** in the 1960's by Metzger *et al.*[73] The compound was highly sensitive to air, and thus isolation and full characterisation proved highly problematic. Since Metzger's report, Wanzlick *et al.*[74] disclosed a straightforward synthetic route to **1.232**, (**Scheme 1.46**). Alkylation of benzothiazole **1.230** with iodomethane afforded salt **1.231** which dimerises on deprotonation with base to afford diazadithiafulvalene electron donor, **1.232**.

Scheme 1.46 Synthesis of DDTF molecule **1.232**.



DDTF molecules incorporate a mixed two nitrogen, two sulfur system. It was thought that nitrogen atoms would confer stability to the radical cation generated after electron transfer. As nitrogen and carbon are more similar in atomic size, the resultant radical cation should have greater aromatic stabilisation due to increased orbital overlap. Therefore, the DDTF system should have a greater driving force for electron-donation than TTF.

Scheme 1.47 Reaction of arenediazonium salt with DDTF.



Initial reactions were performed on diazonium salt **1.233**,[75] with DDTF molecule **1.232** (**Scheme 1.47**). However, the reaction did not proceed as predicted and product **1.234** was isolated from the reaction. After electron transfer and loss of N_2, the radical formed by 5-*exo*-trig cyclisation was trapped by diazadithiafulvalenium radical cation, $DDTF^{\bullet+}$ resulting in adduct **1.236**, paralleling the chemistry of TTF. However, the greater ability of nitrogen to stabilise the positive charge leads to fragmentation of the adduct and production of keteniminium salt **1.237**. Hydrolysis yields **1.238** and **1.239** and subsequent elimination of heterocyclic zwitterion **1.240** affords product **1.234**.

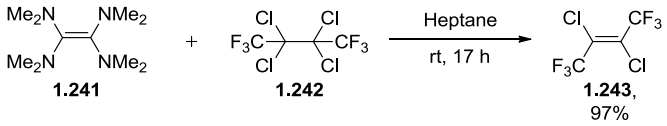
Further experimentation revealed that electron donor **1.232** was not powerful enough to reduce C-I bonds.[75] Along with the fact that the rearrangements of intermediates led to undesired products, it was clear that changes in the molecular design of the electron donor were required to overcome these limitations.

1.6.3 *Tetrakis*(dimethylamino)ethylene, TDAE

TDAE **1.241**, first disclosed in 1950[76] and was reported to effect the dechlorination of highly activated polyhalogenated compounds *e.g.* **1.242** by Carpenter[77] in 1965. Later he reported

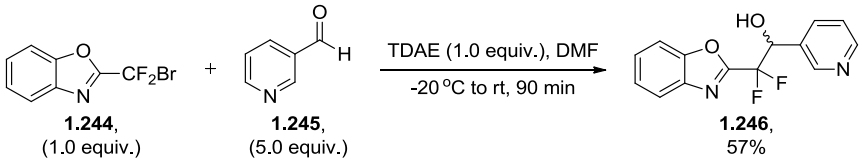
TDAE's application in carbon-fluorine reductive bond cleavage of activated polyfluorinated compounds.[78]

Scheme 1.48 Dechlorination with TDAE.



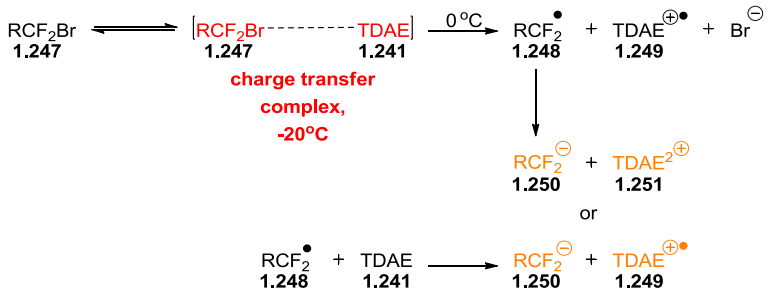
However the reagent received little attention and was not utilised for many years, until Médebielle *et al.*[79] synthesised a *β,β*-difluoro-*α*-heteroarylated alcohol **1.246** in the late 1990's in a TDAE mediated process.

Scheme 1.49 Médebielle *et al.* used TDAE in reduction of activated bromides.



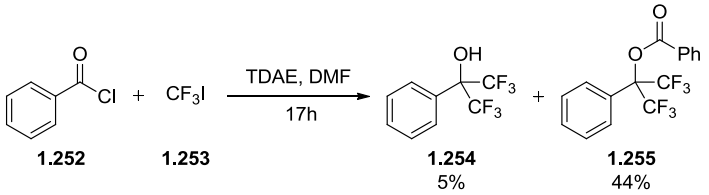
At low temperatures (-20 °C) the reaction is believed to proceed *via* the formation of a charge-transfer complex between **1.247** and TDAE **1.241**, with a deep red colouration being observed. Gradual increase in temperature brings about a colour change to orange as the complex decomposes, generating anion **1.250** and $TDAE^{2+}$ **1.251**. The anion's life-span is sufficiently long to nucleophilically attack aromatic aldehydes affording products like alcohol **1.246**.

Scheme 1.50 Mechanism for generation of reactive anion **1.250**.



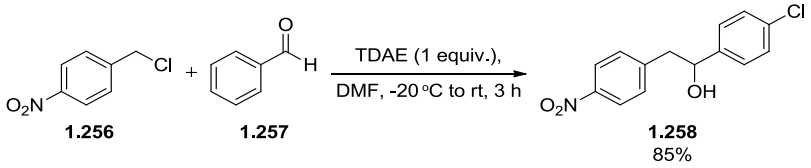
Médebielle *et al*. expanded the reaction scope to the synthesis of esters.[80] Trifluoromethyl anions were generated by double electron transfer to trifluoromethyl iodide **1.252**. Sequential attack by two trifluoromethyl anions at acid chloride **1.253**, affords alcohol **1.254**. Esterification of alcohol **1.254** with benzoyl chloride **1.252** yields ester **1.255**.

Scheme 1.51 Reaction of acid chloride with trifluoromethyl anions.



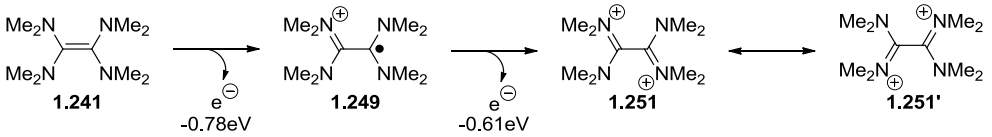
The mild conditions that the electron transfer was performed under meant that Médebielle was able to sever carbon-halogen bonds to generate benzyl anions, which could then nucleophilically attack aldehydes and esters. These promising initial results were followed up in the reaction of nitrobenzyl anions with aromatic aldehyde **1.257** to afford alcohol **1.258** (**Scheme 1.52**), *via* the reduction of benzyl nitro chloride **1.256**.[81]

Scheme 1.52 Reaction of benzyl anion with aldehyde.



In contrast to TTF, TDAE does not gain aromaticity on oxidation but the greater π-donating power of nitrogen (as opposed to sulfur in TTF) more effectively stabilises positive charge in the corresponding radical cation **1.249** and dication **1.251**. The two reversible one electron oxidations occur at $E_{1/2}$ = -0.78 and $E_{1/2}$ = -0.61 V (*vs.* SCE in MeCN)[79] for the TDAE → $TDAE^{\bullet+}$ (**1.241** → **1.249**) and $TDAE^{\bullet+}$ → $TDAE^{2+}$ (**1.249** → **1.251**), respectively (**Scheme 1.53**).

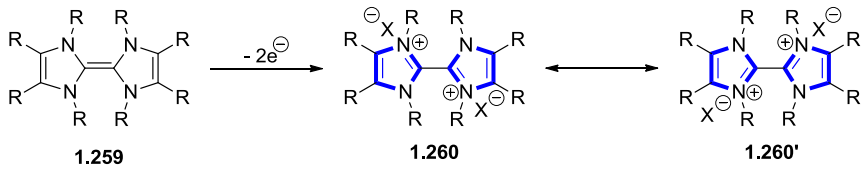
Scheme 1.53 Oxidation of TDAE to dication.



Although TDAE is a more powerful electron donor than TTF, and is capable of the reduction of activated or electron-deficient organic halides as described above, it is still not sufficiently powerful to reduce unactivated aryl halides. However, this research clearly highlights that inclusion of nitrogen in future electron-donating reagents would be beneficial.

Therefore in order to synthesise neutral organic electron donors with stronger redox potentials the logical next step was to combine the electron-donating features of the TTF and TDAE in one structure, a tetraazafulvalene **1.259**. The corresponding oxidised salt, **1.260** of tetraazafulvalene **1.259** would benefit from a gain in aromatic stabilisation energy (shown in blue, **Scheme 1.54**) and greater stabilisation of positive charge which is delocalised by four strongly π-electron-donating nitrogens (as opposed to sulfurs).

Scheme 1.54 Template for new electron donors.

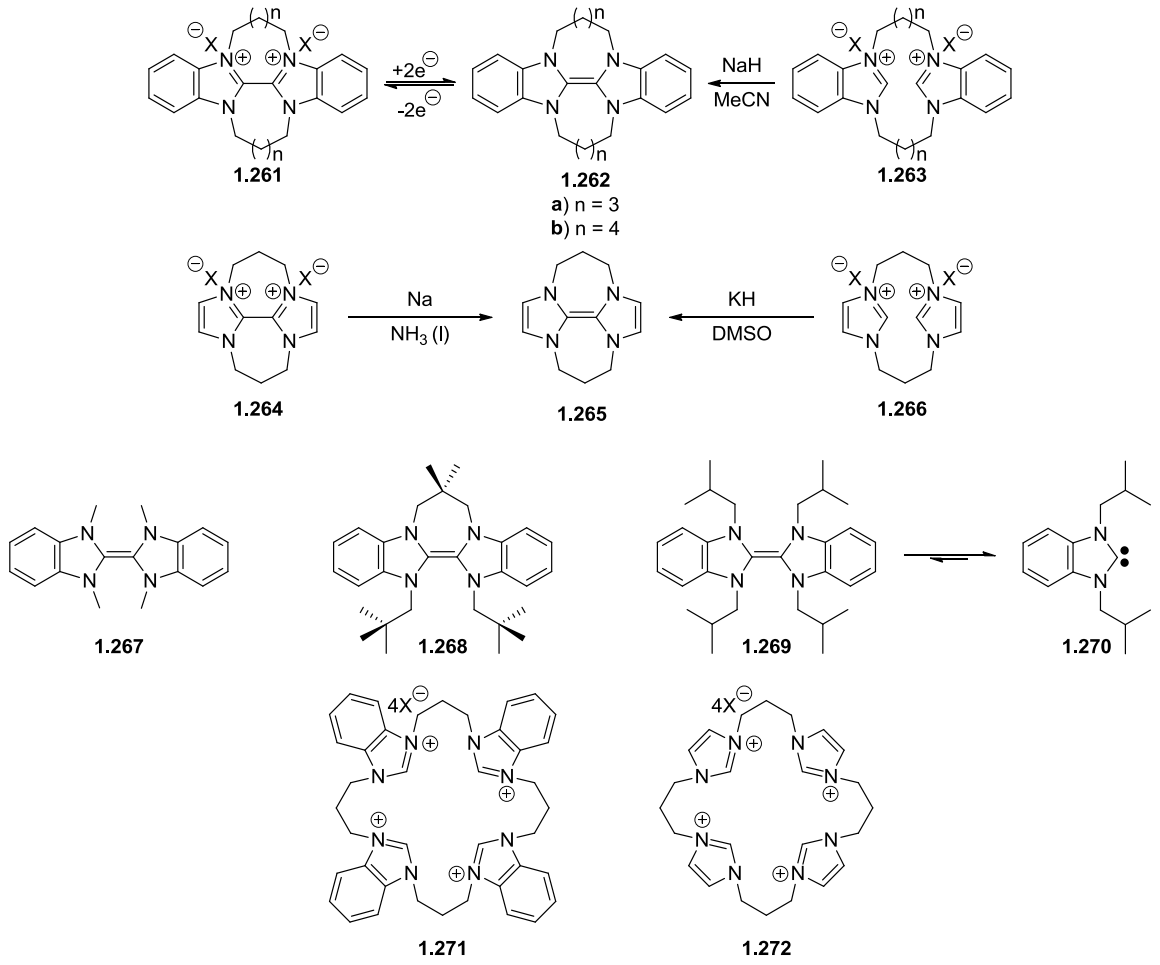


1.7 Super Electron Donor Reagents, SEDs:

1.7.1 Tetraazafulvalenes

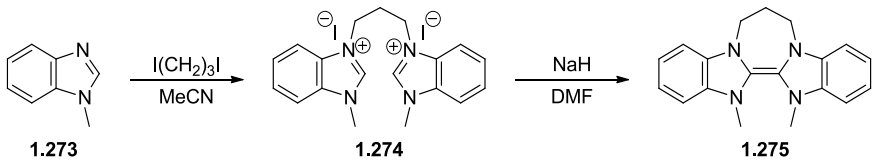
Some tetraazafulvalenes with generic structural features of **1.259** already existed in the literature[3,82-87] but had not been studied for the purpose of synthetic electron transfer chemistry. The di-tethered benzimidazole **1.262** and imidazole **1.265** derived tetraazafulvalene systems had been successfully synthesised by Thummel *et al.*[83-85] and Taton and Chen,[3] respectively, while Lappert *et al.*[86] had reported the synthesis of unbridged tetraazafulvalene **1.267** and Hahn *et al*. had investigated the formation of **1.268** and the dissociation of **1.269** into benzimidazol-2-ylidene **1.270**. Although the dimerisation of *N*-heterocyclic carbenes[4] and the Wanzlick equilibrium[88] is pertinent to the formation of tetraazafulvalenes it will not be discussed in great detail in this section on SED but further details can be found in **Results and Discussion: Chapter 3**.

Scheme 1.55 Known tetraazafulvalenes.



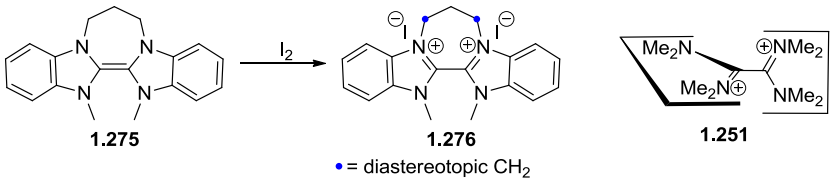
The synthesis of *bis*-tethered salts **1.263** and **1.266** (precursors to tetraazafulvalenes) was complicated due to the simultaneous formation of the corresponding macrocyclic tetramer byproducts **1.271** and **1.272** respectively.[85,89,90] Accordingly early work in our laboratories focused on the comparatively easily prepared benzimidazole-derived tetraazafulvalene **1.275** (**Scheme 1.56**).[91] Benzimidazolium salt **1.274** was synthesised from cheap starting materials by the alkylation of methylbenzimidazole **1.271**, subsequent deprotonation of **1.274** allowed the preparation of **1.275** on the mmol scale. The propylene tether was anticipated to confer stability to the tetraazafulvalene dimer **1.275**. Electrochemical investigations by Ames *et al.*[92] into tetraazafulvalenes had revealed that **1.275** was one of few tetraazafulvalene examples to have a reversible oxidative wave in its cyclic voltammogram. This study also revealed that in general longer propylene tethering gave stronger redox potentials than ethylene bridges presumably by permitting greater charge separation in the corresponding oxidised salt, by allowing increased rotation of the benzimidazole rings around the central single C-C bond in **1.276**.

Scheme 1.56 Benzimidazole-derived tetraazafulvalene **1.275**.



Treatment of disalt **1.274** with base in deoxygenated DMF under argon yielded tetraazafulvalene **1.275** as a highly air-sensitive transparent yellow solution.[91] ^{13}C-NMR spectroscopy verified the formation of dimer **1.275**, identifying the characteristic central alkene signal of the quaternary carbon at δ = 123.1 ppm. No trace of the resonances at 230 ppm typical of *bis*- or *mono*-benzimidazole-2-ylidenes was evident.

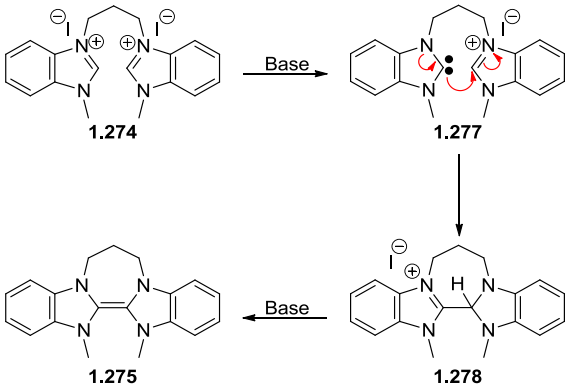
Scheme 1.57 Reduction of tetraazafulvalene **1.275** with iodine.



1.275 was oxidised with easily reduced iodine to forming C_2-tethered **1.276**. Molecular modelling of $TDAE^{2+}$ **1.251**, had indicated that a twisting to orthogonal planes would minimise repulsion between the two positively charged amidinium units. As such it was expected that the 3-carbon bridge in disalt **1.276**, would undergo a helical twist, conferring rigidity to the molecule and imparting diastereotopicity to the two CH_2 groups adjacent to nitrogen. Indeed, ^{1}H-NMR spectroscopy proved this to be the case, while assurance that the alkene in dimer **1.275** had been formed cleanly was provided by HRMS, which showed a mass of **1.276**-I^-.

The reaction mechanism for the formation of tetraazafulvalene **1.275** likely proceeds *via* deprotonation of **1.274** generates *mono*- carbene **1.277**, with intramolecular nucleophilic attack of the benzimidazol-2-ylidene on adjacent benzimidazolium affording the new C_2-tethered benzimidazolium salt **1.278**. Deprotonation of **1.278** affords desired tetraazafulvalene **1.275**.[4]

Scheme 1.58 Mechanism for generation of donor **1.275**.



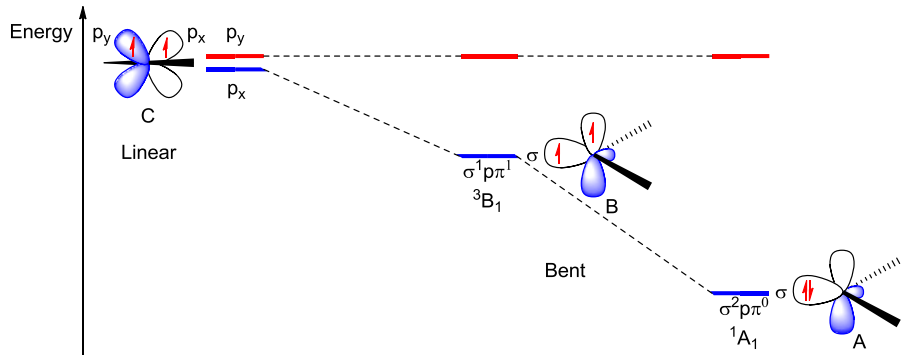
Imidazolinium[4,93] and thiazolium[94] intermediates analogous to **1.278** have been characterised by Alder *et al.*[93] and Chen and Jordan,[94] respectively. These intermediates suggest that tetraazafulvalene and diazadithiafulvalene compounds are formed *via* a nucleophilic attack of a carbene on an azolium, superseded by deprotonation (the same mechanism operates for 'proton-catalysed dimerisation', where the reaction between two carbenes is initiated by addition of a proton forming an azolium; *see* **Results and Discussion: Chapter 3**). The alternative mechanism involving the direct dimerisation of two *N*-heterocyclic carbenes is not thought to occur (*vide infra*, **Figure 1.4**) and would not form intermediates like those observed by Alder *et al.*[4,93] and Chen and Jordan.[94]

1.7.2 Carbenes

Carbenes are neutral molecules with a divalent carbon having only six electrons in its valence shell. The geometry of the carbene can be either linear or bent. The linear geometry is based on a sp-hybridised carbene carbon atom leading to two energetically degenerate p-orbitals (p_x, p_y). This linear geometry is an extreme and most carbene carbon atoms adopt a sp^2-hybridised non-linear geometry. In the transition from sp-hybridised to sp^2-hybridisation the energy of the non-bonding p-orbital (p_y), called the p_π-orbital, does not significantly change. The sp^2-hybridised carbon has a non-bonding sp^2-hybrid orbital, called the σ-orbital, with partial s-character and so is stabilised relative to the original p-orbital.

The two non-bonding electrons of the carbene can occupy the two empty orbitals (σ and p_π) in one of two different ways (**Figure 1.2**). Either both electrons can be paired with anti-parallel spin in the σ-orbital, giving singlet state **A** or they can be distributed one electron in each of the σ-orbital and p_π-orbital with parallel spin leading to triplet state **B**.[95,96]

Figure 1.2 Frontier orbitals and possible electron configurations of carbene atoms.



The multiplicity of the carbene defines its reactivity; singlet carbenes with filled σ- and empty p_π-orbitals are ambiphilic where as triplets carbenes with two unpaired electrons can be considered diradicals. The multiplicity of the ground state (for both **A** or **B**) is determined by the relative energies of the σ- and p_π-orbitals and is strongly influenced by the steric and electronic effects of substituents *α* to the carbene carbon. If the energy for pairing electrons in the lower energy σ-orbital is larger than the energy gap between the σ- and p_π-orbitals then a triplet state will be favoured (quantum chemical calculations showing that the singlet ground state **A**, is stabilised when there is a 2 eV energy between σ-orbital and p_π-orbital, conversely a gap of less than 1.5 eV favours triplet ground state **B**).

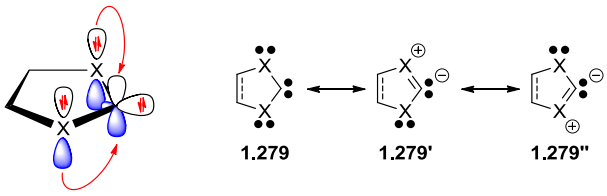
N-Heterocyclic carbenes (NHCs) with nitrogen neighbouring the carbene carbon, adopt singlet state **A** because it is stabilised relative to the triplet state **B** by both inductive and mesomeric effects:

- the negative inductive effect of electronegative nitrogen - lowers the energy of the sp^2-hybrid σ-orbital by withdrawing electron density, therefore increasing σ-p_π energy gap (as p_π-orbital energy is unchanged).
- the mesomeric interactions of the lone π-electron pairs on nitrogen (**Figure 1.3**), donate electron density to the empty carbon p_π-orbital raising its relative energy thus also increasing σ-p_π energy level gap (as σ-orbital energy is unchanged).

Carbenes with σ-electron donating and π-accepting neighbouring atoms have increased σ-orbital energy and decreased p_π-orbital energy thus the σ-p_π energy level gap is decreased, therefore favouring triplet state with an increasing linear geometry. Additionally, carbenes with neighbouring atoms bearing bulky substituents favour the triplet state, as both non-bonding orbitals are forced towards a linear structure, so that they a degenerate p_x- and p_y-orbitals.[97]

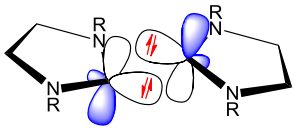
NHCs adopt a bent geometry and mesomeric interactions also lead to the N-C bonds acquiring partial double-bond character, to some extent establishing a four-electron, three-centre π-system, **1.279**.

Figure 1.3 Electronic configuration and resonance structures of five-membered X_2C carbenes, where X is π-electron-donating atom *e.g.* nitrogen.



As mentioned above, an alternative dimerisation mechanism for the formation of tetraazafulvalene **1.275** would be the direct coupling of two singlet carbenes (**Figure 1.4**). This would involve the HOMO, filled σ-orbital of one NHC overlapping with the LUMO, p_π-orbital of the other. This would likely be subject to a high energy barrier as the nitrogens donate π-electrons into this 'empty' p_π-orbital raising its energy level and its electron density, therefore this 'direct dimerisation' is very improbable.

Figure 1.4 Alternative and unlikely dimerisation mechanism, directly combining *N*-heterocyclic carbenes.



1.7.3 Super-electron-donors – a radical beginning

Having successfully synthesised a new, previously unprepared benzimidazole-derived donor **1.275**, a series of reactions with aryl iodides was undertaken to establish the electro-reductive capability of the reagent. Subsequent experimentation indicated that aryl iodides **1.280a-d** afforded cyclic indoline products **1.281a-d** in excellent yields, while ether **1.280e** yielded 2,3-dihydrobenzofuran **1.281e**.

Scheme 1.59 Reduction of aryl iodides and 5-*exo-trig* cyclisation of the aryl radical cyclisation onto alkenes.

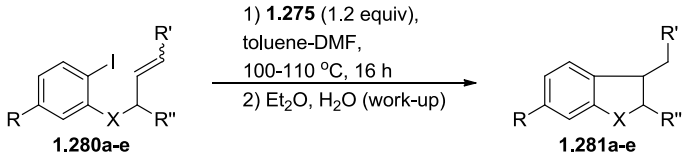
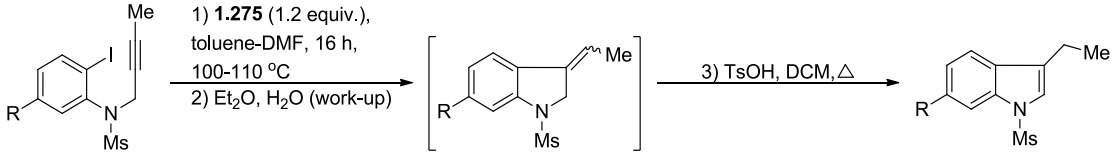


Table 1.1 Yields of cyclised products **1.281a-e** obtained by reductive cyclisation of aryl iodides **1.280a-e** with benzimidazole-derived tetraazafulvalene **1.275**.

Aryl Iodide **1.280**	X	R	R'	R''	Product % Yield **1.281**
a	NMs	H	H	H	80
b	NMs	H	Me	H	88
c	NMs	OMe	H	H	87
d	NMs	H	$-(CH_2)_3-$	= R'	89
e	O	H	H	H	65

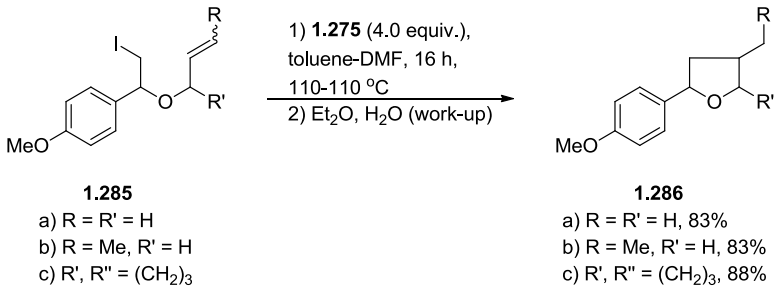
The reaction of electron donor **1.275** with **1.282** afforded indoles **1.284a** and **b**. Cyclisation onto the alkyne appendage generates the indolenine systems **1.283a** and **b**, which were not isolated but aromatised to the corresponding indoles by reaction under mild acid conditions.

Scheme 1.60 Indole synthesis using tetraazafulvalene **1.275**.



Alkyl iodides were also successfully reduced with **1.285** affording tetrahydrofurans **1.286** in excellent yield (**Scheme 1.61**).

Scheme 1.61 The radical cyclisation of alkyl iodides mediated by tetraazafulvalene **1.275**.

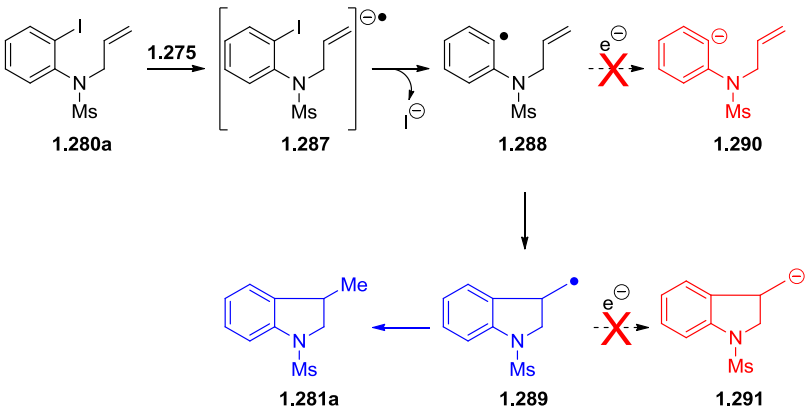


1.285
a) R = R' = H
b) R = Me, R' = H
c) R', R'' = $(CH_2)_3$

1.286
a) R = R' = H, 83%
b) R = Me, R' = H, 83%
c) R', R'' = $(CH_2)_3$, 88%

The products observed are characteristic of radical cyclisations, indicating tetraazafulvalene **1.275** was a single electron donor. Transfer of an electron from donor **1.275** to aryl iodide - **1.280a** would produce radical anion intermediate **1.287**. C-I σ-bond scission generates free radical **1.288**, which undergoes 5-*exo-trig* cyclisation yielding new radical **1.289**. Finally hydrogen abstraction affords indoline, **1.281a**. It is possible that anions **1.290** and **1.291** could form *via* the transfer of a second electron to free radicals **1.288** or **1.289**, respectively. However, this was highly improbable, as aryl anions do not undergo cyclisation with alkenes unless all other reactions are precluded.[6] In these reactions they would be more likely to undergo reaction nucleophilic attack on solvent DMF, but no products resulting from this were observed.

Scheme 1.62 Aryl iodides do not form anions when reacted with donor **1.275**.

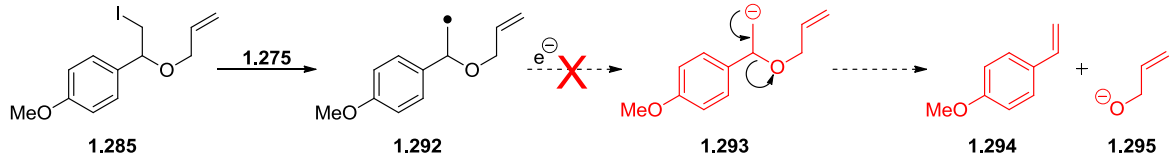


1.280a **1.287** **1.288** **1.290**

1.281a **1.289** **1.291**

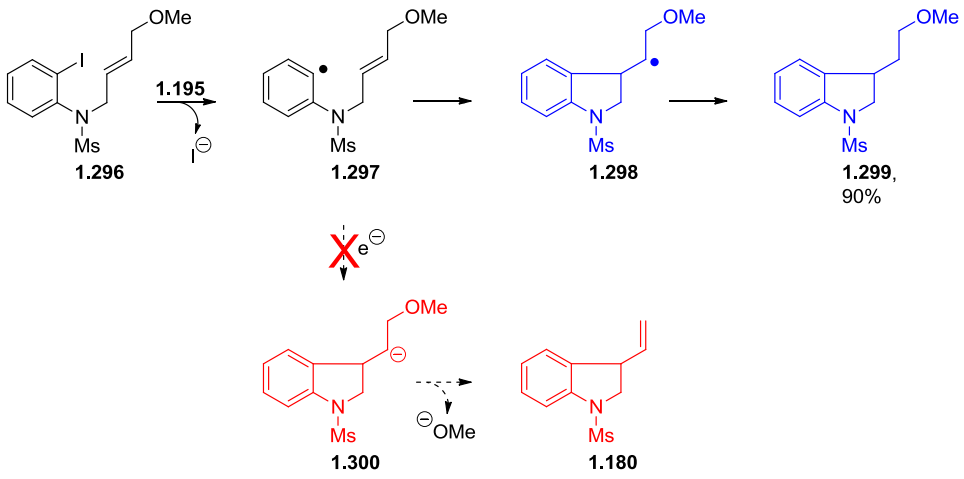
Furthermore, had the reduction of alkyl iodides **1.285** generated alkyl anion **1.293**, then elimination of alkoxide would be expected to follow but neither the styrene **1.294** nor the alcohol from **1.295** resulting from such a process were observed.

Scheme 1.63 Alkyl iodides do not form anions when reacted with donor **1.275**.



In order to confirm tetraazafulvalene **1.275** was behaving as a SET reagent it was further scrutinised with substrates **1.296** and **1.301**. If carbanion **1.300** was generated then rapid elimination to alkene **1.180** would occur, but this was not the case and only indoline **1.299** was isolated in an excellent 90% yield.

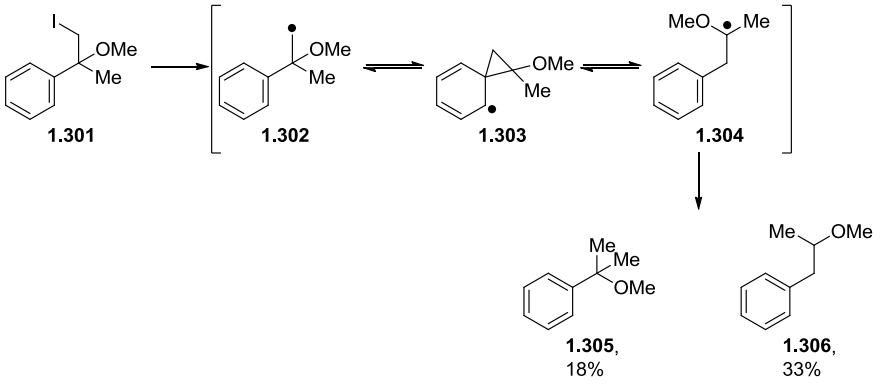
Scheme 1.64 Experimental proof of SET from SED **1.275**.



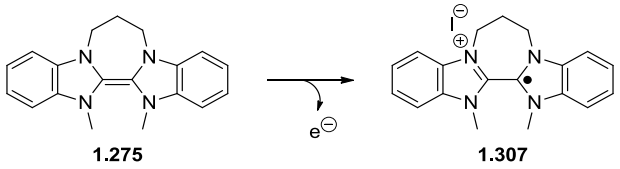
Additionally, alkyl iodide **1.301** yielded ether **1.305** without elimination of methoxide. However the major product isolated was ether **1.306** and could have only resulted from the neophyl rearrangement of radical **1.302** (**Scheme 1.65**).

Tetraazafulvalene **1.275** had been shown to be an excellent SET reagent, capable of reducing alkyl and aryl halides to the corresponding radical intermediates. Being the first neutral organic molecule to mediate these challenging reductions marked it as the first ever Super Electron-Donor, SED. In contrast to TTF, no radical-polar crossover reaction is observed, as the radical-cation **1.307** (**Scheme 1.66**) is much less susceptible to coupling with the radical intermediates generated. Thus, no rearrangement or fragmentation similar to the case of DDTF occurs, an additional benefit.

Scheme 1.65 Neophyl radical rearrangement after SET.



Scheme 1.66 Single electron transfer from donor **1.275**, forming cation **1.307**.



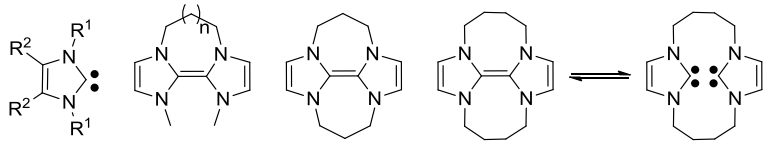
1.7.4 Di-tethered imidazole-derived tetraazafulvalene – new potential

The gain in aromatisation energy, the driving force for electron donation can be clearly seen in the transition from **1.275** to **1.307**. In efforts to synthesise even more powerful SED reagents the subsequent efforts in our laboratories would look to tetraazafulvalenes that would gain more aromatic stabilisation energy in their corresponding oxidised salts.

As already mentioned other tetraazafulvalenes were known in the literature, where Thummel *et al.*[83] had failed in attempts to synthesise pure **1.265** (**Scheme 1.67**) by electrochemical means, while Taton and Chen[3] had succeeded, synthesising the doubly propylene-tethered tetraazafulvalene by both 'Birch type' reduction from oxidised salt **1.264** and by deprotonation of **1.266** (see page 38). Initially it would appear that preparation of imidazole-derived tetraazafulvalenes would be straightforward, however it was known that imidazol-2-ylidenes **1.308** were stable to dimerisation[98] and the attempts by Taton and Chen[3] to synthesise *mono*-or unbridged **1.309a** and **b**, respectively were unsuccessful. Indeed, the extension of the propylene tethers by a single methylene unit likely afforded yellow tetraazafulvalene **1.310** at -50 ºC but on warming to ambient temperature only the white solid *bis*-carbene **1.311** was isolated. This perfectly demonstrates the precarious nature of C=C

central alkene bond when formed between two imidazol-2-ylidenes. Ames *et al*.[92] carried out electrochemical investigations which provided corroborating evidence. While the imidazole-derived tetraazafulvalenes had more powerful negative reduction potentials than their benzimidazole analogues, typically more negative than $E_{1/2}$ = -1.1 V *vs.* SCE (DMF), their cyclic voltammograms were by and large irreversible, pointing to their inherent instability. Furthermore, theoretical calculations predicted the C=C bond energy in imidazole-derived tetraazafulvalenes to be only 4 kJ mol^{-1},[99] thus rather than **1.265** setting a precedent with other imidazole-derived tetraazafulvalenes following it actually became a solitary anomalous example.

Scheme 1.67 Alternative tetraazafulvalenes which might gain more aromatisation energy on oxidation.



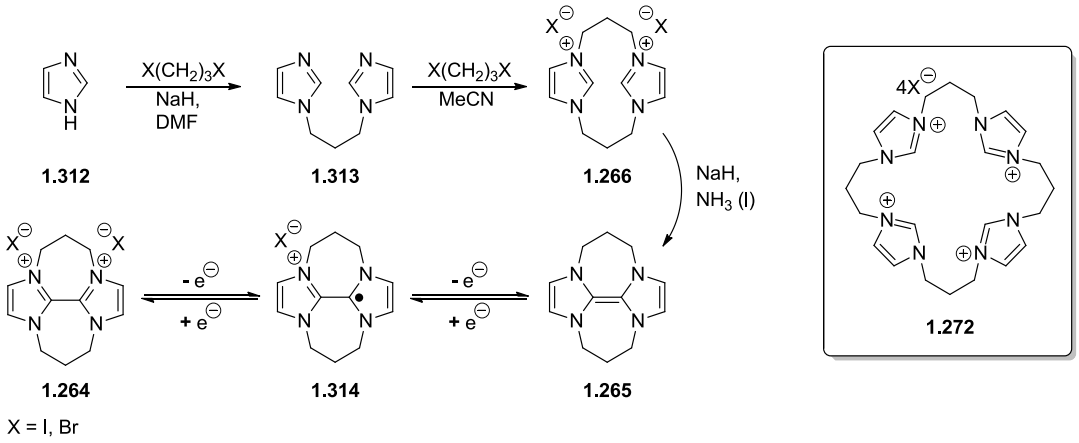
Based on the above, although the dibutylene bridged **1.310** was more powerful than di-propylene tethered **1.265**, the former's rapid decomposition to the corresponding dibutylene tethered *bis*-carbene, **1.311** meant that it could be discounted as a SED candidate.[3]

The only viable candidate for new imidazole-derived tetraazafulvalene SED was **1.265** but it possessed a powerful redox potential for sequential loss of electrons of $E_{1/2}$ (MeCN) = -1.37 and -1.18 V *vs.* SCE[83,89,92] (**Scheme 1.68**, X = Br).

1.7.5 Generation of aryl anions by double electron transfer

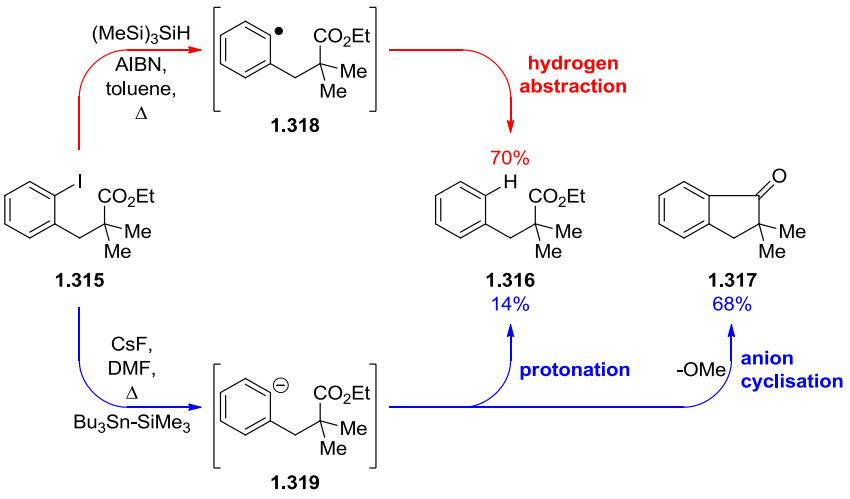
In order to investigate its application in organic synthesis a ready supply of **1.265** would be required. Careful experimentation resulted in robust reaction conditions to prepare the imidazolium salt **1.266** from imidazole **1.312** and diiodopropane, minimising formation of undesired tetramer **1.272**.[89] After evaporation of ether extracts, the treatment of **1.266** with sodium hydride in liquid ammonia afforded tetraazafulvalene **1.265** as a highly oxygen-sensitive yellow crystalline solid that could be stored under anhydrous and anaerobic conditions allowing it to be prepared in over 100 mmol quantities. Alternatively, donor **1.265** could be prepared *in situ* using degassed DMF as solvent on less than 1 mmol scale.

Scheme 1.68 Formation imidazole-derived tetraazafulvalene **1.265**.



In light of the report by Andrieux and Pinson[59] it was somewhat surprising find that SED **1.275** did reduce aryl iodides to aryl anions by two sequential electron transfers. The redox potentials for sequential loss of electrons from donor **1.275** are quoted as $E_{1/2}$(DMF) = -0.76 and -0.82 V *vs.* SCE[91] for dication and radical cation, respectively, much more negative than the reduction of aryl radicals to aryl anions E^0 = +0.05 V *vs.* SCE.[59] Murphy *et al.*[89] were keen to investigate whether tetraazafulvalene **1.265** could achieve such a transformation but first a substrate that unambiguously distinguished the formation of aryl anions as opposed to aryl radicals would be required.

Scheme 1.69 Discrimination of aryl radical from aryl anions by reaction of **1.315**.

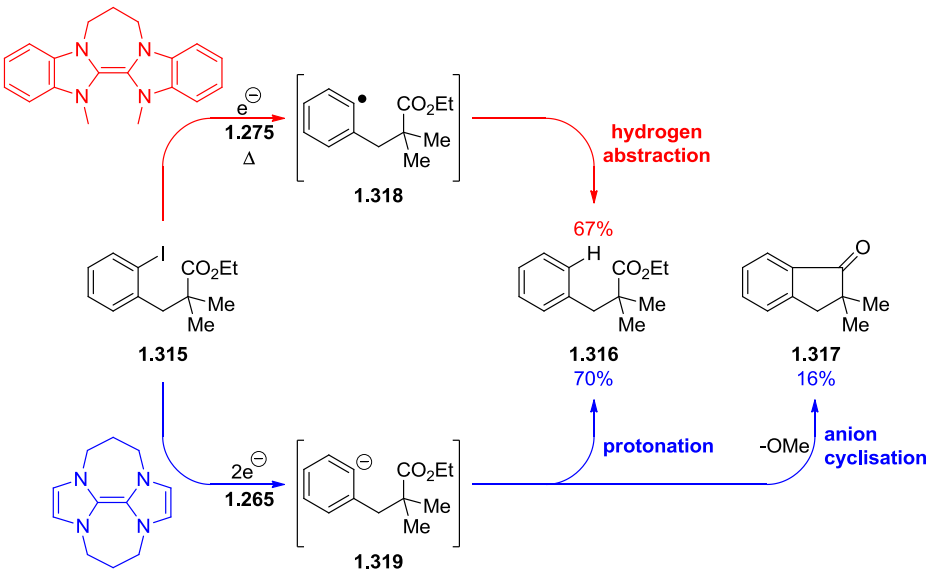


Heating of iodoester **1.315** in the presence of tris(trimethylsilylsilane) and radical initiator azobisisobutyronitrile (AIBN) in toluene, afforded reduced arene **1.316** exclusively without

any trace of indanone **1.317** (**Scheme 1.69**). Arene **1.316** is entirely consistent with aryl radical intermediates expected from these standard radical generating conditions. Iodoester **1.318** was then reacted with trimethy(tributylstannyl)silane and fluoride ions (CsF), standard conditions for the generation of aryl anions from aryl iodides. Indanone **1.317** was afforded in 68% yield together with reduced arene **1.316** in 14% yield. The cyclisation of indanone clearly establishes the formation of aryl anions **1.319** and validates iodoester **1.315** as a suitable diagnostic test substrate to discriminate SET transfer from double electron transfer.

Reaction of SED **1.275** with **1.315** afforded reduced arene **1.316** exclusively, consistent with the formation of aryl radicals and with experimental results already observed with SED **1.275** (**Scheme 1.70**).

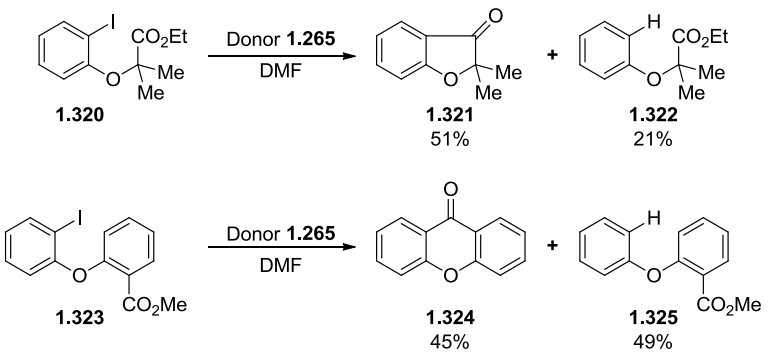
Scheme 1.70 Reduction of iodoester **1.315** with SED **1.265** and **1.275** generating aryl anions and radical, respectively.[89]



The failure of **1.275** to reduce aryl radical to aryl anion despite having a strong enough potential to do so can be attributed to differences between standard and actual redox potentials for aryl radicals to aryl anions under experimental conditions. Andrieux and Pinson[59] under their reaction conditions saw the peak attributed to this reduction at -0.64 V *vs.* SCE, and it was thought that under the conditions used for electron donation from **1.275** it could be even more negative than this. Clearly a stronger SED was necessary to reduce aryl iodides to aryl anions.

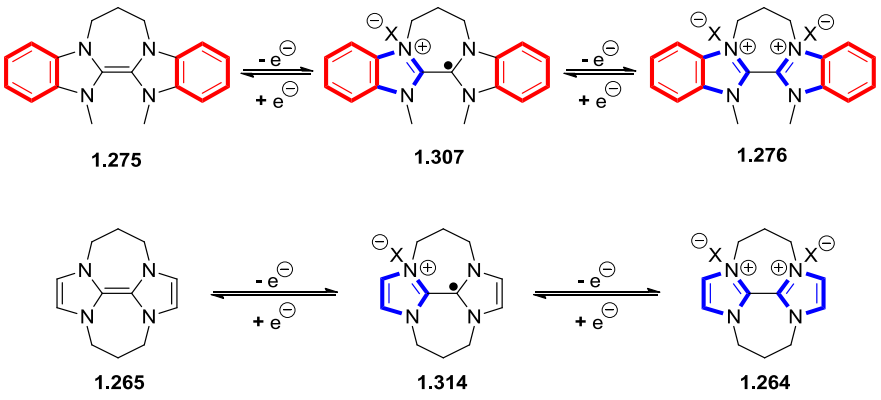
Murphy *et al.* established that reaction of iodoester **1.315** with imidazole-derived tetraazafulvalene **1.265** at ambient temperature afforded desired indanone **1.317** in 16% yield along with 70% of the reduced arene **1.316**.[89] Formation of indanone **1.317** established tetraazafulvalene **1.265** as the first neutral organic electron donor capable of cleaving C-I σ-bonds of aryl iodides and could truly be considered a SED. Arene **1.316** could arise from deprotonation of dication **1.264** or radical cation **1.314** (**Scheme 1.68**) by aryl anion **1.319** or hydrogen atom abstraction by its radical analogue **1.318**, and thus 16% yield of indanone reflects the minimum amount of aryl anion generated by the reaction.

Scheme 1.71 Further examples of double electron transfer.



Two further examples, **1.320** and **1.323** in which steric demands[100] should favour faster cyclisation of aryl anions onto carbonyl groups were examined (**Scheme 1.71**). Indeed improved yields of cyclised products were observed. However, again reduced products **1.322** and **1.325** were isolated, thus again yields of 51% and 45% for the cyclised product represent a minimum amount of respective aryl anions generated.

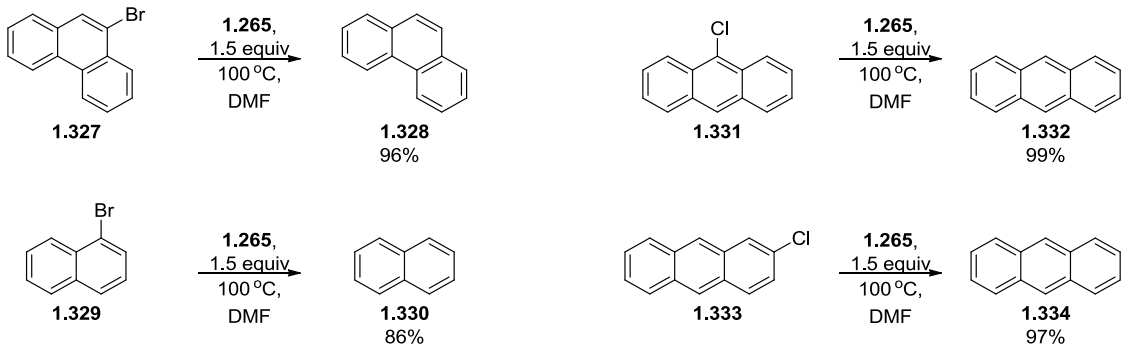
Scheme 1.72 Depiction of aromaticity gained by electron donation in donors **1.275** and **1.265**.



From the experimental results, it was clear that imidazole-derived SED **1.265** was more powerful than benzimidazole-derived **1.275** and these observations were in line with electrochemical studies.[83-85,92] The difference in redox potentials corresponds to difference in the aromatisation energy gained upon oxidation. SED **1.275** already possesses some aromaticity shown in red, while aromaticity gained upon electron donation is shown in blue (**Scheme 1.72**).

The differences in the reorganisation energies associated with transitions from neutral to positively charged cations also provide insight into the differing redox potentials observed. As previously mentioned, ^{1}H-NMR spectra show the NCH_2 protons of the trimethylene bridge in dication **1.276** to be diastereotopic (δ = 4.25-4.61ppm 2H, m and 5.25-5.32ppm 2H, m) thus indicating a rigid helical twist (**Scheme 1.57**). These observations are not mirrored in dication **1.264**, where the presence of a simple triplet for the NCH_2 protons (δ = 4.61ppm 8H, *t*, *J* = 6.0, 4 x CH_2) points to free movement and no helicity. The central C-C bond is increasing in length for both dications. However, the angle between the planes of the heterocyclic rings in benzimidazole-derived **1.275** become increasingly less planar in dication **1.276** (16º to 42º) in contrast to transition from imidazole-derived **1.265** to dication **1.254** (10º to 1.5º), therefore a greater reorganisation energy is anticipated for the transition from benzimidazole-derived **1.275** to **1.276**. Computation performed by Tuttle[89] also indicated that the transition from imidazole-derived **1.265** to dication **1.254** was more favourable than the transition from benzimidazole-derived **1.275** to **1.276**. The maintenance of planarity in imidazole-derived **1.265** during electron transfer and transition to **1.264** was also suggested to be beneficial, in that the intimate complex would be stabilised if interactions occur with the π-system of acceptor arene.

Scheme 1.73 Reaction of donor **1.265** with aryl bromides and chlorides.



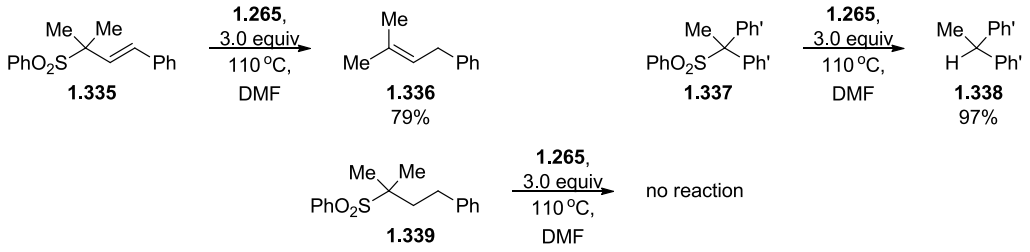
Having established that SED **1.265** transfers two electrons to iodoarenes, Murphy *et al.* demonstrated its powerful redox potential on more challenging bromo and chloro aromatic

compounds (**Scheme 1.73**).[89] The benzimidazole-derived **1.275** (5.0 equiv.) failed to reduce 1-bromonaphthalene **1.329** and afforded a meagre 7% phenanthrene from the reduction of 9-bromophenanthrene **1.327**. In contrast, imidazole-derived **1.265** readily reduced bromo-substituted aromatics in excellent yield employing only 1.5 equivalents, as well as successfully reducing chloroanthracenes **1.331** and **1.333**.

1.7.6 Reductive cleavage of sulfones and sulfonamides

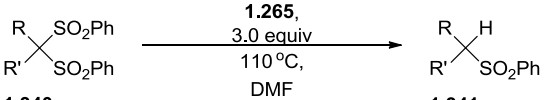
Schoenebeck *et al*. successfully extended the reactivity of SED **1.265** through reductive deprotection of inductively-activated or π-activated sulfones and sulfonamides.[101] Deprotection of these groups are typically mediated by highly aggressive metal containing reducing reagents *i.e.* alkali metals or SmI_2 with HMPA.[102] Electrochemical reduction has also been employed to cleave tosylsulfonamides at -2.3 to -2.4 V *vs.* SCE, making their removal a challenge for the organic chemist.[103]

Scheme 1.74 Reaction of donor **1.265** with activated and unactivated sulfone groups.



Sulfones adjacent to phenyl **1.337** or conjugated to phenyl **1.335** were smoothly converted to the corresponding hydrocarbons in excellent yield while 'unactivated' substrate **1.339** did not react, therefore demonstrating a degree of selectivity (**Scheme 1.74**). Schoenebeck also successfully cleaved *gem*-dimethyl sulfones **1.340** to monosulfones **1.341** in excellent yields (94-98%, **Scheme 1.75**).

Scheme 1.75 Reduction of *gem*-disulfones to monosulfones.

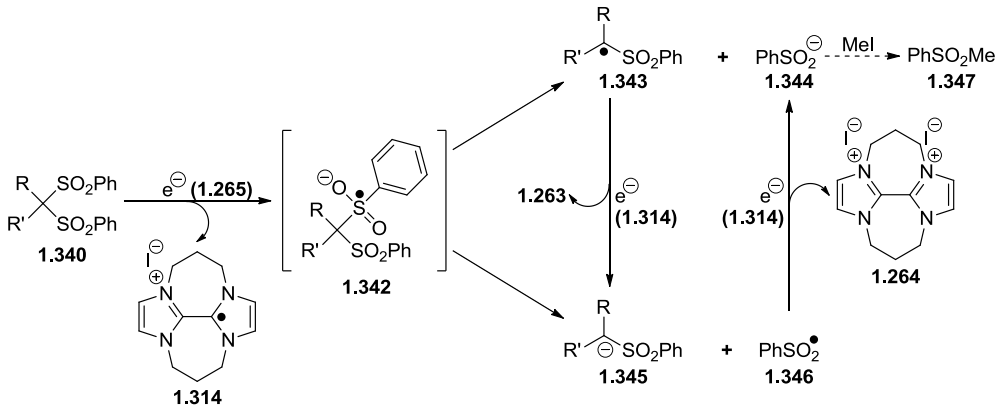


1.340
a) R = R' = Me
b) R,R' = $(CH_2)_4$
c) R = Me, R' = CH_2CH_2Ph
d) R, R' = $(CH_2)_5Ph$

1.341
a) R = R' = Me, 97%
b) R,R' = $(CH_2)_4$, 96%
c) R = Me, R' = CH_2CH_2Ph, 98%
d) R, R' = $(CH_2)_5Ph$, 94%

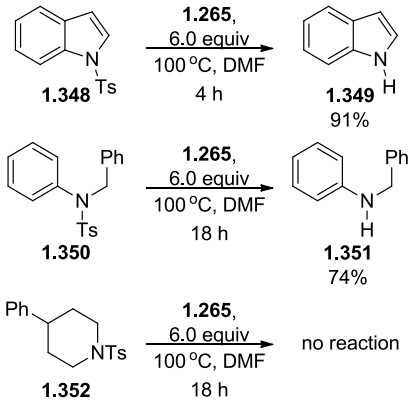
Consideration of the mechanism of the process suggests that single electron transfer to the arenesulfonyl group generates radical anion **1.342** which undergoes instantaneous scission of the C-S σ-bond yielding one of two possible radical anion pairs, either alkyl radical **1.343** and sulfinate anion **1.344** or carbanion **1.345** and sulfonyl radical **1.346**. No matter how fragmentation occurs a second electron transfer from radical cation **1.314** affords anion pair **1.344** and **1.345**. Existence of sulfinate anion **1.344** was proved by trapping with excess methyl iodide affording phenyl methylsulfone **1.347** in excellent yield (86%).

Scheme 1.76 Electron transfer mechanism for the cleavage of disulfone **1.340**.



Computational studies showed that **1.335**, **1.337** and **1.340** had a low activation energy associated with the LUMO having good overlap with σ*-orbital of scissile C-S bond. This results in instantaneous dissociation after electron transfer and thus it follows that an electron is more readily accepted. By contrast, **1.339** was shown to have poor LUMO overlap with C-S σ*-orbital and hence electron transfer does not lead to fragmentation.

Scheme 1.77 Reaction of tosyl protected amides with donor **1.265**.



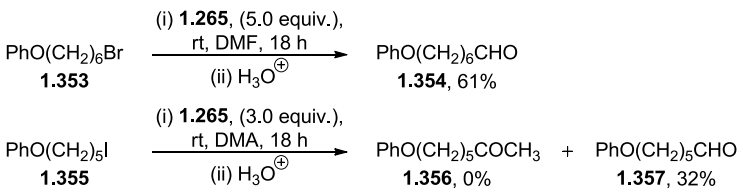
Utilising six equivalents of SED **1.265**, the challenging reductions of indole **1.348** and aniline **1.350** sulfonamides were successfully demonstrated, affording cleaved products in 91% and 74% yield, respectively (**Scheme 1.77**). However no reaction was observed with piperidinesulfonamide **1.352**.

Computational analysis of the radical anions derived from **1.348** and **1.350** indicates spontaneous fragmentation followed by a loose association of the respective fragments.[101] The associated complex is proposed to be a three electron N-S bonded intermediate. In the case of the complex derived from indolesulfonamide **1.348**, the negative charge would principally be associated with the indole, possibly reflecting aromatic stabilisation of the developing anion. In contrast, the charge of the intermediate complex formed from anilinesulfonamide **1.350**, appears to be principally associated with the arenesulfonyl unit. Although sulfones and sulfonamides have redox potentials (typically -2.3 V *vs.* SCE[104]) more negative than the redox potential of donor **1.265** ($E_{1/2}$ = -1.20 V *vs.* SCE in DMF[92]), they can successfully be reduced provided their respective radical-anions undergo rapid fragmentation, and thus there must be adequate orbital overlap between the LUMO and the σ*-orbital of S-X bond (where X = C, N) to allow electrons to be accommodated by their respective fragments.

1.7.7 Isolation of Aldehydes *via* trapping of an SED

Thomson *et al*. had noted that reaction of di-tethered imidazole-derived tetraazafulvalene (DIT) **1.265** with alkyl halides afforded minute traces of aldehydes, observable in the ^{1}H-NMR spectra of crude material after neutral work-up and thus initiated investigations into their origin.[105] Acid work-up afforded increased yields of aldehydes suggesting that they required liberation from protection during work-up.

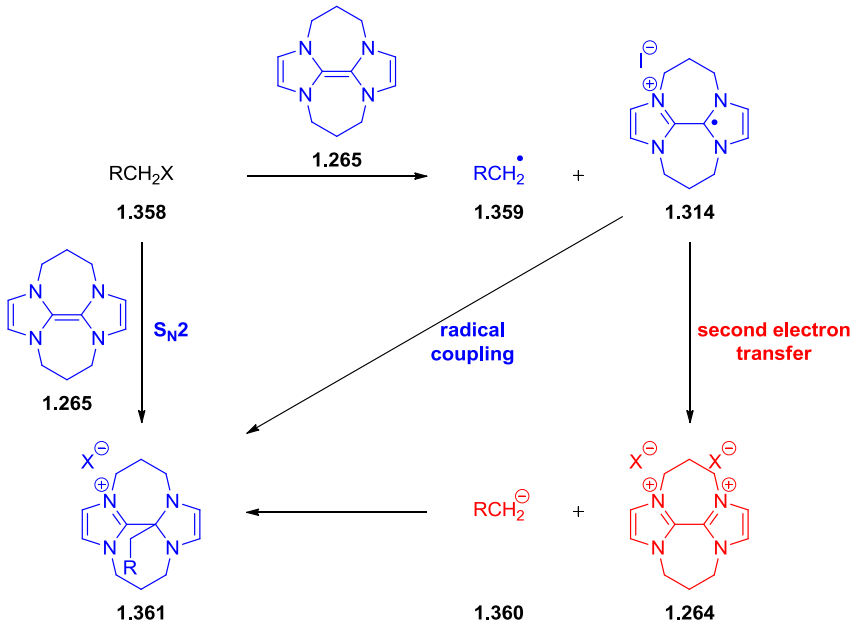
Scheme 1.78 Reaction of DIT **1.265** with alkyl halide affording aldehydes.



The aldehydes observed were one carbon longer than their precursor alkyl halides. It was reasoned that the additional carbon could originate from either DMF or DIT **1.265** itself. However, if DMF was the source (attacked by carbanion *i.e*. **1.360**, generated after double electron transfer) then replacement of DMF in the reaction with dimethylacetamide (DMA)

should afford ketone **1.356** (**Scheme 1.78**). Ketone **1.356** was not observed, only aldehyde **1.357**, demonstrating that aldehydes arise from a route not involving DMF and most likely arising from the DIT moiety **1.265**.

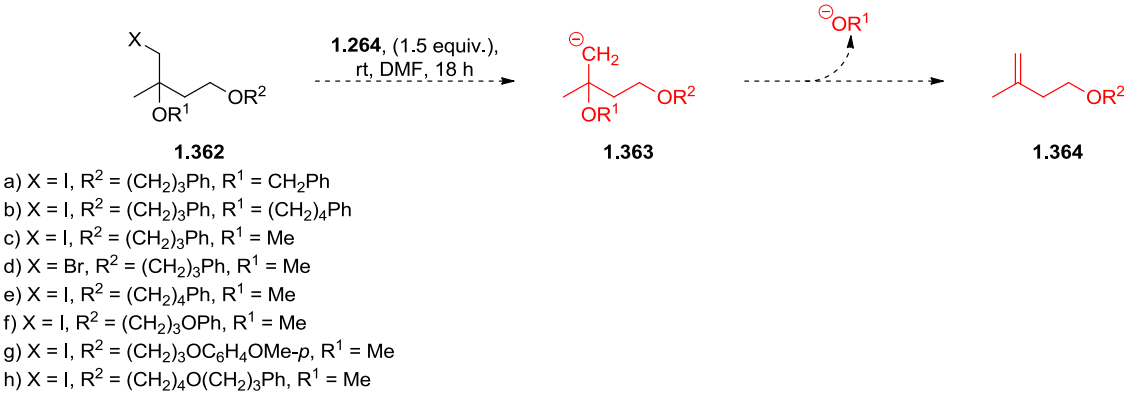
Scheme 1.79 Possible reaction mechanism for the formation of **1.361**.



DIT **1.265** could react with alkyl halide **1.358** by three possible reaction mechanisms, nucleophilic attack by the electron-rich double-bond driven by the gain of aromaticity in **1.361**, coupling of single electron transfer intermediates, radical **1.359** and radical cation **1.314** or attack of anion **1.360** on dication **1.264** generated after a double electron transfer process (**Scheme 1.79**). Each mechanism affords the aminal intermediate **1.361** which liberates aldehydes on work-up (*vide infra*).

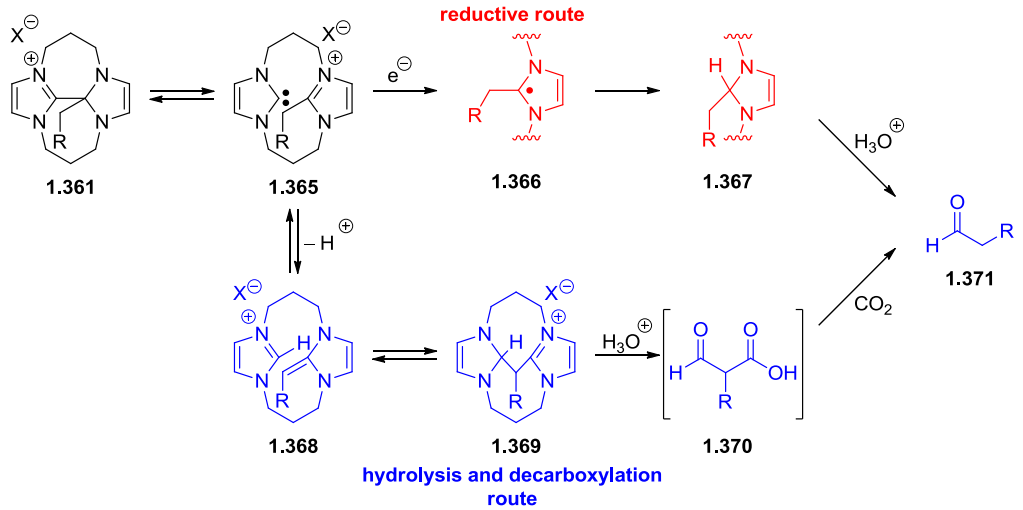
The reaction of DIT **1.265** with alkyl halides **1.362**, primed for the elimination of alkoxide from corresponding anion **1.363** in the event of double electron transfer, failed to generate alkenes **1.364** expect from this reaction process (**Scheme 1.80**). Therefore a sequential or concerted two electron transfer mechanism can be discounted and intermediate **1.361** must arise either *via* S_N2 or radical coupling mechanism.

Scheme 1.80 Failed alkene generation.



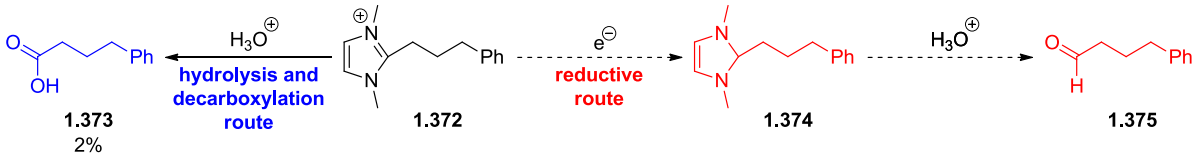
The liberation of aldehydes from **1.361** could take place by either a reductive route (**Scheme 1.81** red) or hydrolysis and decarboxylation (blue) path. Both involve an equilibrium between **1.361** and carbene **1.365**.[105] The reductive route proceeds *via* a transfer of an electron from DIT **1.265** to **1.365**, a possible explanation for the requirement of excess donor. Hydrogen abstraction and acid work-up of imidazoline **1.367** afford aldehyde product. In the alternative mechanism, an intramolecular deprotonation by carbene **1.365** generates enediamine **1.368**, the electron-rich alkene nucleophilically attacks the imidazolium ring producing **1.369** which can form aldehyde acid **1.370** on workup and liberate the final product aldehyde **1.371** *via* decarboxylation.

Scheme 1.81 Reaction mechanism for aldehyde formation.



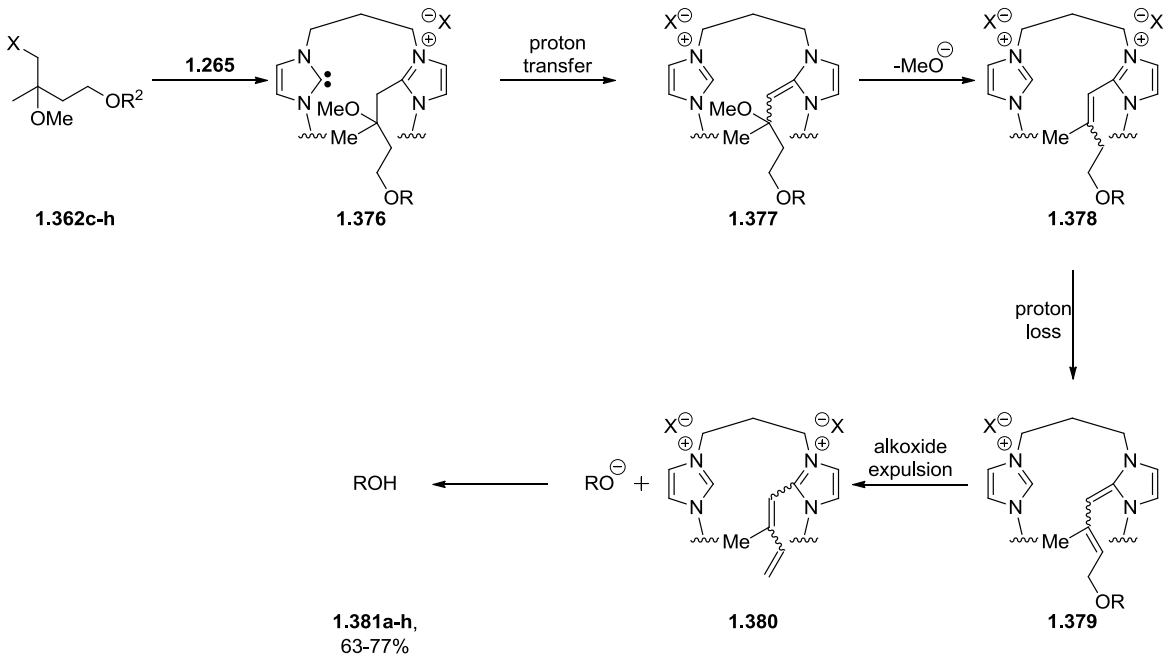
Schoenebeck *et al.* probed the reaction mechanism with imidazolium substrate **1.372**, analogous to intermediate **1.365**. Reaction of **1.372** with DIT **1.265** followed by acid workup should afford aldehyde **1.375** if the reductive mechanism is in operation, but it was not observed. Conversely acid hydrolysis to afford **1.373** (analogous to **1.370**) would support a hydrolysis decarboxylation mechanism and indeed acid **1.373** was afforded, although in low yield.

Scheme 1.82 Evidence for hydrolysis and decarboxylation.



Intermediate **1.365** is common to both mechanisms and further evidence of its existence was sought. Trapping of alkyl iodides **1.362** would afford **1.376**, again analogous to **1.365**. However, through a series of deprotonation and eliminations **1.376** should afford methanol and alcohol **1.381**. The isolation of **1.381** can be taken as positive evidence for the trapped intermediate **1.376** and thus also intermediates **1.365** and ultimately **1.361**.

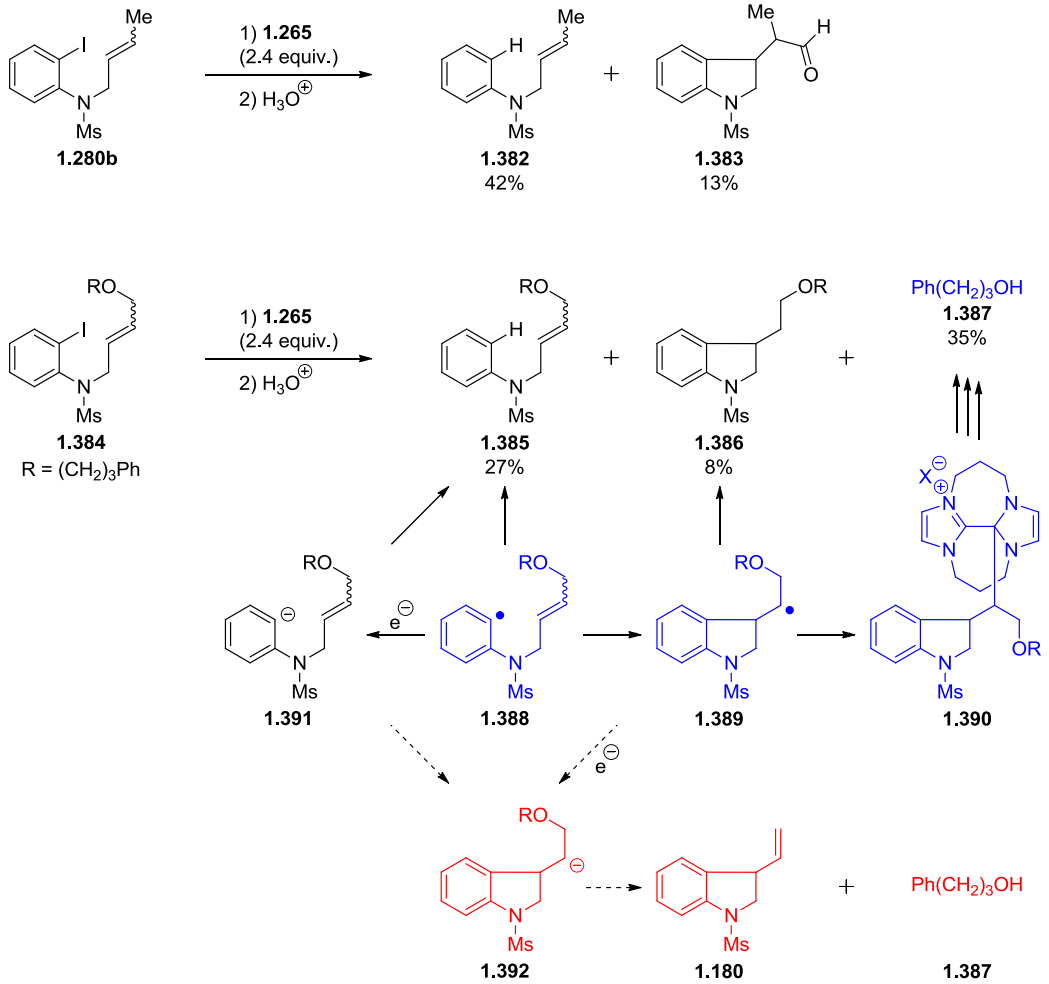
Scheme 1.83 Liberation of alcohols supporting formation of intermediate **1.376**, analogous to **1.365**.



Alkyl iodides **1.362c-h** provided the corresponding alcohols **1.381** in good yields[105] supporting the proposed intermediates and ultimately formation of aldehydes *via* hydrolysis of **1.361**.

Finally the nature of the trapping was investigated with aryl iodides unable to undergo S_N2 reaction (**Scheme 1.84**). Formation of aldehyde **1.383**, consistent with a radical trapping mechanism, was observed. Additionally, isolation of alcohol **1.387** from the reduction of **1.384**, in the absence of vinyl indolenine **1.180** (eliminating the possibility of an anionic reaction mechanism) further supported a radical cation trapping mechanism and subsequent formation of intermediates associated with the proposed reaction path.

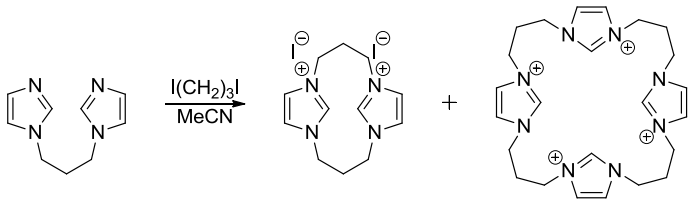
Scheme 1.84 Generation of aldehyde **1.383** and alcohol **1.387** consistent with radical trapping.



1.7.8 *bis*-Pyridinylidene, an enediamine super-electron-donor

The imidazole-derived tetraazafulvalene core provides a strong redox potential for electron donation however, imidazol-2-ylidenes refuse to dimerise with the exception of one favourable anomalous example, the di-tethered imidazolium salt **1.266**[3] (**Section 1.7.1**). While the tetraazafulvalene formation of DIT **1.265** from precursor salt **1.266** is facile, the synthesis of the salt is extremely laborious. The issue is entirely associated with the formation of macrocyclic by-product **1.274**, which can be minimised by making additions of di-iodopropane over a period of one month and is removed by skilful recrystallisation. Therefore a new structure would need to be explored if new SEDs were to be developed and readily generated. The new structure motif would still have to satisfy the previously established criteria for super-electron donation *i.e.* gain in aromatisation by electron donation, and stabilisation of the corresponding oxidised cations by nitrogen π-electrons. Based on this solution the *bis*-pyridinylidene donor **1.395** was developed in our laboratories (**Scheme 1.86**).[106,107]

Scheme 1.85 Formation of undesired macrocycle **1.274**.

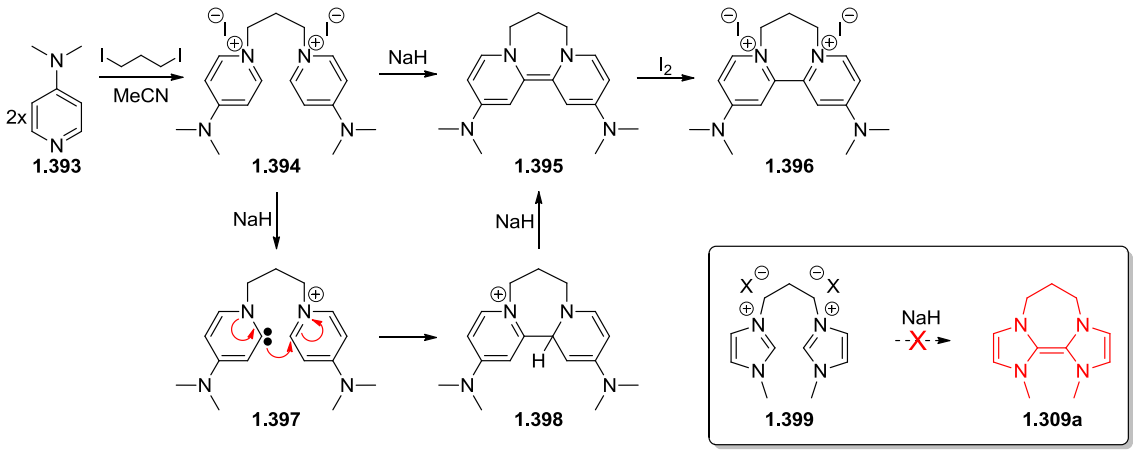


1.313 **1.266** **1.274**

The *bis*-pyridinylidene donor **1.395** (**Scheme 1.86**) is the most recent SED to be developed within the group.[106,107] Despite this its relative ease of preparation and strong redox potential have ensured it also the most extensively researched.[2,107-112] The electron-rich alkene, central to activity in SED forms the reactive core, binding two pyridinyl units at the carbon adjacent to the ring nitrogen. A 4-dimethylaminopyridine analogue was proposed, and it was hoped that the four electron-donating nitrogens, each adding π-electron density to the system would act in a similar manner to tetraazafulvalenes **1.275** and **1.265**, making a more negative redox potential of the neutral organic electron donor **1.395** and also stabilising positive charge in the respective radical cation and dications formed upon oxidation. The *bis*-pyridinium salt **1.394** was easily prepared from cheap 4-dimethylaminopyridine **1.393** and 1,3-diiodopropane. However, the 2-position of *bis*-pyridinium salt **1.394** is less acidic than the respective 2-position of benzimidazolium salts *i.e.* **1.274** and **1.276**. Thus, there was the

possibility that deprotonation might occur at the propylene tether affording a benzylic anion rather than the desired carbene intermediate **1.397**. Additionally, it was unclear whether a pyridin-2-ylidene carbene such as **1.397** would react to form **1.395**. Attempts to synthesise the analogous *mono*-tethered **1.309a** by deprotonation of imidazolium salt **1.399** had failed.[3] Fortunately these concerns were not borne out. Garnier treated *bis*-pyridinium salt **1.394** with sodium hydride in liquid ammonia which formed a dark purple solution.[106,107] Evaporation of ammonia, extraction with diethyl ether and subsequent solvent removal afforded *bis*-pyridinylidene **1.395** as an air-sensitive purple solid. The reaction mechanism is thought to be analogous to the formation of SED **1.265** and **1.275**.

Scheme 1.86 Synthesis of *bis*-pyridinylidene donor **1.395**.

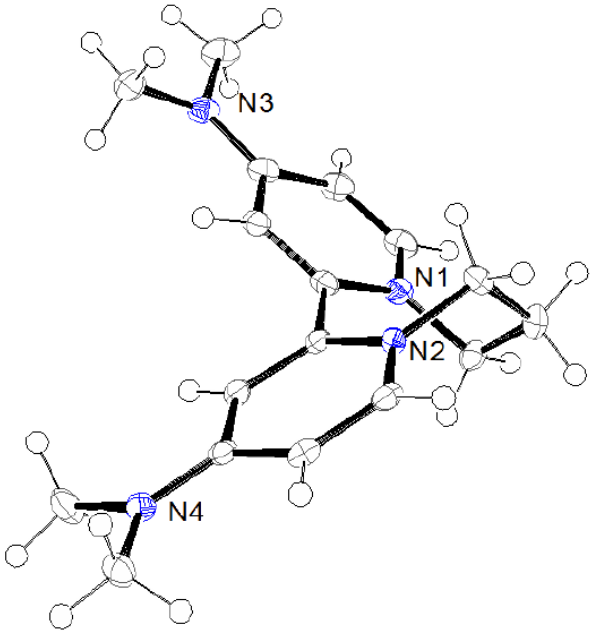


A characteristic ^{13}C-NMR signal at δ = 116 ppm positively identified the formation of the central electron-rich alkene. Further proof of successful synthesis was forthcoming when the *bis*-pyridinylidene was reacted with iodine, yielding oxidised diiodide **1.396**. As with its benzimidazole analogue **1.276** (derived from donor **1.275**), diiodide **1.396** shows non-equivalent methylenes adjacent to nitrogen by ^{1}H-NMR analysis. This diastereotopicity must again reflect non-coplanarity of the two positively charged ring systems, undergoing a helical twist in order to minimise charge interactions. This is clearly demonstrated in the X-ray crystal structure obtained by Garnier (**Figure 1.5**).[106,110]

The electrochemical characterisation of *bis*-pyridinylidene donor **1.395** revealed a single reversible two-electron peak at $E_{1/2}$ (DMF) = -1.24 V in DMF *vs.* SCE, making it the strongest SED at the time of publication. The clean single two-electron peak in the cyclic voltammogram indicates loss of the second electron occurs at essentially the same potential

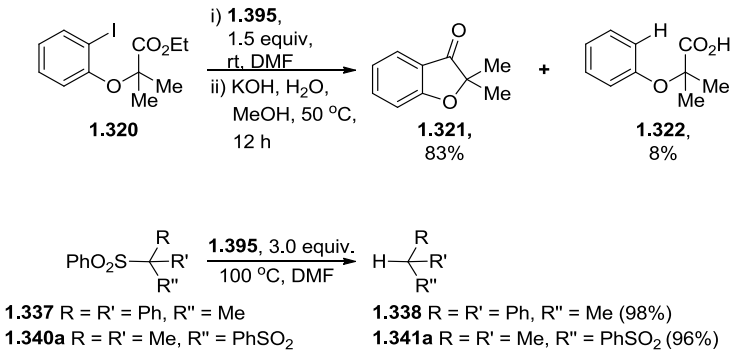
as the first, whereas cyclic voltammogram of donor **1.265** showed a very slight shoulder on both oxidation and reduction peaks indicating second electron loss is only slightly more difficult than the first.

Figure 1.5 X-ray crystal structure of dication **1.396**.[106,110]



Having established that the new donor **1.395** had successfully been synthesised and that it had an electro-reductive potential of the same order as donor **1.265**, Garnier began to investigate its properties with substrates used to examine **1.265**.[89,101] Again formation of cyclic ketone **1.321** from iodoester **1.320** confirms that aryl anions were formed by double electron transfer to **1.320** by *bis*-pyridinylidene donor **1.395** (**Scheme 1.87**), in line with cyclic voltammetry observations.

Scheme 1.87 Initial substrates used to investigate reactivity of *bis*-pyridinylidene donor, **1.395**.[107]

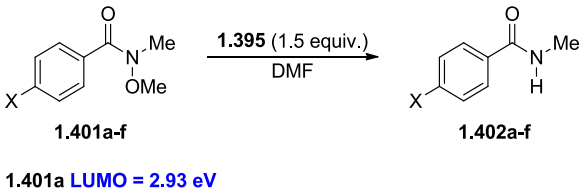


The 83% yield of indanone **1.321**[107] represents the minimum amount of aryl anion generated but is a significant improvement on the more modest 53% observed with donor **1.265**. The *bis*-pyridinylidene donor **1.395** was also given a more severe test with reduction of sulfones **1.337** and **1.340a** one of the most difficult organic reductions. In all of the test cases, the sulfonyl group was successfully cleaved affording excellent yields of reduced products, **1.338** and **1.341a**.

1.7.9 N-O σ-bond scission in Weinreb amide derivatives

Cutulic *et al*. examined the reactivity of SED reagent **1.395** with Weinreb amides and observed the reductive cleavage of the N-O σ-bonds.[112] Although the reaction was successfully applied to a wide variety of substrates, reactivity proved to be intimately dependent on the structure of the Weinreb amide.

Scheme 1.88 Reduction of Weinreb amides.



1.401a-f **1.402a-f**

1.401a LUMO = 2.93 eV

Table 1.2 Reaction conditions and yields of amides **1.402a-f** obtained from the reduction of Weinreb amides **1.401a-f** with *bis*-pyridinylidene donor **1.395**.

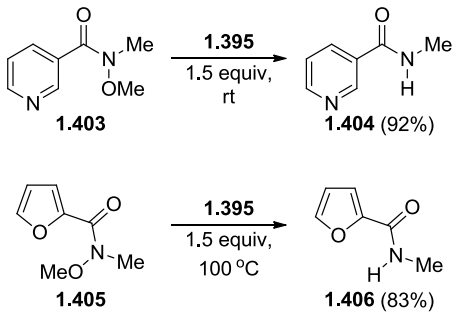
Weinreb amide **1.401**	X	Temperature ^{o}C	Amide **1.402** % Yield
a	H	25	**80**
b	F	25	**88**
c	Cl	25	**83**
d	CN	25	**87**
e	OMe	100	**81**
f	NMe_2	100	**86**

Mono-aromatic Weinreb amides **1.401a-d** with or without electron-withdrawing groups in the *para* position smoothly afforded reduced amides **1.402a-d** in excellent yields at room temperature with only 1.5 equivalents of *bis*-pyridinylidene donor **1.395** (**Scheme 1.88**,

Table 1.2). However electron-rich aromatic amides **1.401e**,**f** exhibited some resistance to the reaction with little conversion being observed at room temperature. Nevertheless at 100 °C cleavage of the N-O σ-bond proceeded smoothly (entry e and f, **Table 1.2**).

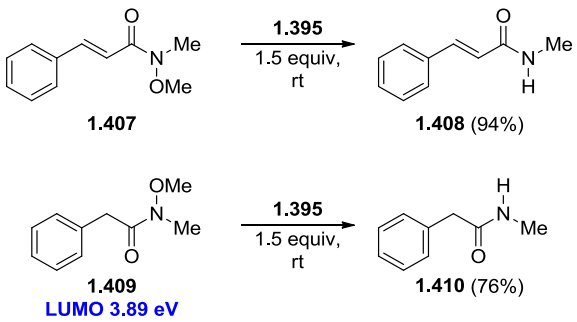
When applied to heteroaromatic Weinreb amides, Cutulic *et al.* found that the N-O σ-bond was cleaved well in the pyridine-derived substrate **1.403** at room temperature but not in the electron-rich furan derivative **1.405**, again requiring elevated temperature for successful N-O σ-bond scission (**Scheme 1.89**).

Scheme 1.89 Reduction of heteroaromatic Weinreb amides.



N-O σ-bond cleavage also progressed smoothly in Weinreb amides with and without the carbonyl group conjugated to the π-system of the arene ring in the cases of **1.407** and **1.409** respectively. Furthermore the synthesis of **1.408** is an example of a selective reduction of the N-O σ-bond over the alkene π-bond.

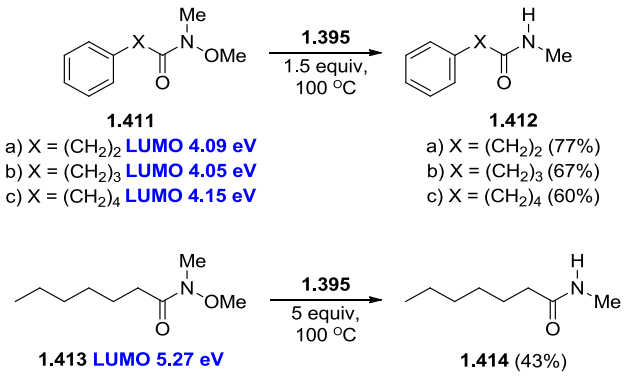
Scheme 1.90 Reduction of conjugated and non-conjugated Weinreb amides.



However, a gradual increase in the distance between the aromatic substituent and the Weinreb amide group in unconjugated amides **1.411a-c** was shown to correspond to a decrease in the reductive cleavage of N-O σ-bond observed. Removal of the aromatic

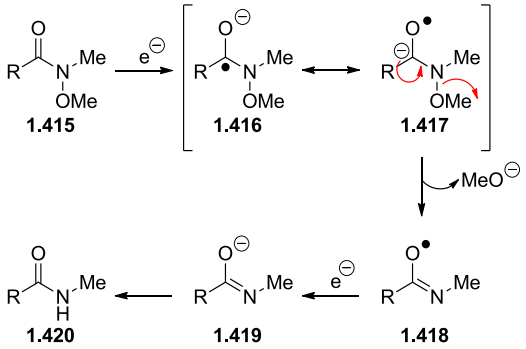
substituent altogether had a significant impact on the reduction of Weinreb amides, with aliphatic substrate **1.413** only being reduced in a modest 43% yield at 100 ºC with 5 equivalents of donor **1.395**.

Scheme 1.91 Reduction of Weinreb amides with extended carbon chains.



These observations provided an insight into the nature of the reaction mechanism. Cutulic *et al.* proposed that a single electron was transferred from *bis*-pyridinylidene donor **1.395** to the π-system of the Weinreb amide **1.415** (either directly or *via* the intramolecular transfer from aromatic system - *vide infra*), that includes the LUMO for the substrate. The LUMO of a Weinreb amide is essentially π* in character and transfer of the electron to the σ*-orbital of the N-O σ-bond brings about its cleavage. The resulting enolyl radical **1.418** could receive a second electron by SET, forming enolate **1.419** which is protonated on work-up, rearranging to stable amide **1.420**.

Scheme 1.92 Proposed reaction mechanism, electron transfer and N-O σ-bond cleavage.

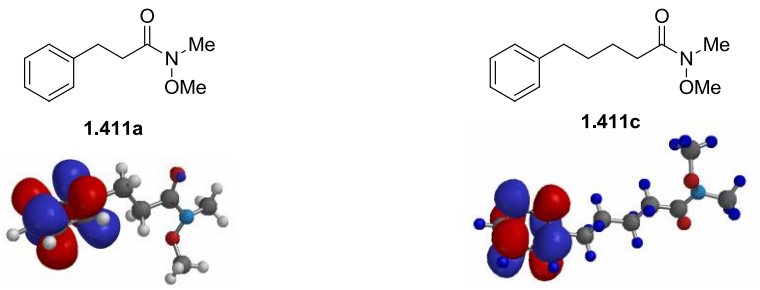


The initial electron transfer was critical for successful reaction. If the first electron was transferred easily to the LUMO of the Weinreb amide then the reaction could be performed

under mild conditions. The more electron-rich the arene is, the more difficult to transfer an electron to it and thus the subsequent N-O σ-bond cleavage becomes more difficult also.

The LUMOs in the homologous series of amides **1.401a**, **1.409**, **1.411a-c** and **1.413** were shown to be associated with the arene in the substrate (**Figure 1.6**). Additionally, it was clear that the LUMO was lowest when it is conjugated to the Weinreb amide in substrate **1.401a**, with an energy of 2.93 eV. When a single methylene group was inserted between the arene and the carbonyl of Weinreb amide as in **1.401**, the LUMO still spanned Weinreb amide group to some extent, however its associated energy increases to 3.89 eV. The insertion of two, three and four methylene groups between arene and carbonyl (substrates **1.401a-c**) brings about a smaller overall change in the energy of the LUMO, 4.05 - 4.15 eV. Accordingly the LUMO energy was highest for aliphatic substrate **1.413** at 5.27 eV. The LUMO correlates with the ease of N-O σ-bond cleavage and is in line with the amount of reduction observed by Cutulic *et al*., who reasoned that an initial single electron donation to the arene ring is followed by an intramolecular electron transfer to the Weinreb amide functionality. Clearly, the intramolecular electron transfer will be hindered when the LUMO is unable to span both groups, and likewise the initial electron transfer will be more difficult in cases where the LUMO is of high energy. Thus in both cases, more forcing conditions need to be employed.

Figure 1.6 LUMO orbitals associated with arene functionality in Weinreb amides.[112]



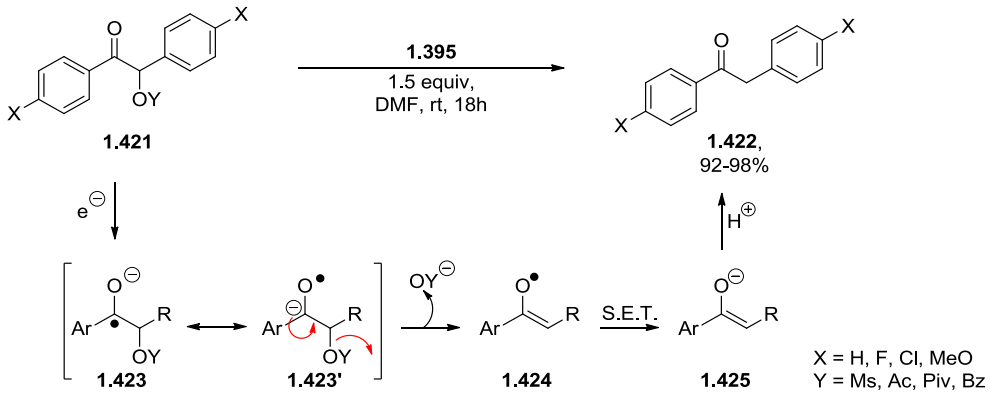
1.7.10 C-O σ-bond scission in acyloin derivatives

Cutulic *et al*. also demonstrated that *bis*-pyridinylidene donor **1.395** could effect the smooth cleavage of C-O σ-bonds in acyloin derivatives in excellent yield at room temperature (**Scheme 1.93**). The nature of the OY group is critical and must be an electron-withdrawing group decreasing the LUMO energy and facilitating departure of the carboxylate anion *i.e.* Y

= mesyl, acetyl, pivaloyl. When Y was methyl, less than 5% conversion was observed even at 100 ºC.

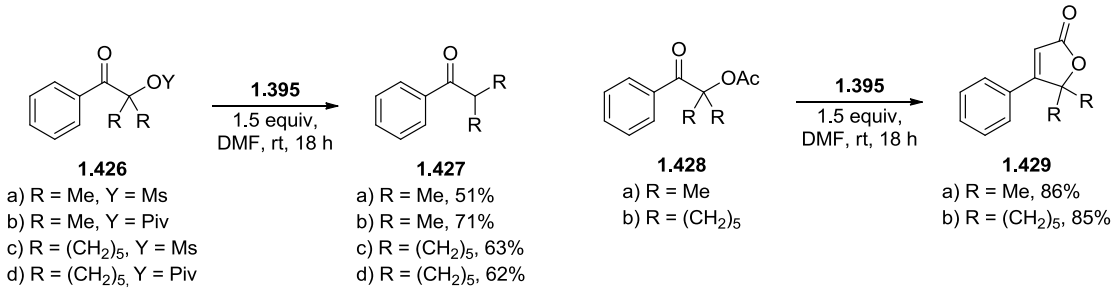
The reaction mechanism is analogous to that of the cleavage of Weinreb amides, in this case with the expulsion of a carboxylate anions from **1.423** (as opposed to methoxide from the Weinreb amides), affording radical **1.424**. A second electron forms enolate **1.425** that is protonated on work up.

Scheme 1.93 Cleavage of C-O σ-bond in acyloin derivatives.[111]



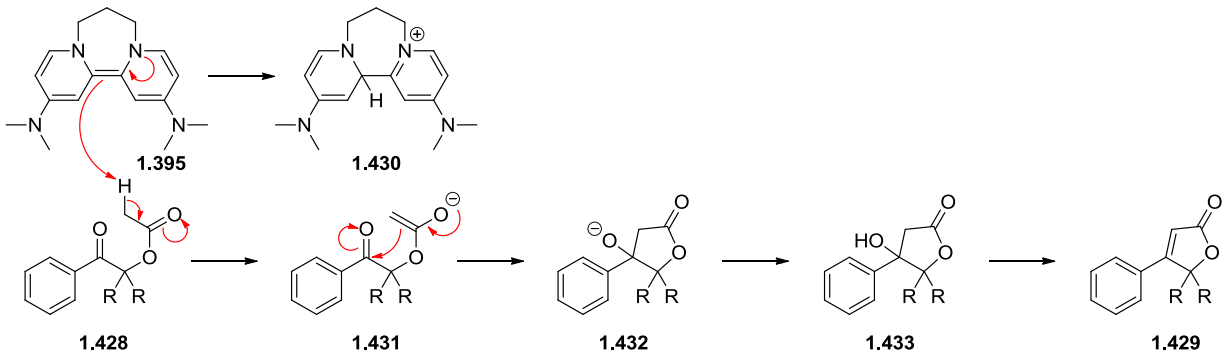
When Cutulic *et al*. replaced the aryl group *β* to the carbonyl with *gem*-dialkyl substrates **1.426** and **1.428**, smooth cleavage of the C-O σ-bond was again observed for mesylate and pivalate analogues **1.426**, affording desoxyacyloin products **1.427** as expected. The acetate analogues **1.428**, however afforded the unsaturated lactones (2-furanones) **1.429**, also known as butenolides.

Scheme 1.94 Formation of desoxyacyloin products **1.427** from mesylates and pivalates, and formation of butenolides **1.429** from acyloin acetates **1.428**.



The formation of butenolides provides strong evidence for the basic nature of the SEDs. Deprotonation of acidic protons *α* to the ester carbonyl group in **1.428** driven by the gain in aromaticity in **1.430** (**Scheme 1.96**), generates an enolate that attacks the benzoyl carbonyl group to form *β*-hydroxylactone **1.432**. On work-up, dehydration of the lactone **1.433** yields butenolide **1.429** (**Scheme 1.95**).

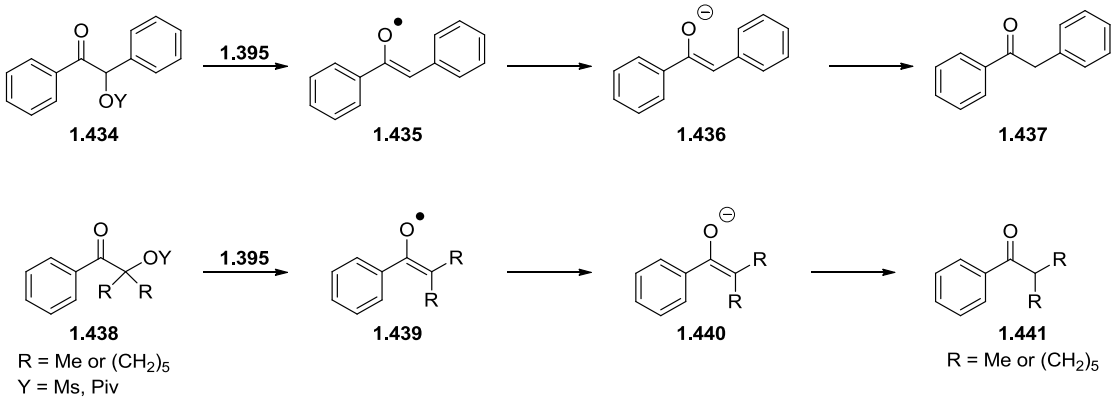
Scheme 1.95 Basic behaviour of *bis*-pyridinylidene donor **1.395** in formation of butenolides **1.429**.



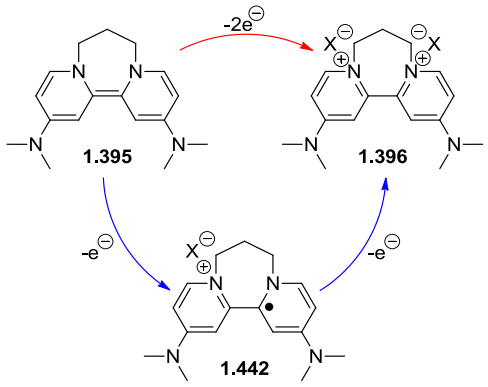
To account for the observed difference in reactivity of acetyl substrates, Cutulic *et al.* proposed formation of a stabilised conjugated π-system in the intermediate **1.436** (**Scheme 1.96**), after electron transfer to di-aryl acetyl substrates **1.434** and subsequent loss of the acetate. *Mono*-aryl substrates would not benefit to the same extent from this stabilised conjugated π-system. Accordingly the alternative deprotonation of acidic protonation *α* to the carbonyl group is preferred in acetyl analogues of **1.438**, no doubt promoted by accelerated enolate cyclisation due to *gem*-dialkyl and reactive rotamer effect.[100] In contrast, mesyl and pivaloyl analogues of **1.438** are without acidic protons and therefore undergo C-O σ-bond cleavage *via* intermediates **1.439** and **1.440**.

It is noteworthy that the formation of reactive intermediates in both the reductive cleavage of N-O[112] and C-O σ-bonds[111] in Weinreb amides and acyloin derivatives respectively requires two sequential electron transfers from donor **1.395**, suggesting formation of intermediate radical cation **1.442** (**Scheme 1.97**).

Scheme 1.96 Proposed intermediates for reaction of acyloins with *bis*-pyridinylidene donor **1.395**.

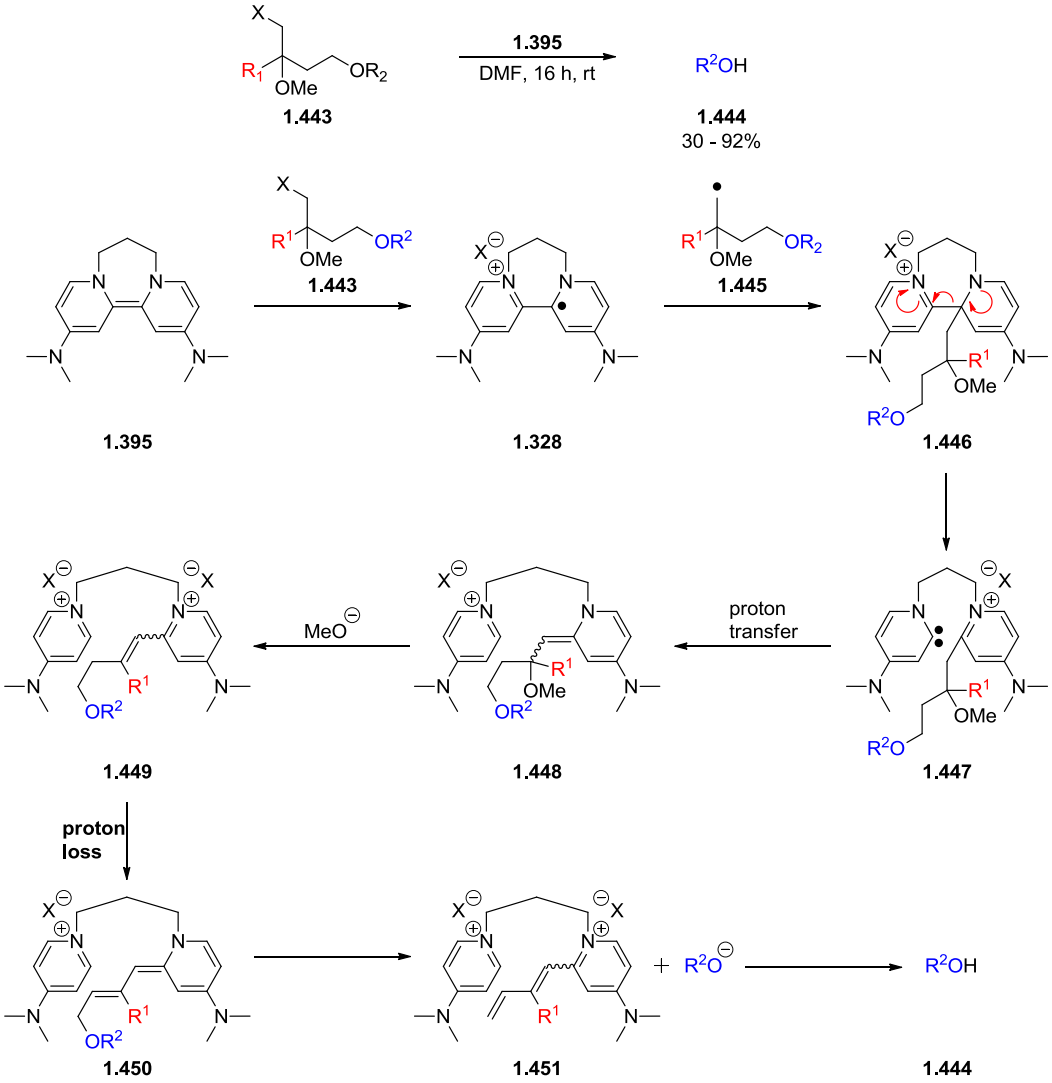


Scheme 1.97 Plausible sequences of electron donation from *bis*-pyridinylidene donor **1.395**.



To probe for the formation of the radical cation **1.442** a trapping investigation with alkyl and aryl iodides **1.443** (**Scheme 1.98**) was undertaken by Sword *et al.*[109] Analogous to the trapping investigations carried out by Schoenebeck *et al.*[105] (**Section 1.7.7**), the successful isolation of expected alcohols **1.444** by Sword *et al.* implies the formation of trapped intermediate **1.446** (analogous to imidazolium **1.361**) which is likely to arise through a radical mechanism.

Scheme 1.98 Liberation of alcohols **1.444** supporting formation of intermediate **1.446** and a radical mechanism.



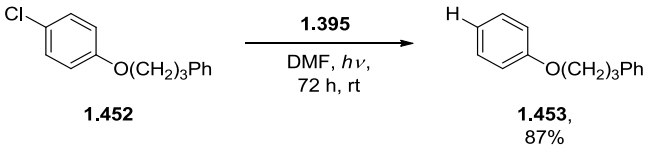
1.7.11 Electron transfer to benzenes by a photoactivated SED

The absorption spectra of deep purple *bis*-pyridinylidene donor **1.395** showed maxima at 260, 350 and 520 nm, indicating that it might be susceptible to near-UV excitation. Indeed, irradiation of *bis*-pyridinylidene donor **1.395** with UV light (365 nm) in the presence of aryl chloride **1.452** successfully afforded dechlorinated arene **1.453** (**Scheme 1.99**), while no reductive cleavage was observed for the thermal reaction (or irradiated blank reactions without **1.395**).[108]

This led Cahard *et al*. to investigate the photoactivation of SEDs using ultra-violet (UV) radiation for the reduction of more challenging non-halogenated benzenes.[108] 1,2-diphenylcyclopropanes were employed to probe acceptance of an electron into the π-system of the aryl ring. Ring-opening is characteristic of phenylcyclopropylcarbinyl radicals such as

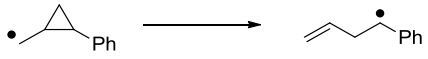
1.454 and has allowed cyclopropanes to find application as probes for very fast radical reactions.[113,114]

Scheme 1.99 Reduction of aryl chloride with UV-excited *bis*-pyridinylidene donor **1.395**.



1.452 **1.453**, 87%

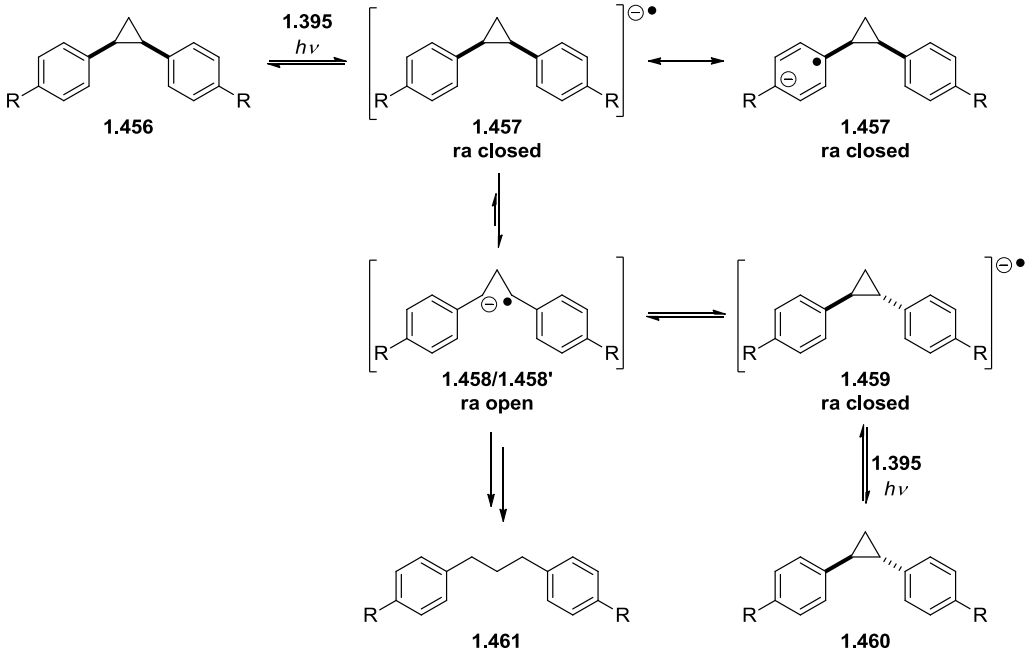
Scheme 1.100 Ring-opening of phenylcyclopropylcarbinyl radical **1.454** to phenylbutenyl radical **1.455**.



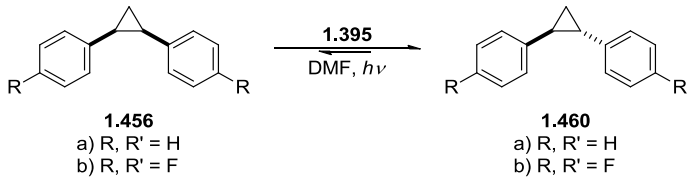
1.454 **1.455**

Therefore stereomutation of a single geometric isomer of 1,2-diphenylcyclopropane, transformation of *cis*- **1.456** to *trans*- **1.460** and *vice versa* or formation of ring-opened 1,3-diphenylpropanes **1.461** would be indicative of the formation of an aryl radical anion, either **1.457** or **1.459** (**Scheme 1.101**). Thus 1,2-diphenylcyclopropanes can act as a diagnostic test for reduction of benzenes by UV-excited *bis*-pyridinylidene donor **1.395**.

Scheme 1.101 Ring-opening of 1,2-diphenylcyclopropyl radical anions.



When 1,2-diphenylcyclopropane **1.456** and **1.460** were reacted with *bis*-pyridinylidene donor **1.395** in DMF under UV irradiation, the stereomutation was indeed observed (while blanks afforded no reaction) confirming the electron transfer from excited **1.395** to an unactivated benzene ring for the first time (**Scheme 1.102**).**Scheme 1.102** Stereomutation of single isomer of 1,2-diphenylcyclopropanes.



1.456
a) R, R' = H
b) R, R' = F

1.460
a) R, R' = H
b) R, R' = F

Table 1.3 Stereomutation observed in cyclopropanes **1.456** and **1.460** mediated by electron transfer from *bis*-pyridinylidene donor **1.395** under UV-irradiation

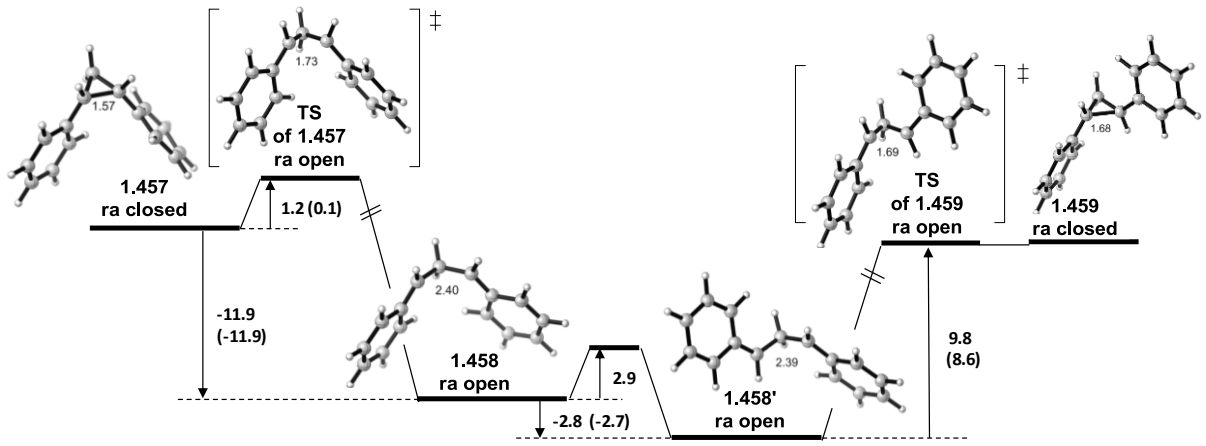
Arene	CP *trans/cis* start ratio	Donor **1.395** equiv.	isolated CP *trans/cis* ratio	isolated % yield
1.456a	2 : 98	3.0	19 : 81	79
1.456b	2 : 98	1.5	14 : 86	59
1.460a	99.5 : 0.5	3.0	95 : 5	88
1.460b	99 : 1	1.5	95 :5	35

Electron transfer to benzene (E^0 = -3.42 V *vs.* SCE) is usually the preserve of highly reductive alkali metals like sodium (E^0 = -2.71 V *vs*. SCE) and lithium (E^0 = -3.04 V *vs*. SCE) in ammonia (**Section 1.1.1**). The redox potentials of the phenyl rings in substrates **1.456a** and **1.460a** were calculated to lie within 0.2 V of benzene,[108] and therefore the reduction of 1,2-diphenylcyclopropane represented unprecedented reductive capability for an neutral organic electron donor.

The stereomutation was more pronounced for *cis*-substrates as expected. Computational calculations by Schoenebeck[108] showed there was essentially no barrier to ring-opening ($\Delta\Delta E^{\neq} = -0.1$ kcal mol^{-1}) in the *cis*-radical anion **1.457** (see **Figure 1.7**). The cleavage is exothermic and therefore reverse ring-closure is disfavoured. The barrier for rotation of ring-opened *cis*-**1.458** to *trans*-**1.458'** is low and feasible. The energy barrier for ring closure of the corresponding opened *trans*-open radical anion **1.458'** is around 9.8 kcal $^{mol-1}$, the same

energy as the transition state itself so in this case ring closure is also disfavoured. However, both *cis*-**1.458** and *trans*-**1.458'** ring-opened radical anions can undergo back-electron transfer forming corresponding singlet biradicals which do spontaneously ring close (the alternative triplet biradical was energetically disfavoured).[108]

Figure 1.7 Reaction path energy profile for 1,2-diphenylcyclopropane. The electronic energies are shown (in kcal/mol^{-1}) and the enthalpies are given in parentheses (at UB3LYP/6-31+G(d) level of theory).[108]



Therefore, the data suggested initial reductive ring-opening was followed by isomerization of ring-opened *cis*-**1.458** and *trans*-**1458'** radical anions. Subsequent oxidation affords a singlet biradical which rapidly ring closes.

Cahard *et al*. found that repeating the reaction for a longer period under more intense UV (100 W, 365 nm) with greater number of equivalents of donor afforded a greater degree of isomerism, along with reductive termination product 1,3-diphenylpropane **1.461**. Similar results under the same conditions were observed when the reaction was performed with DIT **1.265** but with increased yields of 1,3-diphenylpropane **1.461**.

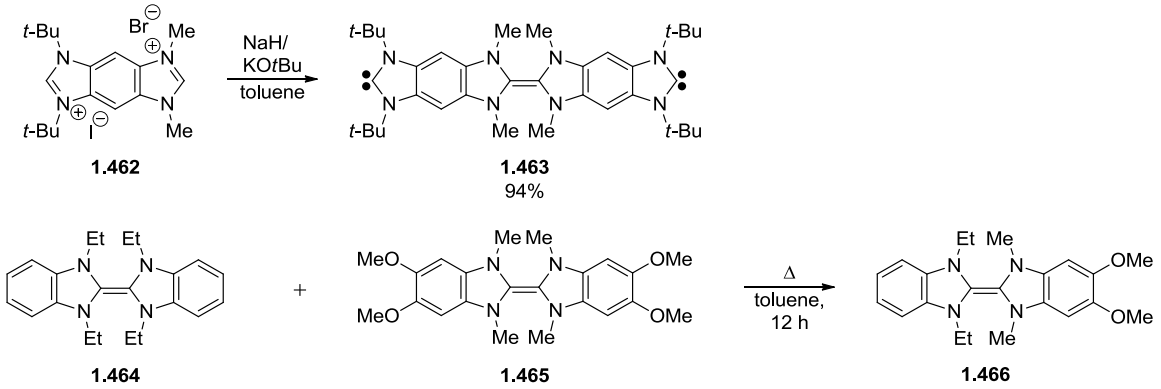
1.8 Other tetraazafulvalenes and organic electron donors:

1.8.1 Janus *bis*-carbenes

Recently Bielawski *et al*. has published formation of tetraazafulvalenes formed by dimerisation of derivatized benzimidazole-2-ylidenes. The 'Janus *bis*-carbene' **1.463**,[115] meaning two faced-carbene, incorporates a tetraazafulvalene core and two carbenes into a single structure. Dimerisation at the sterically less hindered 1,3-dimethyl end of the molecule takes place while the *t*-butyl groups provide sufficient hindrance to form stable *bis*-carbene.

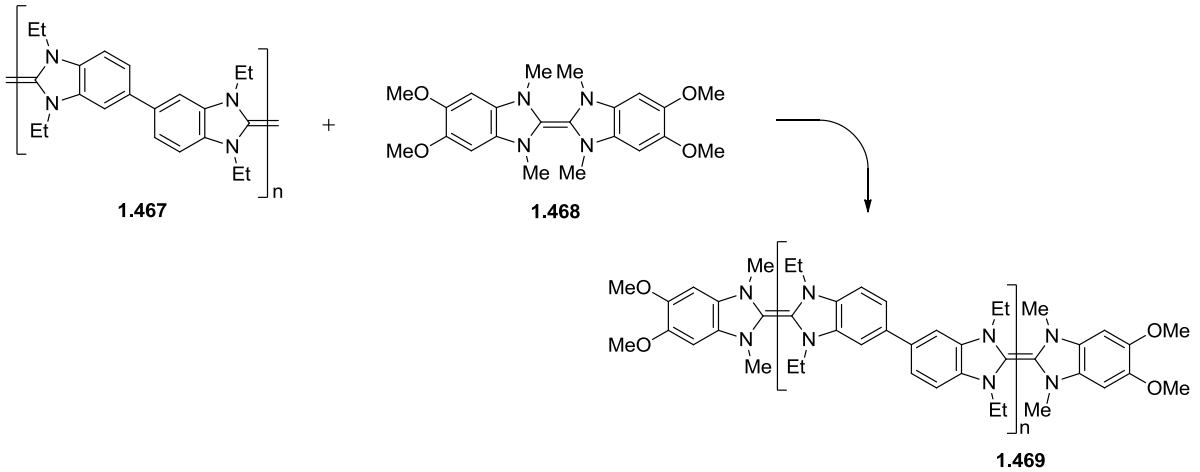
Interestingly Bielawski *et al*. report an example of a tetraazafulvalene cross-over product **1.466** on heating stoichmeteric quantities **1.464** and **1.465** in toluene at 100 ºC for 12 h.[116] **1.464**/**1.465**/**1.466** were afforded in 2:1:1 ratio.

Scheme 1.103 Bielawski tetraazafulvalenes.



Dimerised product **1.466** is analogous to the imidazolin-2-ylidene 'Wanzlick equilibrium'[117-119] cross-over product investigated separately by Lemal *et al*.[120,121] and Denk *et al*.[122] and the equilibrium is still the subject of debate.[4] Bielawski *et al*. do not refer to **1.466** as an explicit example of a Wanzlick equilibrium but instead as the product resulting from the 'dynamic nature of the carbene-based polymerizations' and they used this method to synthesise short polymer chains with functionalized end-groups, **1.469** (**Scheme 1.104**). Although these are interesting molecules and were later ligated to metal centres, being derived from benzimidazole means they will have no greater redox potential than SED **1.275**.

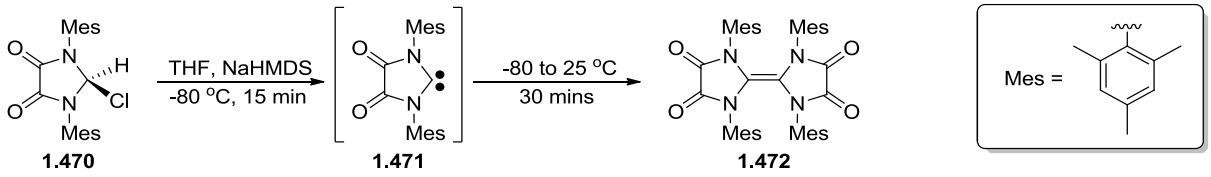
Scheme 1.104 Tetraazafulvalenes and dynamic polymerisation.



1.8.2 Diamido tetraazafulvalene

Interested in modifying the electronic properties of carbenes, Ganter *et al*. synthesised **1.472** hoping to isolate electron deficient carbene **1.471**.[123,124] It was hoped that the desired cyclic five-membered diamido carbene **1.471** would exhibit enhanced metal ligation by being a good acceptor of back-donated π-electrons. However diamido carbene **1.470** was not isolated but instead neutral tetraazafulvalene dimer **1.472**.

Scheme 1.105 Formation of tetraazafulvalene **1.472**.



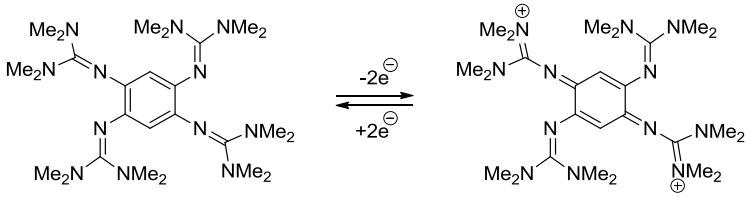
1.470 **1.471** **1.472**

Unusually **1.472** is stable to both moisture and oxygen and cyclic voltammetry showed a reversible wave in cyclic voltammetry at $E_{1/2}$ = -1.33 V *vs.* Fc/Fc^+ (in CH_2Cl_2) attributed to the reduction of the carbonyl moiety.

1.8.3 Tetraguanidino substituted benzenes and Wurster's salts

Himmel *et al*.[125-129] have also investigated electron-rich guanidine-derived benzenes, often forming inorganic complexes by chelation to metals. The neutral organic aromatic compound **1.473** shows a single two-electron wave by CV, with 2 π-electrons being transferred at -0.32 V *vs.* SCE in acetonitrile. Although **1.473** is a mild reducing reagent, it has yet to be applied in organic synthesis. **1.473** actually loses aromaticity on oxidation to **1.474**. Thus, it is no surprise that it is a less powerful reducing reagent than tetraazafulvalenes **1.265** and **1.275** or *bis*-pyridinylidene **1.395**.

Scheme 1.106 1,2,4,5-*tetrakis*guanidinobenzene synthesised by Himmel.

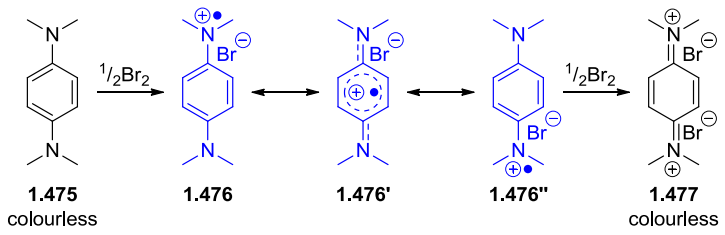


1.473 **1.474**

Computational calculations by Himmel *et al*. suggest **1.473** is a stronger electron donor than **1.265** in the gas phase, however in a polar solvent the bulk dication is poorly stabilised in contrast to **1.265** and so, from a practical point of view, tetraazafulvalenes are far superior electron donors.

The guanidine-derived benzenes of interest to Himmel find their origins in compounds known for over a century, *p*-phenylenediamines.[130,131] These systems are easily oxidised to the corresponding radical cations 'Wursters salts', due to the latter's high degree of resonance stabilisation.[132] The radical cations are typically stable in alcohol-water solutions at pH 3-6. *N*,*N*,*N'*,*N'*-Tetramethyl-*p*-phenylenediamine (TMPPD) **1.475** forms a blue solution of semiquinone **1.476'** upon single electron oxidation, while *N*,*N'*-dialkylated affords red and *N*-alkyl,*N'*-aryl generates light blue or green solutions.[133]

Scheme 1.107 Wurster's Blue.



Staab *et al*.[134-137] investigated aromatics with higher degrees of dimethylamino substitution 1,2,4,5-*tetrakis*(dimethylamino) benzene **1.478** and 2,3,6,7-*tetrakis*(dimethylamino) naphthalene **1.481** (**scheme 1.108**).

Scheme 1.108 Oxidation of *tetrakis*(dimethylamino)benzene and naphthalene.

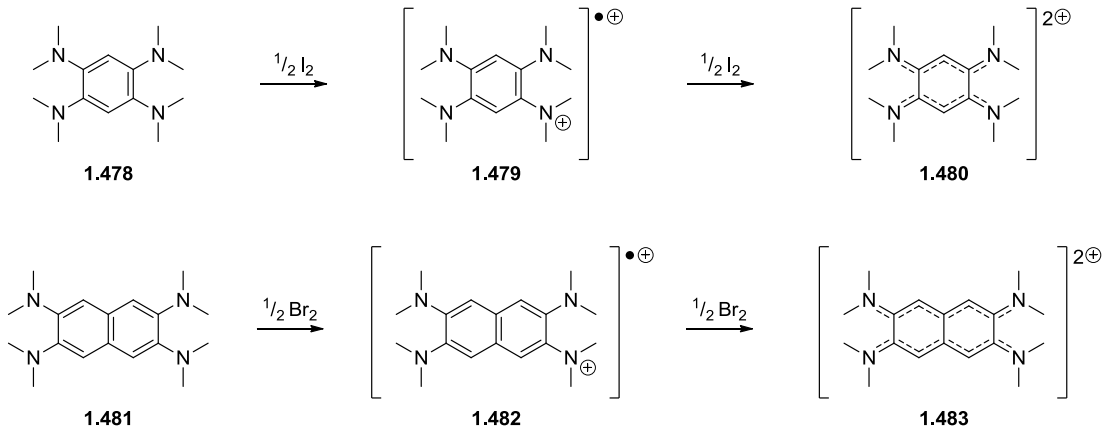


Table 1.4 Redox potentials for *exo*-cyclic aromatic amines.[135,136]

Arene	E_1 *vs.* Ag/Ag^+ (MeCN)	No. of Electrons	E_2 *vs.* Ag/Ag^+ (MeCN)	No. of Electrons
1.475	-0.206 V	1	+0.378 V	1
1.478	-0.266 V	2	+1.266 V	1
1.481	-0.08 V	1	+0.16 V	1

Comparing the cyclic voltammetry of **1.475**, **1.478** and **1.481** (**Table 1.4**) Staab *et al*. found that 1,2,4,5-*tetrakis*(dimethylamino) benzene **1.478** was strongest reducing reagent, capable of donating two electrons at the same redox potential and, strangely, a third electron at a much more positive potential.[136] In contrast Wursters blue, **1.475**[136] and 2,3,6,7-*tetrakis*(dimethylamino) naphthalene, **1.481**[135] typically undergo single-electron transfer. The corresponding radical cations of the latter two are also reported to be more persistent with the positive charge in oxidised salts delocalised over all four nitrogens in both **1.480** and **1.483**.[134]

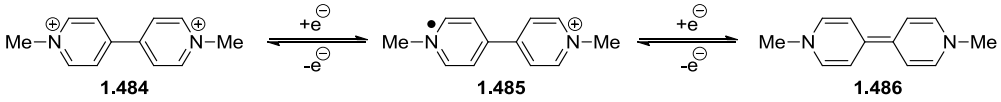
X-ray crystallographic analysis of dication **1.480** reveals loss of aromaticity with the formation of two planar cyanine resonance stabilised π-systems. The two mesomeric systems deform the six membered ring and are twisted relative to one another at 49º, minimising repulsion of positive nitrogens in a similar manner to TDAE cation **1.251** where the angle is 72º.[135] Similarly, in **1.483** two separate delocalised π-systems are established. In contrast to **1.480**, the rigidity of the bicyclic ring system is such that the ring is unable to undergo deformation. Thus, steric hindrance between the dimethylamino groups means they are unable to become fully co-planar with the mesomeric system.

1.8.4 Viologens

Endocyclic incorporation of nitrogen into aromatic compounds has proven a highly efficient method of generating neutral electron-donating compounds. Viologens are *N*,*N'*-di(alkyl)-4,4'-bipyridinium salts (although the name is commonly used to refer to their corresponding reduced neutral fulvalenes as well), the archetypical example being methylviologen **1.484**, also known as paraquat. Methylviologen **1.486** (MV^0)[138-142] has been described as the prototypical electron donor[140] and was first discovered by the reduction of *N*,*N'*–dimethyl-4,4'-bipyridinium **1.484** (MV^{2+}) over 80 years ago by Michaelis.[139,142] The planar non-

aromatic **1.486** is made up of alternating double and single bonds and is a moderately powerful (reversible) electron transfer reagent, donating two electrons *via* two separate SET events at $E_{1/2}$ = -0.84 V and -0.43 V *vs.* SCE (in MeCN).

Scheme 1.109 Methylviologen **1.486**



Takahashi *et al*. synthesised extended viologens with an additional aromatic group linking the pyridinium units (**Scheme 1.110**).[143] The additional gain in aromatic stabilisation energy makes the extended viologens marginally more powerful electron donors (**Table 1.5**) than parent **1.486**. Interestingly the cyclic voltammograms of **1.489a** and **b** show two reversible SET reductions, indicating formation of stable radical cation **1.488a**,**b** and dication **1.487a**,**b**. While **1.490** undergoes a single reduction, donating two electrons at an identical potential.

Scheme 1.110 Takahashi's extended viologens.[143]

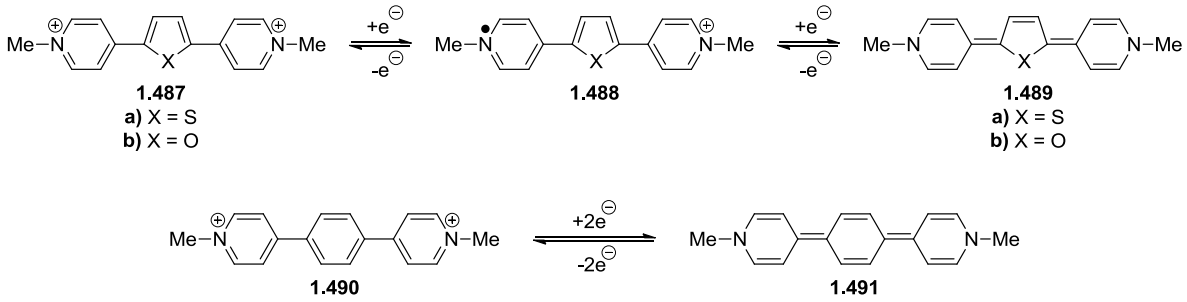
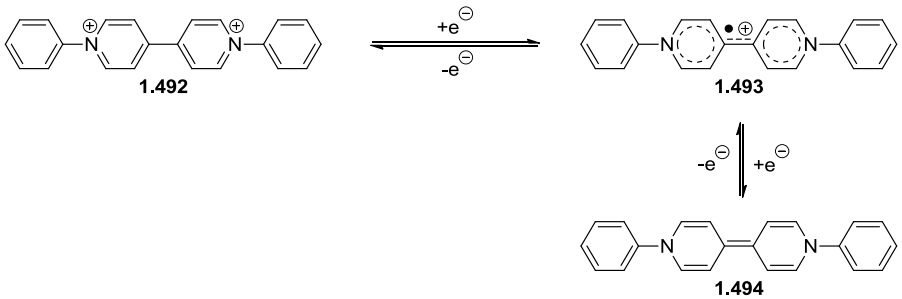


Table 1.5 Redox potential for viologens.

Viologen	E_1 *vs.* SCE (MeCN)	E_2 *vs.* SCE (MeCN)	No. of Electrons	Dication
1.486	-0.85 V	+0.43 V	2	**1.484**
1.489a	-0.84 V	-0.69 V	2	**1.487a**
1.489b	-0.93 V	-0.74 V	2	**1.487b**
1.491	-0.91 V	N/A	2	**1.490**

Vaid *et al.*[144,145] looked to make the redox potentials of viologens more negative by extending the linear chain of aromatics beyond three units (**Scheme 1.111**). Initial investigations were undertaken with phenyl viologen **1.494** (PV^0).[144] Cyclic voltammetry of PV^0 **1.494** showed two single electron transfers at $E_{1/2}$ = -0.94 V and -0.68 V *vs.* Fc/Fc^+ (THF). While X-ray crystallographic data were not obtainable for PV^0 **1.494**, in the radical cation, $PV^{\bullet+}$ **1.493** the two central pyridine rings are coplanar with a twist of only 1º while the dihedral angle between the pyridinyl and the terminal phenyl rings is 37º. Alternate shorter and longer bonds are consistent with a molecule half-way between aromatic dication and quinoid neutral molecule, indicative of a delocalised core which does not extend to the terminal phenyl ring. All the heterocyclic rings in PV^{2+} **1.492** are twisted out of plane by approximately 37º to their neighbouring rings. Thus PV^0 **1.494** has more in common with MV^0 **1.486** than Takahashi's extended viologen **1.491**. The reduction of dication **1.495** did however form fully delocalised conjugated viologen **1.492**.[145] Cyclic voltammetry revealed that **1.496** gains aromaticity by donation of a total of four electrons. Oxidation occurs in three stages *via* two single electron transfers at $E_{1/2}$ = -2.86 V and -2.49 V and one double electron transfer at $E_{1/2}$ = -1.48 V *vs.* Fc/Fc^+.

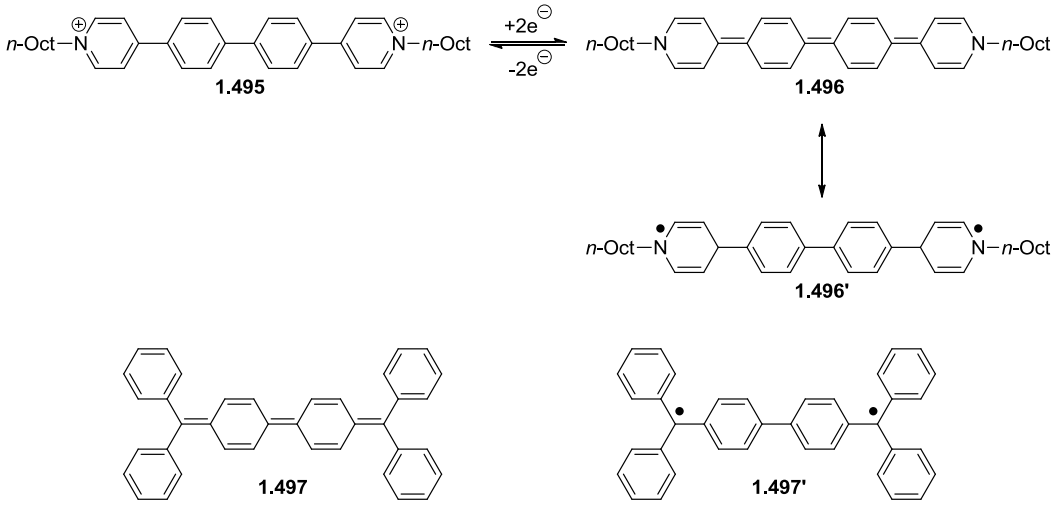
Scheme 1.111 Phenyl viologen synthesised by Vaid *et al.*



Additionally Vaid *et al*. noted that the conflicting analysis by ^{1}H-NMR, ESR and X-ray crystallography of the extended neutral viologen showed evidence for dual existence in the ground state, with the two possible resonance structures being that of closed-shell, fully quinoid **1.496** and biradical **1.496'** (**Scheme 1.112**). Vaid *et al*. suggest that in a neutral extended viologen with a very long chain of phenylene rings, at some point the energetic stabilization gained by converting a long chain of quinoid rings to aromatic rings will be greater than the energy lost by breaking one π-bond, and a diradical of the type **1.496'** will become favoured over the fully quinoid structure. Ultimately, the precise electronic structure **1.496** could not be determined but is very similar to that of Chichibabin's hydrocarbon,[146,147]

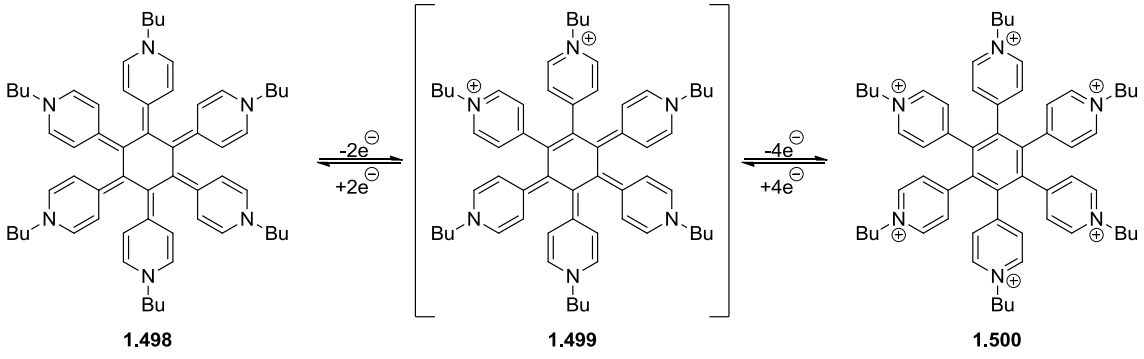
which can be considered either as closed-shell singlet with their two central rings in a quinoid form **1.497** or as biradical **1.497'** with two aromatic central rings.

Scheme 1.112 Chichibabin's hydrocarbon **1.497** and the successfully extended viologen **1.496** by Vaid *et al*.



At the time of its publication **1.496** was the most powerful neutral organic electron donor known[145] and Vaid *et al*. continued to explore the redox properties of viologens (**Scheme 1.113**).

Scheme 1.113 Redox activity observed in *hexakis*(4-(*N*-butylpyridylium))benzene.



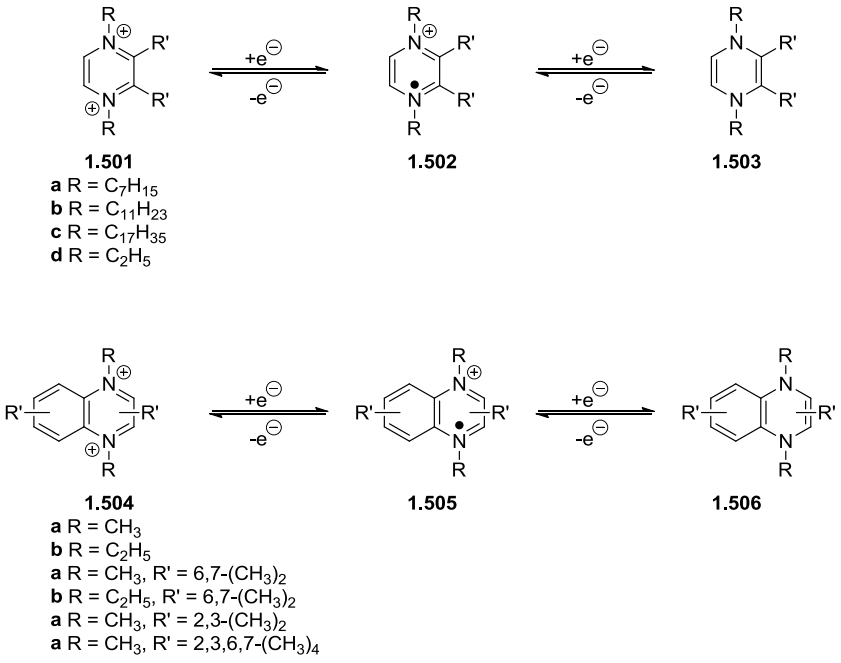
Macrocyclic **1.500** receives six electrons at two reversible redox potentials.[148] An unprecedented four electrons were transferred in a single oxidation at $E_{1/2}$ = -1.14 V *vs.* Fc/Fc^+ forming intermediate dication **1.499** (that could not be isolated), the dication then undergoes further two electron oxidation at $E_{1/2}$ = -1.33 V affording hexacation **1.498**.

Despite aromaticity being gained over a total of seven six-membered rings, **1.500** is only a moderate electron donor and in fact **1.496** is stronger reducing reagent, again this is due to the significant rearrangement energy required to make the transition from **1.500** to **1.498**.

1.8.5 Pyrazinium salts

In contrast to viologens, the redox properties of the structurally similar pyrazinium salts have received significantly less attention. In 2005 Schmittel *et al*. reported the relatively negative redox potentials of pyrazinium ionic liquids **1.501** (**Scheme 1.114**), $E_{1/2}$ = -1.16 V and -0.20 V *vs.* Fc/Fc^{+}.[149]

Scheme 1.114 Formation of 1,4-dihydropyrazines **1.503** and 1,4-dihydroquinoxaline **1.506**.



Over a decade earlier, a number of researchers including Kaim *et al*. were investigating the formation of stable *N*,*N*-dialkylated pyrazine **1.502** and quinoxaline **1.505** radical cations.[150-153] As 1,4-dihydropyrazines **1.503** and 1,4-dihydroquinoxaline **1.506** possess redox potentials significantly stronger than TTF, typical $E_{1/2}$ = -0.40 V and +0.50 V *vs.* SCE it is somewhat surprising that they have not been applied in synthesis. Indeed, comparing the redox potential of 1,4-diethyl-1,4-dihydropyrazines **1.503d** ($E_{1/2}$ = -0.67 V and +0.36 V)[153] with TDAE ($E_{1/2}$ = -0.78 and $E_{1/2}$ = -0.61 V)[154] and TTF ($E_{1/2}$ = +0.32 V and +0.70 V)[63] all versus SCE the first redox potential is almost as strong as TDAE while the second redox potential is approximately the same as first redox potential of TTF. These types of redox potential should

allow **1.503** and **1.506** to mediate electron transfer chemistry. In fact with such a significant difference between the first and second redox potentials, single electron transfer might be possible with formation of relatively stable oxidised radical cations **1.502** and **1.505**.

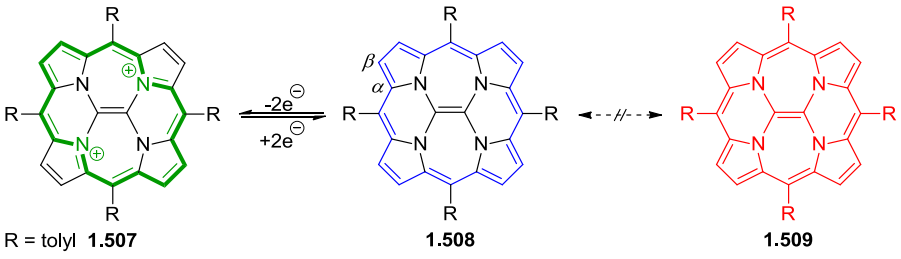
Table 1.6 Reduction of 1,4-dihydropyrazines **1.503** and 1,4-dihydroquinoxaline **1.506**.

1,4-dihydro-pyrazine	E_1^{red} *vs.* SCE (MeCN)	E_2^{red} *vs.* SCE (MeCN)	No. of Electrons	Dication
1.503d	-0.67 V	+0.36 V	2	**1.501d**
1.506a	-0.30 V	+0.60 V	2	**1.504a**
1.506b	-0.34 V	+0.58 V	2	**1.504b**
1.506c	-0.44 V	+0.48 V	2	**1.504c**
1.506d	-0.41 V	+0.48 V	2	**1.504d**
1.506e	-0.39 V	+0.38 V	2	**1.504e**
1.506f	-0.48 V	+0.29 V	2	**1.504f**

1.8.6 Antiaromatic porphine

Most recently Vaid investigated the redox properties of a completely organic porphyrin,[155] replacing the metal element typically found at the core of porphyrin with a C=C double bond, forming enetetramine **1.508** (**Scheme 1.115**).

Scheme 1.115 Antiaromatic porphine **1.508** synthesised by Vaid.



The simplest porphyrin is porphine **1.510** and like any standard porphyrin it contains 18 π-electrons in a conjugated system and is aromatic (shown in bold purple), being in resonance with **1.510'**. Similarly **1.507** appears to be aromatic (bold green), in contrast to the reduced 20-π-electron periphery of the porphine ring system in **1.508**. The 20 π-electrons contained in conjugated alternate single and double carbon-carbon bonds mean **1.508** is antiaromatic (shown in blue).

The cyclic voltammogram of **1.508** shows four reversible electron transfer at $E_{1/2}$ = -0.26, -0.59, -1.91 and -2.17 V *vs.* Fc/Fc^+ (THF). The redox potentials at -0.26 V and -0.59 V are attributed to the reduction of **1.507** forming **1.508**, while the waves at -1.91 V and -2.17 V correspond to the reduction of the porphine ring forming anion and dianion, respectively. **1.508** exhibits more negative redox potentials than typical metalloporphines on account of it containing an easily oxidised enetetramine core. Transformation from an antiaromatic compound **1.508** to an aromatic compound **1.507** provides an additional driving force. The characterisation of the porphine structures by NMR support the aromatic and antiaromatic nature of **1.507** and **1.508,** respectively. A typical diatropic ring current is established in aromatic **1.507** with *β*-pyrrole protons being observed at δ = 9.44 and 9.47 ppm in ^{1}H-NMR, while they are found considerably upfield in antiaromatic **1.508** at δ = 2.38 and 2.67 ppm, diagnostic of paratropic current. Similarly carbons of central C=C bond are shielded in aromatic dication **1.508**, being found at 102.6 ppm by ^{13}C-NMR, while they are deshielded in neutral antiaromatic **1.508** at 135.4 ppm, in accordance with diatropic and paratropic current, respectively.

Despite the redox potential of **1.508** being oxidized at a potential about 1.0 V more negative metalloporphine ($E_{1/2}$ = +0.4 V *vs.* Fc/Fc^+), it is still significantly weaker than the SED developed in our laboratories and viologens explored by others. This interesting example does however highlight the benefit of going from an antiaromatic compound to aromatic compound which in principle could afford more negative redox potentials, conceivably in smaller molecules which undergo less structural reorganisation on oxidation.

1.9 Thesis aims

Through selected examples this review has illustrated the power of electron transfer chemistry when applied to organic synthesis and highlighted some of the key reagents capable of mediating electron transfer chemistry. The aim of this thesis is thus:

- to expand the scope of substrates amenable to functional group transformations *via* reductive electron transfer processes mediated by the known super-electron-donors currently in use within our laboratories.
- to apply electron transfer chemistry of super-electron-donors to the synthesis of small molecules as groundwork for later applications in natural product synthesis.
- to develop new easily synthesised organic compounds capable of powerful reductive electron transfer chemistry.

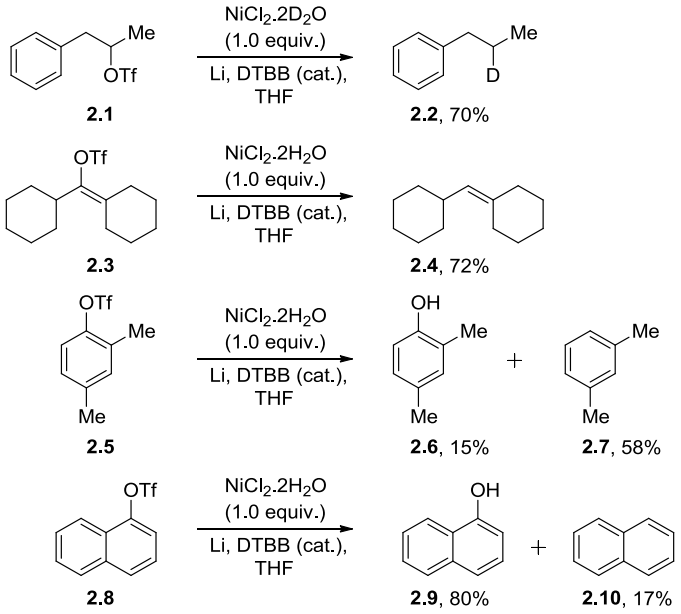
2 RESULTS AND DISCUSSION – Cleavage of Trifluoromethanesulfonyl Esters and Amides with *bis*-Pyridinylidene

2.1 Introduction

The trifluoromethanesulfonyl (triflyl) group makes important contributions in organic chemistry, due to its strong electron-withdrawing effect. Aryl triflate esters find extensive use in metal-mediated cross-coupling reactions,[156,157] and in this regard they differ from other aryl sulfonate esters. In addition, aryl triflates[158] have also been used to modulate the reactivity of aryl rings towards electrophiles at key stages during synthetic sequences; once this role has been fulfilled, their removal (C–O cleavage)[158-160] to form arenes or deprotection (S–O bond cleavage) to form their parent phenols is required; deprotection of aryl triflates has been accomplished with a number of reagents,[161-164] such as Et_4NOH,[161] $LiAlH_4$;[162] electrochemical reduction affords mainly deprotection (S–O cleavage), together with some C–O cleavage;[163] and solvolysis of particular aryl triflates in trifluoroethanol with K_2CO_3[164] gives C–O cleavage.

In contrast, alkyl triflates are excellent alkylating agents even towards mild nucleophiles, undergoing facile displacement of triflate anion (C–O bond cleavage). Alkyl triflates are such sensitive electrophiles that their deprotection to their parent aliphatic alcohols (S–O bond cleavage) has never been reported. This contrasts with alkyl tosylates, for example, which have been reduced to their parent alcohols.[165-172] The reductive cleavage of alkyl and aryl triflates has also been reported by Yus *et al.*[159,160] with very divergent outcomes (**Scheme 2.1**). For instance, exclusive C-O σ-bond scission was observed when alkyl and enol triflates **2.1** and **2.3** were reacted with a $NiCl_2$-Li-arene (cat.) combination (using 4,4-di-*tert*-butyl-biphenyl, DTBB, as arene) affording alkane **2.2** and alkene **2.4**, respectively with complete removal of the triflyl group. In the case of aryl triflates **2.5** and **2.8**, less selectivity was observed with S-O and C-O σ-bond cleavage being observed yielding mixtures of the corresponding phenols and deoxygenated arenes. The mechanism for this reaction is not currently understood.

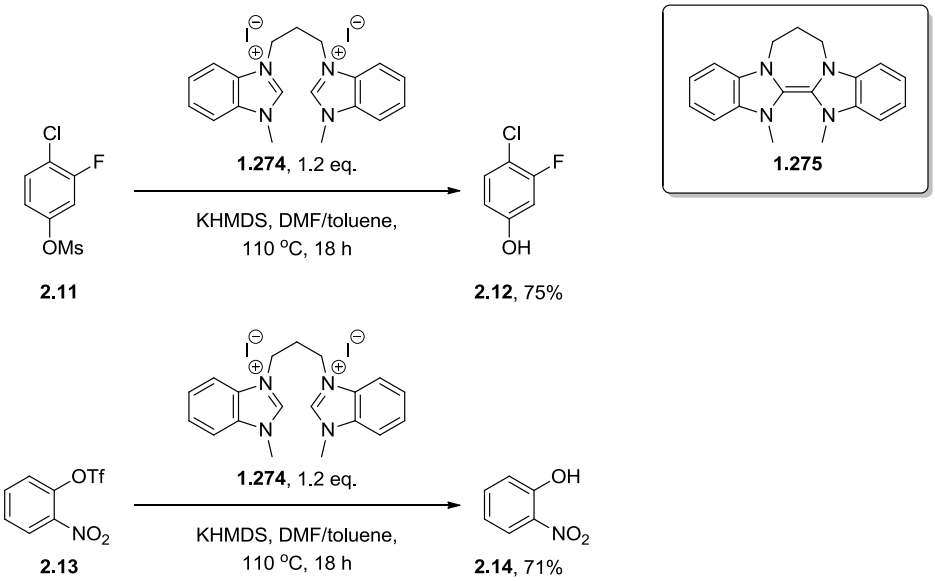
Scheme 2.1 Reductive cleavage of triflates by Yus *et al*.[159,160]



Additionally Yus *et al*. have successfully effected the cleavage of the C-O σ-bond of alkyl triflates using lithium powder and naphthalene.[173]

The deprotection of highly activated aryl methanesulfonate esters has been demonstrated within our own research group by Schoenebeck (**Scheme 2.2**).[174]

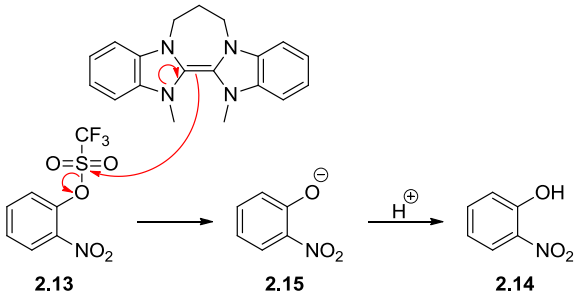
Scheme 2.2 Cleavage of aromatic sulfonate esters to phenols by benzimidazole-derived tetraazafulvalene **1.275**.



Successful O-S σ-bond scission was observed for the reaction of the aryl mesylate **2.11** with benzimidazole-derived tetraazafulvalene **1.275**. Additionally Schoenebeck[174] showed that reaction of **1.275** with the highly electronegative aryl triflate **2.13** readily afforded the corresponding phenol **2.14**.

The reaction mechanism was not established, however Schoenebeck hypothesised that the reaction could be mediated by nucleophilic attack of electron-rich tetraazafulvalene **1.275** at the sulfur atom.[174]

Scheme 2.3 S_N2 at sulfur of triflate.

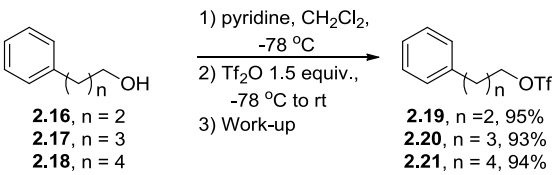


Thus an initial result generated within our laboratories by Schoenebeck and the general lack of understanding around the cleavage of trifluoromethanesulfonate esters represented the perfect prompt to undertake further investigations with neutral organic super electron donors.

2.2 Reduction of Alkyl Triflates with *bis*-Pyridinylidene, Enediamine 1.395

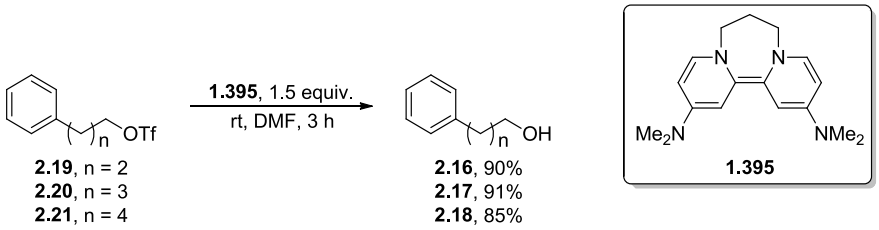
Simple alkyl and aryl triflates are readily afforded by reaction of corresponding alcohols or phenols with trifluoromethanesulfonic anhydride in dry dichloromethane at 0 ºC or less in presence of base, such as triethylamine or pyridine.[175] The alkyl triflates **2.19-2.21** chosen as candidates for primary investigation (**Scheme 2.4**), were prepared in excellent yield by dissolving the corresponding alcohol in dry CH_2Cl_2 and pyridine (1.0 equiv.) at -78 ºC before adding trifluoromethanesulfonic anhydride (1.5 equiv.).

Scheme 2.4 Synthesis of alkyl trifluoromethanesulfonate esters.



Research was initiated with the more powerful and readily available, pure *bis*-pyridinylidene donor **1.395**, $E_{1/2}$ = -1.20 V *vs.* SCE in DMF (compared to $E_{1/2}$ = -0.82 and -0.76 V *vs.* SCE in DMF for **1.275**) and alkyl triflates **2.19-2.21** in DMF. Under these conditions alkyl triflates **2.19-2.21** were smoothly converted to their parent alcohols **2.16-2.18** in excellent yields (85-91%), at neutral pH at ambient temperature (**Scheme 2.5**).

Scheme 2.5 Conversion of alkyl triflates **2.19-2.21** to aliphatic alcohols **2.16-2.18** with *bis*-pyridinylidene SED **1.395**.



The trifluoromethanesulfonyl functional group is extremely electronegative and an outstanding leaving group for alkylation reactions. It is therefore possible that the reaction could proceed *via* three different mechanisms (**Scheme 2.6**):

- nucleophilic attack by the electron-rich *bis*-pyridinylidene **1.395**
- nucleophilic attack at carbon by the DMF solvent
- electron transfer from *bis*-pyridinylidene **1.395**

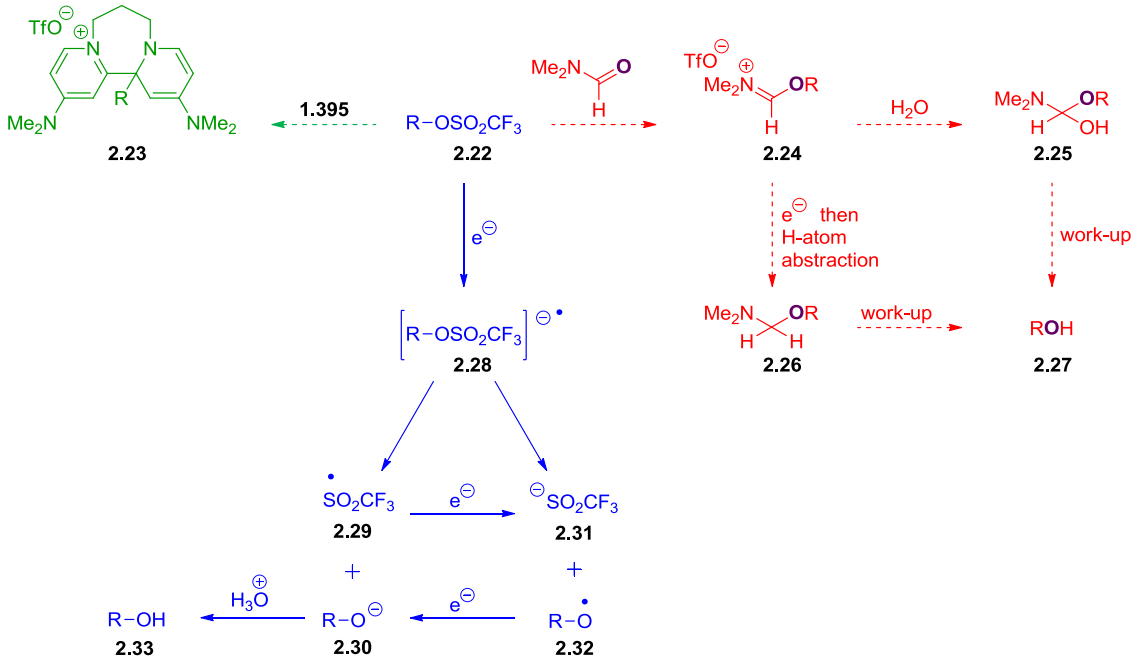
It is conceivable that **1.395** driven by gain of aromatic stabilisation energy in **2.23**, could act as a nucleophile attacking the excellent carbon electrophile adjacent to triflate (**Scheme 2.6**, green). However it is difficult to see how alcohol products could now be released from alkylated **2.23** and thus this pathway can be eliminated. Substitution at the sulfur atom of an alkyl triflate is unprecedented with nucleophilic attack always occurring at the carbon adjacent to triflyl functional group, thus this possibility can be discounted also.

Alternatively nucleophilic attack by DMF on the triflate would afford imidate salt **2.24** which could be directly hydrolysed to alcohol **2.27** or could undergo further reduction and hydrogen abstraction generating aminol ether **2.26**, that in turn yields alcohol **2.27** on work-up (**Scheme 2.6**, red). Crucially in this hypothesis the oxygen of the DMF (bold purple) would be incorporated into the final alcohol product. To probe for the involvement of DMF in the reaction mechanism, another member of our team[176] performed a reaction using ^{18}O-labelled

DMF (13% enrichment). No incorporation of ^{18}O was observed in the alcohol product and thus the reaction must be mediated by a process that excludes DMF as a nucleophile.

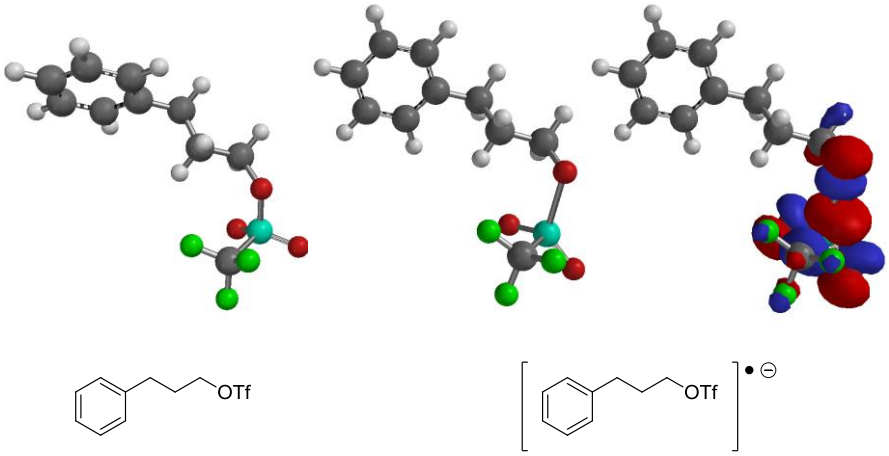
Therefore it is reasonable to conclude that the reaction is mediated by an electron transfer process (**Scheme 2.6**, blue), in line with the typical reactivity already observed for *bis*-pyridinylidene donor **1.395**.[107,108,110-112,177] Electron transfer to triflate **2.22** would form radical anion **2.28**. Scission of the O-S σ-bond in the radical anion **2.28** could potentially occur in one of two possible ways with formation of either (i) a sulfonyl radical **2.29** and alkoxide anion **2.30** or (ii) sulfinate anion **2.31** and oxyl radical **2.32**. In either case a rapid second electron transfer from the highly reductive reaction medium ultimately yields the same final alkoxide and sulfinate anion pair **2.30** and **2.31**, respectively, which on work-up affords the final alcohol product **2.33** and trifluoromethanesulfinic acid.

Scheme 2.6 The three possible reaction mechanisms for cleavage of triflates with *bis*-pyridinylidene **1.395** in DMF.



DFT calculations (6-31 G*) on the radical-anion of **2.19** support the O-S σ-bond scission of alkyl triflates. The SOMO is delocalised on the trifluoromethanesulfonate unit and the expected stretching of the O-S σ-bond is also observed, increasing from 1.61 Å in the neutral triflate to 2.39 Å in the radical anion (**Figure 2.1**).

Figure 2.1 DFT computational simulation of phenylpropyl triflate **2.19** (left), its radical-anion with stretched O-S σ-bond (centre) and the orbital depiction of the SOMO in the radical anion (right) [Spartan'04 using DFT 6-31G*].



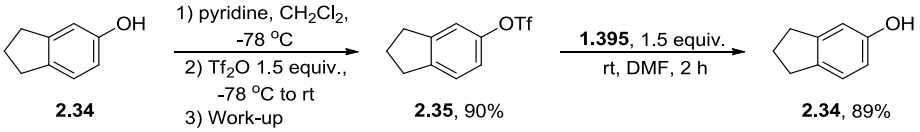
The deprotection of alkyl triflate electrophiles to their corresponding aliphatic alcohols is unprecedented. Alkyl triflates are superb nucleofuges and are known to be between 2 x 10^4 and 2 x 10^5 more reactive than corresponding tosylates.[178] Thus, the ability of *bis*-pyridinylidene **1.395** to act only as an electron donor in the presence of such highly sensitive electrophiles highlights its exceptional prowess as a powerful super-electron-donor.

2.3 Reduction of an Aryl Triflate and Trapping of the Sulfinate Anion

The reactivity of *bis*-pyridinylidene donor **1.395** with aryl triflates was also explored**.**

Under the same reaction conditions used for the cleavage of alkyl triflates, the reaction of triflate **2.35** with *bis*-pyridinylidene donor **1.395** successfully regenerated phenol **2.34** in excellent yield.

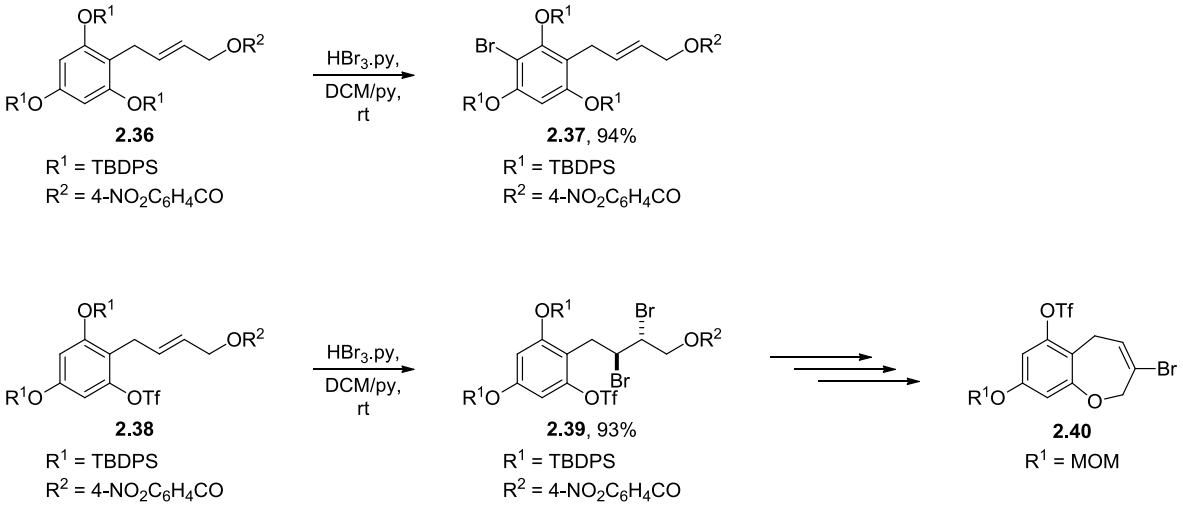
Scheme 2.7 Reductive cleavage of aryl trifluoromethanesulfonate ester **2.35**.



The use of aryl triflates as protecting groups is significantly less frequent than the corresponding tosylates. However Ohgiya *et al.*[161] successfully employed the electron-

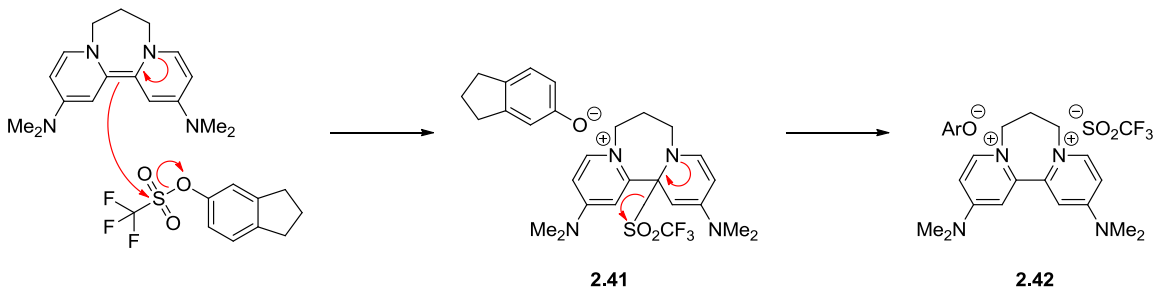
withdrawing effects of the triflyl group to decrease the nucleophilicity of the aromatic system in **2.38** (**Scheme 2.8**), which undergoes selective bromination of the alkene bond and successfully affords desired dibromide **2.39**, a precursor to a key natural product intermediate **2.40**. In contrast, when all three phenol hydroxy groups were protected as *tert*-butyldiphenylsilyl ethers in the analogous **2.36**, the increased electron-density led to the formation of **2.37** *via* the undesired bromination of the aryl ring. Deprotection of the triflyl group in **2.39** to the corresponding phenol is then required before further elaboration.

Scheme 2.8 Inductive modulation of an aromatic system *via* triflyl protection.[161]



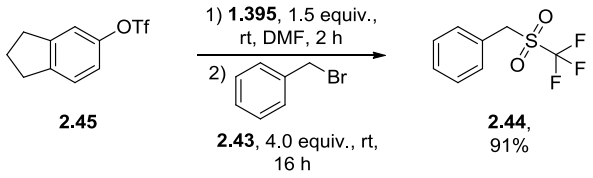
Unlike alkyl trifluoromethanesulfonate esters, it is possible that cleavage of aryl trifluoromethanesulfonate esters is mediated by the nucleophilic attack at the sulfur atom of triflyl group by *bis*-pyridinylidene **1.395** (as previously suggested by Schoenebeck[174] for SED **1.275**).

Scheme 2.9 Proposed nucleophilic attack of *bis*-pyridinylidene donor **1.395** at the triflyl sulfur atom.



Both the electron transfer and the S_N2 mechanism are driven by a gain of aromatic stabilisation energy upon oxidation of **1.395** to the corresponding pyridinium dication *e.g.* **2.42** and in both processes a sulfinate anion is generated. Reaction with a suitable alkylating reagent should afford the corresponding triflyl sulfone, providing evidence for the existence of the sulfinate anion. Thus, the reduction of aryl triflate **2.35** was repeated, stirring for 2 h with *bis*-pyridinylidene donor **1.395** in DMF at ambient temperature (**Scheme 2.10**), before benzyl bromide (4.0 equiv.) was added and allowed to stir overnight. Standard work-up and column chromatography yield the desired sulfone, trifluoromethylsulfonylmethylbenzene **2.44** in excellent yield, completely consistent with the formation of a nucleophilic sulfinate anion **2.31**.

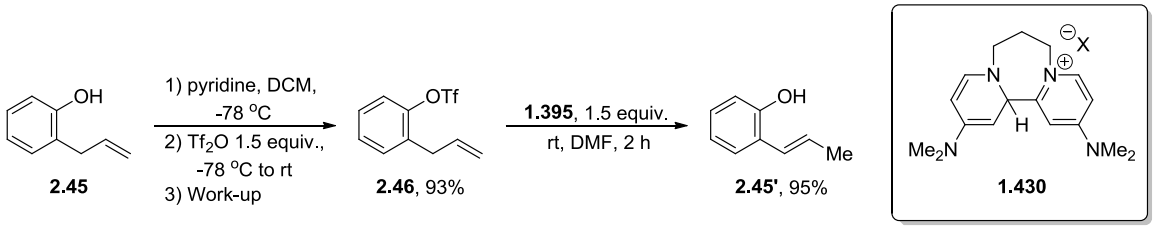
Scheme 2.10 Trapping of sulfinate anion with benzyl bromide electrophile.



2.4 Selective Reduction of Triflate Esters

Having successfully demonstrated the cleavage of both alkyl and aryl triflates, the reductive cleavage of triflates in the presence of other functional groups was now investigated. Allyl trifluoromethanesulfonate ester **2.46** was smoothly converted to phenol **2.45**, in excellent yield (**Scheme 2.11**). No reduction of the olefin moiety was observed. However interestingly the terminal C=C double bond was isomerised to the more thermodynamically stable conjugated styrene **2.45'**. The isomerisation is most likely to occur due to *bis*-pyridinylidene donor **1.395** behaving as a base and forming partially aromatised intermediate **1.430**.[111]

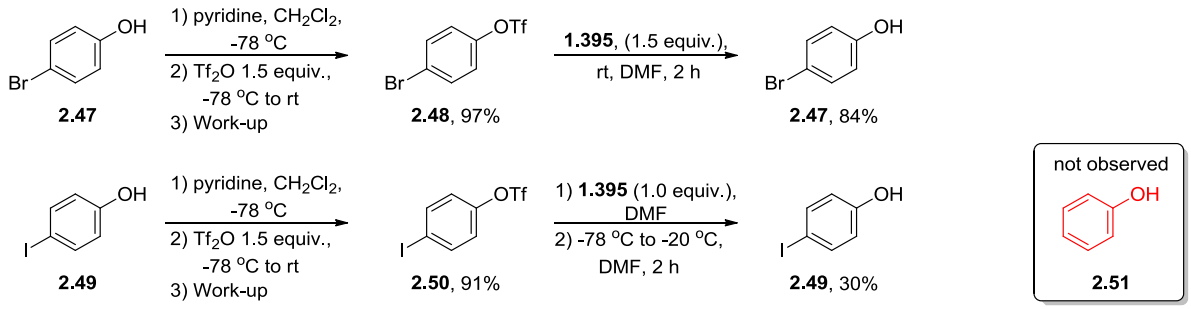
Scheme 2.11 Selective reduction of triflyl group over olefin.



The selective reduction of the carbon-halogen bond versus triflate in aromatic compounds was also investigated. Previous investigations have established that 3.0 equivalents of SED **1.395** at 100 °C reduce aryl bromides in good yield, with the more easily reduced 9-bromoanthracene being fully converted to anthracene with 1.5 equivalents at room temperature.[107]

The bromo and iodo aromatic trifluoromethanesulfonate esters, **2.48** and **2.50** were prepared and examined on reaction with *bis*-pyridinylidene donor **1.395** (**Scheme 2.12**).

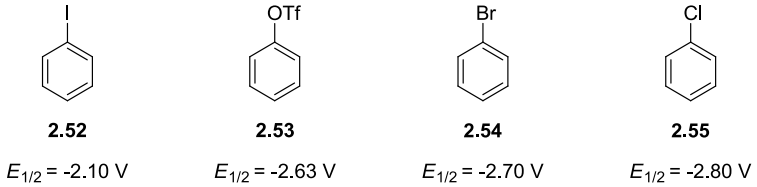
Scheme 2.12 Reduction of halo aryl trifluoromethanesulfonate ester.



Pleasingly selective cleavage of the triflate functional group was observed when **1.395** (1.5 equiv.) was reacted with **2.48** at room temperature, exclusively affording 4-bromophenol **2.47** in good yield, the first chemoselective cleavage of a triflate group over a halogen. The reduction of analogous **2.50** also afforded a single product, the detriflated 4-iodophenol **2.49**, however the recovered yield was significantly lower than for 4-bromophenol **2.47**.

Considering that the relative reduction potential of PhOTf **2.53** and PhBr **2.54** as individual species are so close to one another, $E_{1/2}$ = -2.63 V and $E_{1/2}$ = -2.70 V *vs*. SCE, respectively[179] (**Figure 2.2**), it is interesting that the selective reduction of triflate over bromide is observed at all when the functionalities inhabit the same aromatic system.

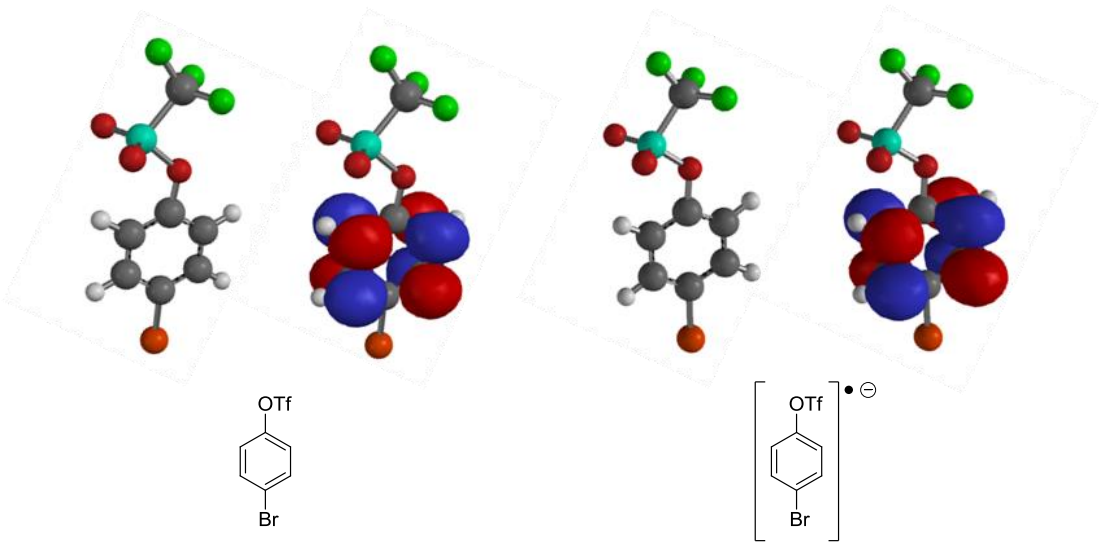
Figure 2.2 Reduction potentials of aryl halides and triflate.[179]



Clearly the experimental results show the O-S σ-bond of the triflate is cleaved in preference to C-Br σ-bond in **2.48**. This might be an indication that the cleavage is taking place by nucleophilic attack at sulfur of the aromatic triflate; alternatively a reductive cleavage might occur through the formation of a complex between *bis*-pyridinylidene donor **1.395** and the substrate **2.48** and this could subsequently favour triflate cleavage.

DFT studies (6-31G*) of *p*-bromophenyl triflate **2.48** show the LUMO located on the π-system of the aromatic ring and the SOMO of the radical anion is also located on the π-system.

Figure 2.3 DFT 6-31G* of *p*-bromophenyl triflate **2.48** (far left) and with LUMO depicted (centre left), *p*-bromophenyl triflate radical-anion (centre right) and with SOMO depicted (far right).

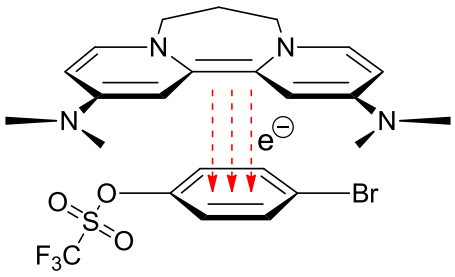


The computational studies suggest the electron transferred from *bis*-pyridinylidene enediamine **1.395** would be likely to be transferred to the aromatic π-system, the LUMO of the *p*-bromophenyl triflate, **2.48** (**Figure 2.3**, centre left). Electron transfer to the π*-orbital of the aromatic system may be facilitated *via* an intimate complex, encouraged to form by favourable Van der Waals interactions between the aromatic substrate and planar **1.395** (**Figure 2.4**).

The computational studies also indicate that, after transfer, the electron resides predominantly in the π*-orbital, the SOMO of the *p*-bromophenyl triflate radical-anion (**Figure 2.3**, far right). Hynes *et al*.[180] have shown that out-of-plane bending and stretching of the C-Br bond,

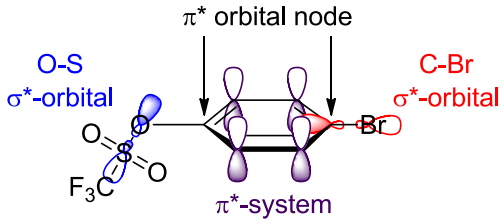
(which is orthogonal to the aromatic system) is required in order to achieve sufficient orbital overlap and mixing between π*-orbital and C-Br σ*-orbital to permit intramolecular electron transfer. In this case electron transfer from the π*-orbital of the aromatic system and the σ*-orbital of the triflyl O-S could be favoured.

Figure 2.4 Intimate complex formation favouring electron transfer to π-system.



However, computation of the SOMO of the *p*-bromophenyl triflate radical-anion indicates that there is an orbital node at the carbon attached to the triflate thus intramolecular transfer would be precluded which may suggest the cleavage of the triflate is mediated *via* a nucleophile mechanism as previously mentioned.

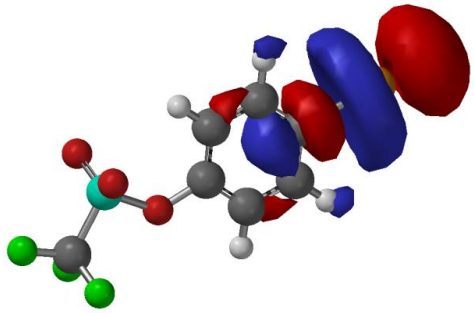
Figure 2.5 Orbital representation of 4-bromophenyl trifluoromethanesulfonate radical anion.



The reduction potentials of PhI **2.52** and PhOTf **2.53** taken as individual cases are $E_{1/2}$ = -2.10 V and $E_{1/2}$ = -2.63 V *vs*. SCE respectively, a difference of 0.53 V *vs*. SCE that clearly favours C-I σ-bond scission. Thus, within the same molecule the C-I σ-bond would be expected to be cleaved preferentially. However the reaction of 4-iodophenyl-1-trifluoromethanesulfonate **2.50** with *bis*-pyridinylidene donor **1.395** afforded only 4-iodophenol and this was the only product observed in the ^{1}H-NMR spectrum of the crude work-up reaction mixture. Computation on substrate **2.50** (Hartree-Fock 6-31 G*) show the LUMO to be the C-I σ*-orbital (**Figure 2.6**) and thus this where the first electron from SED **1.395** would be

expected to be transferred, subsequently resulting in scission of C-I σ-bond contradicting the experimental observations.

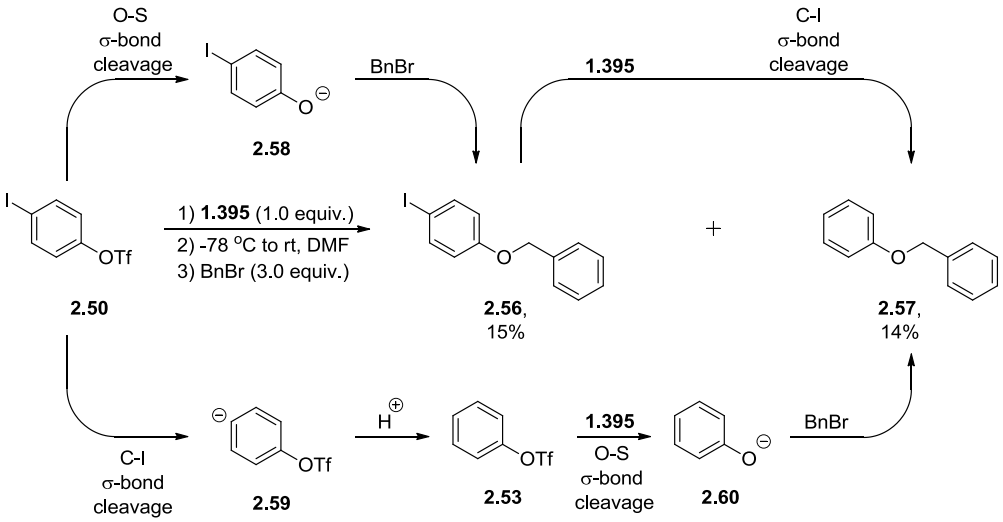
Figure 2.6 Hartree-Fock 6-31 G* of *p*-iodophenol triflate **2.50**.



The modest mass recovery of 4-iodophenol (30%) raises doubts about the selectivity of reaction. No cleavage of the O-C σ-bond of triflates has been observed by the reduction with **1.395** so generation of benzene and loss to the vacuum can be discounted. Phenol **2.51** could be generated if both O-S and C-I σ-bond cleavage were to occur. The relatively high boiling point of 182 ^{o}C should result in significant amounts visible by ^{1}H-NMR of the crude reaction but this is not the case. However, in an attempt to determine the fate of any intermediate anions formed by the reduction of 4-iodophenyl triflate **2.50** the reaction was repeated, adding benzyl bromide (3 equiv.) to the reaction mixture. After work-up and purification, two benzyl ethers **2.56** and **2.57** were isolated in 15% and 14%, respectively (**Scheme 2.13**). 1-(Benzyloxy)-4-iodobenzene **2.56** can only arise through O-S σ-bond cleavage and alkylation of phenoxide **2.58**. (Benzyloxy)benzene **2.57** can occur by two possible paths with either the further reduction of **2.58** by **1.395** bringing about C-I σ-bond scission or initial C-I bond cleavage generating aryl anion **2.59** which is protonated to afford phenyl triflate intermediate **2.53**. Reduction of triflate **2.53** and O-S σ-bond scission generates phenoxide **2.60** which, on reaction with benzyl bromide, affords the benzyl ether **2.57**.

Isolation of **2.57** proves that reduction of the C-I σ-bond is occurring in competition with O-S σ-bond cleavage of the triflyl group and this may be the reason for low isolated yield of 4-iodophenol **2.49**. However it should also be noted that the overall mass recovery for this trapping experiment was lower than anticipated which may be an indication that some alternative processes are occurring, generating side-products that either have a low boiling point or are lost in aqueous on work-up.

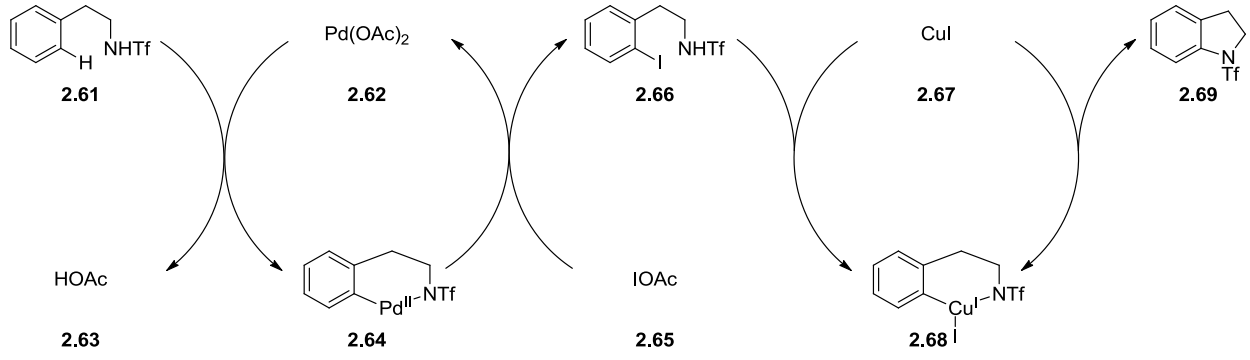
Scheme 2.13 Reduction of **2.50** and trapping of anionic intermediates generating benzyl ethers **2.56** and **2.57**.



2.5 Reduction of Triflamides with *bis*-Pyridinylidene, Enediamine 1.395

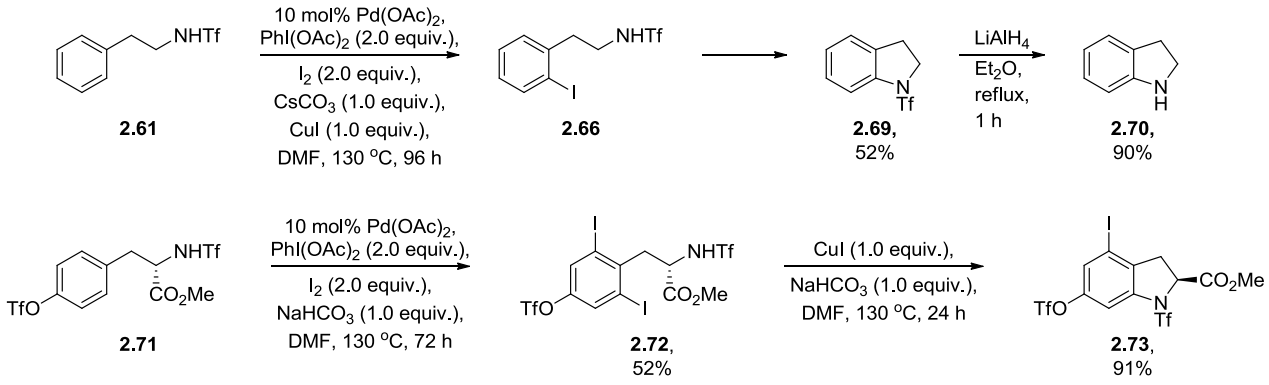
The triflyl group has successfully been employed for the protection of amines and utilised in chemistry where the acidity of the NH moiety was crucial for promoting reactivity. The high electronegativity of the triflyl group ensured that it was the protecting group of choice for phenylethylamine in the C-H activation chemistry of Yu *et al*.[181] and outperformed acetyl-, trifluoroacetyl-, Boc-, Troc- and benzenesulfonyl- alternatives.[181] The increased acidity of the triflamide functional group is thought to promote the formation of the Pd-N bond in palladacycle **2.64** (**Scheme 2.14**) which is critical for the reactivity observed in either a 'one-pot' tandem reaction process or sequence of individual reactions mediated by palladium C-H activated iodination and subsequent copper-mediated amination (**Scheme 2.15**).

Scheme 2.14 The C-H iodination and subsequent intramolecular amination developed by Yu *et al*.[181]



The triflamide effectively acts as a directing group ensuring the activation of the C-H bond *ortho* to the amidoethyl substituent occurs selectively by formation of the favourable six-membered palladacycle **2.64**. A range of indolines as well as an example of a tetrahydroisoquinoline were successfully synthesised using this procedure (**Scheme 2.15**).

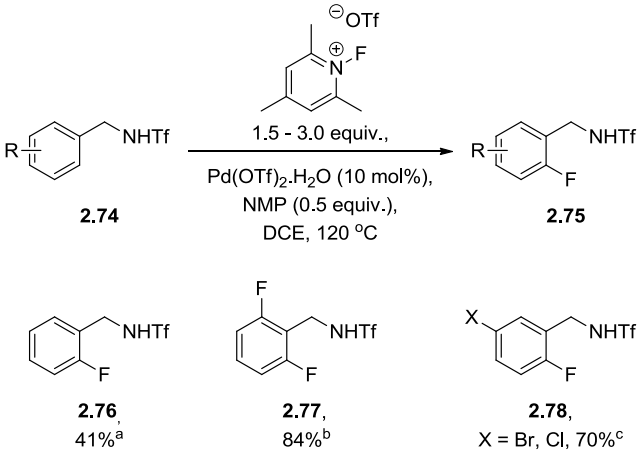
Scheme 2.15 Triflamide directed synthesis of indolines *via* 'one-pot' tandem process (top) and sequence of individual reactions (bottom).[181]



Only one example of a triflamide deprotection was demonstrated, using lithium aluminium hydride in diethyl ether to afford free indoline **2.70** from precursor **2.69**.

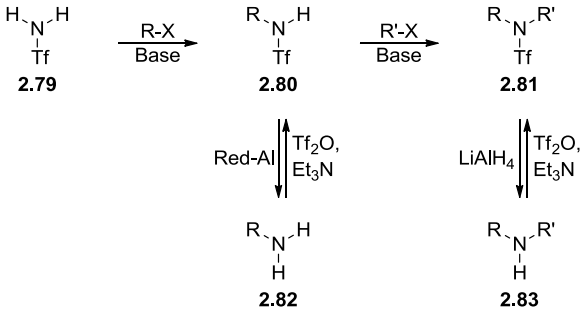
Yu *et al*. later reported the expedient *ortho*-fluorination of triflamide-protected benzylamines using *N*-fluoro-2,4,6-trimethylpyridinium triflate, palladium triflate and *N*-methylpyrrolidinone (NMP) in dichloroethane (DCE) (**Scheme 2.16**).[182]

Scheme 2.16 Triflamide-directed fluorination, a = 4.0 h, NMP substituted with DMF; b = 4.0 h; c = 2.0 h.[182]



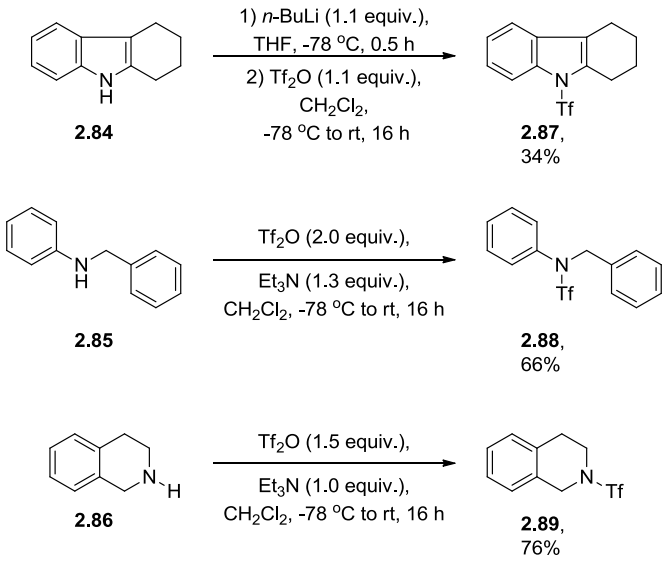
Aryl and alkyl triflamides act as protected and activated forms of aryl and alkyl amines, respectively, and have been particularly useful for the preparation of secondary amines via the *mono*-alkylation of primary triflamides (**Scheme 2.17**).[183-186]Deprotection of the product secondary triflamides to the parent amine (S–N σ-bond cleavage) is required at the end of the synthetic sequence and reduction by $LiAlH_4$ is one successful approach to this deprotection,[187] while Red-Al cleaves primary and secondary triflamides.[187,188]

Scheme 2.17 Synthesis of primary and secondary amines *via* triflamide protection/deprotection.



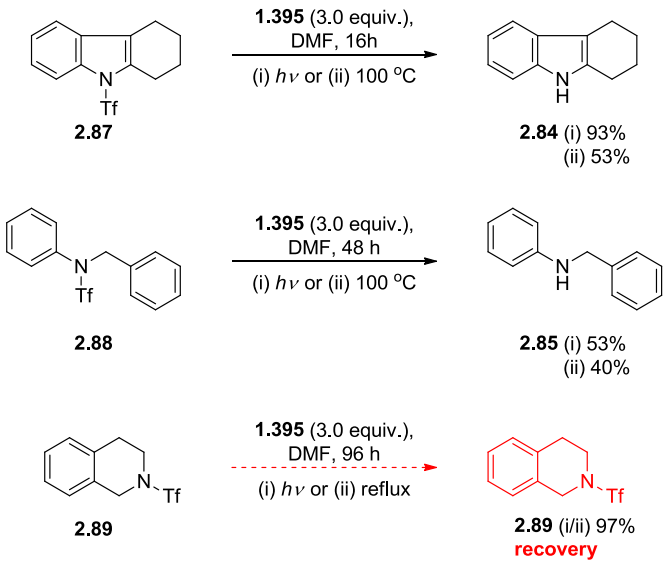
A range of test triflamides was desirable to investigate the reactivity of *bis*-pyridinylidene donor **1.395**. Aromatic, phenyl and benzyl triflamides **2.87**, **2.88** and **2.89**, respectively, were prepared in reasonable to good yield (**Scheme 2.18**).

Scheme 2.18 Synthesis of trifluoromethanesulfonamides.



While phenyl **2.88**[185,189] and benzyl **2.89** triflamides were afforded *via* the direct reaction of parent amines with triflic anhydride in the presence of triethylamine base, the reaction of indole **2.84** under the same conditions failed to yield the protected triflamide **2.87**. The deprotonation of indole **2.84** with *n*-butyllithium followed by reaction with triflic anhydride was necessary.

Scheme 2.19 Reductive cleavage of trifluoromethanesulfonamides with *bis*-pyridinylidene donor **1.395**.



No cleavage of aliphatic triflamide **2.89** occurred under UV or thermal conditions, with almost quantitative recovery of the start material being observed. The degree of N-S σ-bond cleavage observed for the triflamides decreases from activated aromatic triflamide, **2.87** to unactivated aliphatic triflamide **2.89**. This possibly reflects the ability of the compound to stabilise the negative charge in the resultant anions or radical anions formed after electron transfer.

2.6 Chapter Summary

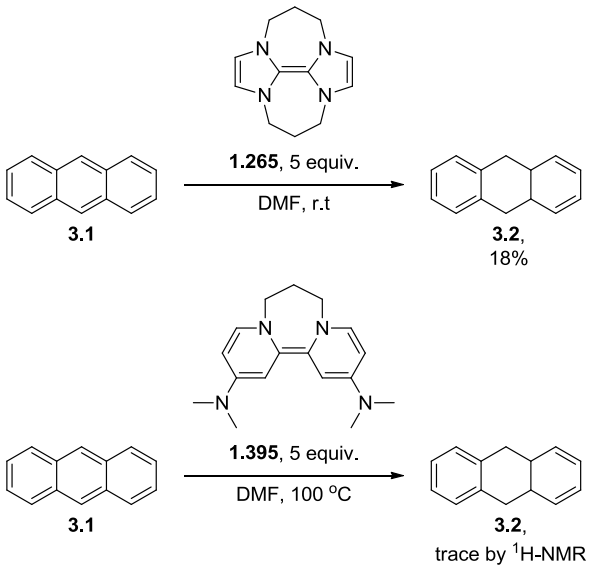
Powerful *bis*-pyridinylidene super-electron-donor **1.395** successfully mediates the conversion of aliphatic and aromatic triflates to corresponding alcohols and phenols. In the case of alkyl triflates, we believe the conversion is mediated by an electron transfer process, while either an electron transfer or S_N2 (at sulfur) mechanism could operate for aryl triflates. The O-S σ-bond of triflates is also selectively cleaved in *p*-bromophenyl triflate **2.48**, in preference C-Br σ-bond. Additionally, activated triflamides are converted to their parent aromatic amines.

3 RESULTS AND DISCUSSION – The Formation of New Highly Reactive Imidazole-Derived Tetraazafulvalenes

3.1 Introduction

Despite the relative reduction potential of imidazole-derived tetraazafulvalene **1.265** and *bis*-pyridinylidene donor **1.395** being very similar $E_{1/2}$ = -1.20 V *vs.* SCE in DMF and $E_{1/2}$ = -1.24 V *vs.* SCE in DMF,[110] Garnier had noted that in practical terms, **1.265** was the more powerful of the two donors providing improved yields of products from difficult-to-reduce substrates *e.g.* anthracene.[106]

Scheme 3.1 Comparison of the reduction of anthracene with SEDs **1.265** and **1.395**.

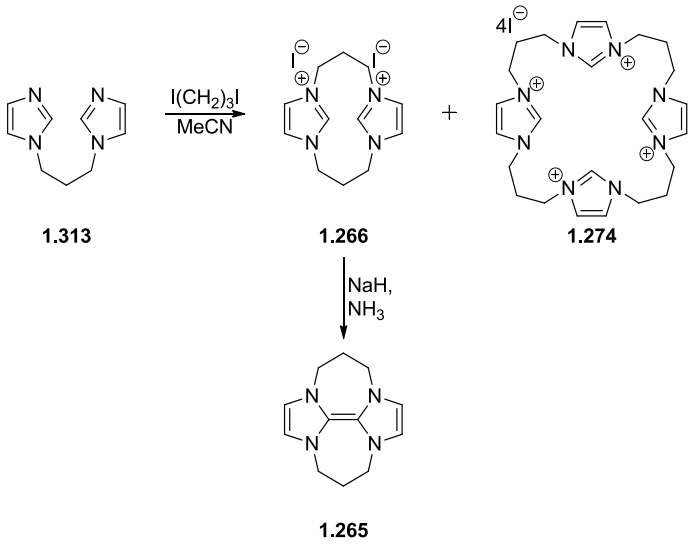


It would be logical then to select imidazole-derived tetraazafulvalene **1.265** as the SED of choice to investigate new challenging reductive chemistry. However, its application in organic synthesis has been hampered by its own problematic synthesis, and thus the readily available *bis*-pyridinylidene donor **1.395** has become the most widely studied super-electron-donor. Imidazole-derived tetraazafulvalene **1.265** was first characterised in 1996[3] while the first publication concerning *bis*-pyridinylidene donor **1.395** did not appear until twelve years

later in 2008.[107] The electron transfer chemistry with **1.265** was not applied in synthesis until 2007.[174] Thus with regards to research of electron transfer chemistry the two donors are separated by a period of only one year. Despite its later arrival, *bis*-pyridinylidene donor **1.395** has been the subject of seven publications,[1,107-112] double that of imidazole-derived tetraazafulvalene **1.265** with a total of only three,[101,107,174] a clear demonstration of the effect that a simplified preparation can have on application of a reagent.

As already mentioned in the Introduction (pages 38-39 and 59) the problem with the preparation of **1.265** is entirely associated with the introduction of the second propylene tether in **1.266** (**Scheme 3.2**) which results in the formation of undesired macrocycle **1.274** along with the product. The deprotonation of **1.266** readily affords desired super-electron-donor **1.265**, but the separation of **1.274** from **1.266** is a skilled operation, requiring careful recrystallisation.

Scheme 3.2 Synthesis of imidazole-derived tetraazafulvalene **1.265** and macrocyclic by-product **1.274**.



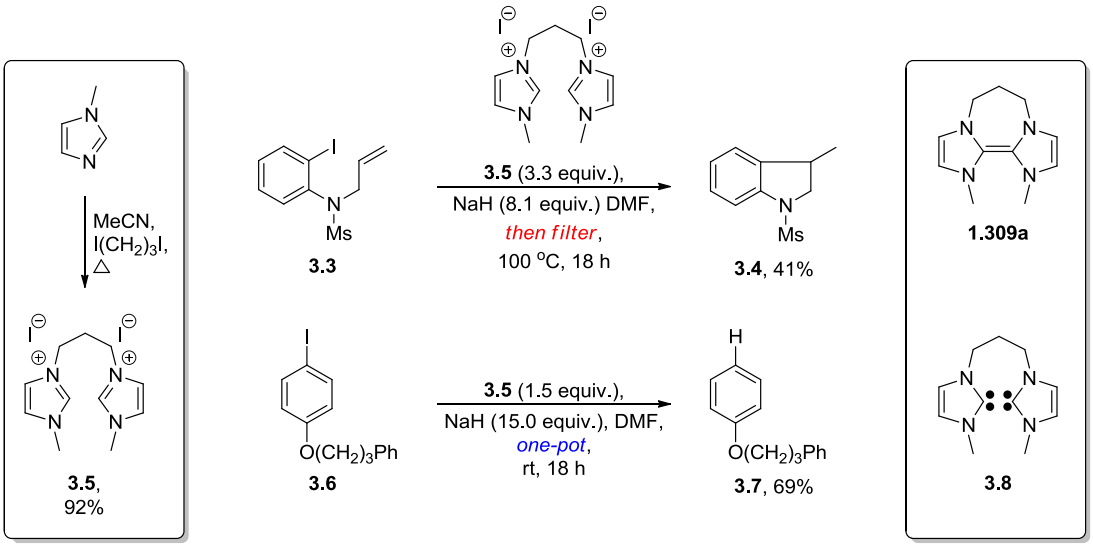
This chapter discusses the issues relating to dimerisation of imidazol-2-ylidenes and synthesis of new imidazole-derived tetraazafulvalenes, circumventing the formation of undesired macrocycles.

3.2 Reduction of Aryl Iodides by Deprotonation of *mono*-Tethered and Unbridged Imidazolium Salts

To prevent the synthesis of undesired macrocycle **1.247** the logical step would be to avoid the double tethering of the imidazole heterocycles. Thomson began to investigate the reductions

of aryl iodides *e.g.* **3.3** (**Scheme 3.3**) with *mono*-trimethylene-tethered imidazolium salt **3.5** (often referred to as '*mono*-tethered **3.5**' in this report) and successfully isolated indoline product **3.4** arising from radical cyclisation.[177,190] Additionally Garnier[106] demonstrated the successful reduction of aryl iodide **3.6** to the aromatic ether **3.7**.

Scheme 3.3 Reductive radical cyclisation observed with *mono*-tethered imidazolium salt **3.5** and base.

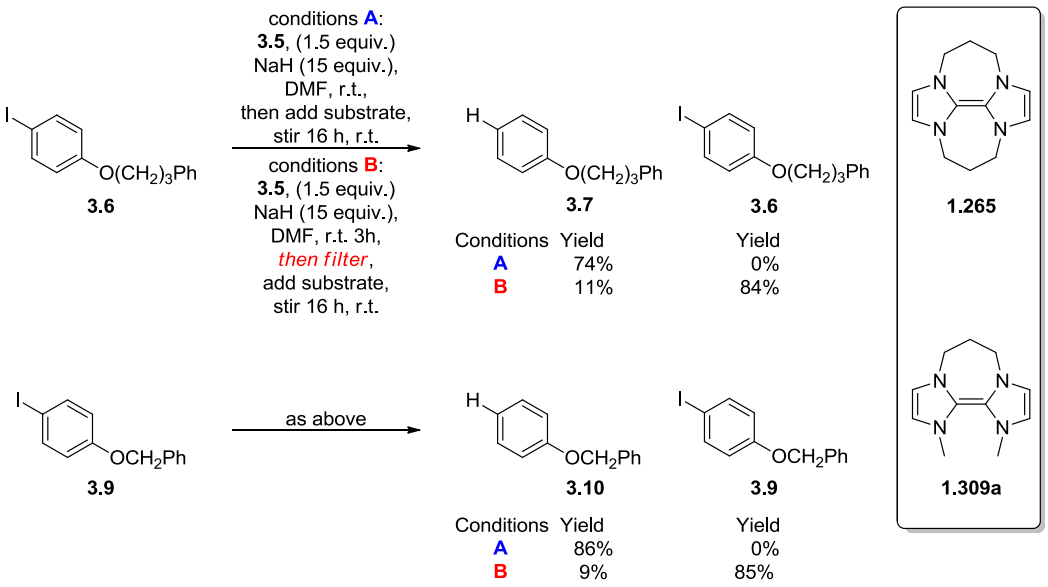


Thomson used a larger excess of imidazolium salt **3.5** (3.3 equiv.) and sodium hydride before adding the filtered supernatant liquid to substrate **3.3** and heating, while Garnier employed only a slight excess of imidazolium salt **3.5** and sodium hydride at room temperature in an unfiltered 'one-pot' procedure. The successful reduction of aryl iodide suggests that tetraazafulvalene **1.309a** has been formed as the observed reductions are indicative of super-electron-donor chemistry but are unknown for *N*-heterocyclic carbene *i.e. bis*-carbene **3.8** (the product of deprotonating **3.5** without formation of the central C=C bond). Furthermore, the result indicated that improved yields of reduced products could be obtained when the reduction was carried out in the presence of excess base.

With a ready supply of aryl iodide **3.6**[106] and **3.9**,[106] further investigations were initiated with *mono*-tethered imidazolium salt **3.5** under two set of conditions **A** and **B**, to see if there was an impact on the amount of reduced product generated in the presence of excess base. Under conditions **A** the aryl iodides were stirred with imidazolium salt **3.5** (1.5 equiv.) and excess sodium hydride in anhydrous DMF for 16 h. In contrast, under conditions **B** the imidazolium salt **3.5** was stirred with excess sodium hydride in anhydrous DMF for 3 h, the solution was then filtered or centrifuged (removing NaH) and then stirred with aryl iodides for 16 h

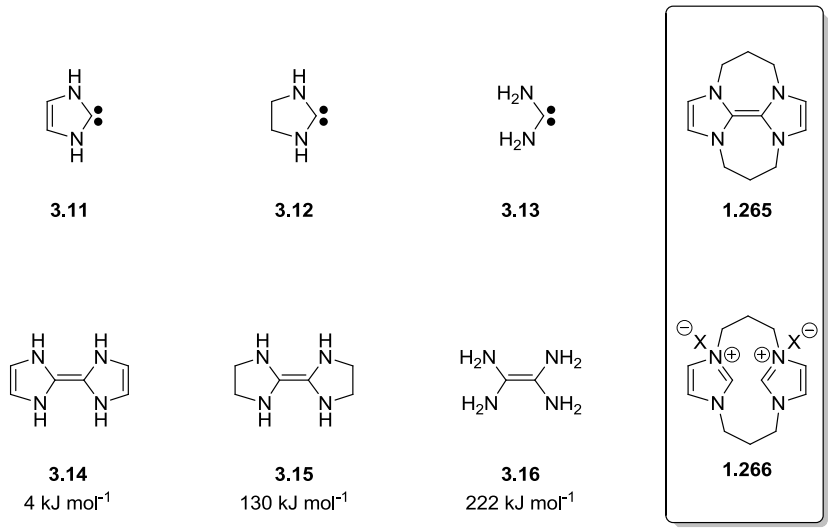
(**Scheme 3.4**, both conditions were conducted under an anhydrous and oxygen-free atmosphere). Significantly improved yields of reduced products **3.7** and **3.10** were observed when the reaction was carried out in the presence of excess base. Garnier had shown in a control blank reactions that omission of **3.5** led to no cleavage.

Scheme 3.4 Reaction of imidazolium salt **3.5** in presence of excess base, conditions **A** *vs.* absence of base, conditions **B**.



The successful reduction of aryl iodides **3.6** and **3.9** are in line with those observations of Thomson[190] and Garnier[106] and supports the *in situ* formation of *mono*-tethered tetraazafulvalene **1.309a**. However, to date only one example of a tetraazafulvalene derived from an imidazolium salt precursor has been isolated and characterised, the doubly-tethered **1.265**, first synthesised by Taton and Chen.[3] Indeed Taton and Chen's attempts to synthesise **1.309a** were unsuccessful[3] and attempts to synthesise any other imidazole-derived tetraazafulvalene met the same fate.[84,92,191] Furthermore, imidazol-2-ylidenes, first disclosed by Arduengo in 1991[192] are understood to be thermodynamically stable to dimerisation,[98] in part due to aromatic stabilisation. The stability of imidazol-2-ylidene **3.11** is reflected in its singlet-triplet energy gap, 354 kJ mol^{-1} (**Figure 3.1**) compared to dihydroimidazol-2-ylidene **3.12** at 290 kJ mol^{-1} and acyclic diaminocarbene **3.13** at 245 kJ mol^{-1}; from these the strength of C=C central bond in corresponding in dimers can be estimated.[193] The innately unstable theoretical dimer **3.14** has a calculated C=C bond strength of 4 kJ mol^{-1} substantially weaker than the non-aromatic **3.15** at 130 kJ mol^{-1} and acyclic **3.16** at 222 kJ mol^{-1}.[3,4,193]

Figure 3.1 Theoretical tetraazafulvalene dimers and C=C bonds strength.

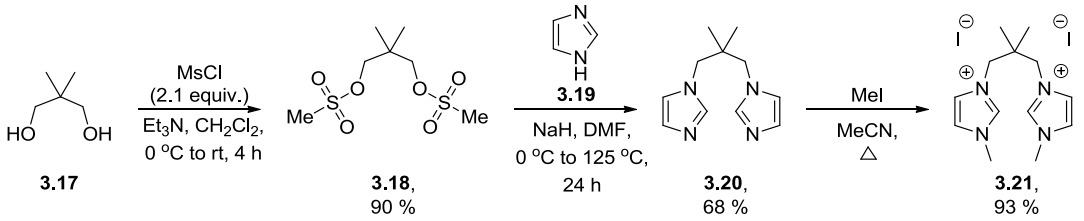


3.3 Synthesis of New *mono*-Tethered Imidazole-Derived Tetraazafulvalenes

Indications from the successful reduction of **3.6** and **3.9** that *mono*-tethered **1.309a** is forming at ambient temperature are extremely surprising and attention next focused on ^{1}H-NMR and ^{13}C-NMR evidence of tetraazafulvalene formation. Imidazolium salt **3.21** (**Scheme 3.5**) was designed so that tetraazafulvalene formation might be promoted compared to *mono*-tethered **3.5**. It would seem that the entropic restrictions imposed by two propylene-tethers of **1.266** and **1.265** ensure formation of tetraazafulvalene is kinetically favourable by the rapid capture of the developing carbene by the adjacent imidazolium group and confer stability to the resulting tetraazafulvalene, **1.265**. The challenge was thus to duplicate these favourable conditions without the use of a di-tethered system and avoid the formation of undesirable macrocycles. We decided to employ the Thorpe-Ingold effect[100] that would result from replacement of the two propylene tethers by a single *gem*-dimethylpropylene tether.

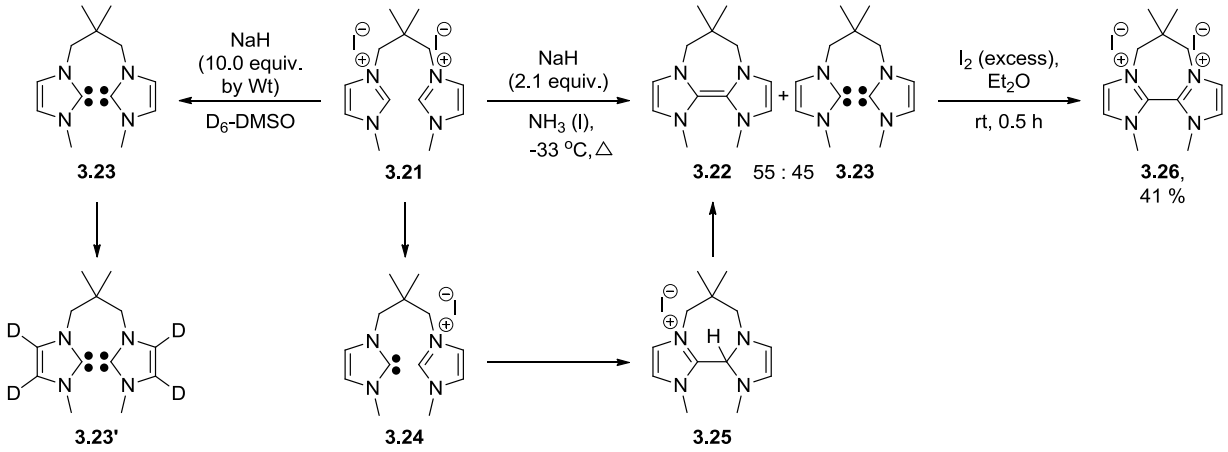
2,2-Dimethylpropane-1,3-diol **3.17** was readily converted to the di-mesylate **3.18** (**Scheme 3.5**). Displacement of the mesylates with imidazolium **3.19** furnishes *bis*-imidazole **3.20** in reasonable yield. Alkylation then affords *bis*-imidazolium **3.21**, in a reasonable overall yield of 57 % in three steps. The synthesis completely avoids the formation of any corresponding by-products *e.g.* macrocycle **1.274**.

Scheme 3.5 Synthesis of *gem*-dimethyl tethered *bis*-imidazolium **3.21**.



It now remained to see if the Thorpe-Ingold effect[100] of the *gem*-dimethyl tether would close the angle between the imidazolium heterocycles sufficiently to promote dimerisation. Sodium hydride (2.1 equiv.) was added to imidazolium **3.21** over 3 hours in an effort to allow the formation of intermediates **3.24** and **3.25** as well as prevent double deprotonation occurring (which leads to *bis*-carbene **3.23**). We were encouraged to discover that this approach afforded tetraazafulvalene **3.22** as the predominant product along with *bis*-carbene **3.23** in a 55:45 ratio, after work-up, as judged by ^{1}H-NMR.

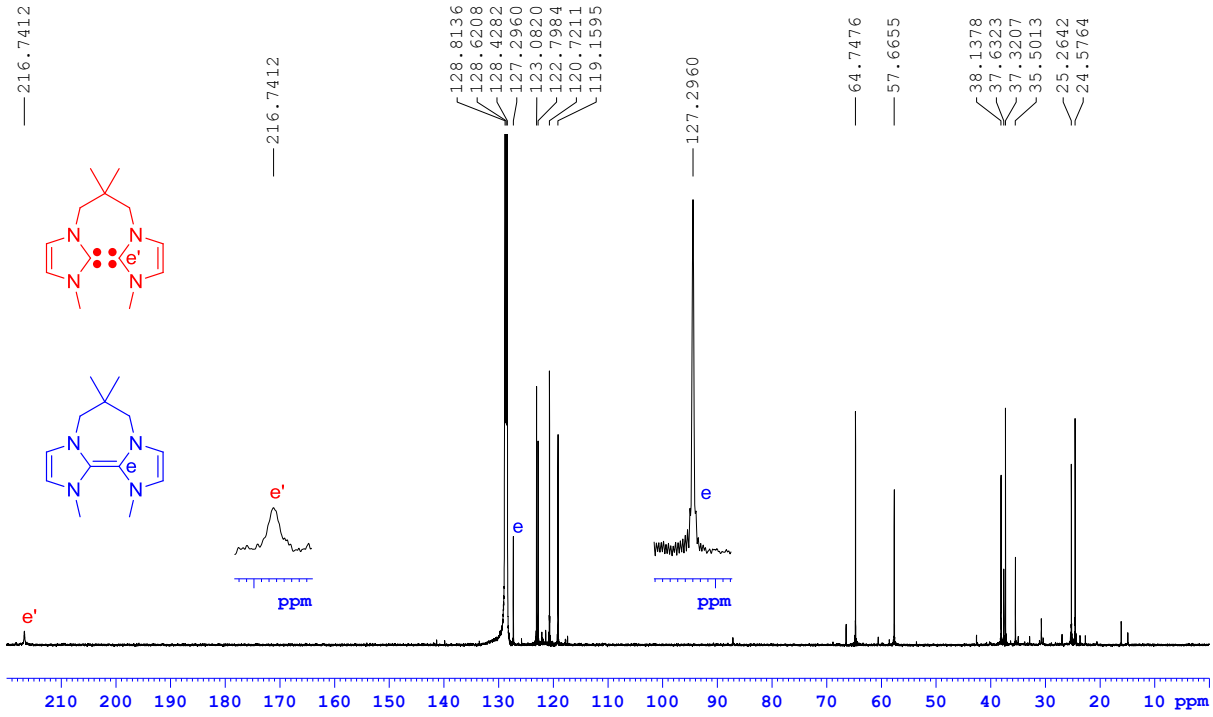
Scheme 3.6 Formation of tetraazafulvalene **3.22** and *bis*-carbene **3.23**.



The ^{1}H-NMR spectrum of the dimer/*bis*-carbene mixture shows the signals associated with tetraazafulvalene **3.22** characteristically upfield of those for carbene **3.23** and in accord with the signals observed for tetraazafulvalene **1.265**. The signals for NCH_2 (c, **Figure 3.3**) and NCH_3 (a) of the tetraazafulvalene **3.22** are found at δ = 2.33 ppm (4H, s) and δ = 2.59 ppm (6H, s), respectively, either side of NCH_2 signal (c) observed in **1.265** at δ = 2.43 ppm (8H, m). While the NCH_3 (a') and NCH_2 (c') signals of *bis*-carbene are significantly downfield at δ = 3.39 (6H, s) and δ = 3.91 ppm (4H, s), respectively. Similarly the alkene protons (b) of **3.22**, at δ = 5.41 ppm (2H, d, J = 2.4 Hz) and δ = 5.48 ppm (2H, d, J = 2.4 Hz) correspond to

those of **1.275**, visible at δ = 5.41 ppm (4H, s). Again the corresponding proton signals of the aromatic *bis*-carbene are further downfield (b'). Crucially the ^{13}C-NMR of the dimer/*bis*-carbene mixture shows characteristic signals for both the central alkene bond of tetraazafulvalene **3.22** at δ = 127.3 ppm (e, **Figure 3.2**) and also the carbene **3.23** at 216.7 ppm (e').

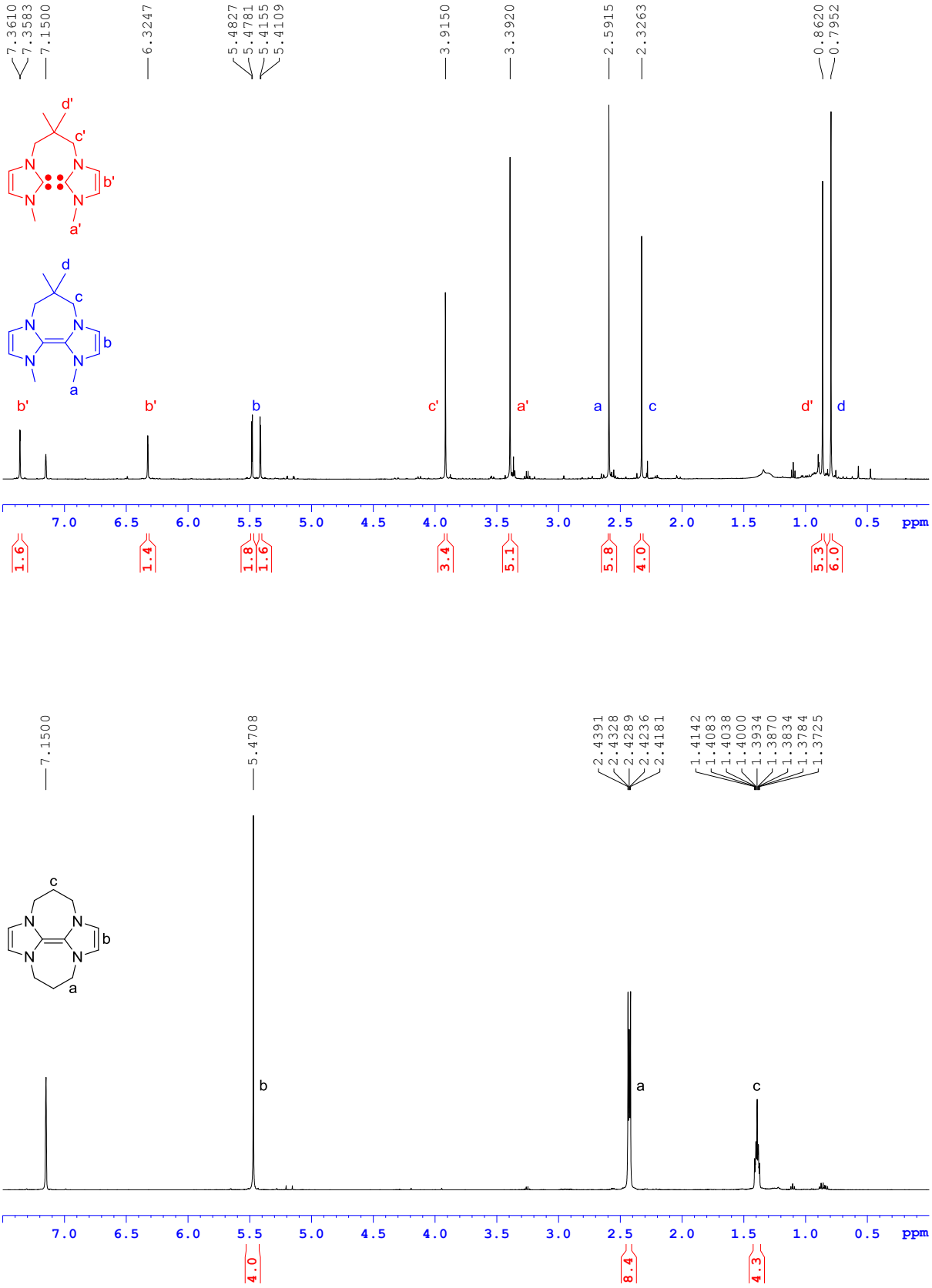
Figure 3.2 ^{13}C-NMR of tetraazafulvalene **3.22** and *bis*-carbene **3.23** (red, top) and di-tethered tetraazafulvalene **1.275** (blue, bottom).



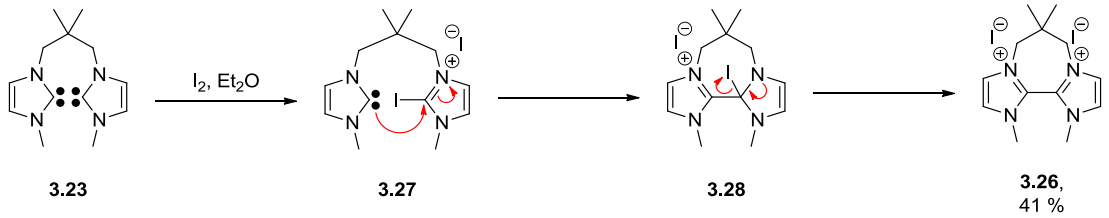
Interestingly carbene **3.23** was almost exclusively afforded when the imidazolium salt **3.21** was reacted with excess sodium hydride in deuterated dimethyl sulfoxide under inert and anhydrous atmosphere. In deuterated dimethyl sulfoxide rapid deuterium exchange of the ring protons in *bis*-carbene **3.23** is observed in line with the observations of Denk.[194]

Looking for further evidence of tetraazafulvalene formation, the 55:45 reaction mixture was oxidised with iodine. Surprisingly the ^{1}H-NMR spectrum showed that it was converted in greater than 90% to bi-imidazolium **3.26**. Presumably iodination occurs only at one carbene forming **3.27**. Nucleophilic attack of the remaining carbene on the 2-iodoimidazolium salt counterpart would displace the iodine to afford final bi-imidazolium **3.26**.

Figure 3.3 ^{1}H-NMR of tetraazafulvalene **3.22** and *bis*-carbene **3.23** (top) and di-tethered tetraazafulvalene **1.275** (bottom).



Scheme 3.7 Proposed mechanism for oxidation of *bis*-carbene **3.23**.



To be certain that the 55:45 mixture of tetraazafulvalene **3.22** and *bis*-carbene **3.23** was being almost quantitatively converted to bi-imidazolium **3.26** a crystal of 18-crown-6-ether (distilled from P_4O_{10}, recrystallised from dry acetonitrile in the glove-box and deoxygenated by repeated freeze-thaw cycles) was added to the combined diethyl ether extracts. The 18-crown-6 was chosen as an internal standard that should be unreactive with either tetraazafulvalene **3.22** or *bis*-carbene **3.23**, and provide a reference point to compare NMR signals before and after oxidation. The solution was divided in two with one portion being evaporated to dryness while the other was oxidised with iodine then evaporated to dryness. If the intensity ratio of a selected peak in oxidised **3.26** to 18-crown-6 is less than the ratio of combined intensity of corresponding peaks in carbene and dimer to 18-crown-6 in the mixture then another product must be forming, but this was not the case (**Figure 3.4**).

Figure 3.4 Calculated ratios of tetraazafulvalene **3.22**, *bis*-carbene **3.23** and bi-imidazolium **3.26** to 18-crown-6.

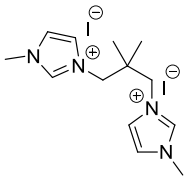
$$\text{Ratio} = \frac{\text{integral of ArH in carbene + dimer}}{\text{integral of 18-crown-6 signal}} = \frac{1.65 + 1.57 + 4.00}{2.53} = 2.85$$

$$\text{Ratio} = \frac{\text{integral of ArH in oxidised } \mathbf{3.26}}{\text{integral of 18-crown-6 signal}} = \frac{4.00}{1.07} = 3.74$$

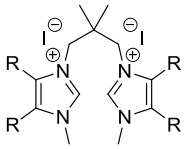
Encouraged by the clean formation of tetraazafulvalene dimer **3.22** as major product we sought to optimise steric interactions further to eliminate *bis*-carbene formation completely. Although the *gem*-dimethyl tether should help close the angle between the imidazole heterocycles a degree of freedom around the N-CH_2 bond might allow the **3.21** to adopt a conformation where the C2 positions were not in close proximity to one another (**Scheme 3.8**). We therefore reasoned that steric bulk at the C4 and C5 positions should restrict the

number of conformations the imidazolium salt can take and should lead to a situation where steric interactions are minimised when the C2 positions are in close proximity to one another.

Scheme 3.8 An alternative proposed transient conformation of imidazolium salt **3.21** and envisaged sterically encumbered **3.29**.



3.21



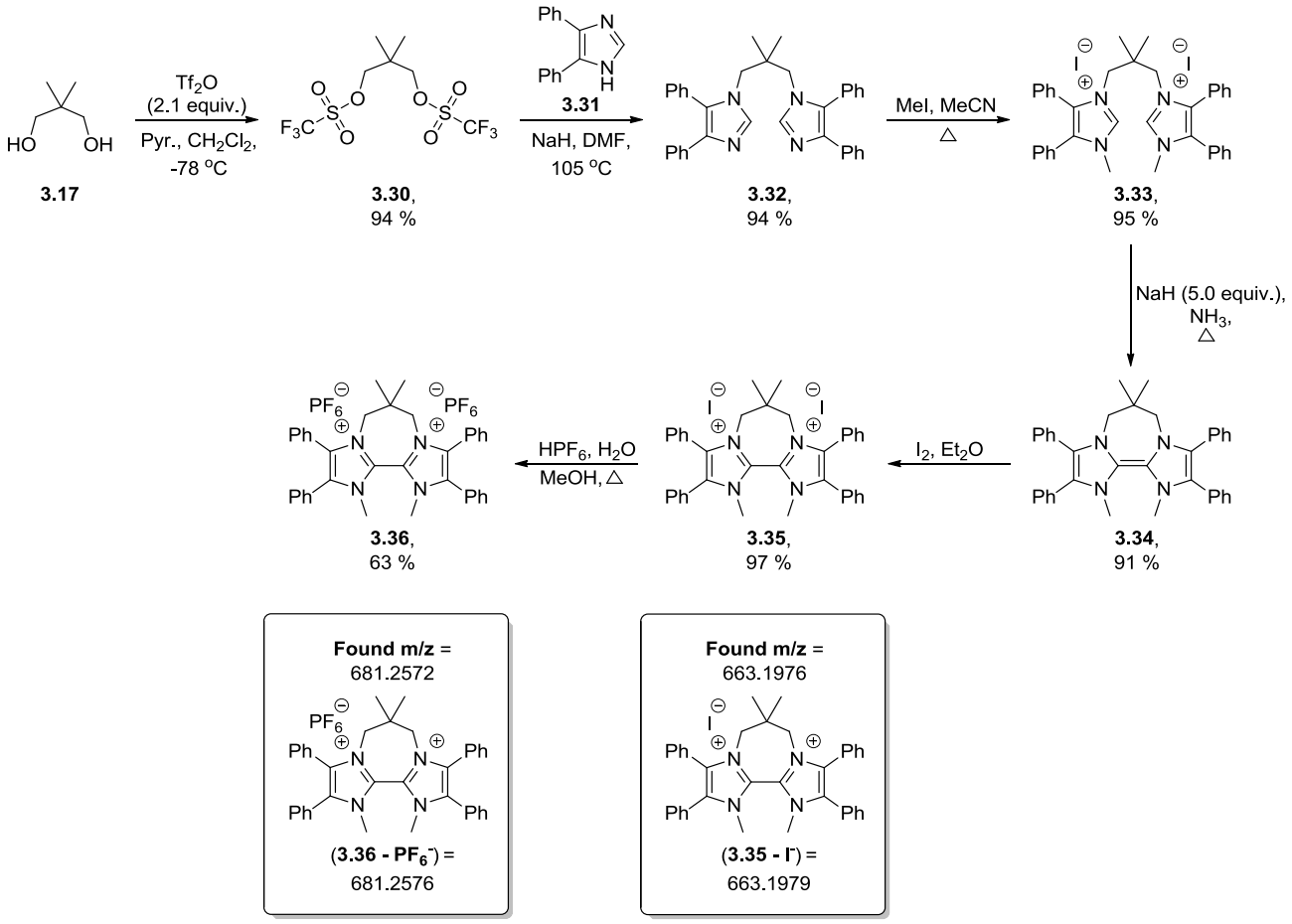
3.29
R = Ar or Alkyl

bis-Imidazolium iodide **3.33** was readily prepared from the triflate **3.30** and commercially available 4,5-diphenylimidazole, **3.31** and methyl iodide (**Scheme 3.9**). On deprotonation of **3.33** in liquid ammonia with sodium hydride (5.0 equiv.) a purple reaction mixture formed. Extraction of the dry solid with diethyl ether in the glove-box and removal of solvent furnished the pure phenyl-substituted tetraazafulvalene **3.34** in excellent yield 91 % (76 % over four steps). The ^{1}H-NMR spectrum showed signals consistent with those of a tetraazafulvalene only. With no alkene protons in 4,5-positions, **3.34** was readily identified by the quaternary carbon signal of the central enetetramine bond at δ = 127.6 ppm, which is characteristic of tetraazafulvalenes.[3]

Again the tetraazafulvalene was oxidised to the corresponding bi-imidazolium **3.35** which was converted to the di-hexafluorophosphate analogue **3.36**. High resolution mass spectrometry further supported the formation of tetraazafulvalene **3.34** finding masses of *m/z* = 663.1879 and *m/z* = 681.2578 corresponding to **3.35-I**$^{-}$ and **3.36-PF$_6$**$^{-}$, respectively for the oxidised salts.

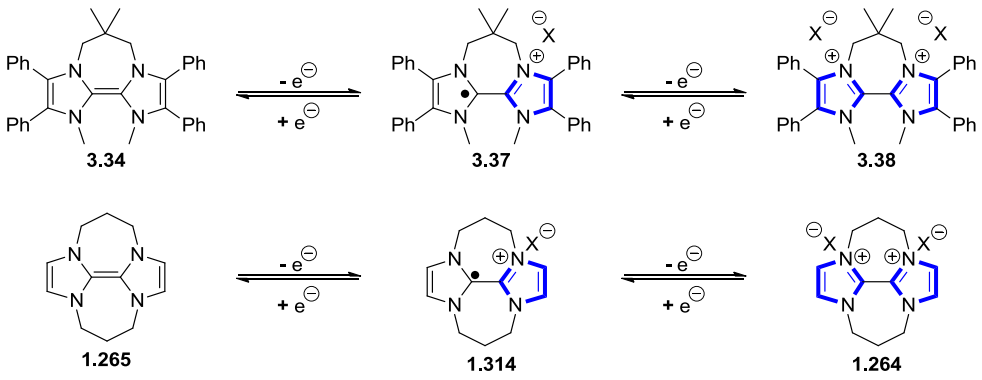
Tetraazafulvalene **3.34** is only the second example of a completely pure imidazole-derived tetraazafulvalene to be stable at room temperature. When stored as a dry solid under inert atmosphere it does not degrade at an appreciable rate, making it amenable to practical laboratory scale organic chemistry. Furthermore, compared to **1.265** its synthesis is comparatively simple and does not suffer from the formation the undesired macrocycles that plague the synthesis of precursor salt **1.266** (**Scheme 3.2**, page 101).

Scheme 3.9 Synthesis of *gem*-dimethyl tethered imidazole-derived tetraazafulvalene **3.34** and subsequent oxidation.



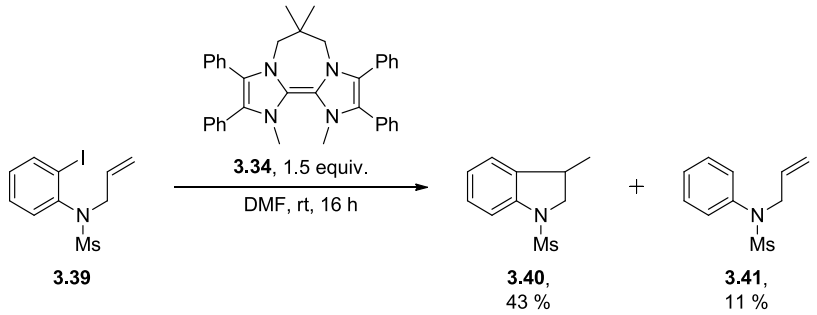
On oxidation of tetraazafulvalene **3.34** to the di-salt **3.38** a gain in aromatic stabilisation energy comparable to that of imidazole-derived tetraazafulvalene **1.265→1.264** would be anticipated and thus it would be reasonable to assume that **3.34** would also be a strong electron-donor capable of transferring two electrons at a similar reduction potential.

Scheme 3.10 Redox expected between tetraazafulvalene **3.34** and bi-imidazolium **3.38**.



Initial investigations with **3.34** into electron transfer chemistry have demonstrated the tetraazafulvalene is capable of reducing aryl iodide **3.39** at room temperature as expected. However, the cyclisation onto an alkene appendage forming indoline **3.40** is diagnostic of aryl radical formation, thus **3.34** is in fact acting here as a powerful single electron donor. The reduction of an aryl iodide to an aryl radical at ambient temperature is unprecedented for a fully characterised super-electron-donor (Garnier has observed similar reactivity, although the super-electron-donor responsible has yet to unequivocally identified or prepared pure and fully characterised).[106,177]

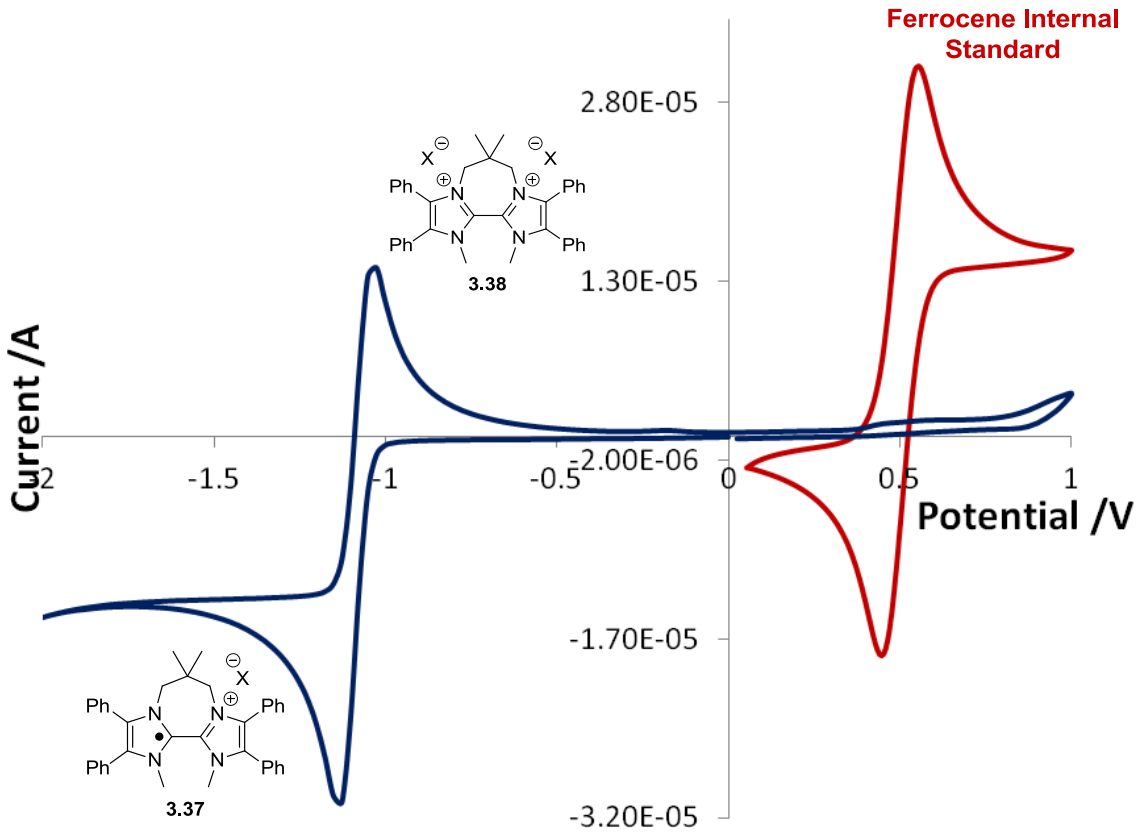
Scheme 3.11 Single electron reduction of aryl iodide **3.39** with tetraazafulvalene **3.34** at room temperature.



3.39 **3.40**, 43 % **3.41**, 11 %

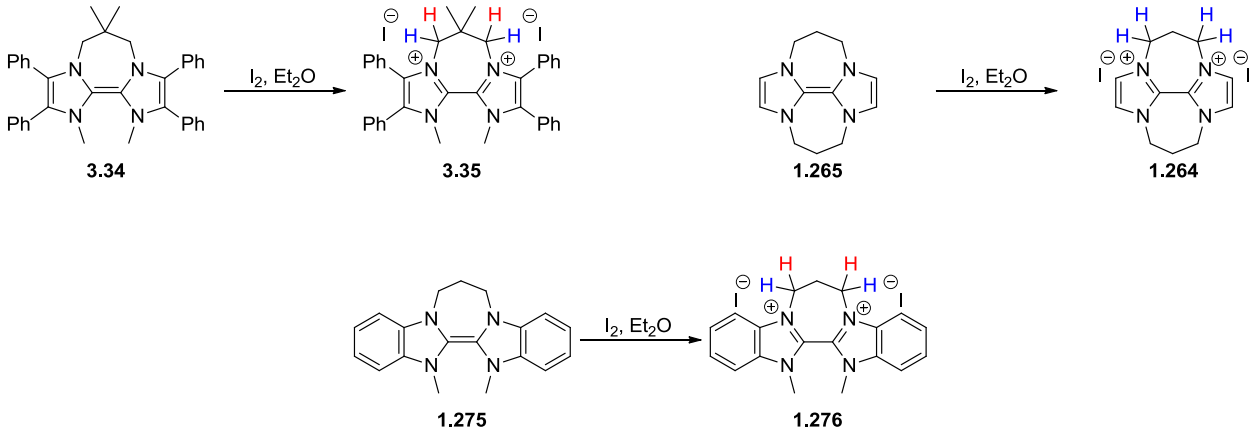
The reactivity of **3.34** suggests radical cation **3.37** (shown in **Scheme 3.10**) formed after a one electron oxidation is relatively stable and is reluctant to oxidise further to dication **3.38**. Initial cyclic voltammogram (CV) analysis of the bi-imidazolium di-triflate **3.38** (**Figure 3.5**) carried out by another member[195] of our laboratory, shows a single reversible one-electron redox wave at $E_{1/2}$ = -1.08 V *vs.* Ag/AgCl (in DMF) equivalent to -1.12 V *vs.* SCE. The CV indicates reduction of dication **3.38** by a single electron is facile, forming stable radical cation **3.37** but further reduction to neutral **3.34** under the experimental conditions does not occur. Single-electron transfer is line in with experimental observations but the CV cannot be taken as the reduction potential for neutral **3.34**, as it corresponds to the transition between dication **3.38** and radical cation **3.37**. In practice, our electron transfer reactions would begin with neutral tetraazafulvalene **3.34** and form **3.37** after a single electron. Thus the redox potential for transition between neutral **3.34** and radical cation **3.37** may be even more negative. Analysis of tetraazafulvalene **3.34** is ongoing.

Figure 3.5 Cyclic voltammogram of tetraphenyl bi-imidazolium di-triflate salt **3.38**, where X = TfO^- (blue wave) and ferrocene standard (red wave); $Bu_4N^+PF_6^-$/DMF, 50 mV s^{-1} scan rate, Ag/AgCl.



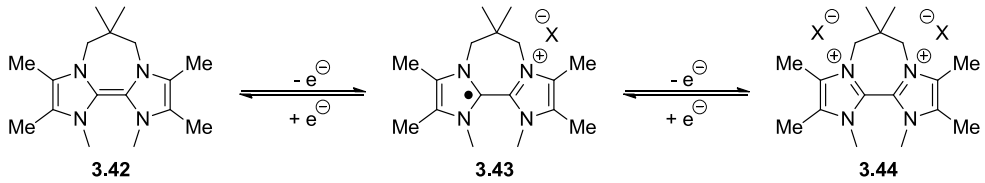
It is possible that the four phenyl substituents of **3.34** are able to delocalise the single electron in the radical cation **3.37** making single electron transfer favourable. In contrast, di-tethered **1.265** (**Scheme 3.10**) does not have same opportunity to delocalise a single electron in radical cation **1.314** and this may be a one reason why **3.34** and **1.265** display different reactivity. It was also noted that on oxidation, benzimidazole-derived tetraazafulvalene **1.275** forms a twisted dication **1.276**, while imidazole-derived tetraazafulvalene **1.265** forms an almost planar bi-imidazolium salt **1.264** requiring significantly less structural reorganisation. Therefore, a greater energy barrier is associated with the formation of dication **1.276** making electron transfer more difficult (**Introduction** page 50).[89,91] In these cases diastereotopicity of methylene protons adjacent to nitrogen is diagnostic of twisted molecules (**Scheme 3.12**) and is visible by ^{1}H-NMR spectroscopy of **3.35**, δ = 3.97 (2H, d, J = 14.6 Hz) and 4.46 ppm (2H, d, J = 14.6 Hz). Therefore, it may also be that significant reorganisation energy is required to form **3.35** and this may favour single electron transfer.

Scheme 3.12 Diastereotopicity of NCH_2 in dications **3.35** and **1.276**.



Tetraazafulvalene **3.42** (**Scheme 3.13**) was designed to probe whether delocalisation of the electron within the radical cation or the need to overcome larger reorganisation energy does indeed have an effect on the electron transfer. The corresponding oxidised radical cation **3.43** and dication **3.44** of tetraazafulvalene **3.42** should be stabilised by a similar gain of aromatic energy as the analogous tetraphenyl substituted **3.34** and di-tethered molecule **1.275** but oxidation of **3.42** should form a twisted dication **3.44** requiring reorganisation similar to oxidation of neutral tetraazafulvalene **3.34** to dication **3.35**. However unlike its tetraphenyl analogue, tetramethyl substituted **3.42** would have no possibility to delocalise the single electron onto phenyl groups at the radical cation intermediate stage, **3.43** (analogous to **3.37**).

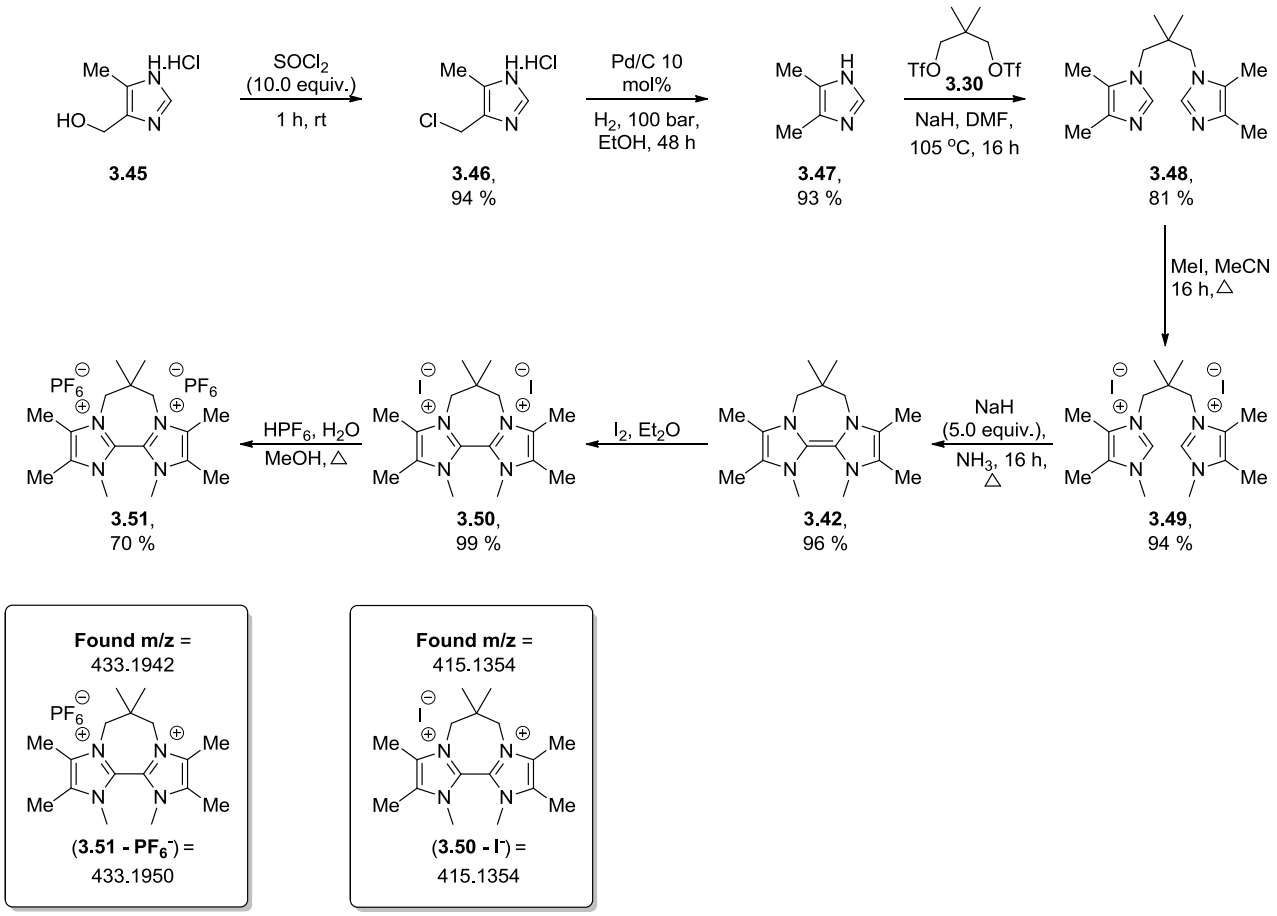
Scheme 3.13 Redox expected between tetraazafulvalene **3.42** and bi-imidazolium **3.44**.



4,5-Dimethylimidazole **3.47** was furnished from commercially available **3.45** in excellent yield following a literature procedure.[196] With the free imidazole in hand the precursor *bis*-imidazolium salt **3.49** (**Scheme 3.14**) was readily afforded following the same method employed for the tetraphenyl analogue **3.33** (**Scheme 3.9**). We were extremely pleased to discover deprotonation of **3.49** afforded the desired tetraazafulvalene **3.42** in excellent yield with no *bis*-carbene formation, validating our hypothesis that the Thorpe-Ingold effect together with imidazolium heterocycles bearing bulky substituents in 4 and 5 positions would

lead to successful 'imidazol-2-ylidene dimerisation'. The vivid yellow crystalline solid was highly soluble in diethyl ether and of course was moisture- and oxygen-sensitive. Again ^{13}C-NMR showed the characteristic central quaternary tetraazafulvalene carbon peak at δ = 127.8 ppm, while high resolution mass spectrometry successfully identified the corresponding oxidised salts, **3.50** and **3.51** (**Scheme 3.14**). The ^{1}H-NMR spectrum of di-iodide salt **3.50** indicates that the molecule is indeed twisted with diastereotopic NCH_2 being visible at δ = 3.75 (2H, d, J = 15.0 Hz, CH_2 4.20 ppm (2H, d, J = 15.0 Hz, CH_2) but further analysis and exploration of its chemistry are the subject of continued investigations with the group.

Scheme 3.14 Synthesis and oxidation of tetramethyl substituted tetraazafulvalene **3.42**.



3.4 Wanzlick Equilibrium and Carbene Dimerisation

The exploration of the reactivity of new super-electron-donors **3.34** and **3.42** is a continued area of research within our laboratories. Having successfully characterised three new *mono*-tethered tetraazafulvalenes at ambient temperature and synthesised two pure examples **3.34**

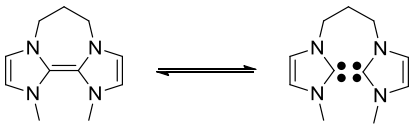
and **3.42**, suitable for investigations into electron transfer chemistry we began to reconsider the initial reductions performed with imidazolium salt **3.5** (**Scheme 3.3** and **3.4**) and what could be inferred from the apparent *in situ* formation of tetraazafulvalene **1.309a**. Under conditions **A**, the reaction is carried out in the presence of excess sodium hydride and clearly affords greater yields of reduced arenes **3.7** and **3.10**, compared to filtered reaction, conditions **B**. This suggests that any tetraazafulvalene dimer **1.309a** formed does not persist in the reaction featuring filtration and therefore the presence of base somehow prolongs the stability **1.309a**.

Other than electron transfer there are two mechanisms by which tetraazafulvalene **1.309a** might be depleted:

- dissociation of **1.309a** into *bis*-carbene **3.8**, the 'Wanzlick equilibrium' (**Scheme 3.15**)
- tetraazafulvalene protonation and subsequent dissociation to imidazolium carbene species **3.61** (**Scheme 3.20**)

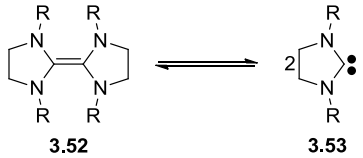
The dissociation of a tetraaminoethylene into its carbene constituent parts is known as the 'Wanzlick equilibrium' and has been studied for 50 years.[88] The fact that more reduced product is obtained in our reaction when it is run in the presence of excess base can afford some insight into these mechanisms which will now be discussed in turn along with key investigations in this area of research.

Scheme 3.15 Wanzlick dissociation of proposed dimer **1.309a**.



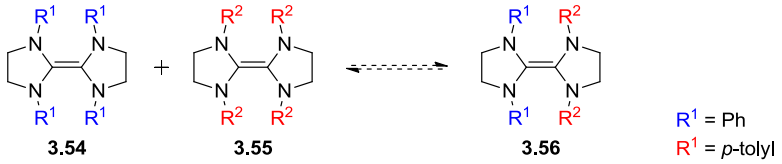
Thirty years before the isolation of the first stable diaminocarbene,[192] Wanzlick sought to synthesise free dihydroimidazol-2-ylidenes[117] *e.g.* **3.53**. He only succeeded in isolating the corresponding imidazolidine dimers, tetraazafulvalenes **3.52** (**Scheme 3.16**). However, his investigations with the dihydroimidazole-derived tetraazafulvalenes afforded products characteristic of nucleophilic carbenes and this led Wanzlick to propose the existence of an equilibrium between tetraazafulvalenes and their dissociated diaminocarbenes, the 'Wanzlick equilibrium'.[118,119,197]

Scheme 3.16 Classical 'Wanzlick equilibrium'.

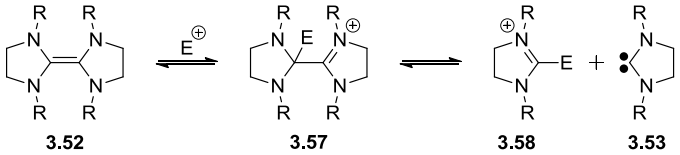


Since its inception, the Wanzlick equilibrium has been a controversial proposal. Early research by Lemal *et al.*[198] showed that no cross-over product **3.56**, formed when tetraazafulvalenes **3.54** and **3.55** were heated under more drastic conditions than the reactions performed by Wanzlick, and thus an equilibrium must not operate (**Scheme 3.17**). Results from Winberg *et al.*[199] also agreed with Lemal's findings. Lemal suggested instead that the dissociation of tetraazafulvalenes **3.52** was initiated by an electrophilic attack on the alkene (**Scheme 3.18**) forming intermediate **3.57** and finally stable azolium salt **3.58** and carbene **3.53** (which can then itself react with an electrophile).

Scheme 3.17 The cross-over experiments performed by Lemal *et al.* did not yield **3.56**.



Scheme 3.18 Lemal *et al*. proposed electrophile-catalysed dissociation of enetetramines.

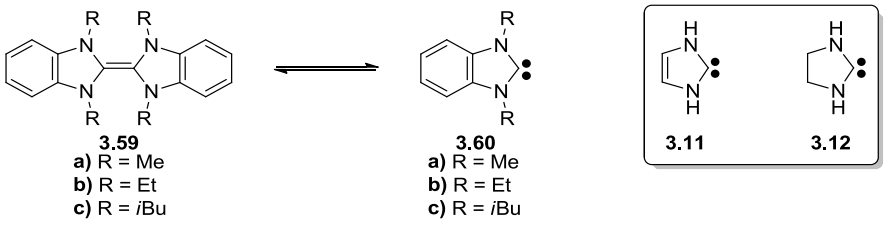


More recently Denk *et al.*[122] reported the successful cross-over of alkyl substituted imidazolidine-derived enetetramines which prompted Lemal and Liu to re-examine their original cross-over experiment, after 6 h at 100 ºC equilibrium product **3.56** was indeed observed. However Lemal and Liu stated that 'a trace impurity, however nefarious, could not prevent the occurrence of unimolecular dissociation, and therefore could not prevent crossover'. In fact they proposed that 'it could catalyze crossing over, for example by cleaving a tetraaminoethylene' *e.g.* **3.52**. Thus they repeated the experiment several times but

in the presence of potassium hydride, this afforded negative cross-over outcome in every case thus reaffirming that the Wanzlick equilibrium was not in operation.

Hahn *et al*.[200] and Lemal *et al*.[121] independently reported (submitted within a month of one another) the dissociation of benzimidazole-derived tetraazafulvalenes **3.59** into their corresponding benzimidazol-2-ylidenes **3.60** (**Scheme 3.19**). Both groups reasoned that benzimidazol-2-ylidene carbenes **3.60** should exhibit stability somewhere between that of thermodynamically stable imidazol-2-ylidenes **3.11** and dihydroimidazol-2-ylidenes **3.12**, with the benzimidazole-2-ylidenes having degree of aromaticity intermediate between the two species. Hahn observed the dissociation of the *iso*-butyl analogue **3.59c**[200] at ambient temperature over 24 h while Lemal reported the dissociation of dimer **3.59a** as well as the *N*-ethyl substituted analogue at elevated temperature (greater than 110 ºC, quenching a sealed NMR sample in liquid nitrogen to trap species in their 'equilibrated' states).[121] In fact, Lemal even reported the emergence of signals corresponding to carbene **3.60a** that disappear on cooling to room temperature.

Scheme 3.19 Dissociation of benzannulated tetraazafulvalene to their corresponding benzimidazol-2-ylidenes.

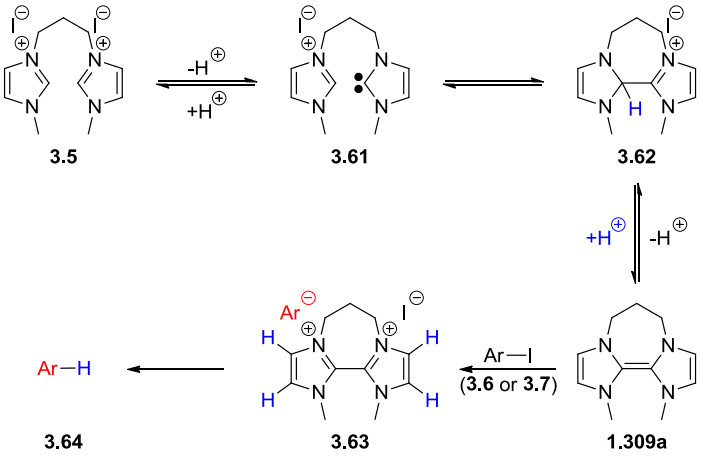


Hahn suggested 'the use of crystalline **3.59c** and carefully purified toluene makes the presence of the electrophile very unlikely' and thus the observed dissociation to **3.60c**, along with the simultaneous observation of both species 'constituted evidence of the equilibrium between the *N*-heterocyclic carbene and the corresponding enetetramine'.[200]

If a true Wanzlick equilibrium was in operation then dissociation would take place regardless of the presence of excess base. In our case this would mean the reduction of aryl iodides **3.6** and **3.9** with **1.309a** would be unaffected by the addition of excess base and **1.309a** would dissociate to *bis*-carbene **3.8** regardless but this is not the case and in fact we observed increased yields of reduced arenes **3.7** and **3.10**. Therefore it is reasonable to conclude that Wanzlick equilibrium is not in operation and the excess base prevents dimer **1.309a**

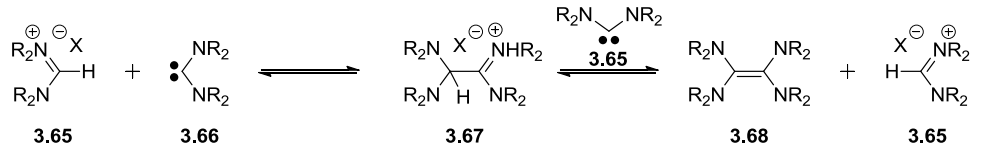
dissociating to *bis*-carbene **3.8**. It therefore seems much more likely that **1.309a** reacts with a proton, as suggested by Garnier[106] (**Scheme 3.20**).

Scheme 3.20 Proton-catalysed dissociation.



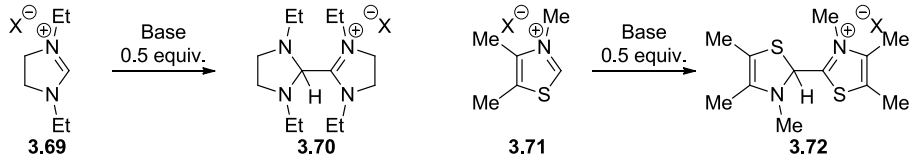
In line with the reactivity of the *bis*-tethered imidazole-derived donor **1.265**, *mono*-tethered tetraazafulvalene dimer **1.309a** is expected to undergo a two-electron oxidation generating bi-imidazolium **3.63** with aryl and iodide counter-anions. Deprotonation of this salt by the aryl anion generates reduced product **3.64** but it is also possible that **1.309a**, driven by gain of aromatic stabilisation energy in **3.62** and **3.61** could act as a base, deprotonating **3.63**. Basic behaviour of *bis*-pyridinylidene donor **1.395** has already been noted by Cutulic[111] and with two additional electron-donating nitrogens adjacent to the C=C bond, one would expect **1.309a** to be even more basic forming **3.62** that dissociates to **3.61** in turn, this is an imidazolium salt with acidic protons and could protonate more molecules of **1.309a** (proton-catalysed dissociation). The dissociation results in loss of reductive reactivity but our results (conditions **A**, **Schemes 3.3** and **3.4**) suggests excess sodium hydride prolongs the lifetime of **1.309a** by competing for protons, preventing dissociation into *bis*-carbene **3.8** and *mono*-carbene **3.61**, thus permitting the reduction of the aryl iodides to reduced arenes in increased yields. These results are in keeping with the electrophile-catalysed dissociation of tetraazafulvalene proposed by Lemal.[120,198] Indeed a dissociation reaction mechanism catalysed by a proton (**Scheme 3.20**) is simply the reverse of the proton-catalysed carbene dimerisation (**Schemes 3.21**)[4] by which tetraazafulvalenes are formed.

Scheme 3.21 Dimerisation by deprotonation can also be considered as proton-catalysed carbene dimerisation.



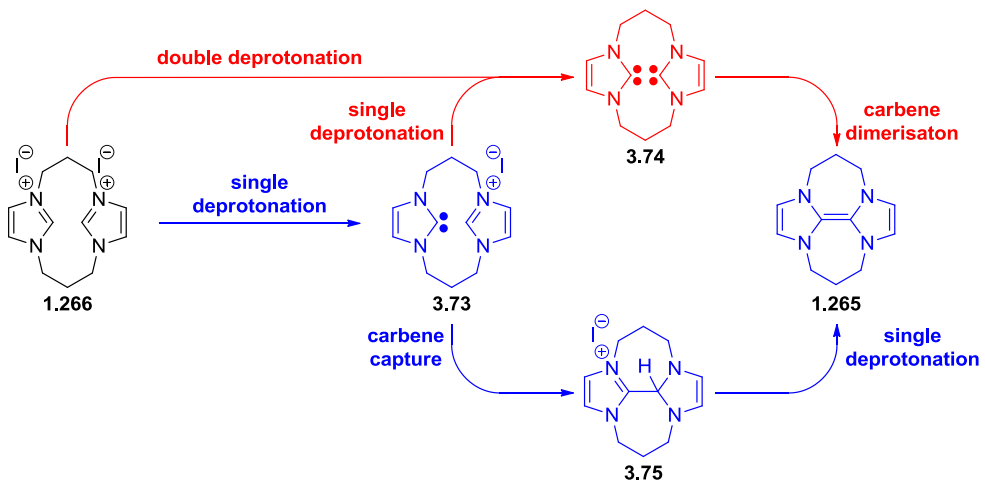
Imidazolium salt **3.62** is a key intermediate common to both the proposed dissociation and dimerisation mechanisms; while the analogous dihydroimidazolium **3.70** [4,93] and thiazolium **3.72**[94] intermediates are known, no such intermediate has been observed for an imidazolium salt.

Scheme 3.22 Unsymmetrical dimer intermediates observed by NMR - dihydroimidazolium **3.70** reported by Alder *et al*.[93] and thiazolium **3.72**, by Jordan and Chen.[94]



Identification of an imidazole-derived intermediate such as **3.62** would suggest dimerisation takes place by a proton-catalysed type mechanism for the dimerisation of imidazol-2-ylidenes (**Scheme 3.23**, blue path) as opposed to a direct 'Wanzlick' type dimerisation of two free carbenes (**Scheme 3.23**, red path. See also **Introduction** pages 37-42 and Alder[4]).

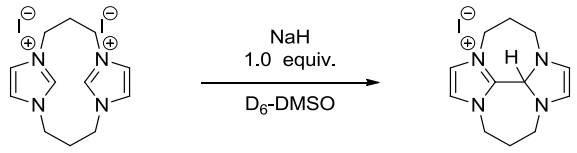
Scheme 3.23 Possible reaction mechanism for tetraazafulvalene formation – direct carbene dimerisation (red) or proton-catalysed dimerisation (blue).



As discussed above and also in the introduction, tetraazafulvalenes that are derived from imidazole are understood to be inherently unstable. In order to replicate the dimerisation intermediates analogous to **3.70**[93] and **3.72**[94] observed we selected imidazolium salt **1.266**, which readily affords imidazole-derived tetraazafulvalene **1.265** on deprotonation (**Scheme 3.2**, page 103).[3]

Imidazolium Salt **1.266** (1.0 equiv.) was ground to a fine powder and was thoroughly mixed with pure sodium hydride (1.0 equiv.). A sample of the mixture was sealed in an NMR tube under nitrogen before being dissolved in d_6-DMSO. Pleasingly the ^{1}H-NMR signals for **1.266** completely disappeared and were replaced with those of unsymmetrical dimer intermediate **3.75** with a single C-C formed at the C2 position of the imidazole heterocycles.

Scheme 3.24 Synthesis of protonated donor intermediate **3.75**.



1.266 **3.75**

The ^{1}H-NMR spectrum of **3.75** showed an absence of signals above δ = 9.00 ppm indicating there are no protons present at the 2-position of the imidazolium ring. Instead an upfield singlet (f, **Figure 3.6**) at δ = 5.10 ppm (1H, s, CH) corresponds to the proton at the bridged 2-position of the 2,3-dihydro-1*H*-imidazole ring, while its alkene protons can be seen as a singlet (e) at δ = 5.71 ppm (2H, s, CH). The aromatic protons of the imidazolium (b) resonate at δ = 7.67 ppm (2H, s, ArH) while deshielded methylene protons (a) adjacent to the nitrogens of imidazolium are a multiplet at δ = 4.35-4.40 ppm (4H, m, CH_2). The remaining eight proton of the four methylenes adjacent to nitrogen (c and d) lie upfield at δ = 2.07-3.45 ppm. The ^{13}C-NMR spectrum of **3.75** (**Figure 3.7**) shows 3 types of CH_2 groups (a, c and d) as expected, between δ = 26.8 and 51.2 ppm, saturated CH (f) is found at δ = 83.7 ppm while unsaturated CH (b and e) of the heterocyclic rings can be seen further downfield at δ = 120.7 and 123.3 ppm. Finally the aromatic quaternary carbon (g) is present at δ = 146.3 ppm.

Figure 3.6 ^{1}H-NMR for protonated donor **3.75**.

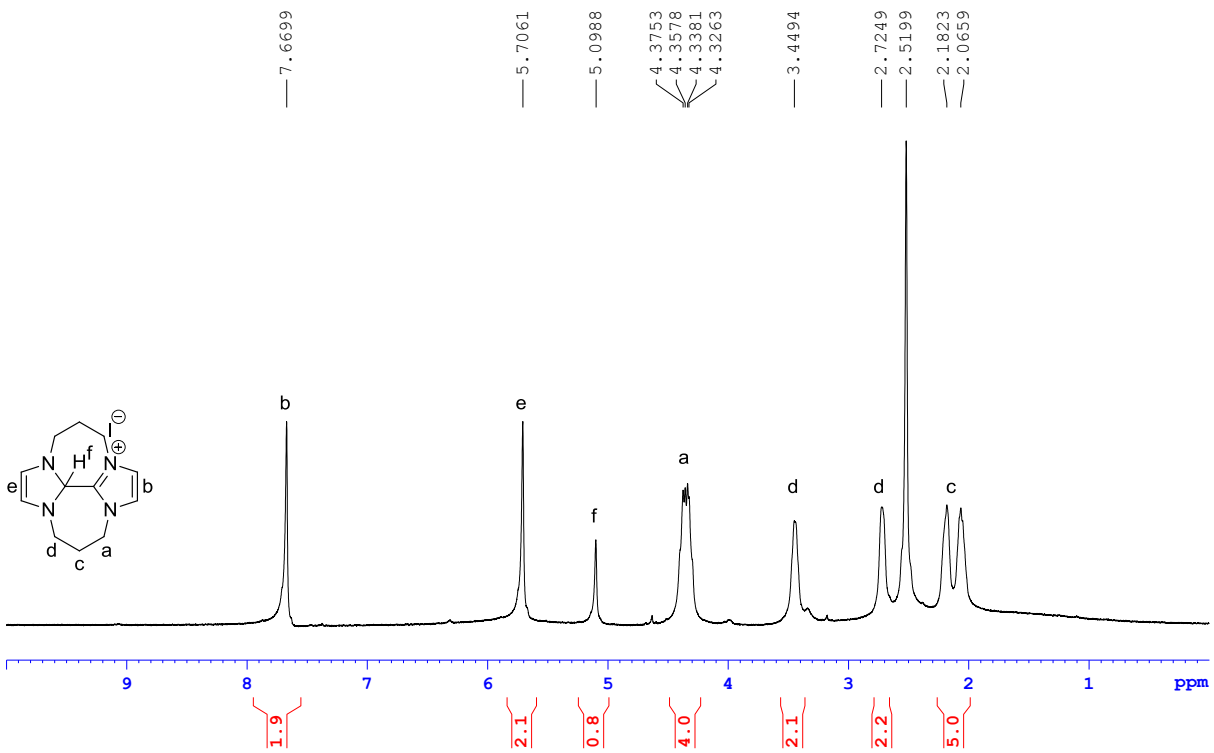
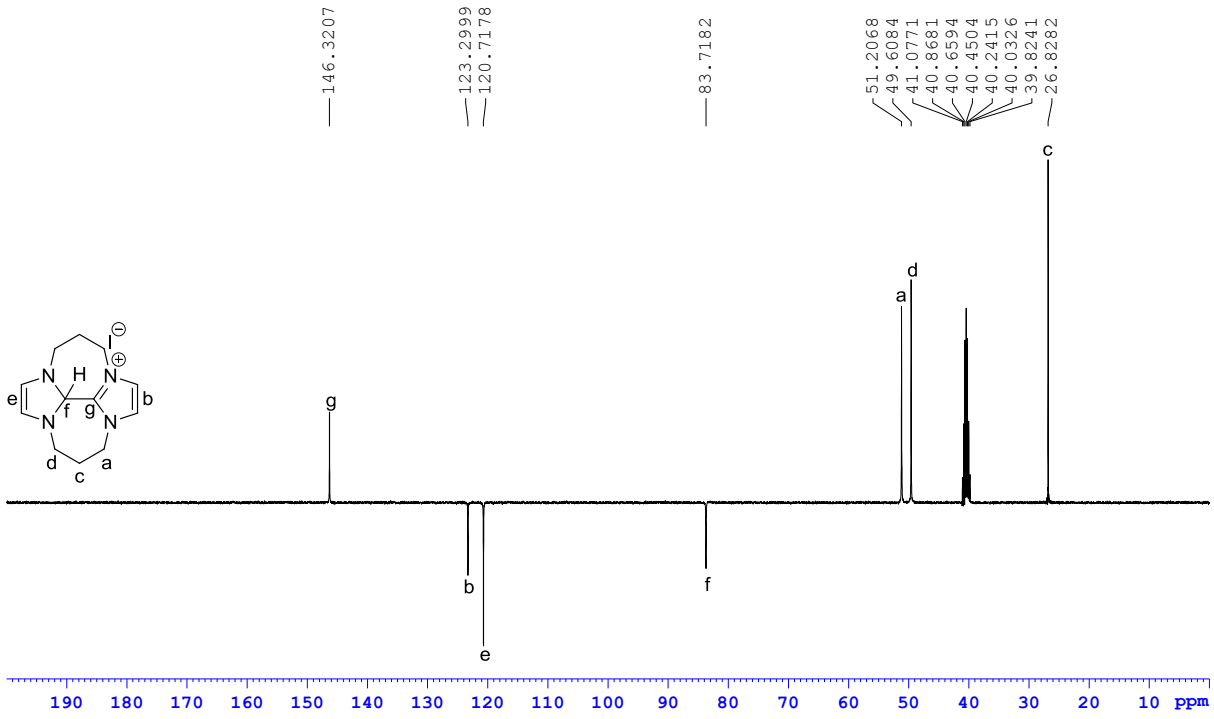


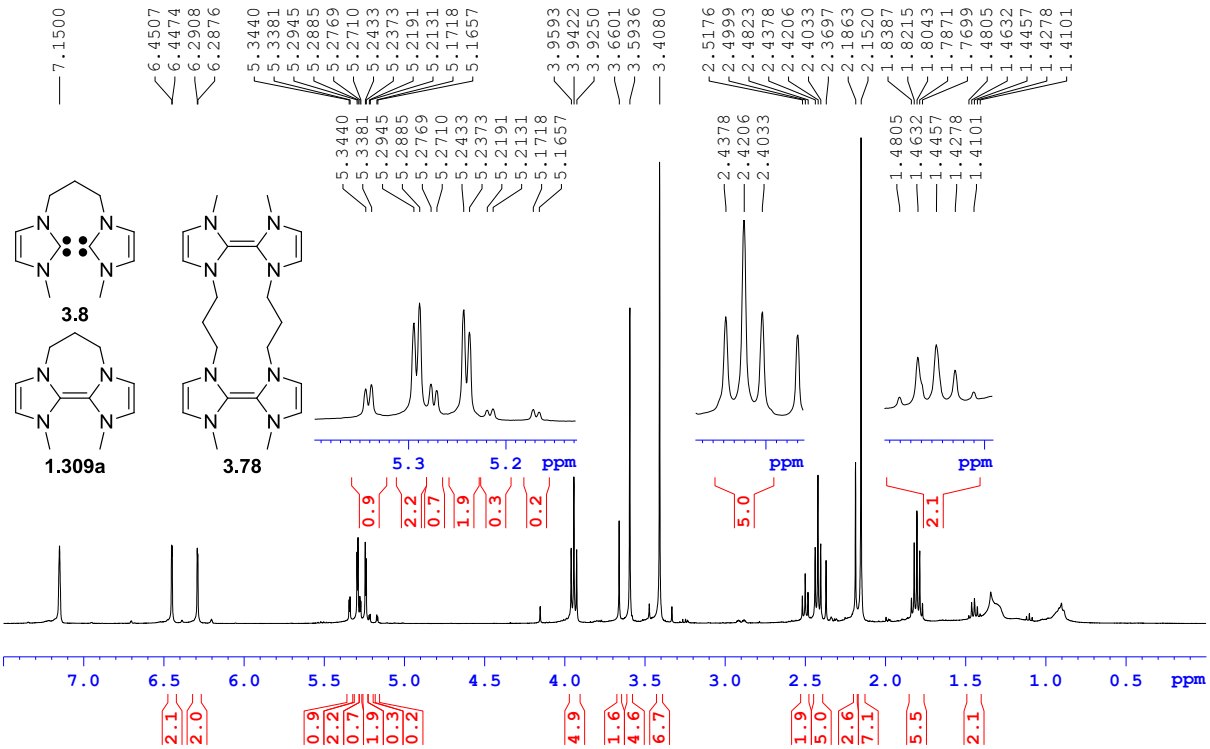
Figure 3.7 ^{13}C-NMR for protonated donor **3.75**.



3.5 Synthesis of "Impossible" Tetraazafulvalenes

The successfully identification of unsymmetrical intermediate **3.75** analogous to **3.70** and **3.72** (**Scheme 3.13**) suggests that imidazole-derived tetraazafulvalene **1.265** is formed by a 'proton-catalysed' dimerisation reaction mechanism. We now looked to spectroscopy to indentify the *mono*-tethered tetraazafulvalene **1.309a** (**Figure 3.8**). Pure imidazole-derived tetraazafulvalene **1.265** is routinely prepared by mixing **1.266** with excess sodium hydride (6-10 equiv.) in a Schlenk flask and then refluxing in liquid ammonia (-33 ºC) under an inert atmosphere (**Scheme 3.2**). After four hours the ammonia is allowed to completely evaporate overnight and dimer is extracted with dry deoxygenated diethyl ether in a glove-box. Removal of solvent affords pure **1.265** as yellow, air-sensitive solid and so we attempted to isolate **1.309a** by the same method. A vivid yellow colour characteristic of **1.265** developed immediately on dissolution of the imidazolium salt **1.265** and sodium hydride. However this was not observed with salt **3.5** and the reaction mixture only took on a very faint green coloration. Extraction of the dry solid with diethyl ether followed by evaporation afforded a trace amount of organic material, which was examined by ^{1}H-NMR in dry deuterated benzene.

Figure 3.8 ^{1}H-NMR for the deprotonation of imidazolium salt **3.5** in liquid ammonia with excess sodium hydride. Structures of plausible products are inset.

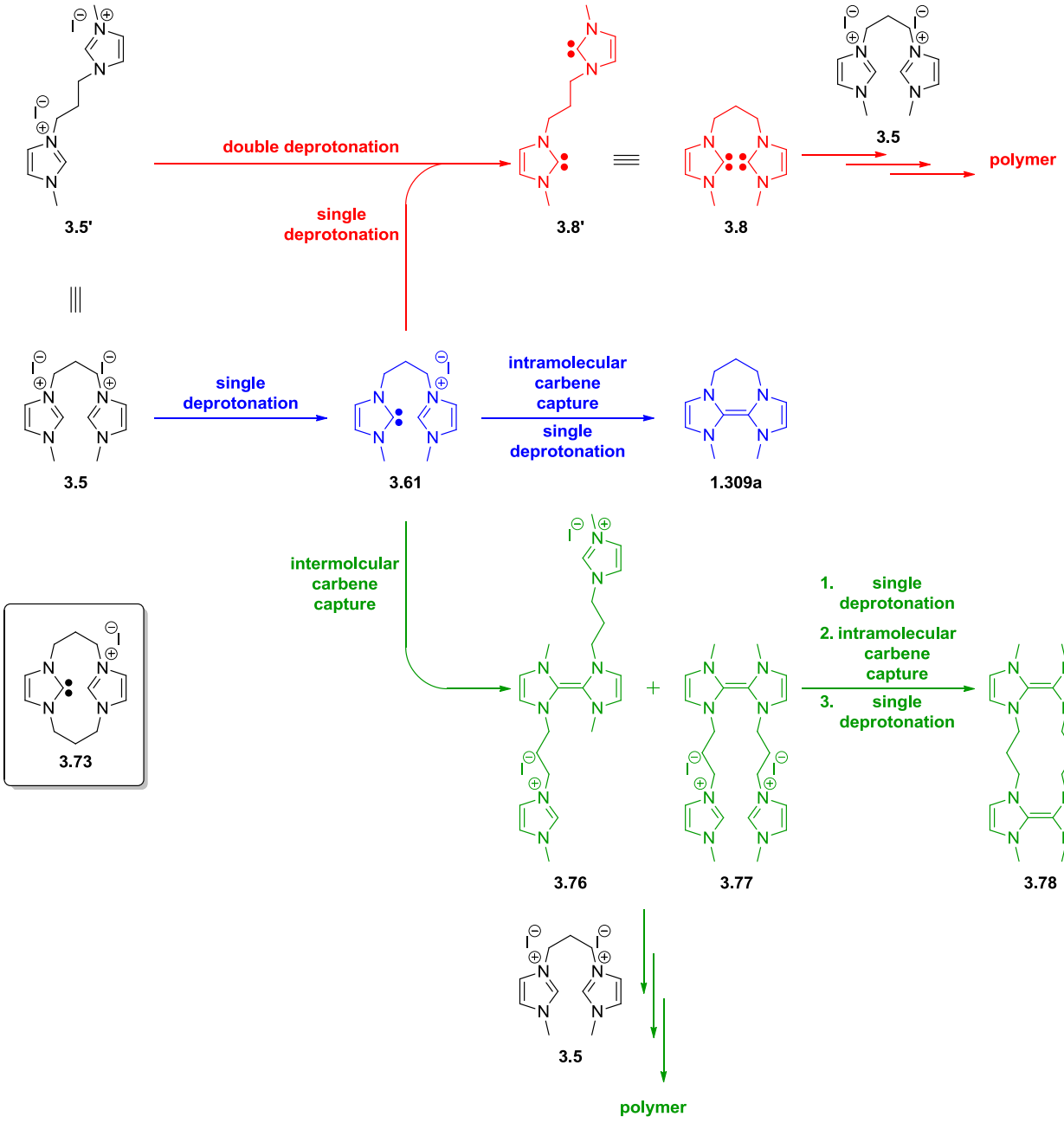


The ^{1}H-NMR spectrum consisted predominantly of *bis*-carbene **3.8**, however signals at δ = 5.25 ppm consistent with CH protons at the 4- and 5-positions of the heterocyclic ring in tetraazafulvalene were visible. The reaction was repeated, refluxing this time for 24 h, during which time the reaction mixture developed stronger yellow/green coloration; this faded somewhat on evaporation of ammonia. The dry solid was extracted with diethyl ether and evaporation of the organic layer under reduced pressure afforded a yellow/orange residue (< 50 mg) that contained a number of components by ^{1}H-NMR spectroscopy (**Figure 3.8**). Two doublets at δ = 6.29 and 6.45 ppm correspond to the *bis*-carbene **3.8** while three pairs of doublets between δ = 5.17-5.34 ppm suggest the formation of tetraazafulvalene-like compounds, for which two possibilities are shown.

The flexibility of *mono*-tethered **3.5** allows the molecule to adopt numerous conformations *e.g.* **3.5'** (**Scheme 3.25**), therefore intramolecular capture of the carbene by the imidazolium counterpart in intermediate **3.61** is kinetically less favourable compared to **3.73**. Thus it is also possible that deprotonation of **3.5** forms *bis*-carbene **3.8** or undergoes intermolecular dimerisation generating **3.76** or **3.77**. Intermolecular dimer **3.77** could then undergo an intramolecular dimerisation to afford macrocycle **3.78**. It is conceivable that reaction of **3.5** with *bis*-carbene **3.8** could also generate macrocycle **3.78** while further reaction of any of the carbene species with imidazolium salts could lead to tetraazafulvalene-derived polymers. Charged species and polymers will not be soluble in diethyl ether which may account for the low yields of organic material recovered after extraction and evaporation of solvent. The formation of macrocycle **3.78** would explain why more than one set of doublet signals characteristic of the heterocyclic protons in tetraazafulvalenes could be seen at δ = 5.17-5.34 ppm.

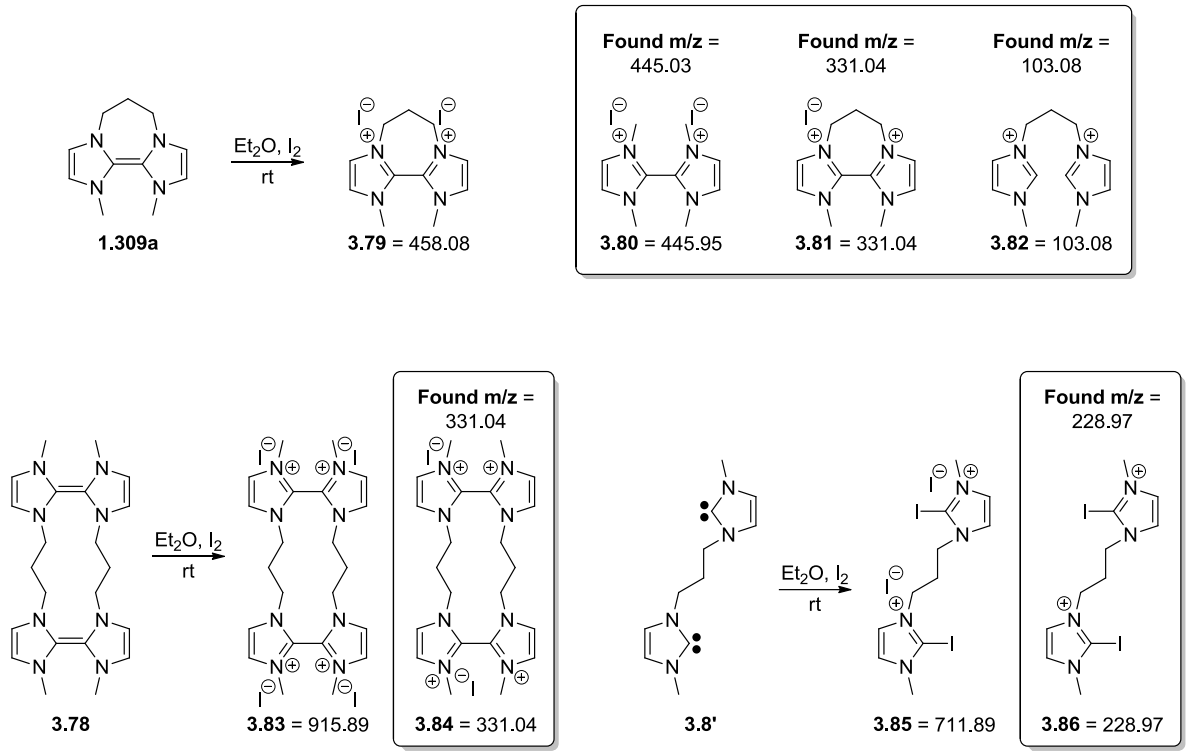
Tetraazafulvalenes can be easily oxidised with iodine to afford the corresponding C2 dimerised iodide salts,[91] and thus **1.309a** would be expected to afford **3.79** (**Scheme 3.26**). Seeking further evidence of imidazole-derived tetraazafulvalene formation by deprotonation, a diethyl ether solution containing the tetraazafulvalene and carbene species was stirred with iodine, and this instantly resulted in formation of a precipitate. The filtered iodide salts were examined by low resolution mass spectrometry. The principal ions found were *m/z* = 445.03, 331.04 and 228.97, which could arise *via* formation of several plausible iodide salts shown in **Scheme 3.26**.

Scheme 3.25 Dimerisation forming **1.309a** by the deprotonation of **3.5** and alternative reaction paths with subsequent by-products.



Despite the NMR and MS being unable to distinguish between plausible products *e.g.* the dimer **1.309a** or macrocycle **3.78**, the experiment does suggest that the *mono*-propylene-tethered tetraazafulvalenes are sufficiently stable as to allow their observation at ambient temperature. Clearly the opportunity for other reactions to take place occurs when forming the C=C by deprotonation and an alternative route that would preclude the formation of undesirable side-products and permits the full characterisation of **1.309a** was desirable.

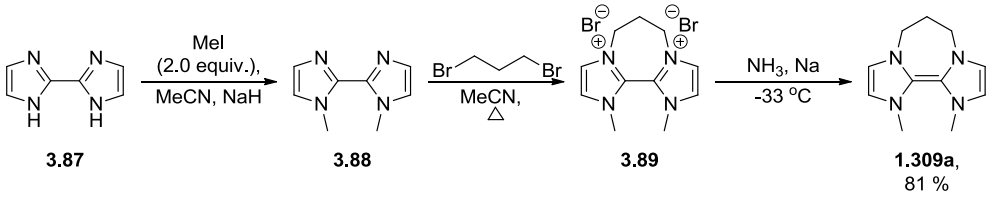
Scheme 3.26 Expected iodide salts generated by oxidation with iodine, along with masses found by mass spectrometry and possible ions they arise from (boxed).

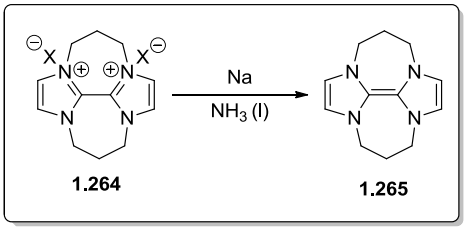


Success in synthesising the *gem*-dimethyl tethered imidazole-derived tetraazafulvalene **3.22**, **3.34** and **3.42**, and the appearance of signals with appropriate chemical shifts to be assigned to tetraazafulvalenes in the deprotonation of **3.5** prompted us to attempt to form tetraazafulvalene **1.309a**. Imidazole-derived tetraazafulvalene **1.265** has also been generated by reduction of bi-imidazolium salt **1.264** (shown in a box, **Scheme 3.27**), with the crucial central C-C bond at the 2-position of imidazole units already in place.[3,83] Thus following Taton and Chen's example,[3] the formation of *mono*-tethered **1.309a** was explored by the reduction of bi-imidazolium salt **3.89** with sodium dissolved in liquid ammonia. Dr. Zhou of our laboratories continued this line of research and synthesised salt **3.89** starting from bi-imidazole **3.87** (**Scheme 3.27**).[92,201] Taking every precaution to exclude oxygen and moisture, **3.89** was dissolved in liquid ammonia under argon within a Schlenk flask. Freshly cut sodium was added until the solution turned blue, and then the ammonia was allowed to evaporate off. Extraction of the dry solid in the glove-box with diethyl ether (freshly dried in the glovebox with sodium and benzophenone) afforded a yellow crystalline solid after evaporation, the first time that this pure *mono*-propylene-tethered imidazole-derived tetraazafulvalene, **1.309a**

sought by us and others had been observed.[3,92] Tetraazafulvalene **1.309a** was characterised by NMR spectroscopy in deuterated benzene freshly dried over molten potassium.

Scheme 3.27 Synthesis of **3.89** and its Birch reduction to *mono*-tethered tetraazafulvalene **1.309a**. (Below) Birch reduction of **1.264** affording tetraazafulvalene **1.265**.[3,83,92,201]

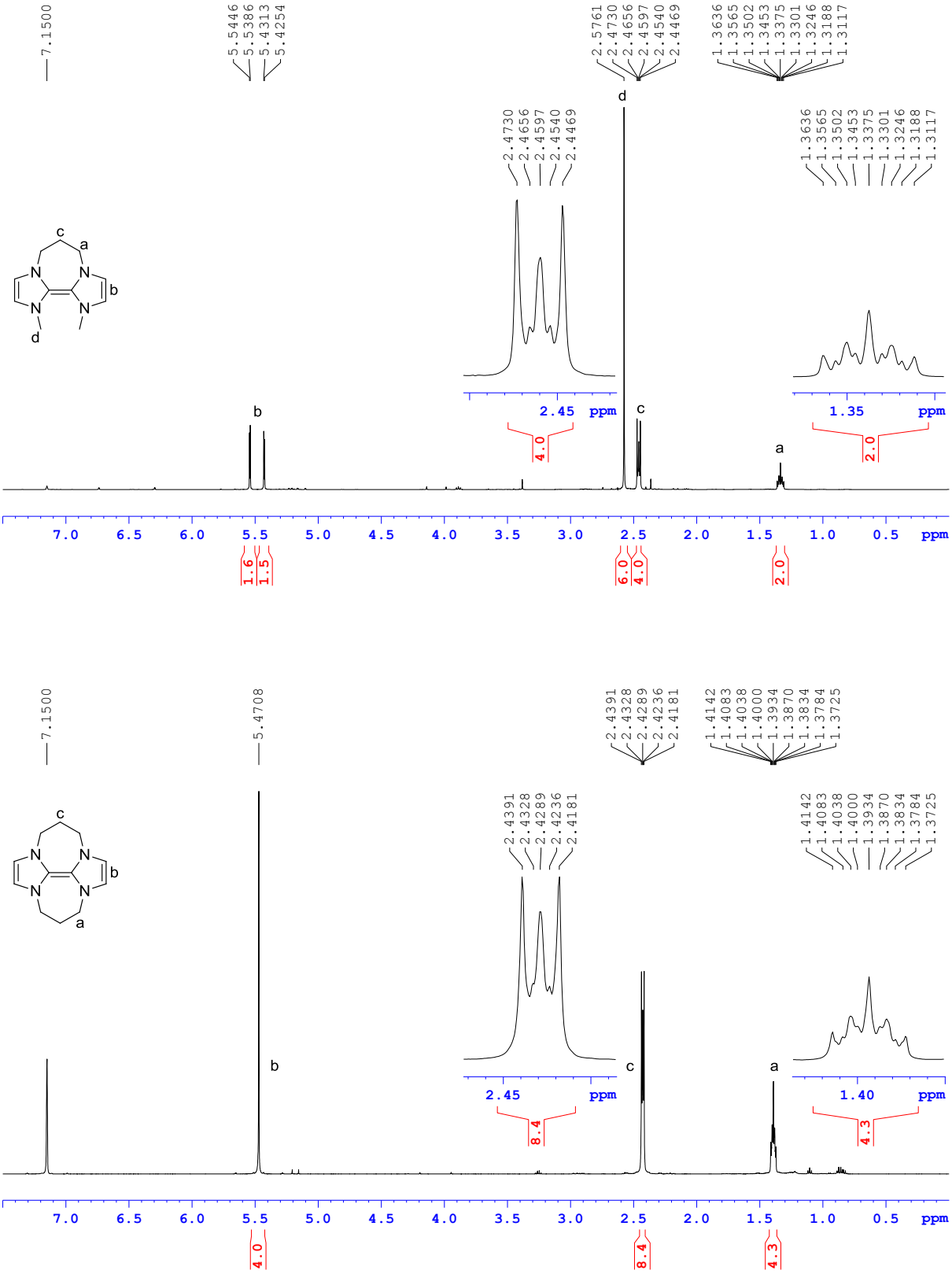




The ^{1}H-NMR spectrum showed the expected upfield shifts of a tetraazafulvalene (**Figure 3.9**), two doublets at δ = 5.43 ppm (2H, d, ^{3}J = 2.4 Hz) and δ = 5.54 ppm (2H, d, ^{3}J = 2.4 Hz). The NCH_2 signal can be seen upfield of the corresponding NMe signal at δ = 2.56 ppm (6H, s), moreover the NCH_2 signal in **1.309a** was a second-order multiplet at δ = 2.44-2.57 ppm (4H, m), as expected within the constraints of the seven-membered ring (and as also seen for di-tethered **1.265**) rather than a simple triplet expected of uncyclised or macrocyclic products. Crucially the ^{13}C-NMR showed the quaternary carbon of the central alkene bond, at δ = 125.9 ppm, characteristic of a tetraazafulvalene. No signals above δ = 200 ppm that would be indicative of *bis*-carbene **3.8** formation were observed.

To further confirm that the structure was that of tetraazafulvalene dimer **1.309a** rather than a related product of higher molecular mass, *e.g.* macrocycle **3.78** or a derived polymer, compound **1.309a** was examined by diffusion-ordered NMR spectroscopy (DOSY).[202,203] DOSY NMR is increasingly being used to determine Formula Weight (FW) or Molecular Weight (MW). It can identify individual components of solution mixtures (comparable to chromatography in NMR terms) which has proven useful for reactive and sensitive species that are difficult or impossible to isolate, thereby precluding other forms of analysis capable of determining molecular weight and thus identity.

Figure 3.9 Comparison of ^{1}H-NMR spectra for di-tethered and *mono*-tethered imidazole-derived tetraazafulvalene **1.309a** (top) and **1.265** (bottom).



The approach first relates the diffusion coefficient to the molecular weight for compounds of known mass, by log *D vs*. log MW. It then possible to measure the diffusion coefficient of the unknown compound and estimate its size, which is inversely proportion to *D*.[202,203] The DOSY experiments on tetraazafulvalene **1.309a** were performed in our NMR suite in a collaboration with Dr. Parkinson. Diffusion coefficient values were determined for seven reference compounds over the molecular weight range 78 – 1203 g/mol to establish a calibration curve against [log D = -0.559 log MW – 7.609 (r^2 = 0.981)]; for which NMR diffusion data from **1.309a** and **1.265** could be assessed (**Table 3.1**).

Table 3.1 Molecular Weight (MW, g/mol) and self-diffusion coefficient (D, m^2/s) data for seven reference compounds used to establish a calibration curve and for the two test compounds *mono*-tethered **1.309a** and di-tethered **1.265**.

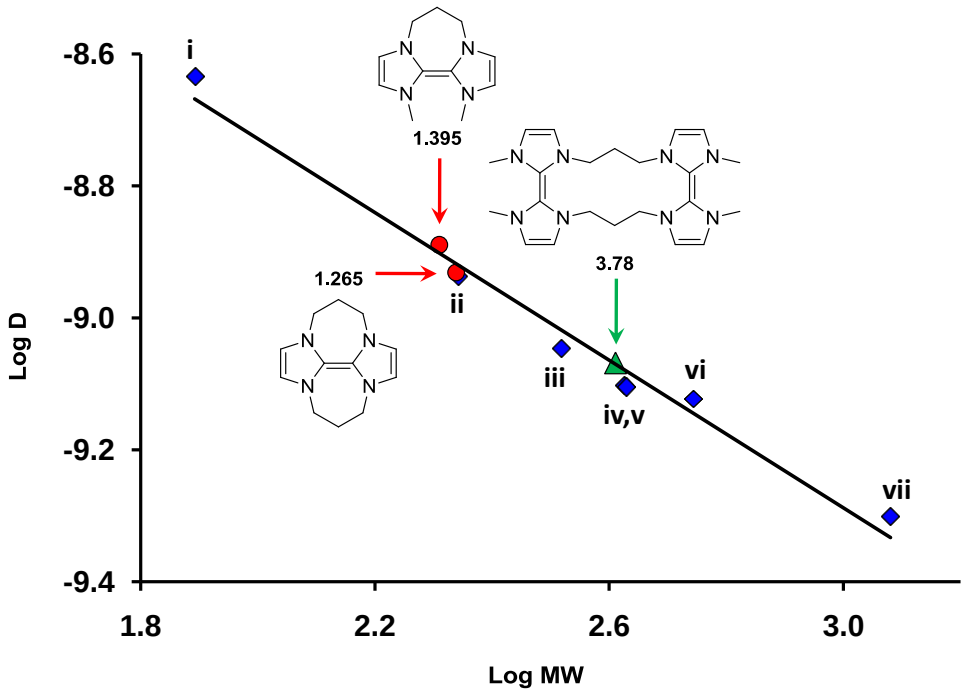
Compound[§]	MW (g/mol)	log MW	10^{-10} D (m^2/s)	log D
i	78	1.892	23.20	-8.694
ii	220	2.342	11.60	-8.936
iii	330	2.519	9.00	-9.046
iv	422	2.625	7.92	-9.102
v	426	2.629	7.87	-9.104
vi	554	2.743	7.54	-9.122
vii	1203	3.080	5.01	-9.300
1.309a	204	2.310	12.90	-8.889
1.265	216	2.338	11.70	-8.931

[§]Reference compounds used: **i** – benzene; **ii** – 4-methyl-2,6-di-tertiarybutylphenol; **iii** - 9,10-diphenylanthracene; **iv** – squalane; **v** - 1,4-*bis*(diphenylphosphinyl)-butane; **vi -** 1,1'-*bis*(diphenylphospinyl)ferrocene; **vii** – Cyclosporine A. Diffusion NMR data were measured for **ii**-**vii** individually as solutions in C_6D_6 and for a mixture of **ii**, **iii**, **iv** and **vi** in C_6D_6 in order to compare results.

Diffusion coefficients measured for the *mono*-tethered species **1.309a** (MW = 204, D_{meas} = 12.9×10^{-10} m^2/s) and for the di-tethered species **1.265** (MW = 216, D_{meas} = 11.7×10^{-10} m^2/s) were consistent with their molecular weights (**Figure 3.10**). The di-tethered imidazole-derived tetraazafulvalene **1.265**, which is known and fully characterised is a particularly good reference point to compare **1.309a**; giving confidence in the correct molecular weight assignment of *mono*-tethered species, **1.309a**, with both being very close together (red

circles). In contrast the theoretical higher molecular mass macrocycle **3.78** (MW = 408 g/mol, calculated diffusion coefficient, D_{calc} = 8.54 × 10^{-10} m^2/s) would be found away from both of these points (green triangle); as would higher oligomers.

Figure 3.10 Plot of log *D vs*. log MW for calibration and **1.309a** and **1.265**.

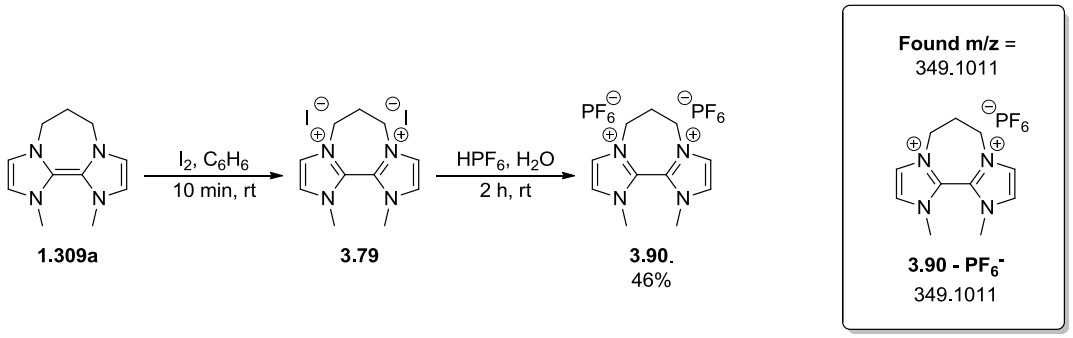


Calibration curve (black line) associated with experimental data from reference compounds **i**-**vii** (**blue diamonds**, **Table 3.1**). Experimental data points for *mono*- and di-tethered keynote compounds, **1.309a** and **1.265** respectively (**red circles**). Reference compounds used: **i** – benzene; **ii** - 4-methyl-2,6-di-tertiarybutylphenol; **iii** – 9,10-diphenylanthracene; **iv** – squalane; **v** - 1,4-*bis*(diphenylphosphino)-butane; **vi** – 1,1'-*bis*(diphenylphospino)ferrocene; **vii** – Cyclosporine A. A linear fit of the calibration data corresponds to log *D* = -0.559 log MW – 7.609 (r^2 = 0.981). Calculated log *D* value (D_{calc} = 8.54 × 10^{-10} m^2/s) for the theoretical macrocycle **3.78** based on a proposed molecule weight MW = 408 g/mol (**green triangle**). Note: the **blue diamond** corresponding to **ii** is obscured by red circle of **1.265**.

The diffusion coefficients measured for **1.309a** and **1.265** were similar to one another and corresponded to values expected for their respective molecular weights of 204 and 216 g/mol; clearly DOSY NMR had demonstrated that the product of the Birch reduction had molecular mass absolutely in line with that of **1.309a**. To further confirm the structure of **1.309a**, it was oxidised to its diiodide salt **3.79** with iodine and then converted to its analogous

hexafluorophosphate salt **3.90** (in 46% yield) by counterion exchange to avoid dealkylation. **3.90** was fully characterised, finding a mass of 349.1011 (**3.90 - PF_6^-**).

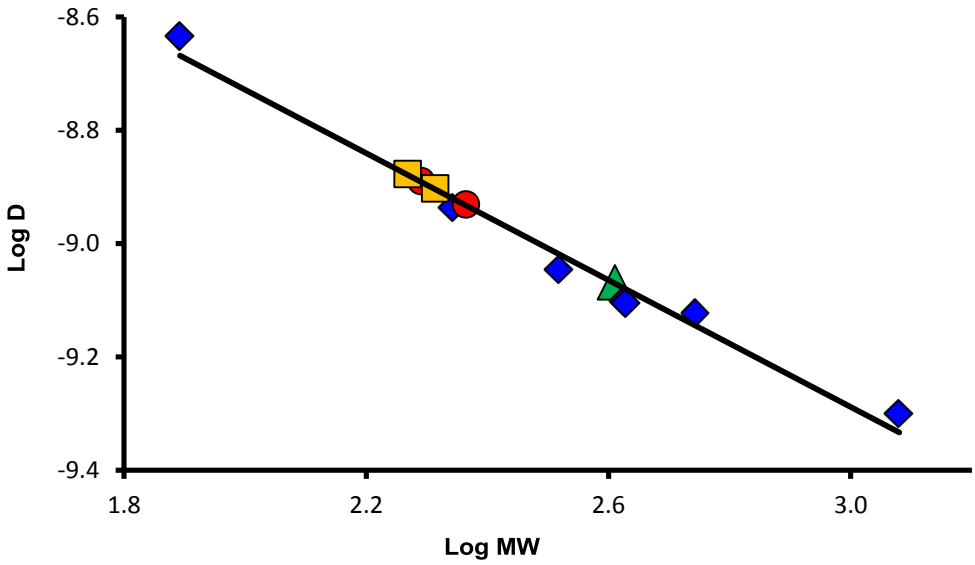
Scheme 3.28 Oxidation of **1.309a** to iodide salt **3.79** and subsequent ion exchange forming bi-imidazolium hexafluorophosphate **3.90**



DOSY investigations (**Figure 3.11**) were also performed on the reaction mixture generated by the deprotonation of imidazolium **3.5** (**Figure 3.8** shows the ^{1}H-NMR spectrum of this mixture. In that NMR spectrum, three pairs of doublets were seen in the δ = 5.2-5.4 region, and each corresponded to a candidate for the desired donor **1.309a**. The two major components (yellow squares) of this reaction mixture also appear to be around the correct molecular weight for tetraazafulvalene **1.309a**, 204 g/mol. Although we have not determined their structure, it is clear that they do not correlate with the calculated mass for theoretical macrocycle **3.78** (408 g/mol), for which log *D* is represented in **Figure 3.11** by the green triangle. The minor third component in the NMR spectrum of **Figure 3.8** was present in too low a concentration to afford a reliable log *D* value in figure 3.11

However the ^{1}H-NMR spectrum of the components of the deprotonation reaction mixture (**Figure 3.8**) does not show the same second-order coupling observed for methylene protons within a seven membered ring that a genuine sample of **1.309a** or indeed di-tethered tetraazafulvalene **1.265** exhibits (**Figure 3.9**). Therefore the exact nature of these compounds remains to be definitively established.

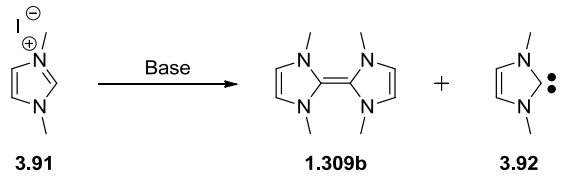
Figure 3.11 Plot of log *D vs.* log MW for calibration and two major components of the reaction mixture generated by deprotonation of imidazolium salt **3.5**.



Calibration curve (black line) associated with experimental data from reference compounds **i**-**vii** (**blue diamonds**, **Table 3.1**). Calculated formula weight for *mono*-tethered **1.309a** and *bis*-carbene **3.8** (**red circles**). Major compounds of reaction the mixture generated by the deprotonation of imidazolium salt **3.5** (**yellow squares**). Reference compounds used: **i** – benzene; **ii** - 4-methyl-2,6-di-tertiarybutylphenol; **iii** – 9,10-diphenylanthracene; **iv** – squalane; **v** - 1,4-*bis*(diphenylphosphino)-butane; **vi** – 1,1'-*bis*(diphenylphospino)ferrocene; **vii** – Cyclosporine A. A linear fit of the calibration data corresponds to log *D* = -0.559 log MW – 7.609 (r^2 = 0.981). Calculated log *D* value (D_{calc} = 8.54 × 10^{-10} m^2/s) for the theoretical macrocycle **3.78** based on a proposed molecule weight MW = 408 g/mol (**green triangle**).

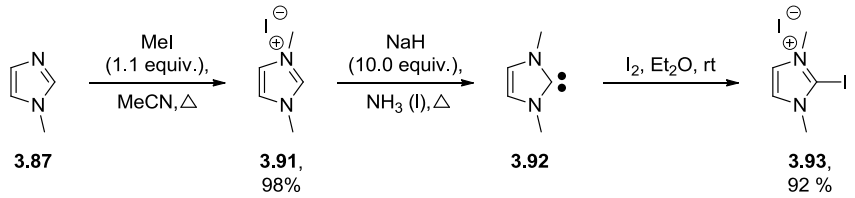
With a genuine sample of *mono*-tethered **1.309a** now synthesised for the first time (by Birch reduction), attention was now directed to the synthesis of non-tethered tetraazafulvalene **1.309b**. The intermolecular dimerisation by deprotonation of dimethyl imidazolium salt **3.91** will be less kinetically favourable than that of intramolecular dimerisation of **1.265**; as such **1.309b** could be expected to provide the most severe challenge being the least thermodynamically and kinetically stable example of an imidazole-derived tetraazafulvalene. However, the reaction products should in principle be simpler, as the exclusion of the propylene-tether should preclude the formation of macrocyclic and oligomer type species and thus only dimer or carbene formation would be expected.

Scheme 3.29 Tetraazafulvalene **1.309b** and carbene **3.92** products expected from the deprotonation of the imidazolium salt **3.91**.



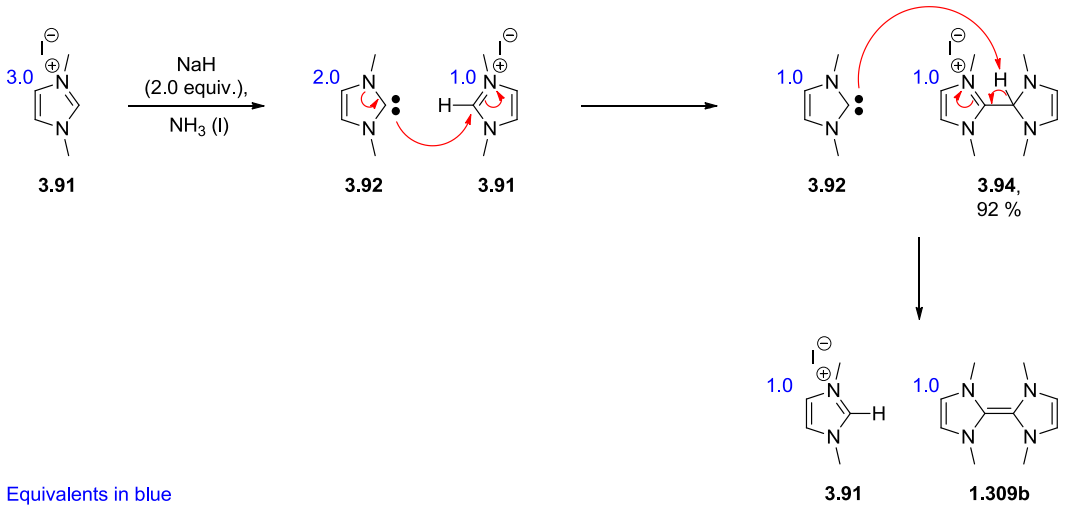
Initially the deprotonation of imidazolium salt **3.91** in liquid ammonia was carried out with 10.0 equivalents of sodium hydride affording the dimethyl imidazol-2-ylidene **3.92** exclusively (after extraction and evaporation). ^{13}C-NMR showed the characteristic C2 carbene signal at 217.1 ppm and oxidation with iodine in diethyl ether afforded the C2 iodinated imidazolium **3.93** in high yield.[204]

Scheme 3.30 Formation of the carbene **3.92** with excess sodium hydride in liquid ammonia and its oxidation to 2-iodo-1,3-dimethyl-1*H*-imidazol-3-ium iodide **3.93**.



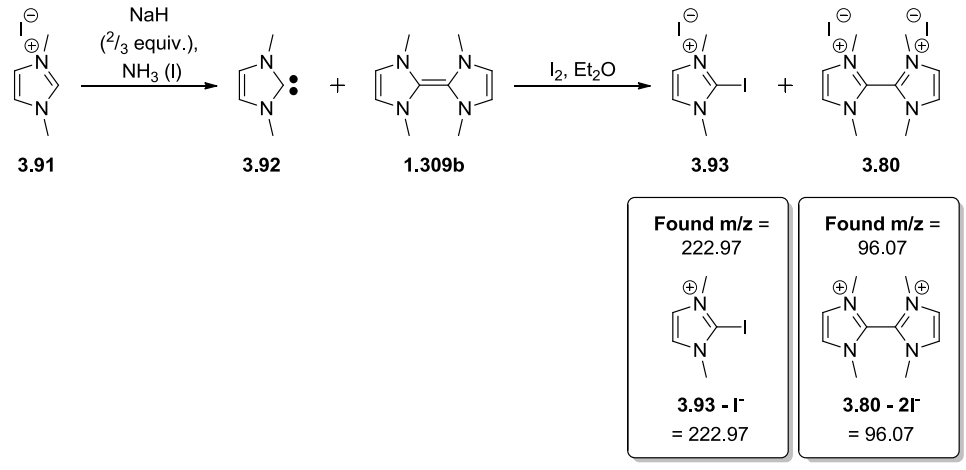
As well as being nucleophilic, *N*-heterocyclic carbenes can act as strong bases[205] with dimethyl imidazol-2-ylidene **3.92** having a pK_a > 21.1.[206-208] By generating 2.0 equivalents of carbene **3.92** in the presence of 1.0 equivalent of the imidazolium **3.91** it was hoped that proton-catalysed dimerisation would afford some tetraazafulvalene **1.309b** (**Scheme 3.31**). Nucleophilic attack of one equivalent of carbene **3.92** on one equivalent of imidazolium salt **3.91** would generate the C_2-tethered intermediate **3.94**. Deprotonation of **3.94** by the remaining equivalent of basic carbene **3.92** would then afford tetraazafulvalene **1.309b** and regenerate imidazolium **3.91**.

Scheme 3.31 Proposed mechanism for the formation of tetraazafulvalene **1.309b** by reaction of 2.0 equivalents carbene **3.92** with 1.0 equivalent imidazolium **3.91**.



After extraction with dry diethyl ether the evaporated residue was analysed after work-up and an upfield singlet at 5.23 ppm in the ^{1}H-NMR spectrum for the alkene protons appeared to be a good indicator that some tetraazafulvalene had been successfully formed along with carbene and some unidentified by-products. Again the reaction mixture was oxidised with iodine and mass spectrum supported the formation of both carbene **3.92** and tetraazafulvalene **1.309b** with mass of 222.97 and 96.07 being observed for the corresponding imidazolium salt **3.93** and **3.80,** respectively.

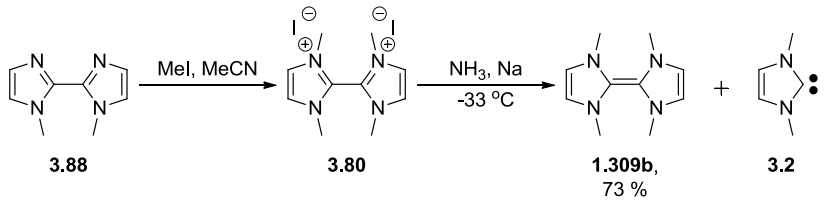
Scheme 3.32 Deprotonation of dimethyl imidazolium **3.91** (3 equivalents) with sodium hydride (2.0 equivalents) and subsequent oxidation of carbene **3.92** and dimer **1.309b** with iodine.



A pure sample of this least stable tetraazafulvalene, **1.309b** was desirable so the Birch reduction of C_2-tethered bi-imidazolium **3.80** was carried out by Dr. Zhou[2] with the same rigour as for *mono*-tethered analogue **1.309a**. Non-tethered tetraazafulvalene **1.309b** was successfully afforded but even under these stringent conditions, carbene **3.92** was also present as a minor product, a clear demonstration of the precarious nature and extreme sensitivity of tetraazafulvalene **1.309b**. Indeed, even using deuterated benzene that was freshly dried over molten potassium, the half-life of **1.309b** was just a few minutes, with the final spectrum being that of carbene **3.92**. Little wonder then that until now it has widely been accepted[4,95,96,209] that the only imidazole-derived tetraazafulvalene that could be observed at room temperature was di-tethered **1.265**.[3] (it is noted that Arduengo refers to carbene dimerisation when the 4,5-position of imidazole bear powerful electron-withdrawing groups and cites unpublished results on 1,3-dimethyl-4,5-*bis*(trifluoromethyl)imidazol-2-ylidene[210]).

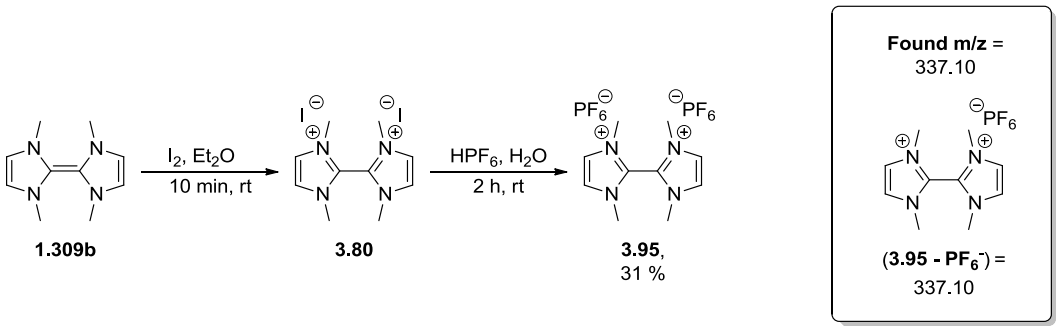
After extraction, the removal of the solvent afforded a uniform yellow solid that turned into an oil in a few minutes. The ^{1}H-NMR spectrum of the unbridged **1.309b** showed signals upfield of those for the carbene and characteristic of tetraazafulvalene; with the methyl groups resonating at δ = 2.53 ppm (12H, NCH_3) and the alkene protons of the heterocyclic rings at δ = 5.44 ppm (4H, CH), while the carbene **3.92** was observed at δ = 3.39 ppm (6H, NMe_2) and δ = 6.27 ppm (2H, CH).

Scheme 3.33 Synthesis of **3.80** and its Birch reduction to unbridged tetraazafulvalene **1.309b** (major product) and carbene **3.92** (minor product).



Again to provide further structure confirmation for the formation of **1.309b** the compound was oxidised with iodine and counter-ions were then exchanged to afford the bi-imidazolium hexafluorophosphate salt **3.95** (31%).

Scheme 3.34 Oxidation of **1.309b** to iodide salt **3.80** and subsequent ion exchange forming bi-imidazolium hexafluorophosphate **3.95** (found ion **3.95 – PF_6^-**).



3.6 Chapter Summary

The formation and characterisation of highly sensitive tetraazafulvalenes **1.309a** and **1.309b** is a significant technical achievement. The deprotonation of the corresponding imidazolium salt **3.5** and **3.91** shows NMR signals characteristic of these tetraazafulvalene formation but cannot be unequivocally assigned to the compounds. The only way to synthesise a pure sample of these tetraazafulvalenes is *via* the Birch reduction of the corresponding bi-imidazoliums, in which a crucial C-C bond binds the imidazole units at the 2-position *e.g.* **3.89** and **3.80**.

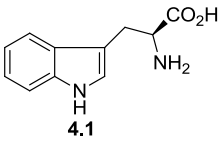
For the first time, pure *mono*-tethered tetraazafulvalenes have been synthesised *via* deprotonation. Two examples of *mono*-tethered tetraazafulvalene **3.34** and **3.42** have successfully been synthesised by employing a combination of Thorpe-Ingold and steric effects. The synthesis of these compounds completely avoids the formation of undesired macrocycles and the tetraazafulvalenes are not so sensitive as **1.309a** and **1.309b** but are expected to be highly reactive like **1.265** making them amenable to investigations into electron transfer chemistry as new super-electron-donors.

4 RESULTS AND DISCUSSIONS – Indole Synthesis *via* Radical Cyclisation Mediated by a Super-Electron-Donor

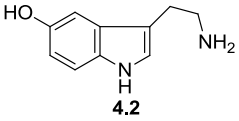
4.1 Introduction

Indoles exhibit a variety of biological activities, exemplified by tryptophan **4.1**, hormones serotonin **4.2** and melatonin **4.3**, the anti-arthritic indomethacin **4.4**, psychotropic LSD **4.5** and the anti-tumour agent vinblastine **4.6**.

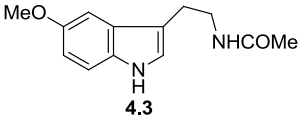
Scheme 4.1 Examples of indoles.



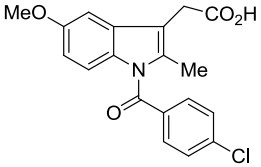
4.1



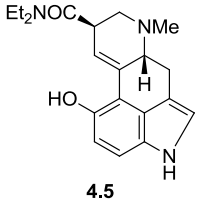
4.2



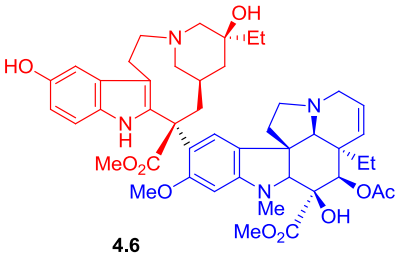
4.3



4.4



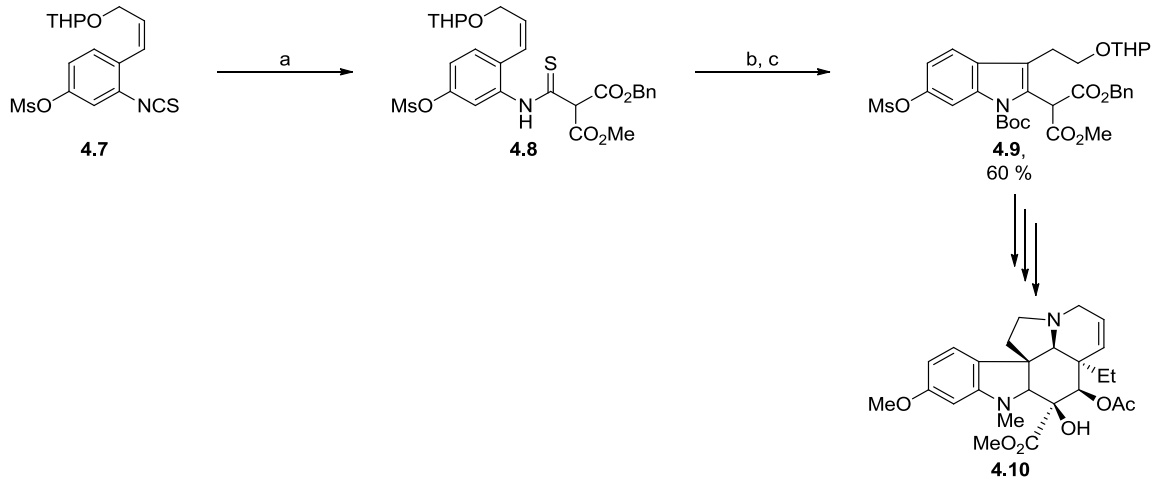
4.5



4.6

Radical cyclisations have successfully been applied to the synthesis of the pyrrole ring in indoles, eloquently demonstrated by Fukuyama's total synthesis of vinblastine **4.6**.[211] The cyclisation using tributyltin hydride and azoisobutronitrile (AIBN) affords indole **4.9** in a 60 % yield (over 3 steps from isothiocyanate **4.7**, **Scheme 4.2**) before it is further elaborated to vindoline **4.10**. Vindoline (blue) is then coupled to catharanthine (red) to afford vinblastine (**Scheme 4.1**).

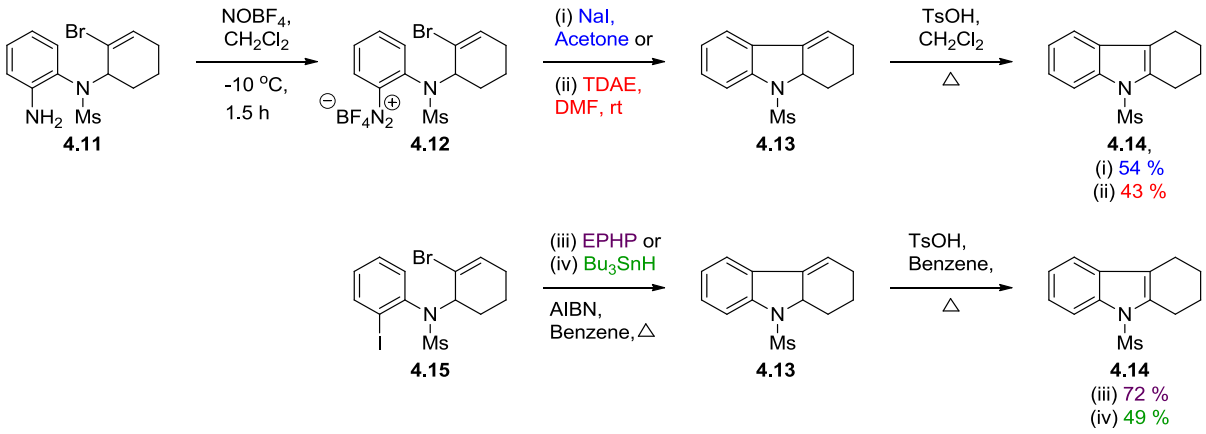
Scheme 4.2 Synthesis of vindoline *via* radical cyclisation of indole **4.9**, carried out by Fukuyama *et al.*[211]



Reaction conditions: (a) benzyl methyl malonate, NaH, THF, 0 °C; (b) AIBN, Bu_3SnH, toluene, 110 °C; (c) Boc_2O, Et_3N, DMAP, CH_2Cl_2, room temperature, 60%

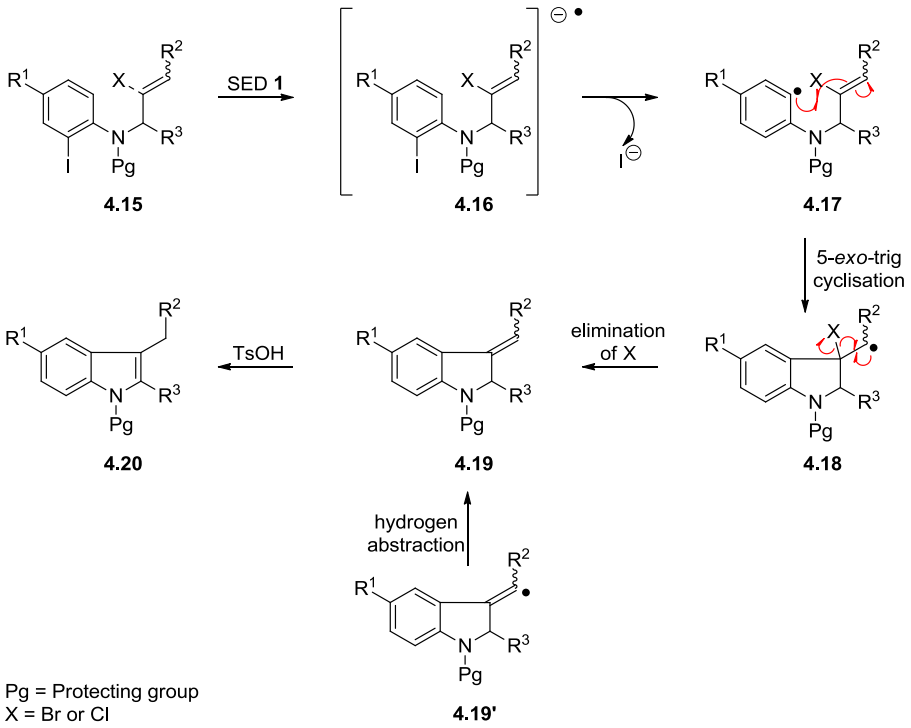
Radical cyclisations have also proved a fruitful avenue of research in our laboratories with indoles being afforded from tautomerisation of indolenines, synthesized *via* radical addition and elimination. Aryl radicals were generated by the reduction of arenediazonium salts mediated by sodium iodide in acetone,[212,213] electrolysis[61] or electron transfer from TDAE.[214] Alternatively the more readily available and easier to handle aryl iodides were converted to aryl radicals *via* abstraction with tributyltin hydride[212,213] or 1-ethylpiperidine hypophosphite (EPHP)[213] both being initiated with AIBN.

Scheme 4.3 Indoles synthesised within the Murphy group *via* addition then elimination of aryl radicals (% yield give starting from **4.11** and **4.14**, respectively).



The Murphy group has an ongoing interest in the clean generation of reactive free radicals and their application in organic synthesis which has led to a drive to move away from metal-mediated reactions in particular those of tributyltin hydride,[215] whose residues are highly toxic and can be difficult to remove. Electrolysis is not always practical for synthesis and the use of organic electron-donors like TTF and TDAE limited the electron-acceptor substrates to arenediazonium salts, until the development of super-electron-donors. Benzimidazole-derived tetraazafulvalene **1.275** had already proved useful as a super-electron-donor, reducing aryl iodides to aryl radicals and this chemistry has already been successfully applied to the synthesis of simple indoline products.[91] We now sought to extend the application of **1.275** to indole synthesis before considering further advances into natural product synthesis. In our plan, the electron transfer from tetraazafulvalene **1.275** into the C-I σ*-orbital would form the radical anion **4.16** which would undergo C-I σ-bond scission, ejecting iodide and generating aryl radical **4.17**. We envisioned cyclisation of the aryl radical onto a halo-alkene[61,212-214] or alkyne appendage in **4.17**. In the case of halo-alkene an alkyl radical would be formed at the carbon adjacent to the halogen in **4.18** and would be primed for the elimination of halo-radical and formation of *exo*-cyclic alkene **4.19**.

Scheme 4.4 Mechanism for aryl radical addition-elimination with halo-alkene appendage or addition-hydrogen abstraction with alkynes.

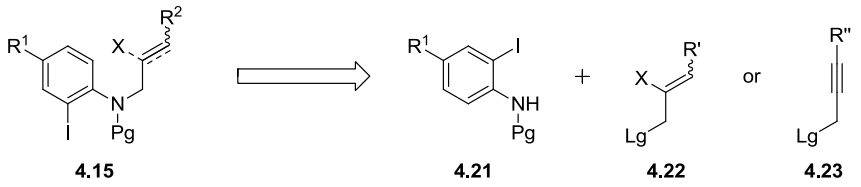


In contrast, cyclisation onto an alkyne would generate an *exo*-cyclic alkene radical **4.19'** which simply abstracts a hydrogen forming indolenine **4.19**. Regardless of the electrophile appendage, tautomerisation of the indolenine **4.19** with acid should afford the thermodynamically more stable indole **4.20**.

4.2 Indole Precursor Synthesis

Indole precursor **4.15** can be disconnected into a protected 2-iodo aromatic amine and a vinyl halide or alkyne.

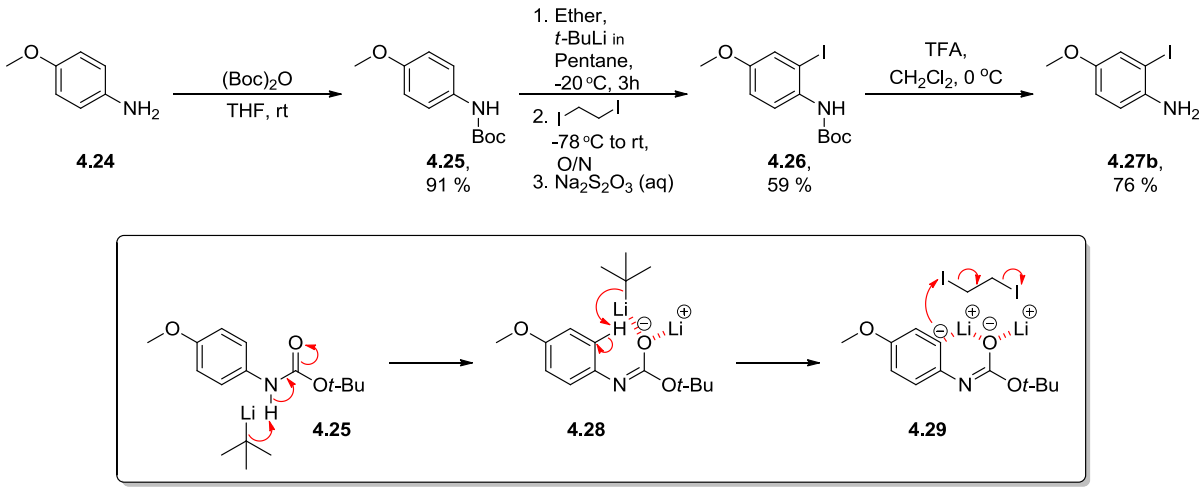
Scheme 4.5 Disconnection of indole precursor.



Pg = Protecting group
Lg = Leaving group
R^1 = H or OMe
X = Br or Cl

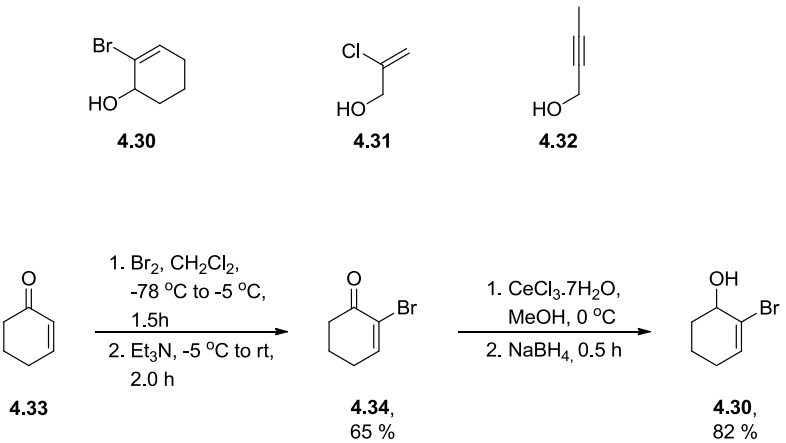
2-Iodoaniline is commercially available however additional analogues derived from anisidine (R^1 = OMe) were targeted as the methoxy group is present in the *para* position in some indoles of interest *e.g.* natural product melatonin **4.3** and pharmaceutical indomethacin **4.4**. 2-Iodoanisidine is not commercially available but can be synthesised from anisidine **4.24**[216-218] (**Scheme 4.6**). Protection of anisidine **4.24** with di-*tert*-butyl dicarbonate furnished *tert*-butyl carbamate **4.25** which was deprotonated with *tert*-butyllithium. The *tert*-butyl carbamate is integral to the synthesis, as it acts as a directing group for *ortho* lithiation. The first equivalent of *tert*-butyllithium deprotonated the nitrogen atom forming the anionic species **4.28**. This then acted as a Lewis base directing the second equivalent of *tert*-butyllithium to the *ortho* position of the aromatic ring. The formation of a lithium metallocycle **4.29** stabilises the anion after deprotonation.[219,220] Subsequent nucleophilic attack on diiodoethane afforded the *ortho*-iodinated **4.26** in good yield after a sodium thiosulfate work-up. Acid-mediated decarboxylation with TFA removed the Boc protecting group affording the free amine **4.27b** in good yield, 76 % (43 % overall).

Scheme 4.6 Synthesis of 2-iodoanisidine and the reaction mechanism of *tert*-butyl carbamate directed lithiation (in the box).[217]



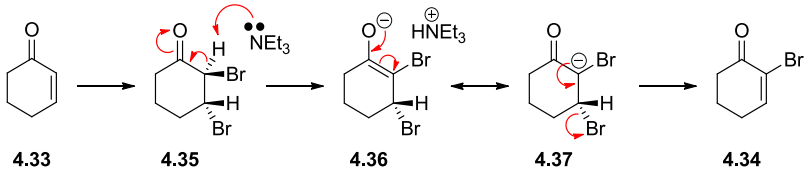
The Mitsunobu reaction[221-223] couples an alcohol to an acidic pronucleophile and would be employed to couple the aromatic amines to unsaturated alcohols in our substrate syntheses. 2-Chloroallyl alcohol **4.31** and but-2-yn-1-ol **4.32** are commercially available, unlike 2-bromoallyl alcohol **4.30** which is readily afforded by bromination/dehydrobromination of cyclohexanone **4.33** in one-pot, followed by Luche reduction[224,225] of the ketone functional group in the resulting vinyl bromide **4.34**.

Scheme 4.7 Synthesis 2-bromoallyl alcohol **4.30**.



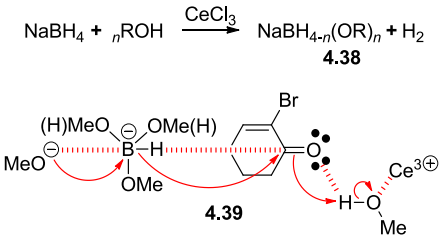
Selective dehydrobromination is promoted by the increased acidity of the proton adjacent to the carbonyl group with anion **4.37**, formed on deprotonation, being resonance-stabilised as the enolate **4.36** (**Scheme 4.8**).

Scheme 4.8 Dehydrobromination mechanism, resonance stabilisation of anion **4.37**.



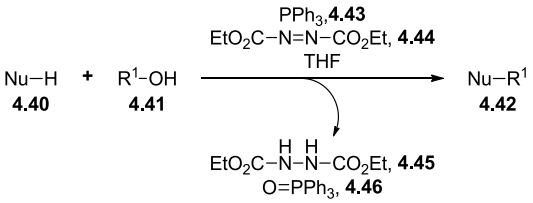
The Luche reduction[224,225] is useful for the selective reduction of a carbonyl group in an *α,β*-unsaturated ketone or aldehyde, in preference to its conjugated alkene. It is proposed that Ce^{3+} cation catalyses the methanolysis of borohydride forming **4.38**, evident by the evolution of hydrogen when cerium chloride is reacted with sodium borohydride in methanol.[224] This 'degradation' of borohydride increases the hardness of species **4.38** promoting selective attack on the harder electrophilic site, the carbonyl. Additionally, it is known that lanthanides bind to hydroxyl in preference to carbonyl so it is likely that reactivity is increased by increasing the acidity of methanol *via* cerium complex **4.39**.

Scheme 4.9 Mechanism for Luche[224] reduction.



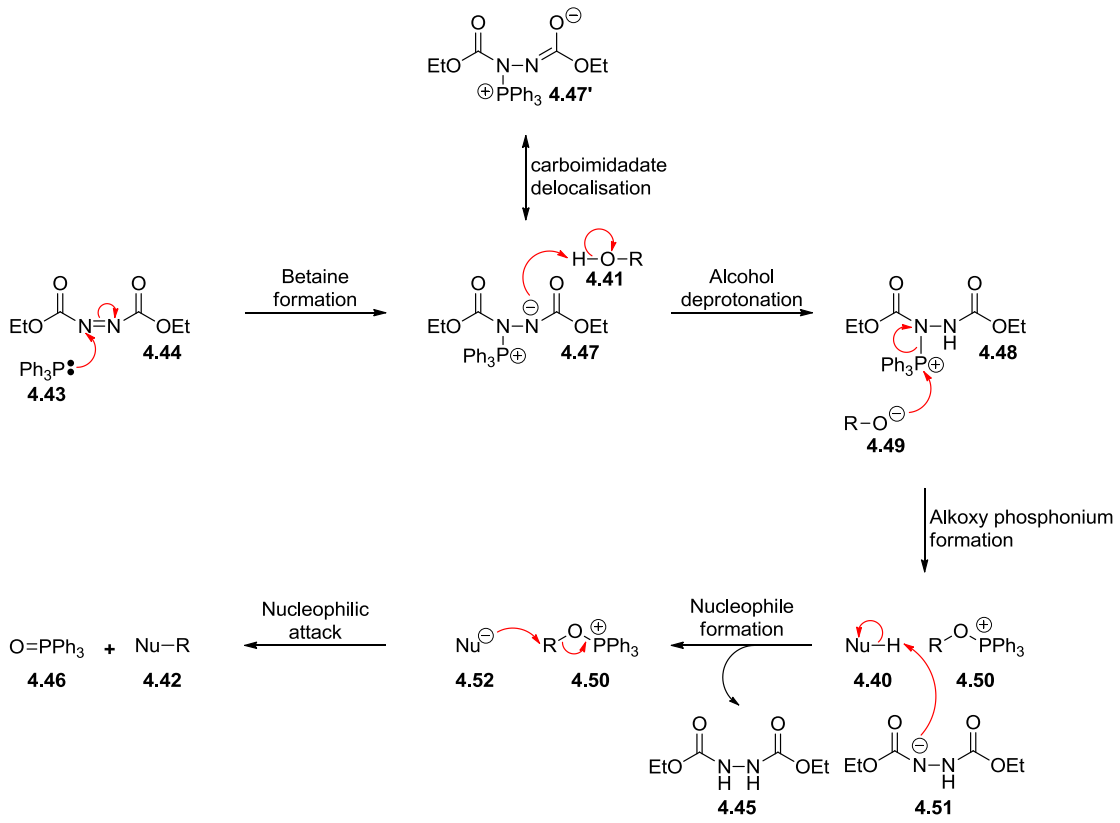
The Mitsunobu reaction[221-223] converts alcohols into good leaving groups in a dehydrative coupling with an acid/pronucleophile. It employs a combination of oxidising azo reagent (usually diethyl azodicarboxylate, DEAD or diisopropyl azodicarboxylate, DIAD) and a reducing phosphine reagent (often trialkylphosphine or triarylphosphine).

Scheme 4.10 The Mitsunobu reaction.



The reaction is initiated by the nucleophilic addition of triphenylphosphine **4.43** to the azo compound DEAD **4.44** forming betaine **4.47** (**Scheme 4.11**). The anion of the betaine is sufficiently basic to deprotonate alcohol **4.41** yielding anion **4.49**, which immediately attacks the phosphonium salt **4.48** generating alkoxyphosphonium salt **4.50** and anion **4.51**. Deprotonation of the acidic pronucleophile **4.40** by **4.51** now generates the true intended nucleophile **4.52** which nucleophilically attacks alkoxyphosphonium salt **4.50** affording alkylated product **4.42** and triphenylphosphine oxide **4.46**.

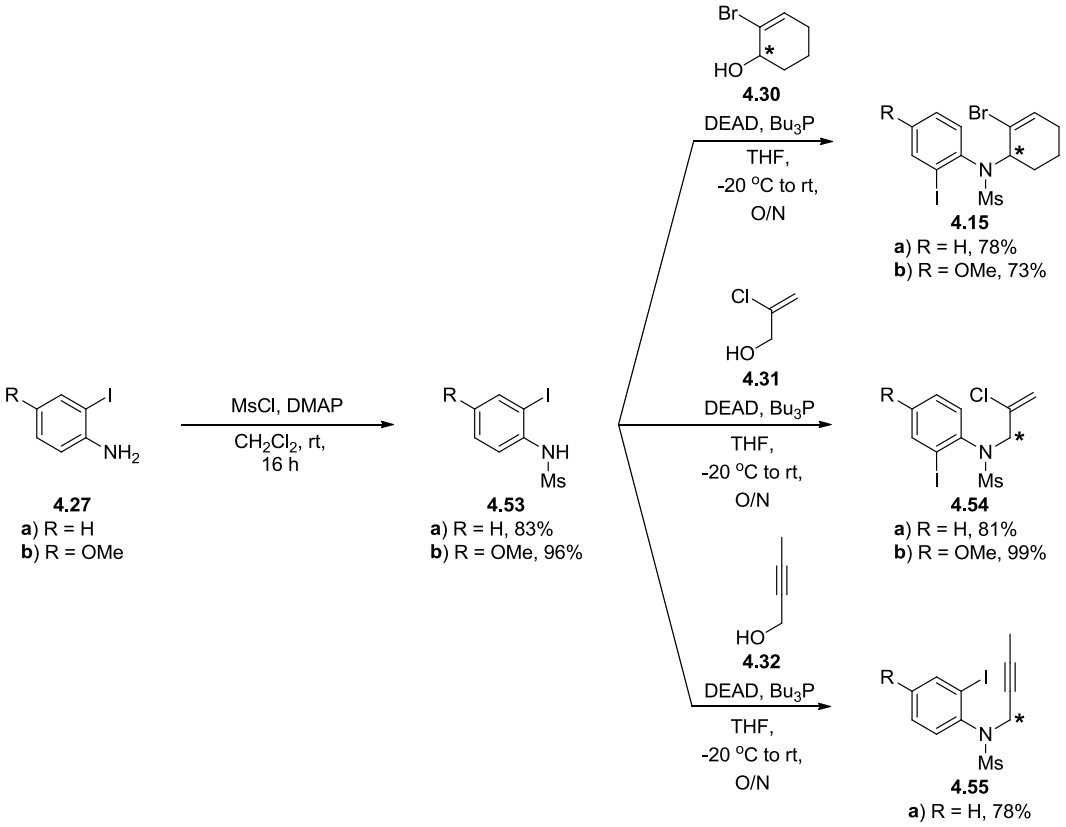
Scheme 4.11 The Mitsunobu reaction mechanism.



The virtue of the Mitsunobu reaction is its ability to utilise a large variety of acidic pronucleophiles under mild and virtually neutral reaction conditions, including carboxylic acids, phenols and imides. However, it is preferable that the pK_a of the acidic pronucleophile is less than 11 and should be no more than 13.5.[183] Aniline has pK_{aH} of 4.6 and pK_a around 30 while *p*-anisidine with an electron donor methoxy group will have pK_a even higher. Thus 2-iodoaniline **4.27a** and 2-iodoanisidine **4.27b** were converted to their corresponding sulfonamides **4.53a** and **4.53b**, respectively (**Scheme 4.12**). The electron-withdrawing sulfonyl group increases the acidity of the remaining hydrogen on nitrogen. With

sulfonamides typically having a pK_a 10 they are suitable pronucleophiles for Mitsunobu coupling.

Scheme 4.12 Synthesis of indole precursors.

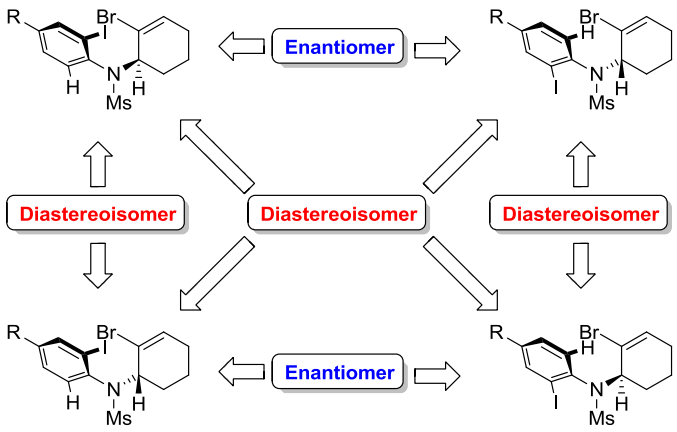


No product was observed for the attempted coupling of cyclic alcohol **4.30** and methanesulfonamide **4.53a** employing Mitsunobu reagents di-isopropyl azodicarboxylate (DIAD) and triphenylphosphine. Azo reagent DIAD is the di-isopropyl analogue of DEAD (di-ethyl) and is thus more sterically encumbered therefore it may be that deprotonation of either the alcohol **4.30** or sulfonamide **4.52** (pronucleophile) is prevented by steric hindrance. Similarly triphenylphosphine is a relatively sterically encumbered phosphine which could potentially hinder the successful formation of alkoxyphosphonium with cyclic alcohol **4.30**, bearing a relatively large atom at the β-position, the vinyl bromide. However, the coupling of **4.30** to **4.53a** has previously been achieved with a DEAD/triphenylphosphine system[212,213] which suggests that the azo reagent is more important in this case. Indeed, replacement of triphenylphosphine with the less hindered tributylphosphine afforded no improvement. However the replacement of DIAD with DEAD (still using tributylphosphine) promoted successful coupling, affording **4.15a** in a 78 % yield (DIAD was initially used in place of DEAD due to transport restrictions on the latter but DEAD was readily afforded from its

hydrazine, diethyl hydrazine-1,2-dicarboxylate by reaction NBS and pyridine[226]). Using DEAD and tributylphosphine the remainder of the desired substrates **4.15b**, **4.54a**,**b** and **4.55a** were afforded in good to excellent yield.

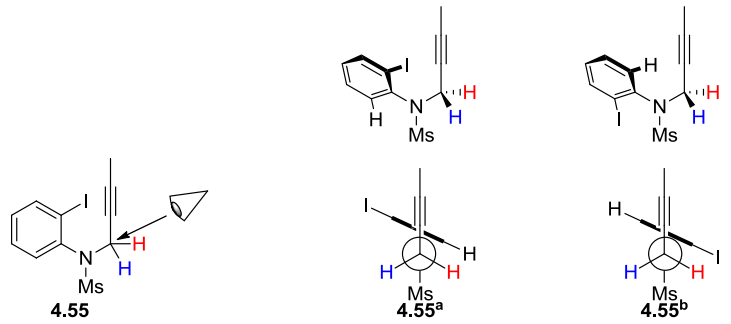
All the coupled products exhibit atropisomerism which arises from restricted rotation about the carbon to nitrogen bonds as a result of the unsaturated appendage being unable to pass the large iodine substituent on the aryl ring. Furthermore coupling of alcohol **4.30** with **4.53** introduces a stereocentre on the allyl substituent of the axially chiral anilide resulting in products with two stereochemical elements – a pair of diastereoisomers.[227] The formation of one enantiomer (pair of enantiomers) almost completely dominates with the other being just visible on the baseline of the ^{1}H-NMR spectrum.

Figure 4.1 Stereochemistry of **4.15a**,**b**.



There are no diastereoisomers formed for **4.54** and **4.55** but atropisomerism places each of the protons on the methylene adjacent to nitrogen in different environments so that two rotamers are possible *e.g.* **4.55^a** and **4.55^b** (**Figure 4.2**). This gives rise to two signals for the methylene at different chemical shifts in the ^{1}H-NMR spectrum, as the protons are different from one another and a large geminal coupling is seen *e.g.* the CH_2 group of **4.55** has two signals of intensity = 1 at δ = 4.02 and 4.67 ppm which are both doublets with a coupling of J = 17.5 Hz. Newman projection looking along the CH_2-N bond shows the two possible rotamers for **4.55**, the aryl ring is represented by the thick bond and the iodide would point out of the page lying either side of alkyne, restricting free rotation. It is now possible to see how the two protons of the methylene are different.

Figure 4.2 A Newman projection of two rotamers possible for **4.55**.

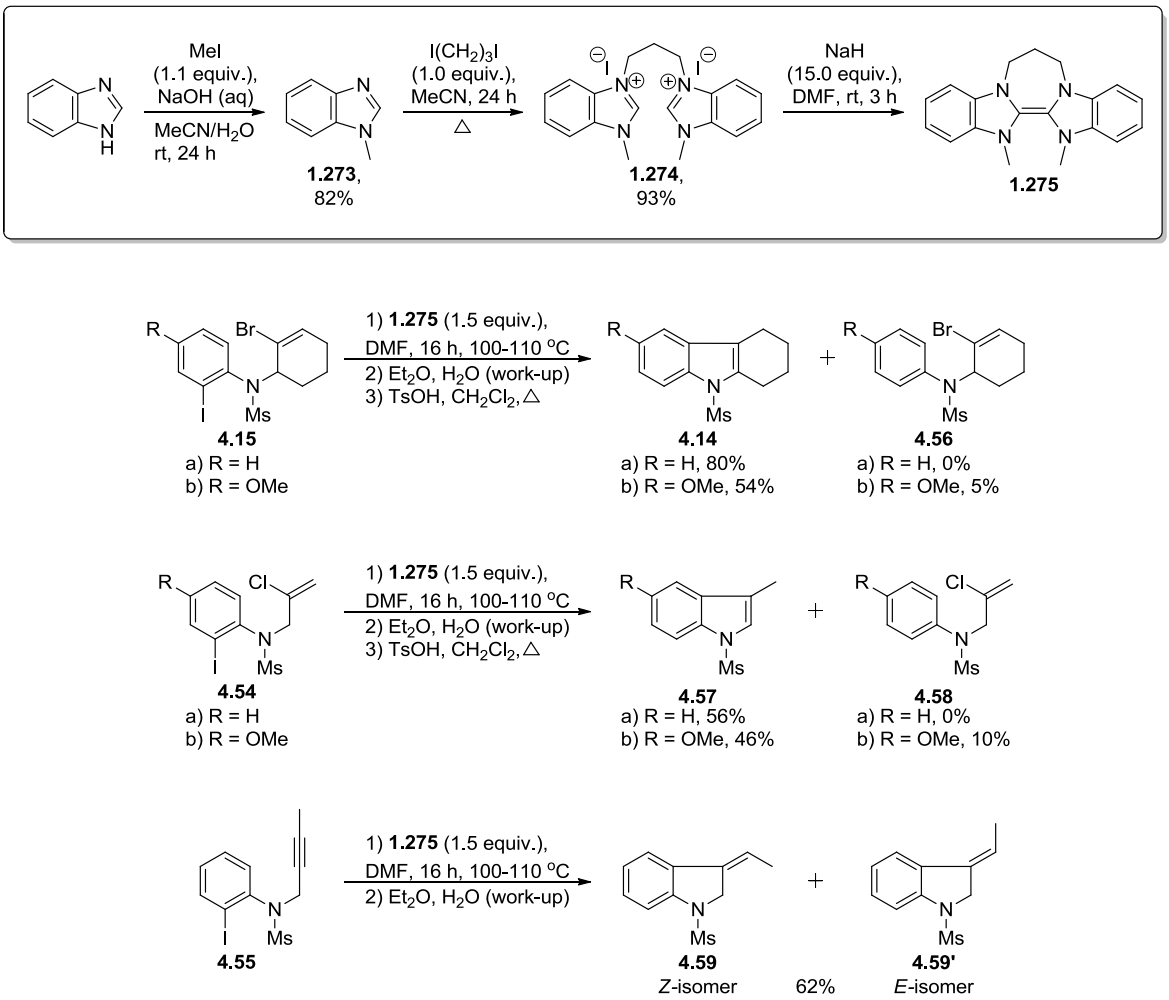


4.3 Indole and Indolenine Synthesis Mediated by a Tetraazafulvalene

Vinyl bromide **4.15a** was the first substrate to be examined with benzimidazole-derived super-electron-donor tetraazafulvalene **1.275** (**Scheme 4.13**). A degassed anhydrous DMF solution of **1.275** was prepared using 1.5 equivalents of the precursor salt **1.274** (box **Scheme 4.13**) before it was heated at 100-110 °C with **4.15a** overnight under an atmosphere of argon. After work-up and rapid column chromatography indole **4.14a** and indolenine **4.13** were isolated as a mixture, with the indolenine being the predominant product. To simplify the purification of the products, the mixture was treated with *p*-toluenesulfonic acid in refluxing dichloromethane. This catalyses the tautomerism of the indolenine **4.13** to the more stable indole **4.14**, which after work-up and purification was isolated in a highly acceptable 80 % yield.

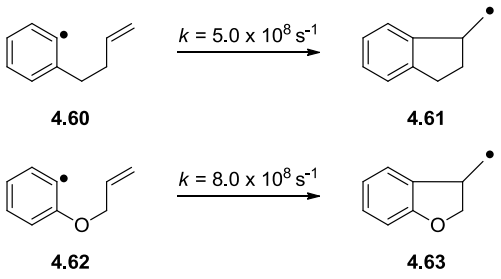
The isolation of cyclised products in high yield indicates the radical addition-elimination process has occurred as desired. Furthermore the product was afforded in higher yield than the previous methods employed within the group (tributyltin hydride[212,213] or 1-ethylpiperidine hypophosphite[213]). 5-*Exo*-trig cyclisation of aryl radicals is known to be rapid[228] (**Scheme 4.14**) so the observation of reduced product **4.56b** from the reduction of **4.15b** (even in a low 5 % yield) is somewhat surprising, particular given the analogous **4.56a** is not observed. ^{1}H-NMR of the crude reaction mixture before purification showed the starting material **4.15b** to be fully consumed but a lower yield of desired indole **4.14b** could be an indication that side-reactions are taking place when the methoxy group is present *meta* to the position of radical formation. reasonable yield although again a small amount of aromatic product **4.58b** was observed for methoxy analogue, being isolated in 10 % yield.

Scheme 4.13 Radical cyclisations mediated by **1.275**, affording indolenines and indoles.



Reaction of vinyl chloride substrates **4.54a**,**b** with 1.5 equivalents of super-electron-donor **1.275** also led to complete consumption of the aryl iodide starting material. After tautomerisation the corresponding indoles **4.57a**,**b** were isolated in

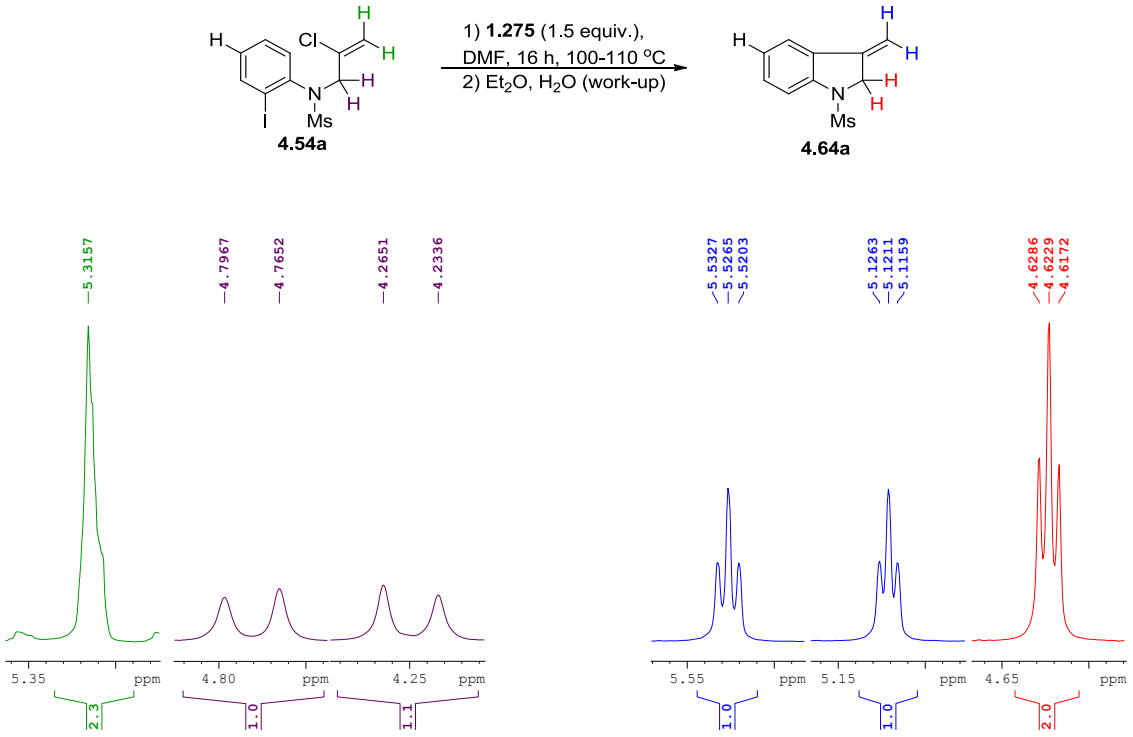
Scheme 4.14 Rate constants for 5-*exo*-trig aryl radical cyclisations.[228]



Reduction of substrate **4.55** with an alkyne appendage similarly yielded successful cyclisation. In this case the product was isolated at the indolenine intermediate stage **4.59** and **4.59'**, affording the *cis*- and *trans*- isomers as an inseparable mixture.

All of the ^{1}H-NMR spectra of crude reaction products were complicated by the presence by products derived from tetraazafulvalene **1.275**, which are soluble in organic solvents (*vide infra*) in contrast to imidazole-derived tetraazafulvalene **1.265** and *bis*-pyridinylidene donor **1.395**. However, loss of atropisomerism in cyclised indolenine intermediate is diagnostic of successful reaction.

Figure 4.3 ^{1}H-NMR of uncyclised aryl iodide **4.54a** and cyclised indolenine **4.64a** which exhibits allylic coupling.



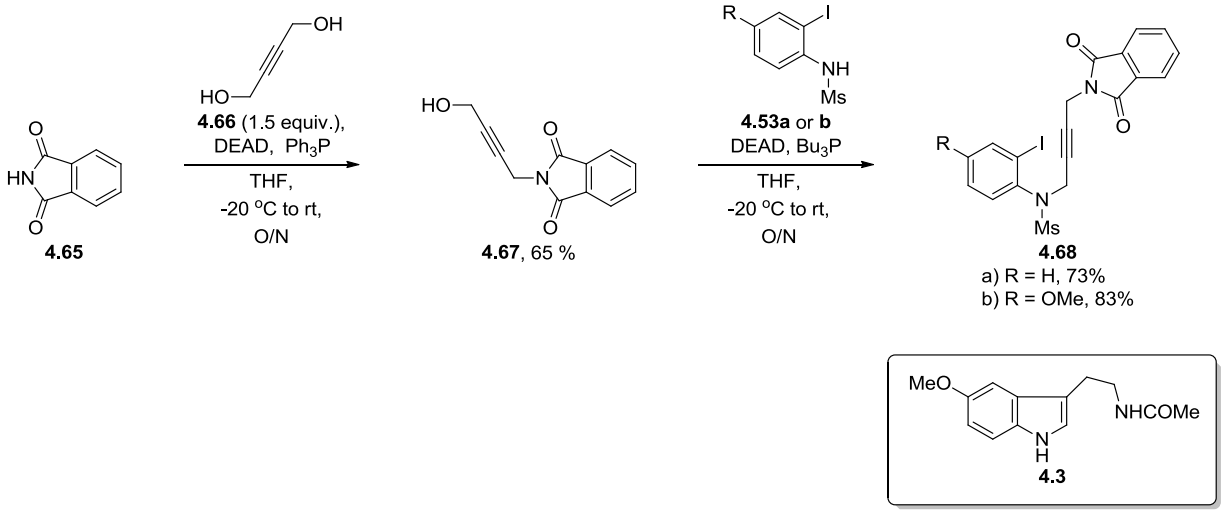
Cyclisation of **4.54a** affords a mixture of indole **4.57a** and indolenine **4.64a** (before tautomerism with TsOH), clearly the disappearance of NCH_2 protons altogether would be indicative of indole formation and we would expect to observe the corresponding aromatic signal. In contrast indolenine formation retains the NCH_2 but its characteristics change. In the aryl iodide **4.54a** the two protons of NCH_2 are different due to atropisomerism (as discussed above) and can be found at δ = 4.25 and 4.78 ppm (purple, centre left, **Figure 4.3**). As each proton experiences a different environment they couple to one another with a large geminal coupling of ^{2}J = 15.8 Hz. Upon cyclisation to indolenine **4.64a** atropisomerism is lost so that

the two protons of NCH_2 no longer differ in their chemical environment, hence they are found a single signal at δ = 4.62 ppm (red, far right, **Figure 4.3**). Furthermore, the geminal coupling of the NCH_2 no longer occurs but a coupling to the CH_2 of the *exo*-cyclic alkene is observed, splitting the signal into a triplet with a long range allylic coupling constant, ^4J = 2.8 Hz. Both *cis* and *trans* protons of alkene experience this coupling and are found downfield of the NCH_2 at δ = 5.12 and 5.52 ppm (blue, centre right, **Figure 4.3**). The observed long range allylic coupling which is promoted in ring structures and is characteristic of indolenine formation, in contrast alkene protons of aryl iodide **4.54a** experience no significant coupling and can be seen at the same chemical shift, a singlet at δ = 5.32 ppm (green, far left, **Figure 4.3**).

4.4 Advances Towards Melatonin

Having successfully isolated indoles and indolenines in good to excellent yield we now sought to apply the methodology to natural product synthesis. Pineal hormone melatonin **4.3** has previously been successfully synthesised by aryl radical cyclisation onto alkyne of **4.68b** using tristrimethylsilylsilane (TTMSS) or EPHP.[229] Substrates **4.68a**,**b** were readily afforded *via* two Mitsunobu couplings, first coupling phthalimide **4.65** to diol **4.66** and then coupling the resulting alcohol **4.67** to sulfonamide **4.53a**,**b**.

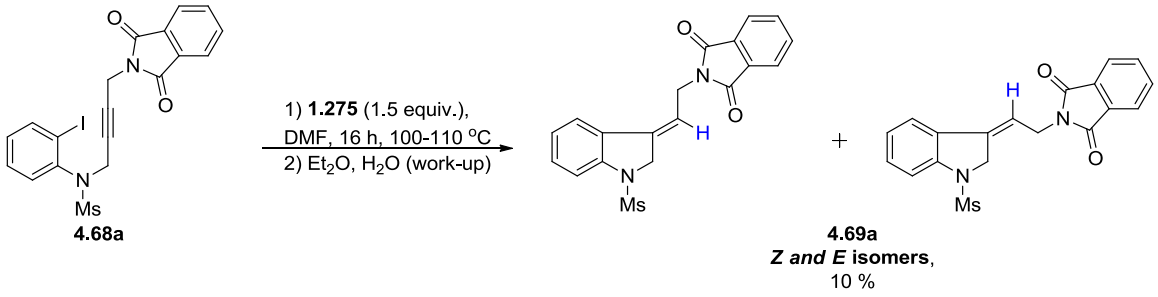
Scheme 4.15 Synthesis of Melatonin precursor **4.68b**.



The 2-iodoaniline-derived **4.68a** moiety was examined as a test substrate before using the methoxy analogue **4.68b** since this precursor was significantly more readily available, being synthesised from **4.53a** as opposed to **4.53b**.

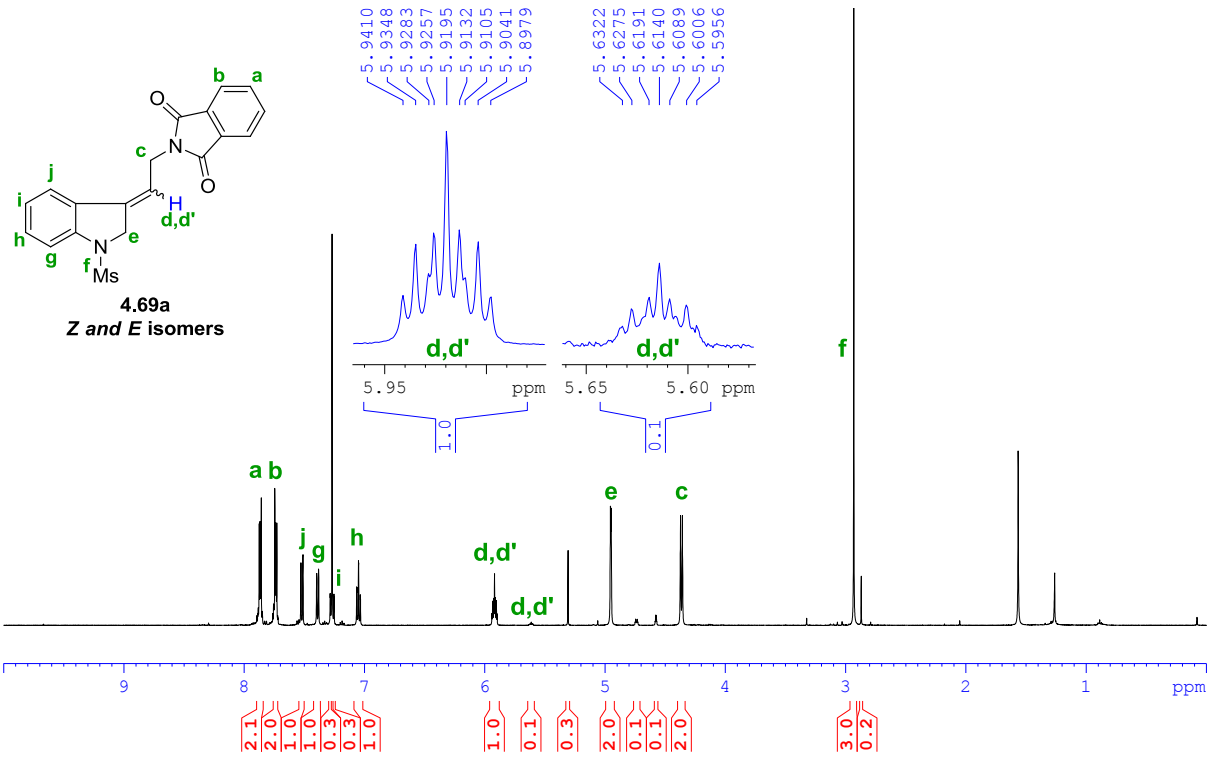
Aryl iodide **4.68a** was reacted with benzimidazole-derived tetraazafulvalene **1.275** by the same method used to synthesise indole and indolenines. The crude reaction mixture was examined by ^{1}H-NMR and found to be rather complicated; however a multiplet with fine allylic type coupling in the alkene region was indicative of success. The crude organic material was purified on silica affording the indolenine **4.69a** as a mixture of *cis*- and *trans*-isomers in 10 % yield.

Scheme 4.16 Cyclisation of **4.68a** to indolenine **4.69a**.



The ^{1}H-NMR spectrum of indolenine **4.69** clearly shows that one geometric isomer predominates, being present in a ratio of 10:1 (**Figure 4.4**)

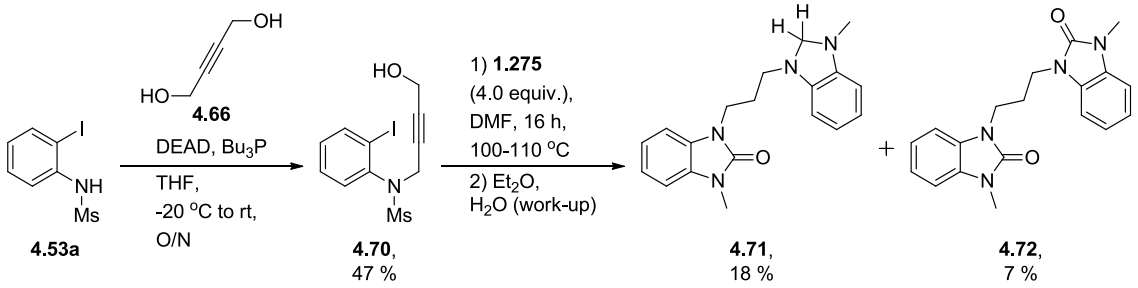
Figure 4.4 ^{1}H-NMR of indolenine **4.69a**.



The 10% yield of **4.69a** was somewhat disappointing as alkyne substrate **4.55a** had undergone smooth cyclisation to indolenine in a respectable yield. The phthalimide protecting group could be interfering with electron transfer from **1.275** by either acting as an acceptor itself or even coming under nucleophilic attack at one of the carbonyl groups. As such the alcohol **4.70** was synthesised without a phthalimide group which could be installed at a later stage if the cyclisation was successful. Substrate **4.70** would provide an interesting challenge for benzimidazole-derived tetraazafulvalene **1.275** as super-electron-donor chemistry had yet to be conducted in the presence of an alcohol functional group. It was possible that the basic super-electron-donor[111] would simply deprotonate the hydroxyl before electron transfer could take place, so 4.0 equivalents of **1.275** were employed in an attempt to promote reduction. Signals in the alkene region that could be assigned to indolenine were absent from the ^{1}H-NMR spectrum of the crude organic worked-up reaction. However aromatic signals that had been visible in the crude reaction mixtures of all previous indole/indolenine cyclisations carried out with **1.275** were visible and in relatively high intensity.

The crude product was purified on silica without the isolation of the desired indole or indolenine but two compounds, **4.71** and **4.72** derived from super-electron-donor **1.275** were isolated.

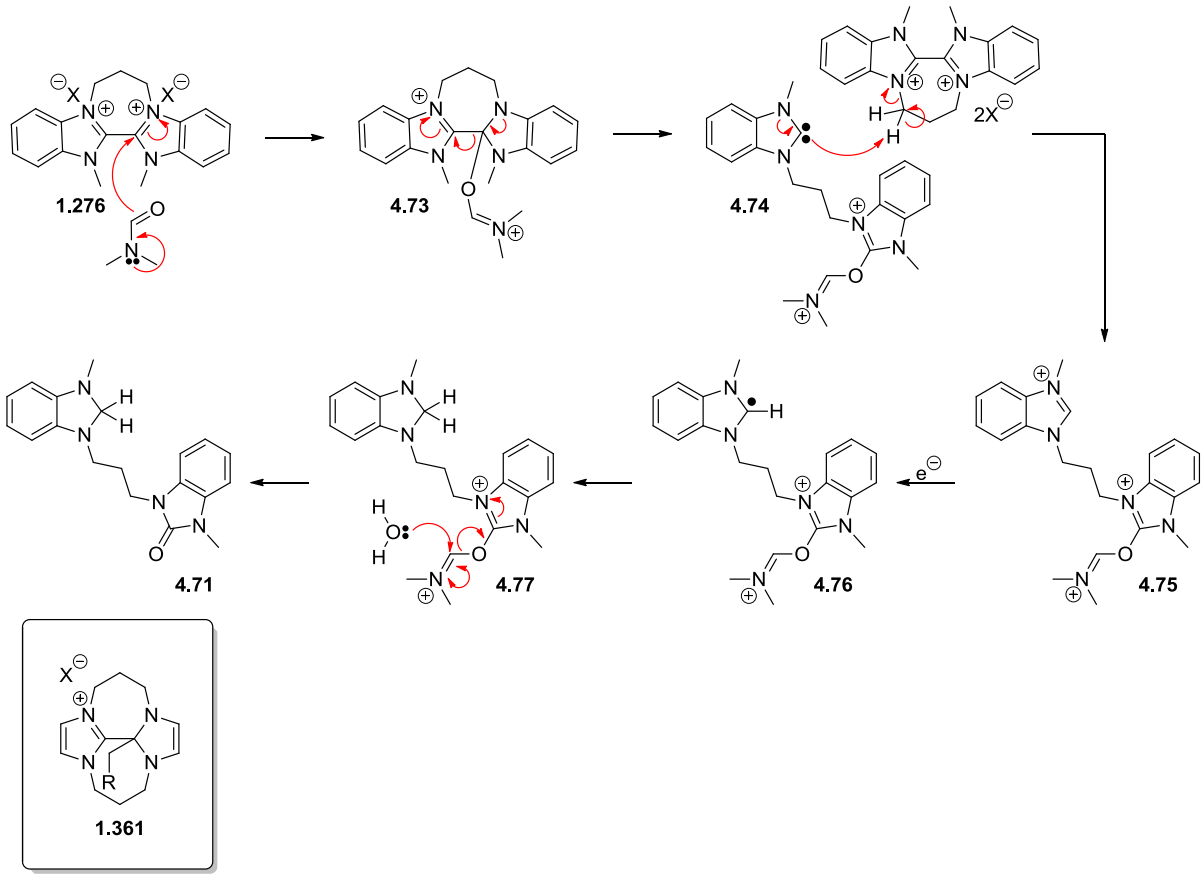
Scheme 4.17 Formation of simultaneously oxidised/reduced **4.71** and oxidised di-urea **4.72**.



Di-urea compounds like **4.72** have already been reported by Thummel[83,85,230] *et al*. and are formed on reaction with benzimidazole-derived tetraazafulvalene with oxygen. In our case **4.72** simply arises on work-up *via* the oxidation of excess **1.275** not consumed in the reaction and is of little further interest. In contrast **4.71** is unusual in that it has been simultaneously oxidised and reduced, one benzimidazole heterocycle forms a urea while the other forms a 2,3-dihydrobenzimidazole.

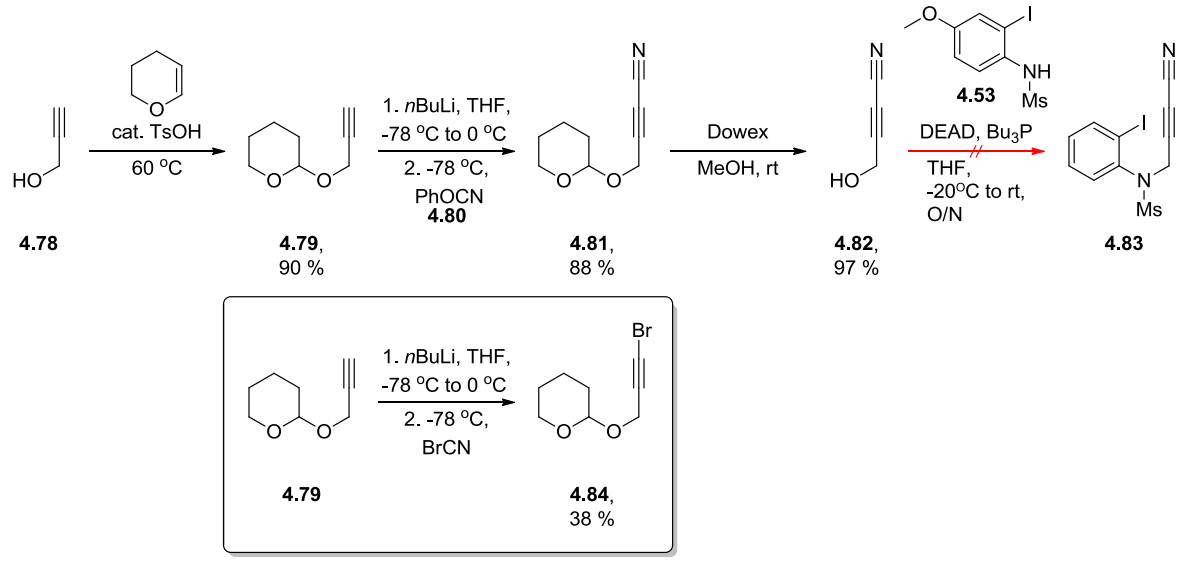
Upon complete oxidative electron transfer tetraazafulvalene **1.275** would form disalt **1.276** which may be susceptible to nucleophilic attack by DMF. There is evidence to suggest cationic species similar to **4.73** (analogous to **1.81**, **Scheme 1.81**) undergo dissociation[105,109] which would a afford benzimidazolium salt and a carbene moiety. Protonation of the carbene would afford dication **4.75** which could be reduced to radical **4.76**; hydrogen abstraction would generate the 2,3-dihydrobenzimidazole in **4.77**, which on work-up affords urea and the final reduced/oxidised species **4.71**.

Scheme 4.18 Proposed reaction mechanism for the formation of oxidised/reduced **4.71**.



Finally an alternative route to melatonin featuring a nitrile masked nitrogen was attempted. Alcohol **4.81**[231,232] can readily be prepared following a known literature procedure *via* the deprotonation of **4.79** and reaction with fresh phenyl cyanate (prepared from phenol and cyanogen bromide[233]). The use of phenyl cyanate is crucial, as lithiation of **4.79** and direct reaction with cyanogen bromide surprisingly afforded the bromoalkyne **4.84**. Unfortunately, having successfully obtained alcohol **4.82**, the Mitsunobu coupling to sulfonamide **4.53** failed and, regrettably, time did not allow for investigation of alternative coupling methods.

Scheme 4.19 Alternative synthesis.



4.5 Chapter Summary

bis-Methylbenzimidazolidene **1.275** successfully effects the reduction of aryl iodides to aryl radicals; subsequent cyclisation onto halo-alkenes or alkynes generates indolenines which are readily tautomerised to the corresponding indoles in good to excellent yield. Indeed indole **4.14** was afforded in higher yield than seen with the previous methods employed within the group (tributyltin hydride[212,213] or 1-ethylpiperidine hypophosphite[213]). However, the application of the methodology to the synthesis of analogues of melatonin precursors afforded poor yields of the desired products. Regrettably, time restrictions have not permitted alternatives to be fully explored. During the course of these investigations, a byproduct derived from benzimidazole-derived tetraazafulvalene **1.275** was successfully identified, *i.e.* **4.71**. Byproduct **4.71** is unusual as it appears that **1.275** has undergone simultaneous oxidation and reduction.

5 CONCLUSIONS AND FUTURE WORK

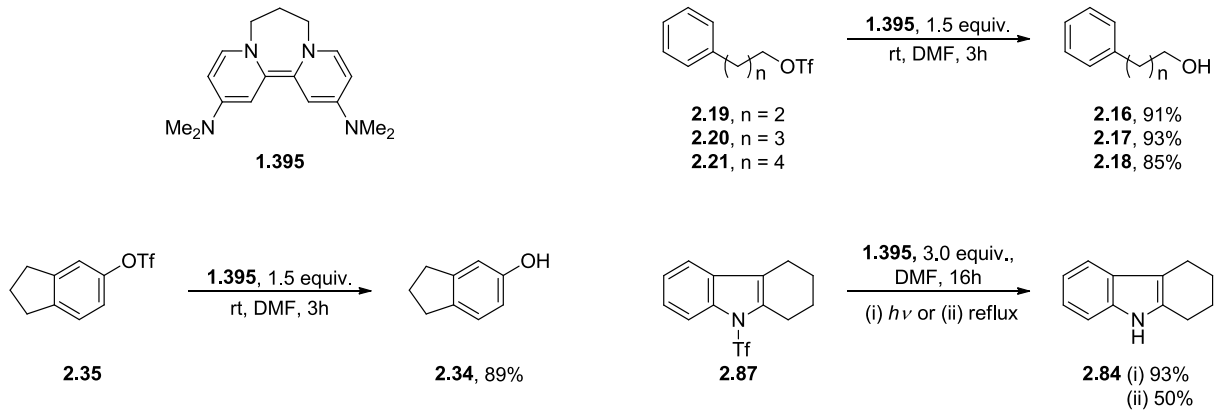
The overarching aims of this research programme were:

- to expand the scope of substrates amenable to functional group transformations *via* reductive electron transfer processes mediated by the known super-electron-donors currently in use within our laboratories.
- to apply electron transfer chemistry of super-electron-donors to the synthesis of small molecules as groundwork for later applications in natural product synthesis.
- to develop new easily synthesised organic compounds capable of powerful reductive electron transfer chemistry.

5.1 The Expanded Substrate Scope of *bis*-Pyridinylidene, Enediamine 1.395

bis-Pyridinylidene donor **1.395** continues to be a useful reagent for effecting chemical transformations. Its reactivity has successfully been extended to the conversion of triflates and activated triflamides to their corresponding alcohols, phenols or amines. In the case of alkyl triflates we believe **1.395** behaves unambiguously as a super-electron-donor, whereas for aryl triflates it is not clear whether electron transfer or nucleophile-electrophile reactions are involved

Scheme 5.1 Triflyl cleavage mediated by *bis*-pyridinylidene donor **1.395**.



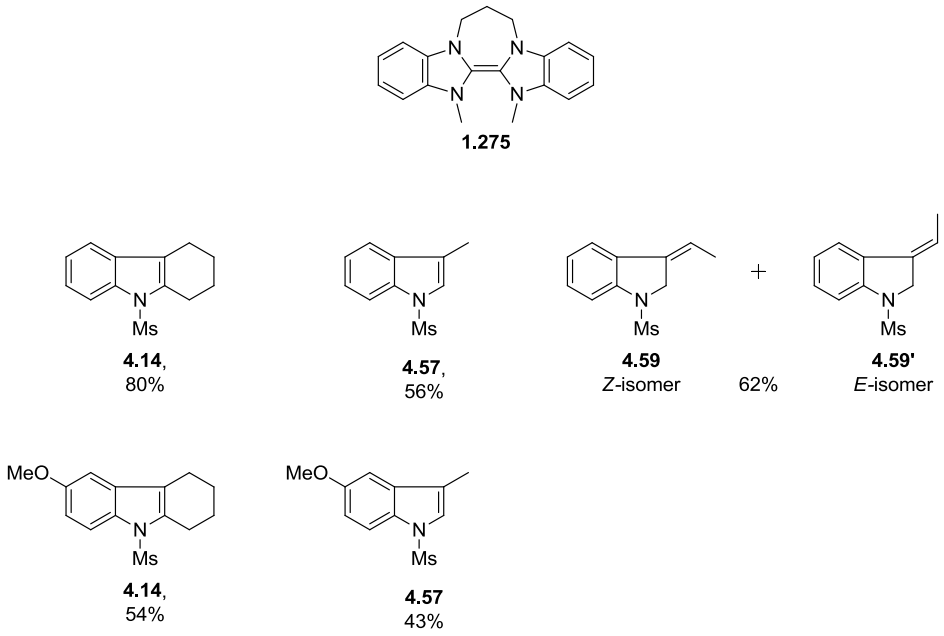
Significant increases in the yield of cleavage of triflamide N-S σ-bonds were observed when the reaction mixture was irradiated with UV-light. Performing reactions with **1.395** under

UV-radiation may be of interest for challenging reductions in the future, indeed it has already proved successful for the reduction of benzenes.[108] Additionally Garnier observed the reduction of aryl bromides at room temperature when irradiated with sunlight, as opposed to UV light.[106] Thus it appears there are great opportunities to explore visible light-mediated electron transfer chemistry with our neutral organic reagents, and future applications may include metal-free Birch reductions.

5.2 Successful Synthesis of Small Molecules

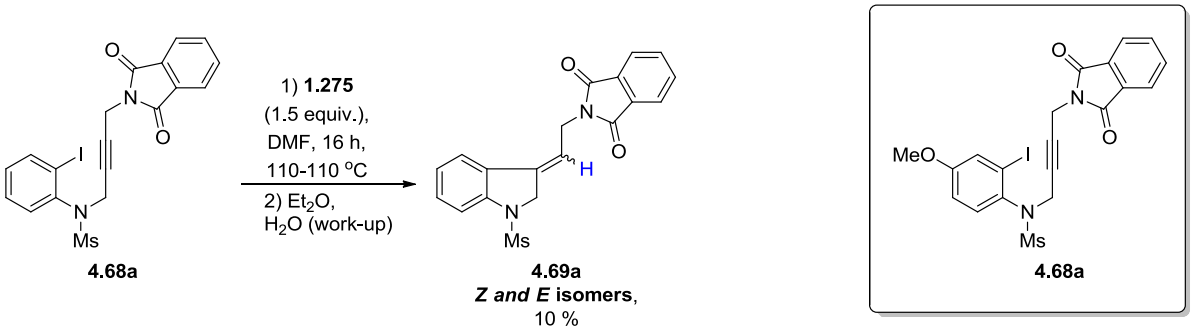
The benzimidazole-derived tetraazafulvalene **1.275** has been shown to successfully reduce aryl iodides to aryl radicals, which subsequently cyclise onto haloalkene and alkyne appendages to afford indolenines. Acid-catalysed tautomerism of the resulting indolenines readily afforded the corresponding indoles.

Figure 5.1 Indole and indolenines afforded by radical cyclisation mediated by benzimidazole-derived tetraazafulvalene **1.275**.



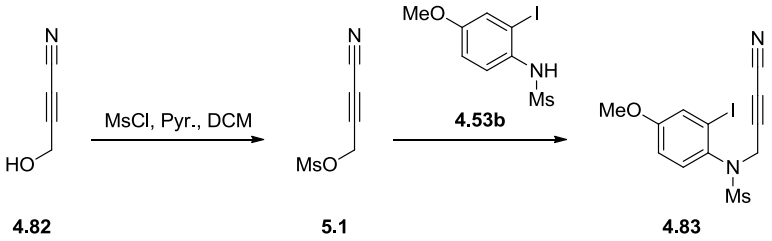
Substrate **4.68a** (**Scheme 5.2**) bearing a phthalamide-protected amine afforded a poor yield of desired indolenine **4.69a**, indicating that the analogous anisidine substrate **4.68b** would also be unlikely to undergo cyclisation to the desired melatonin precursor.

Scheme 5.2 Cyclisation of test substrate **4.68a** with benzimidazole-derived tetraazafulvalene **1.275**.



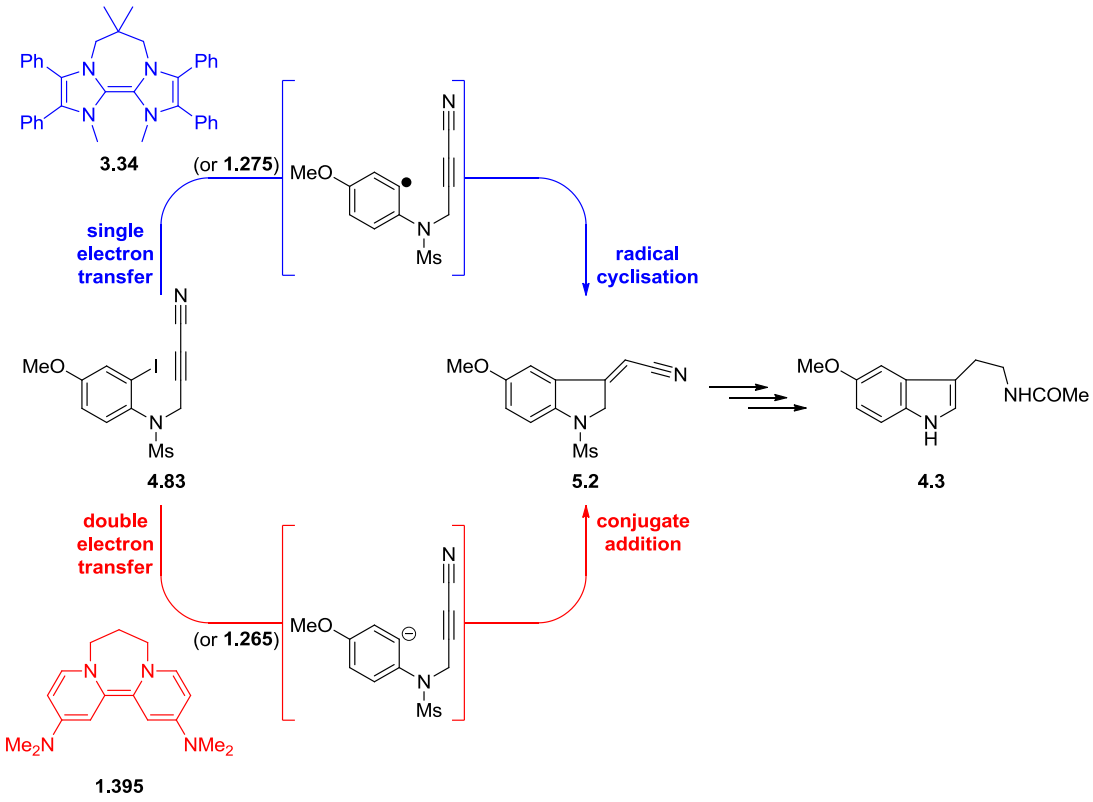
Unfortunately the Mitsunobu coupling of alcohol **4.82** bearing a nitrile protected amine, to sulfonamide **4.53b** failed, and prevented the synthesis of desired substrate **4.83**. However this coupling issue might be simply overcome by converting the alcohol into a sulfonate *e.g.* **5.1** which should readily undergo nucleophilic substitution with **4.53b** under basic conditions (**Scheme 5.3**).

Scheme 5.3 Alternative synthesis of substrate **4.83**.



The nitrile substrate **4.83** may provide a more flexible approach to the synthesis. The cyclisation could possibly be mediated by a radical route using single electron donor **1.275** or new *tetrakis*(phenyl) biimidazolidene **3.34** (blue route **Scheme 5.4**). Alternatively an ionic mechanism might be followed *via* conjugate addition of an aryl anion (red route **Scheme 5.4**) generated by the double electron transfer from either imidazole-derived tetraazafulvalene **1.265** or *bis*-pyridinylidene donor **1.395**. The tautomerisation of indolenine **5.2** would afford the corresponding indole, with reductive acylation and deprotection of the sulfonamide affording the final desired indole natural product, melatonin **4.3**.

Scheme 5.4 Proposed alternative approach to melatonin.



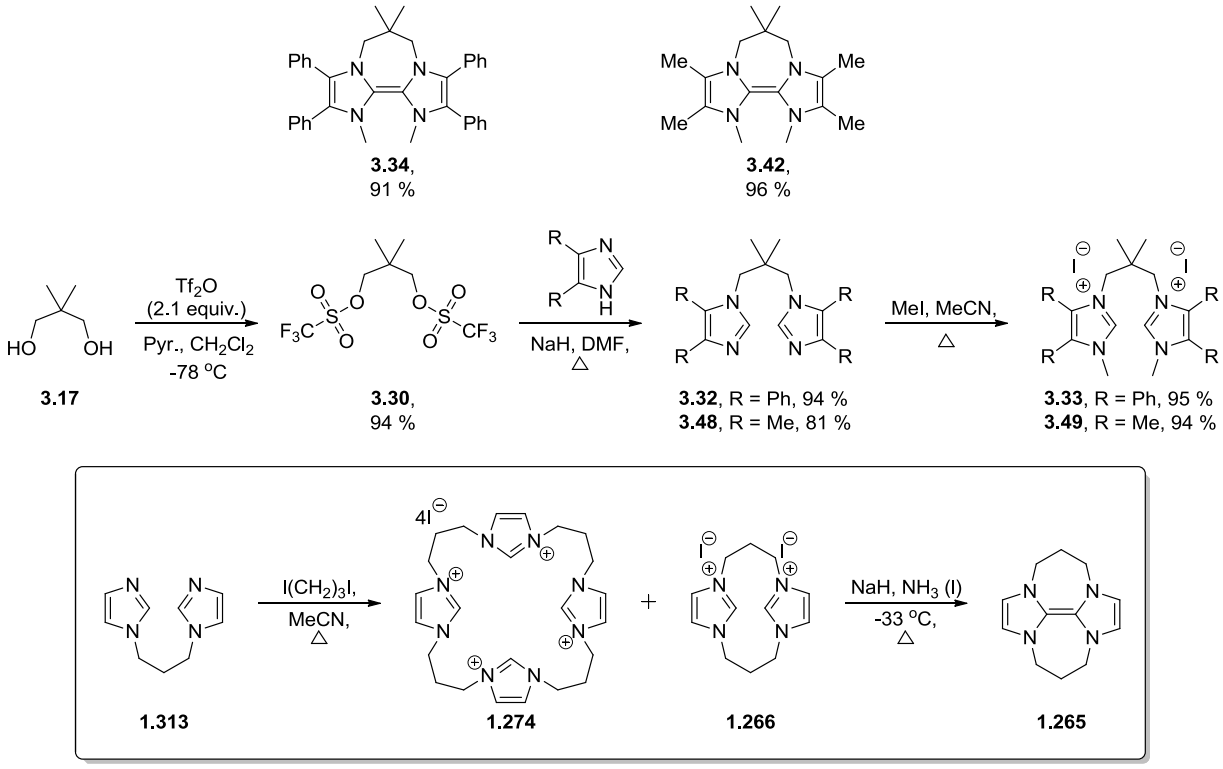
5.3 New Easily Synthesised Super-Electron-Donors:

5.3.1 Synthesis and scope for further insight

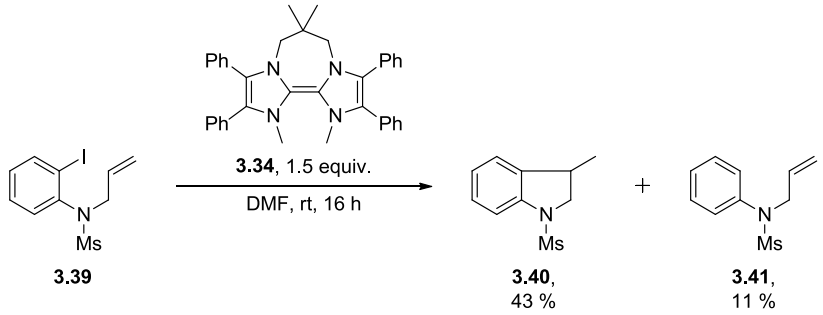
The ease with which *bis*-pyridinylidene donor **1.395** is prepared will ensure that it continues to be a useful reagent for research within our laboratories. In this regard two new possibilities for research now exist with powerful imidazole-derived super-electron-donors, *tetrakis*(phenyl) biimidazolidene **3.34** and *hexakis*(methyl) biimidazolidene **3.42** (**Scheme 5.5**). Both can be prepared in excellent yield from their precursor imidazolium salts **3.33** and **3.49** respectively. This new approach to imidazolium salts **3.33** and **3.49** completely avoids the formation of undesirable macrocycles such as **1.274**, which plague the synthesis of **1.266**.

Tetrakis(phenyl) biimidazolylidene **3.34** is the first definitively characterised super-electron-donor to reduce an aryl iodide to an aryl radical at room temperature, successfully effecting the radical cyclisation of **3.40** to indoline **3.41** (**Scheme 5.6**). The exploration of this chemistry and further electrochemical analysis of tetraazafulvalene **3.34** (and its oxidised salts) are currently being undertaken by other members with our research team.

Scheme 5.5 Formation of new potential super-electron-donors, imidazole-derived tetraazafulvalene, **3.34** and **3.42**.



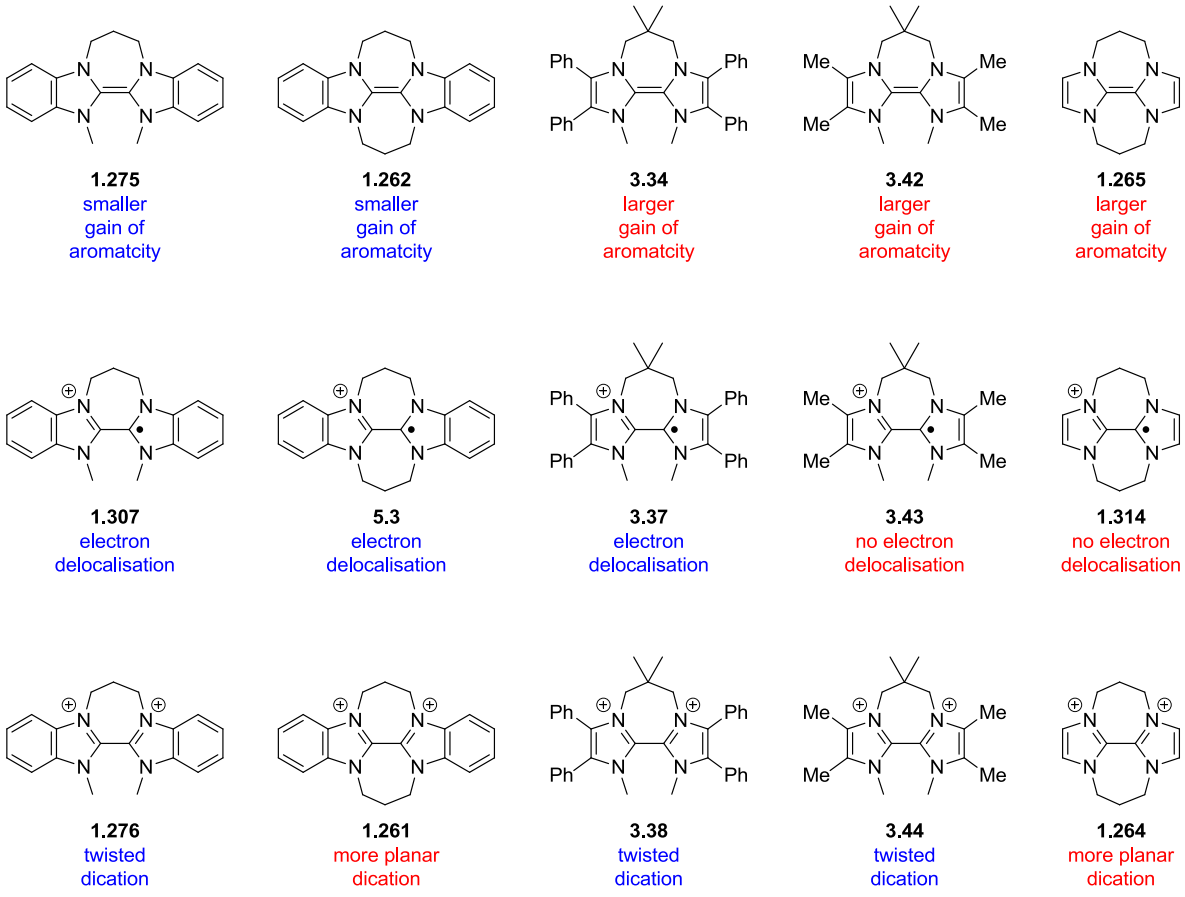
Scheme 5.6 Single electron reduction of aryl iodide **3.39** with tetraazafulvalene **3.34** at room temperature.



Hexakis(methyl) biimidazolylidene **3.42** and *tetrakis*(phenyl) biimidazolylidene **3.34** could provide some insight into the factors that determine whether a super-electron-donor transfers one or two electrons to aryl halides. The reduction potential of super-electron-donors is thought to be influenced by the gain in aromatic stabilisation of the corresponding oxidised dications, the reorganisation energy associated with formation of radical cations and dications and the ability of the radical cation to delocalise the single electron. Varying these factors

could lead to a better understanding of the driving forces for electron donation and enable superior super-electron-donor design. This could be achieved by comparing the reactivity and the electrochemical and spectroscopic properties of tetraazafulvalene **3.34** and **3.42** (and their corresponding radical cations and dication) along with a range of other super-electron-donor reagents.

Figure 5.2 A range of tetraazafulvalenes that could provide further understanding of super-electron-donors. Based on current understanding features expected to favour a single electron transfer are highlighted in blue while features expected to favour a double electron transfer are coloured red.

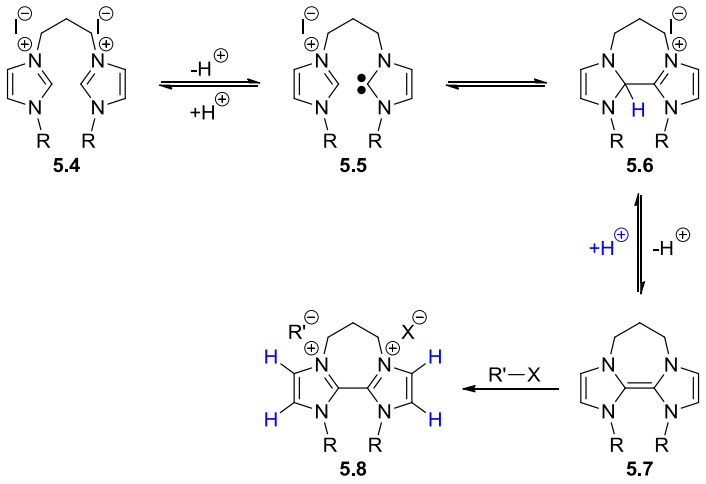


5.3.2 Catalytic application

The catalytic electron transfer from super-electron-donors to substrates is an unmet synthetic challenge. The use of substoichiometric quantities of reductant makes the process highly desirable and the possibility to carry out the chemistry at relatively low redox potentials compared to substrate reduction mediated by direct electrochemistry[234] offers further advantages.

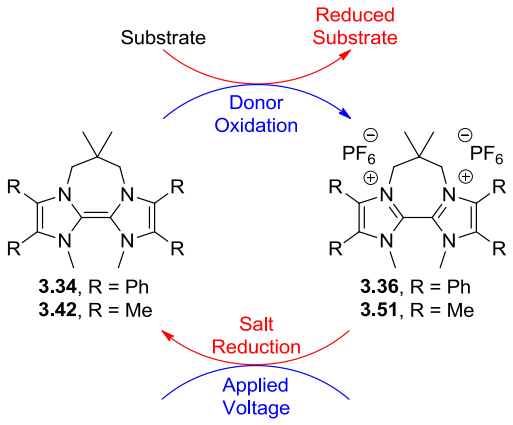
The presence of acidic protons on oxidised imidazolium salts *e.g.* generic **5.8** is thought to impede catalysis. Instead of transferring electrons, the electrochemically generated tetraazafulvalene **5.7** acts as a base, deprotonating **5.8** and thus losing redox activity and dissociating into imidazolium salts **5.5** and **5.4** (as discussed in **Chapter 3**). This establishes a proton-catalysed dissociation with the imidazoliums protonating the desired tetraazafulvalene super-electron-donor, **5.6** and preventing catalytic reduction of the substrate by **5.6**.

Scheme 5.7 Proton-catalysed dissociation.



Therefore the absence of acidic protons in *tetrakis*(phenyl) biimidazolium **3.36** and *hexakis*(methyl) biimidazolium **3.51** should offer significant advantages for electrochemical catalysis and prevent loss of redox activity by this proton-catalysed dissociation.

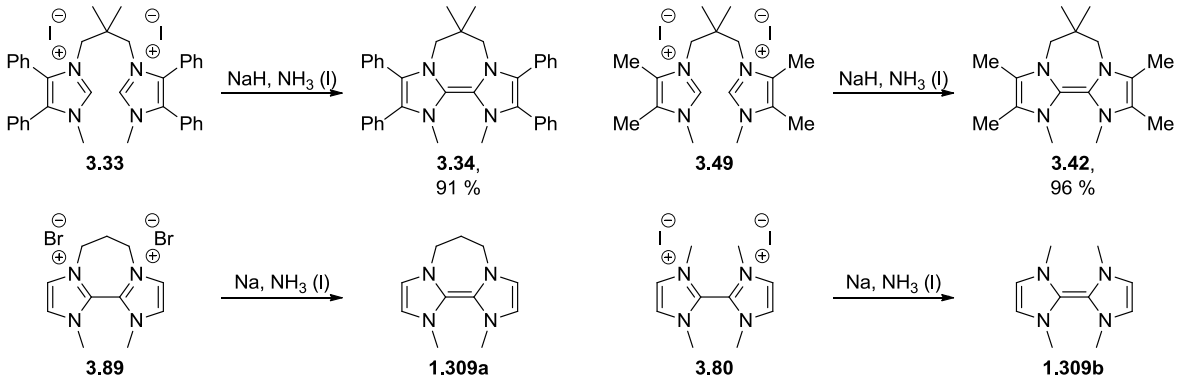
Scheme 5.8 Proposed catalytic generation of super-electron-donors, tetraazafulvalenes **3.34** and **3.42** and their catalytic reduction of substrates.



5.3.3 Closing remarks

The research undertaken during this Ph.D. has been both highly challenging and rewarding. In particular I feel very fortunate to have played a pivotal role in the synthesis of highly reactive tetraazafulvalenes and there is clearly scope for new exciting electron transfer chemistry with tetraazafulvalene **3.34** and **3.42**.

Scheme 5.9 The formation of new tetraazafulvalene **3.34** and **3.42** by deprotonation and the formation of highly reactive *mono*-propylene-tethered tetraazafulvalene **1.309a** and non-tethered **1.309b** Birch reduction.



The observation of tetraazafulvalene-like ^{1}H-NMR signals on deprotonation of simple alkylimidazolium salts suggested that imidazole-derived tetraazafulvalene may be forming and this led to our group successfully isolating the highly reactive *mono*-tethered **1.309a** and non-tethered **1.309b** by the Birch reduction. Until now the chemistry community considered these compounds too unstable to synthesise[3,4,92] and their synthesis is a significant technical achievement.

6 EXPERIMENTAL DETAILS

6.1 General Information

Infra-red spectra were recorded on Perkin Elmer Spectrum One FT-IR spectrometer as films applied on sodium chloride plates or mixed and pressed into potassium bromide disks.
Melting points were recorded using either a Griffin or a Gallenkamp melting point apparatus.
Proton NMR (^{1}H) spectra were recorded on Bruker AV500, AV400 and AV3 spectrometer at 500.16, 400.03 and 400.13, MHz respectively. Carbon NMR (^{13}C) spectra were similarly recorded at 125.75 MHz on Bruker AV500, AV400 and AV3 spectrometer at 125.75, 100.59 and 100.61, MHz respectively. Using a JMOD sequence the ^{13}C-NMR signals were assigned to CH_3, CH_2, CH and C. The NMR experiments were carried out in deuterochloroform ($CDCl_3$), d_6-dimethylsulfoxide (DMSO-d_6), d_3-acetonitrile (MeCN-d_3), d_8-tetrahydrofuran (THF- d_8) and d_6-benzene (C_6D_6). The chemical shifts (δ) are quoted in parts per million (ppm). Multiplicities are abbreviated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br., broad; for the ^{1}H-NMR spectra. The coupling constants (J) are reported in Hertz (Hz). In cases, where superimposition of the signals of two, or more, isomers occurred, the signals have been reported as multiplets (m), unless the coupling constants of each isomer could be ascertained.

High resolution mass spectra were recorded at the EPSRC National Mass Spectrometry Service Centre, Swansea on a LTQ Orbitrap XL micromass instrument using Nanospray Ionisation (NSI), Electrospray Ionisation (ESI), Gas-phase Chromatography (GC) or Atmospheric Pressure Chemical Ionisation (APCI) and masses observed are accurate to within 5 ppm.

All Gas Chromatography Mass Spectrometry (GC-MS) was performed on Thermo Finnigan PolarisQ Ion Trap Mass Spectrometer/Trace GC instrument with ZB-5 column (30 metres), at 1mL/min He gas flow rate and temperature range of 50 to 320 °C with an increment of 10 to 20 °C/min.

Flash chromatography was performed using silica gel 60 (200-400 mesh). Thin layer chromatography (TLC) was performed using Merck silica gel 60 F_{254} precoated aluminium plates and was visualised under Mineralight UVGL-58 lamp (254 nm). The plates were developed with acidic methanolic vanillin solutions or potassium permanganate.

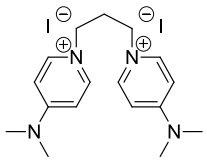
All reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. As required, organic solvents were dried and / or distilled prior to use. Tetrahydrofuran, dichloromethane, hexane, diethyl ether and toluene were dried and deoxygenated with a Pure-Solv 400 solvent purification system by Innovative Technology Inc., U.S.A. and the moisture content of the solvents was analysed using a Karl Fischer coulometer (METTLER TOLEDO DL39).

All reactions requiring anhydrous conditions were performed in flame-dried apparatus under a nitrogen or argon atmosphere. Organic extracts were, in general, dried over anhydrous sodium sulfate (Na_2SO_4).
Glovebox experiments were carried out in an oxygen-free, moisture-free glovebox. Solvents and reagents to be used in glovebox experiments were degassed under reduced pressure for at least 30 min, then purged with argon prior to being sealed. Reagents or reaction mixtures were then transferred to the glovebox port and the port was evacuated then purged with nitrogen at least ten times before transfer into the glovebox. Hydrogenation reactions were carried out on a Cook hydrogenation apparatus (Chas W. Cook and Sons, Ltd., Scientific apparatus makers, model 583-11-71-6).

The IUPAC names of some compounds were obtained using ChemDraw Ultra version 12.0.

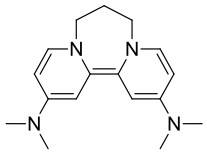
6.2 Chapter 2 Experimental: Cleavage of Trifluoromethanesulfonyl Esters and Amides with *bis*-Pyridinylidene

Synthesis of 1,1'-(propane-1,3-diyl)*bis*(4-(dimethylamino)pyridin-1-ium) iodide, 1.394.[107]



A solution of 4-dimethylaminopyridine (4.58 g, 37.5 mmol, 2.5 eq.) and 1,3-diiodopropane (4.44 g, 15 mmol, 1eq.) in acetonitrile (100 mL) was stirred at reflux overnight, under an inert atmosphere. After cooling, the solid was filtered. Diethyl ether (20 mL) was added to the filtered acetonitrile solution, precipitating more of the solid. The solid was washed with diethyl ether (3 x 30 mL) and dried under vacuum to give 1,3-*bis*(*N'*,*N'*-dimethyl-4-aminopyridinium)propane diiodide **1.394** (7.34 g, 90.6 %) as a white powder; mp 283 - 285°C [Lit. mp 280 - 285 °C][107]; ^{1}H-NMR (400 MHz, DMSO-d_6) δ = 2.36 (2H, quintet, J = 7.2 Hz, CH_2), 3.20 (12H, s, CH_3), 4.27 (4H, t, J = 7.2 Hz, NCH_2), 7.05 (4H, d, J = 7.7 Hz, ArH) and 8.30 ppm (4H, d, J = 7.7 Hz, ArH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ = 31.0 (CH_2), 39.8 (CH_3), 53.6 (CH_2), 107.8 (CH), 141.8 (CH) and 155.8 ppm (C).

Synthesis of N^2,N^2,N^{12},N^{12}-tetramethyl-7,8-dihydro-6*H*-dipyrido[1,2-a:2',1'-c][1,4]diazepine-2,12-diamine, 1.395.[107]

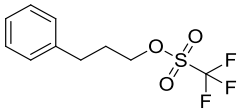


A mixture of 1,3-*bis*(*N*,*N*-dimethyl-4-aminopyridinium)propane diiodide (8.10 g, 15 mmol, 1 eq.) **1.394** and NaH (60% dispersed in mineral oil, 6 g, 150 mmol, 10 eq.) was placed under argon in a Schlenk flask equipped with a dry-ice cooler. The mixture was washed with hexane and the hexane removed. While stirring, ammonia gas was condensed into the flask (70 mL), the mixture was kept under reflux for 4 h and then the ammonia was allowed to evaporate over 3 h, followed by putting under vacuum. The solid was then extracted with diethyl ether, the solvent was removed and the residue dried under vacuum to give *N*,*N*,*N'*,*N'*-tetramethyl-7,8-dihydro-6H-dipyrido[1,2-a;2',1'c][1,4]di-azepine-2,12-diamine **1.395** (3.56 g, 83.4%) as a purple-black, moisture-sensitive and oxygen-sensitive powder; ^{1}H-NMR (400 MHz, C_6D_6) δ = 1.00 (2H, quintet, J = 6.3 Hz), 2.46 (12H, s), 3.03 (4H, t, J = 6.3 Hz), 4.91 (2H, dd, J = 7.5, 2.2 Hz), 5.14 (2H, d, J = 2.2 Hz), 5.64 ppm, (2H, d, J = 7.5 Hz); ^{13}C-NMR

(100 MHz, C_6D_6) δ = 24.5 (CH_2), 40.8 (CH_3), 52.6 (CH_2), 95.8 (CH), 96.2 (CH), 116.0 (C), 138.7 (CH), 143.7 (C).

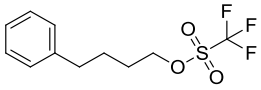
General procedure A - preparation of triflates: Alcohol or phenol starting material (1.0 eq.) was dissolved in dry CH_2Cl_2 (2 mL), pyridine (1.0 eq.) was added and the flask cooled to -78 °C. A solution of trifluoromethanesulfonic anhydride (1.5 eq.) in CH_2Cl_2 (2 mL) at -78 °C was added dropwise to the stirred alcohol or phenol solution. The dry-ice bath was removed and the reaction mixture was allowed to warm to room temperature. Water (10 mL) was then added, followed by CH_2Cl_2 (10 mL). The reaction solution was then washed with further portions of water (3 x 10 mL) and brine (1 x 10 mL), dried over Na_2SO_4 and the solvent was evaporated. The crude organic residue was purified on silica gel eluting with CH_2Cl_2 to afford the corresponding pure trifluoromethanesulfonate ester.

Synthesis of 3-Phenylpropyl-1-trifluoromethanesulfonate, 2.19.[235,236]



3-Phenylpropan-1-ol **2.16** (0.08 mL, 0.6 mmol, 1.0 eq.) was reacted according to procedure **A** to afford 3-phenylpropyl-1-trifluoromethanesulfonate **2.19** as a colourless oil (0.153g, 0.57 mmol, 95%); ν_{max} (thin film)/cm^{-1} 3066, 3030, 2935, 2865, 1498, 1455, 1412, 1246, 1207, 1145, 984, 930, 831, 800, 747, 700, 615, 576 and 519; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.14-2.20 (2H, m, CH_2), 2.78 (2H, t, J = 7.3 Hz, CH_2), 4.54 (2H, t, J = 6.3 Hz, CH_2), 7.20 (2H, d, J = 7.4 Hz, ArH), 7.25 (1H, t, J = 7.4 Hz, ArH) and 7.33 ppm (2H, t, J = 7.4 Hz, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 31.1 (CH_2), 31.5 (CH_2), 76.9 (CH_2), 119.0 (q, J_{CF} = 318 Hz, CF_3), 126.9 (CH), 128.7 (CH), 129.1 (CH) and 139.8 ppm (C). Regrettably the reactive nature of alkyl triflates was not conducive to characterisation by mass spectrometry and data could not be obtained for this compound.

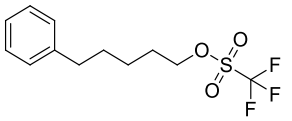
Synthesis of 4-Phenylbutyl-1-trifluoromethanesulfonate, 2.20.



4-Phenylbutan-1-ol **2.17** (150 mg, 1.0 mmol, 1.0 eq.) was reacted according to procedure **A** to afford *4-phenylbutyl*-1-*trifluoromethanesulfonate* **2.20** as a colourless oil (263 mg, 0.93 mmol, 93%) ν_{max} (thin film)/cm^{-1} 3064, 3029, 2944, 2864, 1497, 1454, 1412, 1246, 1206, 1146, 991, 932, 838, 748, 700, 615, 578 and 526; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.75-1.81

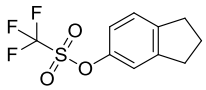
(2H, m, CH_2), 1.84-1.90 (2H, m, CH_2), 2.69 (2H, t, J = 7.4 Hz, CH_2), 4.58 (2H, t, J = 6.3 Hz, CH_2), 7.18 - 7.32 ppm (5H, m, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 27.0 (CH_2), 28.9 (CH_2), 35.2 (CH_2), 77.8 (CH_2), 119.0 (q, J_{CF} = 318 Hz, CF_3), 126.4 (CH), 128.6 (CH), 128.8 (CH) and 141.5 ppm (C); regrettably the reactive nature of alkyl triflates was not conducive to characterisation by mass spectrometry and data could not be obtained for this compound.

Synthesis of 5-Phenylpentyl-1-trifluoromethanesulfonate, 2.21.[237]



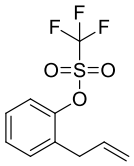
5-Phenylpentan-1-ol **2.18** (164 mg, 1.0 mmol, 1.0 eq.) was reacted according to procedure **A** to afford 5-phenylpentyl-1-trifluoromethanesulfonate **2.21** as a colourless oil (279 mg, 0.94 mmol, 94%) ν_{max} (thin film)/cm^{-1} = 3030, 3934, 2865, 1412, 1247, 1207, 1145, 930, 799, 746 and 616 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.55-1.61 (2H, m, CH_2), 1.66-172 (2H, m, CH_2), 1.84-1.90 (2H, m, CH_2), 2.69 (2H, t, J = 7.4 Hz, CH_2), 4.58 (2H, t, J = 6.3 Hz, CH_2), 7.17 - 7.22 (3H, m, ArH) and 7.26 - 7.31 ppm (2H, m, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 25.0 (CH_2), 29.5 (CH_2), 31.0 (CH_2), 35.9 (CH_2), 77.8 (CH_2), 119.0 (q, J_{CF} = 317 Hz, CF_3), 126.2 (CH), 128.7 (CH), 128.7 (CH) and 142.2 ppm (C). regrettably the reactive nature of alkyl triflates was not conducive to characterisation by mass spectrometry and data could not be obtained for this compound.

Synthesis of 2,3-Dihydro-1*H*-inden-5-yl trifluoromethanesulfonate, 2.35.[238]



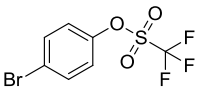
2,3-Dihydro-1*H*-inden-5-ol **2.34** (201 mg, 1.5 mmol, 1.0 eq.) was reacted according to procedure **A** to afford 2,3-dihydro-1*H*-inden-5-yl trifluoromethanesulfonate **2.35** as a colourless oil (359 mg, 1.35 mmol, 90%); [Found: (M)$^+$, 266.0220. $C_{10}H_9F_3O_3S$ requires (M)$^+$, 266.0219]; ν_{max} (thin film)/cm^{-1} = 2957, 2850, 1611, 1593, 1480, 1423, 1250, 1212, 1142, 1100, 933, 870, 852, 608, and 502; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.15 (2H, quintet, J = 7.4 Hz, CH_2), 2.93 (2H, t, J = 7.4 Hz, CH_2), 2.96 (2H, t, J = 7.4 Hz, CH_2), 7.02 (1H, dd, J = 8.2, 2.4 Hz, ArH), 7.12 (1H, d, J = 2.4 Hz, ArH) and 7.25 ppm (1H, d, J = 8.2 Hz, ArH); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 26.1 (CH_2), 32.7 (CH_2), 33.3 (CH_2), 117.7 (CH), 119.1 (q, J_{CF} = 319 Hz, CF_3), 119.2 (CH), 125.8 (CH), 145.0 (C), 147.2 (C) and 148.6 ppm (C).

Synthesis of 2-Allylphenyl trifluoromethanesulfonate, 2.46.[239]



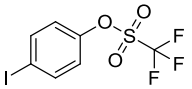
2-Allylphenol **2.45** (268 mg, 2.0 mmol, 1.0 eq.) was reacted according to procedure **A** to afford 2-allylphenyl trifluoromethanesulfonate **2.46** as a colourless oil (493 mg, 1.85 mmol, 93%); [Found: $(M)^+$ 266.0219 $C_{10}H_9F_3O_3S$ requires $(M)^+$, 266.0219]; ν_{max} (thin film)/cm^{-1} = 3085, 2985, 2923, 1642, 1488, 1454, 1422, 1250, 1214, 1140, 1105, 1073, 891, 181, 767 and 606; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.49 (2H, dt, J = 6.6, 1.3 Hz, CH_2), 5.11-5.18 (2H, m, $=CH_2$), 5.89-5.97 (1H, m, =CH) and 7.28-7.36 ppm (4H, m, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 34.3 (CH_2), 117.8 (CH_2), 119.0 (q, J_{CF} = 318 Hz, CF_3), 121.7 (CH), 128.5 (CH), 128.7 (CH), 131.8 (CH), 133.2 (C), 134.9 (CH) and 148.3 ppm (C).

Synthesis of 4-Bromophenyl trifluoromethanesulfonate, 2.48.[156]



4-Bromophenol **2.47** (346 mg, 2.0 mmol, 1.0 eq.) was reacted according to procedure **A** to afford 4-bromophenyl-1-trifluoromethanesulfonate **2.48** as a colourless oil (591 mg, 1.94 mmol, 97%); [Found: $(M)^+$ 303.9011. $C_7H_4BrF_3O_3S$ requires $(M)^+$, 303.9011]; ν_{max} (thin film)/cm^{-1} = 3103, 1481, 1428, 1401, 1251, 1216, 1174, 1141, 1071, 1013, 886, 832, 779, 750, 628, 607 and 525; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.18 (2H, d, J = 9.0 Hz, ArH) and 7.60 ppm (2H, d, J = 9.0 Hz, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 119.0 (q, J_{CF} = 319 Hz, CF_3), 122.4 (C), 123.4 (CH), 133.8 (CH) and 148.8 ppm (C).

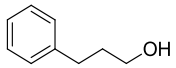
4-Iodophenyl-1-trifluoromethanesulfonate, 2.50.[156,240]



4-Iodophenol **2.49** (201 mg, 1.5 mmol, 1.0 eq.) was reacted according to procedure **A** to afford 4-iodophenyl-1-trifluoromethanesulfonate **2.50** as a colourless oil (482 mg, 1.37 mmol, 91%); [Found $(M)^+$, 351.8871. $C_7H_4F_3IO_3S$ requires $(M)^+$, 351.8872]; IR ν_{max} (thin film) = 3098, 1479, 1428, 1250, 1215, 1141, 940, 886, 829, 747, 606 and 522 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.05 (2H, d, J = 8.8 Hz, ArH) and 7.78 ppm (2H, d, J = 8.8 Hz, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 93.5 (C), 119.0 (q, J_{CF} = 319 Hz, CF_3), 123.7 (CH), 139.8 (CH) and 149.8 ppm (C).

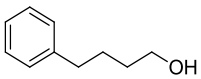
General procedure B - reductions of triflates: *bis*-pyridinylidene donor **1.395** (128 mg, 0.45 mmol, 1.5 eq.) was dissolved in degassed DMF (2 mL) in a glove-box. This solution was directly pipetted onto the dry and degassed selected substrate (0.3 mmol, 1.0 eq.). The mixture was left to stir for 2 h at ambient temperature, then added to water (75 mL), before extracting with diethyl ether (4 x 50 mL). The combined organic layers were then washed with water (2 x 50 mL), brine (50 mL) and dried over Na_2SO_4. The crude organic residue, obtained after evaporation under reduced pressure, was eluting with ethyl acetate on silica gel (unless otherwise stated), to afford the pure corresponding products as reported.

Synthesis of 3-Phenylpropan-1-ol, 2.16.[241]



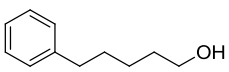
3-Phenylpropyl-1-trifluoromethanesulfonate **2.19** (81 mg, 0.3 mmol, 1.0 eq.), was reacted according to procedure **B** to afford 3-phenylpropan-1-ol **2.16** as a colourless oil, (37 mg, 0.27 mmol, 90%); ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.62 (s, OH), 1.89-1.95 (2H, m, CH_2), 2.72 (2H, t, J = 7.7 Hz, CH_2), 3.70 (2H, t, J = 6.5 Hz, CH_2), 7.20-7.23 (3H, m, ArH) and 7.31 ppm (2H, t, J = 7.4, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 32.4 (CH_2), 34.5 (CH_2), 62.6 (CH_2), 126.2 (CH), 128.7 (CH), 128.8 (CH) and 142.1 ppm (C).

Synthesis of 4-Phenylbutan-1-ol, 2.17.[241]



4-Phenylbutyl-1-trifluoromethanesulfonate **2.20** (85 mg, 0.3 mmol, 1.0 eq.), was reacted according to procedure **B** to afford 4-phenylbutan-1-ol **2.17** as a colourless oil, (41 mg, 0.28 mmol, 91%); ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.60-1.65 (2H, m, CH_2), 1.69-1.75 (2H, m, CH_2), 2.66 (2H, t, J = 7.6 Hz, CH_2), 3.68 (2H, t, J = 7.6 Hz, CH_2), 7.18-7.20 (3H, m, ArH) and 7.27-7.31 ppm (2H, m, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 27.8 (CH_2), 32.6 (CH_2), 36.0 (CH_2), 63.2 (CH_2), 126.1 (CH), 128.6 (CH), 128.7 (CH) and 142.6 ppm (C).

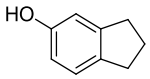
Synthesis of 5-Phenylpentan-1-ol, 2.18.[241]



5-Phenylpentyl-1-trifluoromethanesulfonate **2.21** (89 mg, 0.3 mmol, 1.0 eq.), was reacted according to procedure **B** to afford 5-phenylpentan-1-ol **2.18** as a colourless oil, (42 mg, 0.26 mmol, 85%); ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.39-1.45 (2H, m, CH_2), 1.59-1.64 (2H, m, CH_2), 1.65-1.70 (2H, m, CH_2), 2.64 (2H, t, J = 7.7 Hz, CH_2), 3.65 (2H, t, J = 6.6 Hz, CH_2),

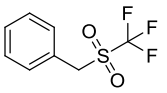
7.18-7.12 (3H, m, ArH) and 7.27-7.30 ppm (2H, m, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 25.7 (CH_2), 31.6 (CH_2), 33.0 (CH_2), 36.2 (CH_2), 63.3 (CH_2), 126.0 (CH), 128.6 (CH), 128.7 (CH) and 142.9 ppm (C).

Synthesis of 2,3-Dihydro-1*H*-inden-5-ol, 2.34.[241]



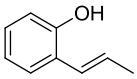
2,3-Dihydro-1*H*-inden-5-yl trifluoromethanesulfonate **2.35** (80 mg, 0.3 mmol, 1.0 eq.), was reacted according to procedure **B** to afford 2,3-dihydro-1*H*-inden-5-ol **2.34** as a colourless oil (36mg, 0.27 mmol, 89%); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.08 (2H, quintet, J = 7.4 Hz, CH_2), 2.84 (2H, t, J = 7.2 Hz, CH_2), 2.87 (2H, t, J = 7.2 Hz, CH_2), 6.61 (1H, dd, J = 8.0, 2.5 Hz, ArH), 6.72 (1H, d, J = 2.0 Hz, ArH) and 7.08 ppm (1H, d, J = 8.0 Hz, ArH); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 26.2 (CH_2), 32.3 (CH_2), 33.4 (CH_2), 111.7 (CH), 113.3 (CH), 123.2 (CH), 136.7 (C), 146.4 (C) and 154.5 ppm (C).

Synthesis of (Trifluoromethylsulfonyl)methylbenzene, 2.44.[242,243]



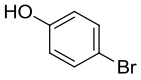
bis-Pyridinylidene donor **1.395** (128 mg, 0.45 mmol, 1.5 eq.) was dissolved in degassed DMF (2 mL) in a glovebox. This solution was directly pipetted onto the dry and degassed 2,3-dihydro-1*H*-inden-5-yl trifluoromethanesulfonate **2.35** (80 mg, 0.3 mmol, 1.0 eq.). The mixture was left to stir for 2 h at ambient temperature, before benzyl bromide (308 mg, 1.8 mmol, 4.0 eq.) was added to the reaction mixture and stirred overnight. The reaction vessel was sealed and removed to a fumehood and water (75 mL) added, before extraction with diethyl ether (5 x 50 mL). The combined organic layers were then washed with water (2 x 50 mL), brine (50 mL) and dried over Na_2SO_4. The crude organic product obtained after evaporation under reduced pressure was purified by column chromatography to give (trifluoromethylsulfonyl)-methylbenzene **2.44** as a white crystalline solid (61 mg, 274 mmol, 91%); mp 100-101 °C [Lit. mp 104 °C]; Found $(M)^+$, 224.0114. $C_8H_7F_3O_2S$ requires $(M)^+$, 224.0113. ν_{max} (KBr)/cm^{-1} = 3007, 2953, 1625, 1494, 1459, 1361, 1202, 1120, 774, 720, 697, 634, 525 and 507 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 4.49 (2H, s, CH_2) and 7.43-7.48 ppm (5H, m, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 56.5 (CH_2), 120.1 (q, J_{CF} = 326 Hz, CF_3), 123.5 (C), 129.6 (CH), 130.4 (CH) and 131.6 ppm (CH).

Synthesis of 2-(Prop-1-enyl)phenol, 2.45'.[244]



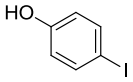
2-Allylphenyl trifluoromethanesulfonate **2.46** (80 mg, 0.3 mmol, 1.0 eq.), was reacted according to procedure **B** to afford 2-(prop-1-enyl)phenol **2.45** as a colourless oil, (38mg, 0.286 mmol, 95%); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.93 (3H, dd, J = 6.6, 1.7 Hz, CH_3), 4.96 (s, OH), 6.23 (1H, dq, J = 15.9, 6.6 Hz, =CH), 6.59-6.63 (1H, m, =CH), 6.81 (1H, dd, J = 8.0, 1.0 Hz, ArH), 6.91 (1H, td, J = 7.7, 7.4, 1.0 Hz, ArH), 7.12 (1H, td, J = 8.0, 7.4, 1.6 Hz, ArH) and 7.32 ppm (1H, dd, J = 7.7, 1.6 Hz, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 19.3 (CH_3), 116.0 (CH), 121.2 (CH), 125.4 (C), 125.7 (CH), 127.7 (CH), 128.3 (CH), 128.7 (CH) and 152.7 (C).

Synthesis of 4-Bromophenol, 2.47.[241]



4-Bromophenyl-1-trifluoromethanesulfonate **2.48** (92 mg, 0.3 mmol, 1.0 eq.), was reacted according to procedure **B** to afford 4-bromophenol **2.47** as a colourless crystalline solid, (44mg, 0.252 mmol, 84%); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.69 (s, OH), 6.73 (d, J = 8.9 Hz, 2H) and 7.35 ppm (d, J = 8.9 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 113.3 (C), 117.5 (CH), 132.8 (CH) and 155.0 ppm (C).

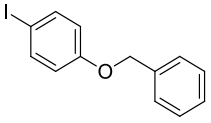
Synthesis of 4-Iodophenol, 2.49.[241]

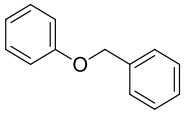


In a glovebox *bis*-pyridinylidene donor **1.395** (85 mg, 0.3 mmol, 1.5 eq.) was dissolved in degassed DMF (5 mL) and sealed in 10 mL round-bottomed flask with a septum and parafilm. Similarly, 4-iodophenyl-1-trifluoromethanesulfonate, **2.50** (106 mg, 0.3 mmol, 1.0 eq.) was weighed out into a 20 mL round-bottomed flask and dissolved in 5 mL degassed DMF (5 mL) before being sealed with a septum and parafilm. The sealed reaction vessels were removed to a fumehood, the 4-iodophenyl-1-trifluoromethanesulfonate solution was cooled to -78 °C under a flow of argon. The solution of DMAP donor **1.395** was transferred to the solution of 4-iodophenyl-1-trifluoromethanesulfonate **2.50** dropwise *via* a cannula. The mixture was warmed to -20 °C and stirred for 2 h, before being quenched with water (10 mL). Additional water (65 mL) was added to reaction mixture in a separating funnel and the aqueous mixture was extracted with diethyl ether (4 x 50 mL). The combined organic extracts

were then washed with water (2 x 50 mL), brine (50 mL) and dried over Na_2SO_4. Evaporation *in vacuo* yielded a crude organic product which was purified on silica gel eluting with 30% hexane in CH_2Cl_2 to afford 4-iodophenol **2.49**, as a white crystalline solid (20 mg, 0.09 mmol, 30%); ν_{max} (KBr)/cm^{-1} = 3007, 2953, 1625, 1495, 1458, 1361, 1203, 1120, 775, 720, 697, 634, 525 and 506; ^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 6.65 (2H, d, J = 8.8 Hz, ArH) and 7.49 ppm (2H, d, J = 8.8 Hz, ArH); ^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 81.5 (C), 119.1 (CH), 138.8 (CH) and 158.2 ppm (C).

Synthesis of 1-(benzyloxy)-4-iodobenzene 2.56[240,245] **and benzyloxybenzene 2.57.**[246,247]

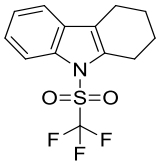




In a glovebox *bis*-pyridinylidene donor **1.395** (284 mg, 1.0 mmol, 1.0 eq.) was dissolved in degassed DMF (10 mL) in and sealed in a 25 mL round-bottomed flask with a septum and parafilm. Similarly, 4-iodophenyl-1-trifluoromethanesulfonate, **2.50** (352 mg, 1.0 mmol, 1.0 eq.) was weighed out into a 50 mL round-bottomed flask and dissolved in degassed DMF (10 mL) before being sealed with a septum and parafilm. The sealed reaction vessels were removed to a fumehood and the 4-iodophenyl-1-trifluoromethanesulfonate solution was cooled to -78 °C under a flow of argon. The solution of DMAP donor **1.395** was transferred to the solution of 4-iodophenyl-1-trifluoromethanesulfonate **2.50** dropwise *via* a cannula. The mixture was warmed to room temperature, before benzyl bromide (513 mg, 3.0 mmol, 3.0 eq.) was added *via* a syringe. After 3 h the reaction quenched with water (20 mL). Additional water (65 mL) was added to the reaction mixture in a separating funnel, and the aqueous mixture was extracted with diethyl ether (50 mL and 4 x 50 mL). The combined organic extracts were then washed with water (2 x 50 mL), brine (50 mL) and dried over Na_2SO_4. Evaporation *in vacuo* yielded crude organic products purified by column chromatography on silica gel eluting with ethyl acetate/hexane (50:50) to afford 1-(benzyloxy)-4-iodobenzene **2.56** as a colourless crystalline solid (47 mg, 0.15 mmol, 15%); mp 61-63 °C (Lit. mp 61-62 °C)[245]; ν_{max} (KBr)/cm^{-1} = 3030, 2906, 2860, 1582, 1568, 1485, 1463, 1454, 1400, 1381, 1282, 1243, 1174, 1115, 824, 800, 745, 697, 644 and 504; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.05 (2H, s, CH_2), 6.77 (2H, d, J = 8.9, ArH), 7.32-7.36 (1H, m, ArH), 7.38-7.43 (4H, m, ArH) and 7.57 ppm (2H, d, J = 8.9, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 70.4 (CH_2), 83.4 (C), 117.7 (CH), 127.8 (CH), 128.5 (CH), 129.0 (CH), 136.9 (C), 138.6 (CH) and 159.0 ppm (C) and benzyloxybenzene **2.57** as a white solid (25 mg, 0.14 mmol, 14%); mp 39-40 °C (Lit. 39-40 °C)[246]; ν_{max} (KBr)/cm^{-1} = 3056, 3034, 2907, 2866, 1599, 1585, 1497, 1468, 1455, 1377,

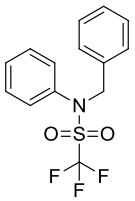
1300, 1246, 1171, 1078, 1029, 1012, 991, 916, 856, 801, 744, 696, 629 and 515; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.08 (2H, s, ArH), 6.96-7.00 (3H, m, ArH), 7.28-7.35 (3H, m, ArH), 7.38-7.41 (2H, m, ArH) and 7.44-7.46 ppm (2H, m, ArH); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 70.3 (CH_2), 115.2 (CH), 121.3 (CH), 127.8 (CH), 128.3 (CH), 128.9 (CH), 129.8 (CH), 137.5 (C) and 159.2 ppm (C).

Synthesis of 9-(Trifluoromethylsulfonyl)-2,3,4,9-tetrahydro-1H-carbazole, 2.87.



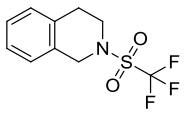
2,3,4,9-Tetrahydro-1*H*-carbazole **2.84** (685 mg, 4.0 mmol, 1.0 eq.) was dissolved in dry THF (10 mL). The reaction vessel was cooled to -78 °C before *n*-butyllithium was added dropwise (4.4 mmol, 1.1 eq.) and stirred for 30 min. Trifluoromethanesulfonic anhydride (1.24 g, 4.4 mmol, 1.1 eq.) in CH_2Cl_2 (10 mL) at -78 °C, under argon was added dropwise to the stirred solution of 2,3,4,9-tetrahydro-1*H*-carbazole. On complete addition, the reaction vessel was warmed to room temperature and stirred overnight. The reaction mixture was quenched with water (25 mL) and washed with further portions of water (3 x 25 mL) and brine (1 x 20 mL) before being dried over Na_2SO_4 and evaporated. The crude organic residue was purified on silica gel, (10% ethyl acetate in hexane), to afford 9-(trifluoromethylsulfonyl)-2,3,4,9-tetrahydro-1Hcarbazole **2.87** as colourless crystals (413 mg, 1.36 mmol 34%); mp = 60-61 °C; [Found: $(M)^+$, 303.0533. $C_{13}H_{12}F_3NO_2S$ requires $(M)^+$, 303.0535]; ν_{max} (KBr)/cm^{-1} = 3437, 2944, 1441, 1412, 1224, 1196, 1151, 1116, and 609; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.86-1.95 (4H, m, CH_2), 2.66-2.69 (2H, m, CH_2), 2.86-2.96 (2H, m, CH_2), 7.30-7.35 (2H, m, ArH), 7.43-7.45 (1H, m, ArH) and 7.93-7.94 ppm (1H, m, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 21.5 (CH_2), 22.2 (CH_2), 23.4 (CH_2), 24.3 (CH_2), 114.6 (CH), 118.8 (CH), 119.3 (q, J_{CF} = 322.7 Hz, CF_3), 121.1 (C), 125.1 (CH), 125.2 (CH), 130.9 (C), 136.1 (C) and 136.5 ppm (C).

Synthesis of *N*-Benzyl-*N*-phenyl-1,1,1-trifluoromethanesulfonamide, 2.88.[185]



N-Benzylaniline **2.85** (277 mg, 1.51 mmol, 1.0 equiv.) in dry CH_2Cl_2 (5 mL) was cooled to -78 °C under an inert atmosphere and triethylamine (202 mg, 2.0 mmol, 1.3 eq.) was added. Trifluoromethanesulfonic anhydride (846 mg, 3.0 mmol, 2.0 eq.) in dry CH_2Cl_2 (5 mL) was added, cooled to -78 °C, to the stirred *N*-benzylaniline solution. The cooling was then removed and the reaction mixture was stirred for a further 16 h. It was then quenched with water (15 mL) and washed with further portions of water (4 x 15 mL) before drying and evaporation. The crude organic residue was purified on silica gel, [10% ethyl acetate in hexane], to afford *N*-benzyl-1,1,1-trifluoro-*N*-phenylmethane-sulfonamide **2.88** as pale yellow crystals, (318 mg, 1.00 mmol, 66%); mp = 76-77 °C (Lit. 78-79 °C)[186]; [Found $(M)^+$, 315.0535. $C_{14}H_{12}F_3NO_2S$ requires $(M)^+$, 315.0531]. ν_{max} (KBr)/cm^{-1} = 3064, 3032, 2925, 2854, 1595, 1493, 1456, 1391, 1229, 1207, 1141, 1086, 1060, 882, 714, 695, 601, 575 and 524 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 4.92 (2H, s, CH_2), 7.13-7.19 (4H, m, ArH) and 7.30-7.34 ppm (6H, m, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 57.7 (CH_2), 120.9 (q, J_{CF} = 321 Hz, CF_3), 128.8 (CH), 129.0 (CH), 129.35 (CH), 129.5 (CH), 129.7 (CH), 129.7 (CH), 134.6 (C) and 136.9 ppm (C).

Synthesis of 2-(Trifluoromethylsulfonyl)-1,2,3,4-tetrahydroisoquinoline, 2.89.[248]

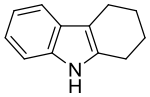


1,2,3,4-Tetrahydroisoquinoline **2.86** (466 mg, 3.5 mmol, 1.0 eq.) was weighed into a clean oven-dried round-bottomed flask equipped with stirrer bar, before being sealed with a septum and parafilm. The sealed vessel was placed under a flow of argon before being diluted with dry CH_2Cl_2 (10 mL). The reaction vessel was cooled to -78 °C and triethylamine (354 mg, 3.5 mmol, 1.0 eq.) was added. Into a second oven-dried sealed round-bottomed flask dry CH_2Cl_2 (10 mL) was cooled to -78 °C under argon. Trifluoromethanesulfonic anhydride (1.48 g, 5.25 mmol, 1.5 eq.) was added to the second reaction vessel at -78 °C before being transferred dropwise to the stirred 1,2,3,4-tetrahydroisoquinoline solution. On completion of addition, the reaction vessel was removed from the dry-ice bath and stirred for a further 2 h. The reaction mixture was quenched with water (25 mL) and washed with further portions of water (4 x 25 mL) before being dried over Na_2SO_4 and concentrated under reduced pressure. The crude organic residue was purified on silica gel, eluting with 10% ethyl acetate in hexane, to afford to afford 2-(trifluoromethylsulfonyl)-1,2,3,4-tetrahydroisoquinoline **2.89** as brown/orange crystalline solid (703 mg, 2.65 mmol, 76%); mp = 193-195 °C (Lit. 192-193 °C)[248]; [Found $(M)^+$, 265.0379. $C_{10}H_{10}F_3NO_2S$ requires $(M)^+$, 265.0379]; ν_{max} (KBr)/cm^{-1}

= 3437, 2949, 1390, 1227, 1190, 1115 and 1026 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.00 (2H, t, J = 5.7 Hz, CH_2), 3.78 (2H, br. s, CH_2), 4.68 (2H, br. s, CH_2), 7.08-7.11 (1H, m, ArH), 7.16-7.20 (1H, m, ArH) and 7.23-7.26 ppm (2H, m, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 29.2 (CH_2), 44.8 (CH_2), 47.9 (CH_2), 120 (q, J_{CF} = 322 Hz, CF_3),126.4 (CH), 127.2 (CH), 127.7 (CH), 129.5 (CH), 131.0 (C) and 132.9 ppm (C).

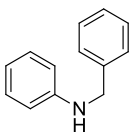
General procedure C – UV reductions of triflamides: *bis*-pyridinylidene donor **1.395** (256 mg, 0.90 mmol, 3.0 eq.) was dissolved in degassed DMF (2 mL) in a glovebox. This solution was directly pipetted onto the dry and degassed selected substrate (0.3 mmol, 1 eq.). The mixture was left to stir overnight under irradiation with UV light, then added to water (75 mL), and extracted with diethyl ether (50 mL and 4 x 50 mL). The combined organic layers were then washed with water (2 x 50 mL), brine (50 mL) and dried over Na_2SO_4. The crude organic residue obtained after evaporation under reduced pressure was purified by column chromatography to give the corresponding products as reported.

Synthesis of 2,3,4,9-Tetrahydro-1*H*-carbazole, 2.84 by general procedure C.[241]



9-(Trifluoromethylsulfonyl)-2,3,4,9-tetrahydro-1*H*-carbazole **2.87** (91 mg, 0.3 mmol, 1.0 eq.) was reacted according to procedure **C**, to afford 2,3,4,9-tetrahydro-1*H*-carbazole **2.84** as a white solid, (48 mg, 0.280 mmol, 93%); ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.87-1.97 (4H, m, CH_2), 2.72-2.76 (4H, m, CH_2), 7.09 (1H, td, 7.4, 1.2 Hz, ArH), 7.13 (1H, td, 7.4, 1.4 Hz, ArH), 7.28-7.30 (1H, m, ArH), 7.47-7.49 (1H, m, ArH) and 7.65 ppm (1H, br. s, NH); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 21.2 (CH_2), 23.6 (CH_2), 23.6 (CH_2), 23.6 (CH_2), 110.5 (C), 110.7 (CH), 118.1 (CH), 119.4 (CH), 121.3 (CH), 128.2 ppm (C), 134.4 (C) and 136.0 ppm (C).

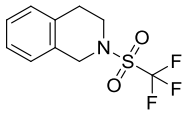
Synthesis of *N*-benzylaniline, 2.85 by general procedure C.[241]



N-Benzyl-1,1,1-trifluoro-*N*-phenylmethanesulfonamide **2.88** (95 mg, 0.3 mmol, 1.0 eq.), was reacted according to procedure **C**, [but irradiating for 2 days] to afford *N*-benzylaniline **2.85** as a white/yellow crystalline solid (29 mg, 0.16 mmol, 53%); ^{1}H-NMR (400 MHz, $CDCl_3$): ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.35 (2H, s, CH_2), 6.67 (2H, d, J = 7.8 Hz, ArH), 6.74 (1H,

t, *J* = 7.3 Hz, ArH), 7.17-7.22 (2H, m, ArH), 7.28-7.31 (1H, m, ArH) and 7.40-7.41 ppm (4H, m, ArH); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 48.7 (CH_2), 113.2 (CH), 117.9 (CH), 127.6 (CH), 127.9 (CH), 129.0 (CH), 129.6 (CH), 139.8 (C) and 148.5 ppm (C).

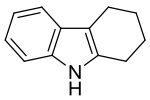
Unsuccessful reduction of 2-(Trifluoromethylsulfonyl)-1,2,3,4-tetrahydroisoquinoline, 2.89.



Reduction of 2-(Trifluoromethylsulfonyl)-1,2,3,4-tetrahydroisoquinoline **2.89** (79.0 mg, 0.300 mmol, 1.0 eq.) as per procedure **C** afforded only recovery of starting material (77.0 mg, 0.291 mg, 97%) ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.00 (2H, t, *J* = 5.7 Hz, CH_2), 3.78 (2H, br. s, CH_2), 4.68 (2H, br. s, CH_2), 7.08-7.11 (1H, m, ArH), 7.16-7.20 (1H, m, ArH) and 7.23-7.26 ppm (2H, m, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 29.2 (CH_2), 44.8 (CH_2), 47.9 (CH_2), 120 (q, J_{CF} = 322 Hz, CF_3),126.4 (CH), 127.2 (CH), 127.7 (CH), 129.5 (CH), 131.0 (C) and 132.9 ppm (C).

General procedure D – thermal reductions of triflamides: Donor **1.395** (256 mg, 0.90 mmol, 3.0 eq.) was dissolved in degassed DMF (2 ml) in a glovebox. This solution was directly pipetted onto the dry and degassed selected substrate (0.3 mmol, 1 equiv.). The mixture was left to stir at 100 °C for the indicated time. Water (75 ml) was added to the cooled reaction mixture and extracted with diethyl ether (50 ml and 4 x 50 ml). The combined organic layers were then washed with water (2 x 50 ml), brine (50 ml) and dried over Na_2SO_4. The crude organic residue obtained after evaporation under reduced pressure was purified by column chromatography to give the corresponding products as reported.

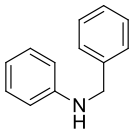
Synthesis of 2,3,4,9-Tetrahydro-1*H*-carbazole, 2.84 by general procedure D.[241]



9-(Trifluoromethylsulfonyl)-2,3,4,9-tetrahydro-1*H*-carbazole **2.87** (91 mg, 0.3 mmol, 1.0 eq.) was reacted according to procedure **D**, to afford 2,3,4,9-tetrahydro-1*H*-carbazole **2.84** as a white solid, (27 mg, 0.16 mmol, 53%); ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.87-1.97 (4H, m, CH_2), 2.72-2.76 (4H, m, CH_2), 7.09 (1H, td, 7.4, 1.2 Hz, ArH), 7.13 (1H, td, 7.4, 1.4 Hz, ArH), 7.28-7.30 (1H, m, ArH), 7.47-7.49 (1H, m, ArH) and 7.65 ppm (1H, br. s, NH); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 21.2 (CH_2), 23.6 (CH_2), 23.6 (CH_2), 23.6 (CH_2), 110.5 (C),

110.7 (CH), 118.1 (CH), 119.4 (CH), 121.3 (CH), 128.2 ppm (C), 134.4 (C) and 136.0 ppm (C).

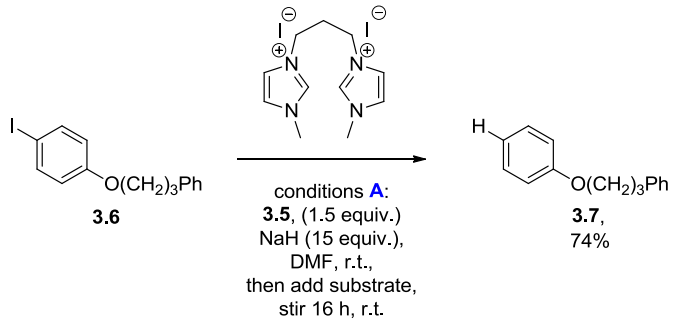
Synthesis of *N*-benzylaniline, 2.85 by general procedure D.[241]



N-Benzyl-1,1,1-trifluoro-*N*-phenylmethanesulfonamide **2.88** (95 mg, 0.3 mmol, 1.0 eq.), was reacted according to procedure **D**, [but irradiating for 2 days] to afford *N*-benzylaniline **2.85** as a white/yellow crystalline solid (22 mg, 0.12 mmol, 40%); ^{1}H-NMR (400 MHz, $CDCl_3$): ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.35 (2H, s, CH_2), 6.67 (2H, d, J = 7.8 Hz, ArH), 6.74 (1H, t, J = 7.3 Hz, ArH), 7.17-7.22 (2H, m, ArH), 7.28-7.31 (1H, m, ArH) and 7.40-7.41 ppm (4H, m, ArH); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 48.7 (CH_2), 113.2 (CH), 117.9 (CH), 127.6 (CH), 127.9 (CH), 129.0 (CH), 129.6 (CH), 139.8 (C) and 148.5 ppm (C).

6.3 Chapter 3 Experimental: Formation of New Highly Reactive Imidazole-Derived Tetraazafulvalenes

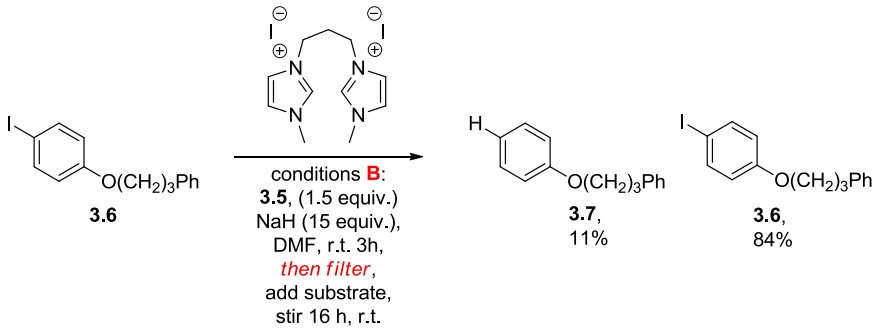
Reduction of 1-iodo-4-(3-phenylpropoxy)benzene 3.6 using 3,3'-(propane-1,3-diyl)*bis*(1-methyl-1H-imidazol-3-ium) 3.5 in presence of excess NaH, conditions A.



Under an inert atmosphere, 3,3'-(propane-1,3-diyl)*bis*(1-methyl-1H-imidazol-3-ium) iodide **3.5** (207 mg, 0.45 mmol, 1.5 eq.) was stirred with sodium hydride (108 mg, 4.5 mmol, 15.0 eq.) in anhydrous DMF (15 mL) at room temperature for 3 h. 1-Iodo-4-(3-phenylpropoxy)benzene **3.6** (101 mg, 0.3 mmol, 1.0 eq.) was added and the mixture stirred for 16 h. The reaction mixture was filtered under reduced pressure, washing excess sodium hydride with anhydrous DMF (4 mL). The organic phase was removed, quenched with distilled water (10 mL) before and diluted with saturated brine (40 mL). The aqueous phase was extracted with diethyl ether (4 x 50 mL), the combined organic layers were washed with

water (3 x 50 mL) and saturated brine (1 x 30 mL), dried over sodium sulfate, filtered and evaporated. The organic residue was redissolved in the minimum volume of solvent (3:2 hexane: CH_2Cl_2) and adsorbed onto a silica column packed in neat hexane, before being eluted with 20 mL portions of solvent (3:2 hexane/ CH_2Cl_2 → 1:1 hexane/ CH_2Cl_2 → neat CH_2Cl_2) to afford pure (3-phenoxy-propyl)benzene **3.7** (50 mg, 0.236 mmol, 74%) The NMR data were in accord with those reported by Garnier;[106] ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 2.15 (2H, m, CH_2), 2.86 (2H, t, J = 7.5 Hz, $PhCH_2$), 4.01 (2H, t, J = 6.3 Hz, OCH_2), 6.93-7.00 (3H, m, ArH) and 7.22-7.35 ppm (7H, m, ArH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 31.1 (CH_2), 32.4 (CH_2), 67.0 (CH_2), 114.8 (CH), 120.8 (CH), 126.1 (CH), 128.6 (CH), 128.7 (CH), 129.6 (CH), 141.8 (C) and 159.3 ppm (C).

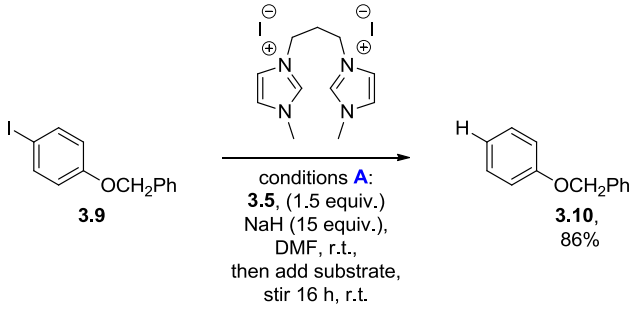
Reduction of 1-iodo-4-(3-phenylpropoxy)benzene 3.6 using 3,3'-(propane-1,3-diyl)*bis*(1-methyl-1H-imidazol-3-ium) 3.5 removal of excess NaH, conditions B.



Under an inert atmosphere 3,3'-(propane-1,3-diyl)*bis*(1-methyl-1H-imidazol-3-ium) iodide **3.5** (207 mg, 0.45 mmol, 1.5 eq.) was stirred with sodium hydride (108 mg, 4.5 mmol, 15.0 eq.) and anhydrous DMF (15 mL) in an oven-dried centrifuge tube at room temperature for 3 h. The contents were then centrifuged, before the organic phase was transferred via cannula, to an argon-purged round-bottomed flask containing 1-iodo-4-(3-phenylpropoxy)benzene **3.6** (101 mg, 0.3 mmol, 1.0 eq.) with stirring. The reaction mixture was stirred for 16 h, quenched with distilled water (10 mL) and diluting with saturated brine (40 mL). The aqueous phase was extracted with diethyl ether (5 x 50 mL), the combined organic was washed with water (3 x 50 mL) and saturated brine (1 x 30 mL), dried over sodium sulfate, filtered and evaporated. The organic residue was adsorbed on to minimum volume of dry silica before packing on silica column packed in neat hexane. The column was eluted with 25 mL of 5% CH_2Cl_2/hexane then 4 x 50 mL CH_2Cl_2/hexane, increasing CH_2Cl_2 to 25% in 5% increments. 1-Iodo-4-(3-phenylpropoxy)benzene **3.6** was recovered as colourless crystals (85 mg, 0.251 mmol, 84%).The NMR spectroscopic data were in accord with those reported by Garnier;[106] ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 2.09-2.16 (2H, m, CH_2), 2.82 (2H, t, J = 7.6 Hz,

$ArCH_2$), 3.94 (2H, t, J = 6.2 Hz, OCH_2), 6.68-6.71 (2H, m, ArH), 7.22-7.24 (3H, m, ArH), 7.30-7.34 (2H, m, ArH) and 7.56-7.59 ppm (2H, m, ArH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 30.9 (CH_2), 32.3 (CH_2), 67.2 (CH_2), 82.8 (C), 117.2 (CH), 126.2 (CH), 128.7 (CH), 128.7 (CH), 138.4 (CH), 141.5 (C) and 159.1 ppm (C) and (3-phenoxypropyl)benzene **3.7** (7 mg, 0.033 mmol, 11%). The NMR spectra were in accord with those reported by Garnier;[106] 1H-NMR (400 MHz, $CDCl_3$) δ = 2.15 (2H, m, CH_2), 2.86 (2H, t, J = 7.5 Hz, $PhCH_2$), 4.01 (2H, t, J = 6.3 Hz, OCH_2), 6.93-7.00 (3H, m, ArH) and 7.22-7.35 ppm (7H, m, ArH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 31.1 (CH_2), 32.4 (CH_2), 67.0 (CH_2), 114.8 (CH), 120.8 (CH), 126.1 (CH), 128.6 (CH), 128.7 (CH), 129.6 (CH), 141.8 (C) and 159.3 ppm (C).

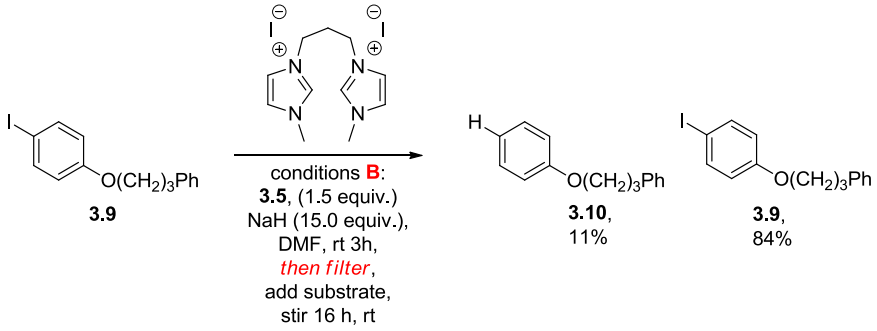
Reduction of 1-iodo-4-(phenylmethoxy)benzene 3.9 using 3,3'-(propane-1,3-diyl)*bis*(1-methyl-1H-imidazol-3-ium) 3.5 in presence of excess NaH, conditions A.



Under inert atmosphere, 3,3'-(propane-1,3-diyl)*bis*(1-methyl-1H-imidazol-3-ium) **3.5** (207 mg, 0.45 mmol, 1.5 eq.) was stirred with sodium hydride (108 mg, 4.5 mmol, 15.0 eq.) in anhydrous DMF (15 mL) at room temperature for 3 h. 1-Iodo-4-(phenylmethoxy)benzene **3.9** (93 mg, 0.3 mmol, 1.0 eq.) was added to the reaction mixture and stirred for 16 h. The reaction mixture was filtered under reduced pressure, washing excess sodium hydride with anhydrous DMF (4.0 mL). The organic phase was removed from the glove-box and the reaction quenched with distilled water (10 mL) before it was diluted with saturated brine (40 mL). The aqueous phase was extracted with diethyl ether (4 x 50 mL), the combined organic was washed with water (3 x 50 mL) and saturated brine (1 x 30 mL), dried over sodium sulfate, filtered and evaporated. The organic residue was adsorbed on to a minimum volume of dry silica before packing on a silica column packed in neat hexane. The column was eluted with 10% ethyl acetate in hexane to afford pure (benzyloxy)benzene **3.10** as a colourless crystalline solid (47 mg, 0.257 mmol, 86%); mp 39-40 °C (Lit. 39-40 °C)[246]; [Found: $(M)^+$ 184.0881 $C_{13}H_{12}O$. $(M)^+$ requires 184.0883]; ν_{max} (KBr)/cm^{-1} = 3056, 3034, 2907, 2866, 1599, 1585, 1497, 1468, 1455, 1377, 1300, 1246, 1171, 1078, 1029, 1012, 991, 916, 856, 801, 744, 696, 629 and 515 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.08 (s, 2H), 6.96-7.01, (m, 3H),

7.28-7.35 (m, 3H), 7.38-7.41 (m, 2H) and 7.44-7.46 (m,2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 70.3 (CH_2), 115.2 (CH), 121.3 (CH), 127.8 (CH), 128.3 (CH), 128.9 (CH), 129.8 (CH), 137.4 (C) and 159.2 (C).

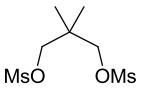
Reduction of 1-iodo-4-(phenylmethoxy)benzene 3.9 using 3,3'-(Propane-1,3-diyl)*bis*(1-methyl-1H-imidazol-3-ium) diiodide 3.5 after removal of excess NaH, conditions B.



3,3'-(Propane-1,3-diyl)*bis*(1-methyl-1H-imidazol-3-ium) diiodide **3.5** (207 mg, 0.45 mmol, 1.5 eq.) was stirred with sodium hydride (108 mg, 4.5 mmol, 15.0 eq.) and anhydrous DMF (15 mL) under the inert atmosphere in an oven-dried centrifuge tube at room temperature for 3 h. The sealed contents were then centrifuged, before the organic phase was transferred via a cannula, to an argon-purged round-bottomed flask containing 1-iodo-4-(phenylmethoxy)benzene **3.9** (93 mg, 0.3 mmol, 1.0 eq.) with stirring. The reaction mixture was stirred for 16 h, quenched with distilled water (10 mL) and diluting with saturated brine (40 mL). The aqueous phase was extracted with diethyl ether (5 x 50 mL), the combined organic layers was washed with water (3 x 50 mL) and saturated brine (1 x 30 mL), dried over sodium sulfate, filtered and evaporated. The organic residue was adsorbed on to minimum volume of dry silica before packing on silica column packed in neat hexane. The column was eluted with 25 mL of 5% CH_2Cl_2/hexane then 4 x 50mL CH_2Cl_2/hexane, increasing CH_2Cl_2 to 25% in 5% increments. Starting material 1-(benzyloxy)-4-iodobenzene **3.9** was recovered as colourless crystals (79 mg, 0.255 mmol, 85%), mp 61-63 °C (Lit. mp 61-62 °C)[245]; ν_{max} (KBr)/cm^{-1} = 3030, 2906, 2860, 1582, 1568, 1485, 1463, 1454, 1400, 1381, 1282, 1243, 1174, 1115, 824, 800, 745, 697, 644 and 504; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.05 (2H, s, CH_2), 6.77 (2H, d, J = 8.9, ArH), 7.32-7.36 (1H, m, ArH), 7.38-7.43 (4H, m, ArH) and 7.57 ppm (2H, d, J = 8.9, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 70.4 (CH_2), 83.4 (C), 117.7 (CH), 127.8 (CH), 128.5 (CH), 129.0 (CH), 136.9 (C), 138.6 (CH) and 159.0 ppm (C) and benzyloxybenzene **3.10** (5 mg, 0.027 mmol, 9%) as a colourless crystalline solid; mp 39-40 °C (Lit. 39-40 °C)[246]; [Found: (M)$^+$ 184.0881 $C_{13}H_{12}O_1$. (M)$^+$ requires 184.0883]; ν_{max} (KBr)/cm^{-1} = 3056, 3034, 2907, 2866, 1599, 1585, 1497, 1468, 1455, 1377, 1300, 1246,

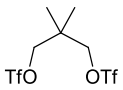
1171, 1078, 1029, 1012, 991, 916, 856, 801, 744, 696, 629 and 515; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.08 (2H, s, ArH), 6.96-7.00 (3H, m, ArH), 7.28-7.35 (3H, m, ArH), 7.38-7.41 (2H, m, ArH) and 7.44-7.46 ppm (2H, m, ArH); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 70.3 (CH_2), 115.2 (CH), 121.3 (CH), 127.8 (CH), 128.3 (CH), 128.9 (CH), 129.8 (CH), 137.5 (C) and 159.2 ppm (C).

Preparation of 2,2-dimethylpropane-1,3-diyl dimethanesulfonate, 3.18.[249]



In a flame-dried round-bottomed flask (250 mL) equipped with a stirrer bar, neopentyl glycol (5.208 g, 50 mmol, 1.0 eq.) and triethylamine (13.94 mL, 100 mmol, 2.0 eq.) were dissolved in dry CH_2Cl_2 (100 mL) under inert atmosphere. Methanesulfonyl chloride (8.13 mL, 105 mmol, 2.1 eq.) was added CH_2Cl_2 to 0 ^{o}C with stirring, and the solution was then added dropwise by syringe to the neopentyl glycol/triethylamine mixture. When the addition was complete, the cooling bath was removed and the reaction mixture was allowed to reach room temperature and was stirred for an additional 4 h before working up with water (3 x 100 mL) and brine (100 mL). The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 2,2-dimethylpropane-1,3-diyl dimethanesulfonate **3.18** as a white solid (11.706 g, 44.0 mmol, 90%): mp = 70-72 °C (lit. mp = 69-71 °C)[1]; ν_{max} (KBr)/cm^{-1} 2995, 2939, 1479, 1411, 1354, 1172, 981, 848, 760 and 527; [Found: $(HNES)^+$ $(M+Na)^+$ 283.0275. $C_7H_{16}O_6S_2Na$ (M+Na) requires 283.0285]; ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 1.07 (6H, s, Me), 3.05 (6H, s, Me) and 4.02 ppm (4H, s, CH_2); ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 21.5 (CH_3), 35.7 (C), 37.5 (CH_3) and 73.4 ppm (CH_2).

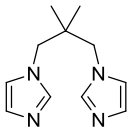
Preparation of 2,2-dimethylpropane-1,3-diyl *bis*(trifluoromethanesulfonate), 3.30.[250,251]



In a flame-dried round-bottomed flask (250 mL) equipped with a stirrer bar, neopentyl glycol (5.208 g, 50 mmol, 1.0 eq.) and pyridine (8.09 mL, 100 mmol, 2.0 eq.) were dissolved in dry CH_2Cl_2 (100 mL) under inert atmosphere. Dichloromethane (80 mL) was measured into a second flame-dried round-bottomed flask (100 mL) under inert atmosphere, before both flasks were cooled to -78 °C. Trifluoromethane sulfonic anhydride (17.8 mL, 105 mmol, 2.1 eq.) was added to the cooled CH_2Cl_2 with stirring, the solution was then transferred dropwise via a cannula to the neopentyl glycol/pyridine mixture with vigorous stirring. On complete addition the cooling bath was removed and the reaction mixture was allowed to

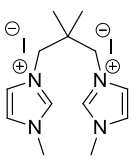
reach room temperature and stirred for an additional 30 min before working up with water (3 x 100 mL) and brine (100 mL). The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* before purifying by flash filtration through silica. Elution with CH_2Cl_2 afforded 2,2-dimethylpropane-1,3-diyl *bis*(trifluoro-methanesulfonate) **3.30**, (17.4 g, 47.2 mmol, 94 %) as a transparent dark pink oil: ν_{max} (thin film)/cm^{-1} 2981, 1480, 1417, 1248, 1210, 1146, 946, 850 and 615; ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 1.14 (6H, s, C(CH_3) and 4.32 ppm (4H, s, CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 20.8 (CH_3), 36.5 (C), 79.25 (CH_2) and 119.0 ppm (q, J = 319.5 Hz, CF_3).

Preparation of 1,1'-(2,2-dimethylpropane-1,3-diyl)*bis*(1H-imidazole), 3.20.



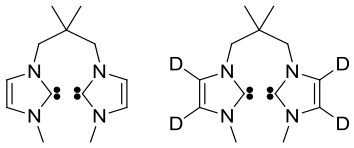
Sodium hydride (7.46g, 60% in mineral oil, 186.4mmol) was washed with dry hexane (2 x 100 mL) under argon. The residual hexane was removed by vacuum. Dimethylformamide (40 mL, dried with activated 4 Å molecular sieve) was added and the suspension was cooled in an ice-water bath. Imidazole (11.54g, 169.5 mmol, 2.1 eq.) in DMF (50 mL) was added carefully. The clear solution obtained was stirred at room temperature for 30 min and 2,2-dimethylpropane-1,3-diyl dimethanesulfonate (20.98 g, 80.7 mmol, 1.0 eq.) in DMF (40 mL) was added. The mixture was heated at 125 °C for 24 h, cooled to room temperature, diluted with CH_2Cl_2 (900 mL), filtered and concentrated. The product was purified by distillation (210˚C/0.01mmHg), to afford 1,1'-(2,2-dimethylpropane-1,3-diyl)*bis*(1H-imidazole) **3.20** as yellow crystalline product (11.2 g, 54.3 mmol, 68%): mp = 80-82 °C; ν_{max} (KBr)/cm^{-1} 3124, 3104, 2970, 2936, 1666, 1636, 1508, 1232, 1110 and 1079; [Found: $(HNES)^+$ $(M+H)^+$ 205.1447. $C_{11}H_{16}N_4$ requires (M+H), 205.1448]; ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 0.97 (6H, s, Me), 3.82 (4H, s, CH_2), 6.86 (2H, s, ArH), 7.08 (2H, s, ArH) and 7.46 ppm (2H, s, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 23.9 (CH_3), 37.4 (C), 56.1 (CH_2), 120.9 (CH), 129.6 (CH) and 138.6 ppm (CH).

Preparation of 3,3'-(2,2-dimethylpropane-1,3-diyl)*bis*(1-methyl-1*H*-imidazol-3-ium) iodide, 3.21.[2]



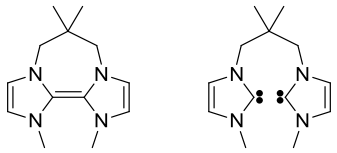
1,1'-(2,2-Dimethylpropane-1,3-diyl)*bis*(1H-imidazole) **3.20** (10.214 g, 50.0 mmol, 1.0 eq.) was dissolved in acetonitrile (50 mL) under an inert atmosphere. Methyl iodide (3.42 mL, 105.0 mmol, 2.1 eq.) was added via a syringe and the reaction mixture was refluxed overnight. Dry diethyl ether was added to the cooled solution and the resultant precipitate was collected, rinsed with dry diethyl ether (3 x 100 mL) and dried in a desiccator. The hygroscopic pure white powder *3,3'-(2,2-dimethylpropane-1,3-diyl)bis(1-methyl-1H-imidazol-3-ium) iodide* **3.21** (22.801 g, 46.7 mmol, 93 %) was stored in a glove-box; mp = 200-202 °C; ν_{max} (KBr)/cm^{-1} 3077, 3056, 1578, 1562, 1474 and 1168; [Found: $(HNES)^+$ $(M-I)^+$ 361.0880. $C_{13}H_{22}I_2N_4$ requires (M-I), 361.0884]; ^{1}H-NMR (500 MHz, DMSO-d_6) δ = 0.96 (6H, s, CH_3), 3.94 (6H, s, CH_3), 4.25 (4H, s, CH_2), 7.79 (2H, t, J = 1.7 Hz, ArH), 7.82 (2H, t, J = 1.7 Hz, ArH) and 9.21 ppm (2H, s, ArH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ = 22.9 (CH_3), 36.9 (C), 37.0 (CH_3), 56.9 (CH_2), 124.3 (CH), 123.8 (CH) and 138.4 ppm (CH).

Preparation of 3,3'-(2,2-dimethylpropane-1,3-diyl)*bis*(1-methyl-1*H*-imidazol-2-ylidene) 3.23 and 3,3'-(2,2-dimethylpropane-1,3-diyl)*bis*(1-methyl-4,5-deutero-1*H*-imidazol-2-ylidene 3.23'.



Sodium hydride (ca. 20 mg) was placed in an NMR tube under the inert atmosphere of a glove-box before dissolving in DMSO-d_6. 3,3'-(2,2-Dimethylpropane-1,3-diyl)*bis*(1-methyl-1*H*-imidazol-3-ium) iodide **3.21** (20 mg) was added to the NMR tube bringing about a colour change from green to blue. The NMR tube was promptly sealed and examined by NMR, which showed the presence of the *bis*-carbene) *3,3'-(2,2-dimethylpropane-1,3-diyl)bis(1-methyl-1H-imidazol-2-ylidene)* **3.23** was cleanly generated *in situ*; ^{1}H-NMR (500 MHz, DMSO-d_6) δ = 0.85 (6H, s, CH_3), 3.68 (6H, s, CH_3), 3.83 (4H, s, CH_2), 7.07 (2H, s, ArH) and 7.38 (2H, s, ArH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ = 24.7 (CH_3), 37.3 (C), 38.1 (CH_3), 57.4 (CH_2), 120.3 (CH), 122.7 (CH) and 212.2 ppm (C). After 1 h the reaction was re-examined, showing *3,3'-(2,2-dimethylpropane-1,3-diyl)bis(1-methyl-4,5-deutero-1H-imidazol-2-ylidene* with complete deuteration of 4 and 5 positions of the imidazol-2-ylidene; ^{1}H-NMR (500 MHz, DMSO-d_6) δ = 0.85 (6H, s, CH_3), 3.69 (6H, s, CH_3) and 3.83 (4H, s, CH_2); ^{13}C-NMR (125 MHz, DMSO-d_6) δ = 24.7 (CH_3), 37.3 (C), 38.1 (CH_3), 57.4 (CH_2), 120.3 (CH/D), 122.7 (CH/D) and 212.2 ppm (C).

Preparation of 1,6,6,11-tetramethyl-5,6,7,11-tetrahydro-1*H*-diimidazo[1,2-a:2',1'-c][1,4]diazepine 3.22 and 3,3'-(2,2-dimethylpropane-1,3-diyl)*bis*(1-methyl-1*H*-imidazol-2-ylidene), 3.23.



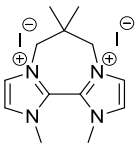
3.22 **3.23**

3,3'-(2,2-Dimethylpropane-1,3-diyl)*bis*(1-methyl-1*H*-imidazol-3-ium) iodide **3.21** (2.441 g, 5.0 mmol, 1.0 eq.) weighed into a Schlenk flask (1 L) and sealed with a septum. Also in a glove-box sodium hydride (0.252 g, 10.5 mmol, 2.1 eq.) was weighed into a specialised dropping funnel before being sealed under inert atmosphere. The Schlenk flask and dropping funnel were removed to a fumehood, before the septum on the Schlenk flask was replaced with a dry-ice condenser under a stream of argon. Salt imidazolium salt **3.23** was dissolved with stirring by the condensation of liquid ammonia (approx. 800 mL) into the Schlenk flask. Still under a stream of argon the dropping funnel was placed between the Schlenk flask and condenser. Liquid ammonia (100 mL) was condensed into the dropping funnel and the dissolved sodium hydride solution was added to the Schlenk flask; this was then repeated a further time. Over a 3 h period liquid ammonia was allowed to repeatedly reflux onto the dry-ice condenser and collect in the dropping funnel before being re-added to the reaction mixture, ensuring that the majority of sodium hydride was transferred. The dropping funnel was then removed and the reaction was allowed to reflux. A colour change in the reaction mixture was observed during the course of the reaction, from colourless to a clear green and eventually a vibrant clear yellow. After 48 h cooling was stopped and the liquid ammonia was allowed to completely evaporate. At room temperature and under an atmosphere of argon, the Schlenk flask was sealed with a septum and transferred to a glove-box. The pink crystalline residue was scraped down with a spatula and extracted with diethyl ether (4 x 500 mL). The clear greenish yellow diethyl ether extracts were concentrated with stirring under vacuum to afford a yellow solid residue containing **3.22** and **3.23** in a 55:45 ratio.

1,*6,6*,11-*tetramethyl-5,6,7*,11-*tetrahydro*-1*H-diimidazo[*1,*2-a:2'*,1*'-c][*1,*4]diazepine* **3.22**: ^{1}H-NMR (500 MHz, C_6D_6) δ = 0.79 (6H, s, CH_3), 2.33 (4H, s, CH_2), 2.59 (6H, s, CH_3), 5.41 (2H, d, J = 2.4 Hz, =CH) and 5.48 ppm (2H, d, J = 2.4 Hz, =CH); ^{13}C-NMR (125 MHz, C_6D_6) δ = 24.6 (CH_3), 35.5(C), 37.3 (CH_3), 57.7 (CH_2), 120.7 (CH), 123.1 (CH) and 127.3ppm (C) and *3,3'-*(*2,2-dimethylpropane*-1,*3-diyl)bis*(1-*methyl*-1*H-imidazol-2-ylidene)* **3.23**; ^{1}H-NMR (500 MHz, C_6D_6) δ = 0.86 (6H, s, CH_3), 3.39 (6H, s, CH_3), 3.91 (4H, s, CH_2), 6.32 (2H, d, J = 1.4 Hz, ArH) and 7.36 ppm (2H, d, J = 1.4 Hz, ArH); ^{13}C-NMR (125 MHz, C_6D_6)

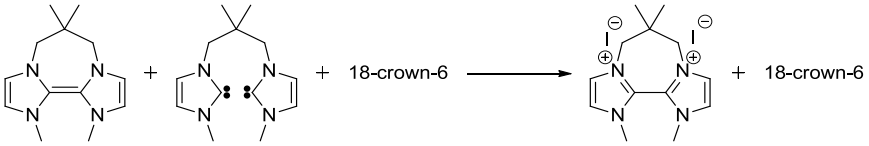
δ = 25.3 (CH_3), 37.6 (C), 38.1 (CH_3), 64.7 (CH_2), 119.2 (CH), 122.8 (CH) and ppm 216.7 (C).

Preparation of 1,6,6,11-tetramethyl-5,6,7,11-tetrahydro-1*H*-diimidazo[1,2-a:2',1'-c][1,4]diazepine-4,8-diium iodide, 3.26.



1,6,6,11-tetramethyl-5,6,7,11-tetrahydro-1*H*-diimidazo[1,2-a:2',1'-c][1,4]diazepine **3.22** and 3,3'-(2,2-dimethylpropane-1,3-diyl)*bis*(1-methyl-1*H*-imidazol-2-ylidene) **3.23** were prepared as a mixture according to the above experiment. When the final ether solution was obtained, iodine was added until precipitation ceased and the colour of the mixture changed to clear brown. The precipitated 1,*6,6*,11-*tetramethyl-5,6,7*,11-*tetrahydro*-1*H-diimidazo[*1,*2-a:2'*,1'-*c][*1,*4]diazepine-4,8-di-ium iodide* **3.26** was collected as shiny needles (1.00 g, 2.06 mmol, 41.1%); [Found: ($HNES^+$) $(M-I)^+$ 359.0728. $C_{13}H_{20}IN_4$ (M-I) requires 359.0727]; ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 1.15 (6H, s, CH_3), 4.06-4.09 (8H, m, CH_2,CH_3), 4.38 (2H, d, *J* = 14.4 Hz, CH_2), 8.27 (2H, d, *J* = 1.7 Hz, ArH) and 8.35 ppm (2H, d, *J* = 1.7 Hz, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 25.2 (CH_3), 38.5 (CH_3), 43.7 (C), 56.7 (CH_2), 127.2 (CH), 128.4 (CH) and 128.9 (C) ppm.

Calibration experiment to see if both 3.22 and 3.23 are converted into product 3.26 on reaction with Iodine.

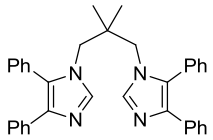


1,4,7,10,13,16-Hexaoxacyclooctadecane (18-crown-6) was distilled from phosphorus(V) oxide under reduced pressure. The solid was recrystallised from dry acetonitrile under inert atmosphere before freeze-pump-thaw deoxygenation using high vacuum and liquid nitrogen. The pure dry 1,4,7,10,13,16-hexaoxacyclooctadecane was then stored in the glove-box.

A mixture of 1,6,6,11-tetramethyl-5,6,7,11-tetrahydro-1*H*-diimidazo[1,2-a:2',1'-c][1,4]diazepine **3.22** and 3,3'-(2,2-dimethylpropane-1,3-diyl)*bis*(1-methyl-1*H*-imidazol-2-ylidene) **3.23** were prepared as per the previous procedure. However, the combined diethyl ether extracts were not immediately evaporated to dryness. A crystal of 1,4,7,10,13,16-hexaoxacyclooctadecane was added and to the extracts, then the organic solution was split into two approximately equal volumes. Iodine was added with stirring to one half of the

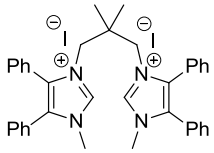
organic solution until further precipitation ceased, then both halves were evaporated to dryness. The intensities of the singlet peak associated with 1,4,7,10,13,16-hexaoxacyclooctadecane, was measured relative (a) to the peaks for products **3.22** and **3.23** in the unoxidised mixture and (b) relative to oxidised 1,6,6,11-tetramethyl-5,6,7,11-tetrahydro-1*H*-diimidazo[1,2-a:2',1'-c][1,4]diazepine-4,8-diium iodide **3.26**. Comparison indicated that the conversion of the carbene/dimer reaction mixture to **3.26** was > 90%.

Preparation of 1,1′-(*2,2*-dimethylpropane-1,3-diyl)*bis*(4,5-diphenyl-1H-imidazole*)*, 3.32.



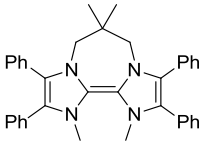
4,5-Diphenyl-1*H*-imidazole (4.516 g, 20.5 mmol, 2.05 eq.) **3.31** was dissolved in anhydrous DMF (50 mL) within a glove box. Sodium hydride (0.492g, 20.5 mmol, 2.05 eq.) was added spatula-wise to the vigorous stirred reaction mixture, allowing effervescence to subside between additions. On complete addition of sodium hydride, the reaction mixture was allowed to stir for an additional 10 min before 2,2-dimethylpropane-1,3-diyl *bis*(trifluoromethanesulfonate) **3.30** (3.683g, 10.0 mmol, 1.0 eq.) was added dropwise, allowing the exotherm to subside. The round-bottomed flask was equipped with a condenser and sealed with a septum before removing to a fumehood and heating at 105 °C overnight. The cooled reaction mixture was poored in water (250 mL) and the precipitate was collected in a Buchner funnel, before being redissolved in ethyl acetate (250 mL) and washed with 2M sodium hydroxide (3 x 100 mL), water (2 x 100 mL) and brine (100 mL). The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford pure 1,1′-(*2,2-dimethylpropane*-1,*3-diyl)bis*(*4,5-diphenyl*-1*H-imidazole)* **3.32** (4.8 g, 9.4 mmol, 94 %) as an off-white solid; mp = 204-212 °C; ν_{max} (KBr)/cm^{-1} 3063, 3040, 2980, 2964, 1601, 1505, 1250, 1174, 775 and 700; [Found: (HNES^{+}) (M+H)$^{+}$ 509.2693. $C_{35}H_{32}N_4$ (M+H) requires 509.2700]; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.66 (6H, s, CH_3), 3.54 (4H, s, CH_2), 7.14-7.22 (10H, m, ArH), 7.39-7.44 (10H, m, ArH) and 7.45 ppm (2H, s, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 24.5 (CH_3), 38.3 (C), 53.3 (CH_2), 126.8 (CH), 127.2 (CH), 128.4 (CH), 129.1(CH), 129.1(C), 129.5 (C), 130.9 (CH), 131.5 (CH), 134.7 (C), 138.1 (CH) and 138.6 ppm (C).

Preparation of 3,3'-(2,2-dimethylpropane-1,3-diyl)*bis*(1-methyl-4,5-diphenyl-1H-imidazol-3-ium) iodide, 3.33.



In a flame-dried round-bottomed flask equipped with a stirrer bar and condenser, 1,1'-(2,2-dimethylpropane-1,3-diyl)*bis*(4,5-diphenyl-1*H*-imidazole) (4.578 g, 9.0 mmol, 1.0 eq.) **3.32** was dissolved in acetonitrile (30 mL) and then sealed under an inert atmosphere. Methyl iodide (1.17 mL, 18.9 mmol, 2.1 eq.) was added via a syringe and the reaction mixture was refluxed overnight. Dry diethyl ether was added to the cooled solution and the resultant precipitate was collected at the pump, before quickly rinsing with dry diethyl ether (3 x 100 mL) and drying in a desiccator. The hygroscopic pure white powder *3,3'-(2,2-dimethylpropane-*1,*3-diyl)bis*(1-*methyl-4,5-diphenyl-*1*H-imidazol-3-ium) iodide* (6.771 g, 8.54 mmol, 95 %) **3.33** was transferred to a glove-box; mp = 180-205 °C; ν_{max} (KBr)/cm^{-1} 3054, 2970, 2877, 1616, 1566, 1443, 1194, 767, 708 and 697; [Found: (HNES^{+}) (M-I)$^{+}$ 665.2128. $C_{37}H_{38}N_4I_2$ (M-I) requires 665.2136]; ^{1}H-NMR (500 MHz, DMSO-d$_6$) δ 0.65 (6H, s, C(CH_3), 3.79 (6H, s, CH_3), 4.01 (4H, s, CH_2), 7.28-7.30 (4H, m, ArH), 7.42-7.44 (4H, m, ArH), 7.47-7.52 (10H, m, ArH) and 7.55-7.58 ppm (2H, m, ArH); ^{13}C-NMR (125 MHz, DMSO-d$_6$) δ 23.3 (CH_3), 35.7 (CH_3), 38.0 (C), 54.3 (CH_2), 125.8 (C), 126.2 (C), 129.8 (CH), 129.9 (CH), 131.0 (CH), 131.1 (CH), 131.6 (CH), 132.0 (CH), 132.5 (C), 132.8 (C) and 138.1 ppm (CH).

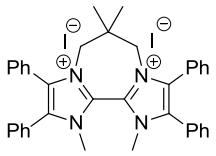
Preparation of 1,*6,6*,11-tetramethyl-2,3,9,10-tetraphenyl-5,6,7,11-tetrahydro-1H-diimidazo[1,2-a:2',1'-c][1,4]diazepine, 3.34.



In a glove-box, 3,3'-(2,2-dimethylpropane-1,3-diyl)*bis*(1-methyl-4,5-diphenyl-1*H*-imidazol-3-ium) iodide **3.33** (3.17 g, 4.0 mmol, 1.0 eq.) and sodium hydride (0.48 g, 20.0 mmol, 5.0 eq.) were weighed into a Schlenk flask (500 mL) and sealed with a septum. The Schlenk flask was removed to a fumehood and the septum replaced with a dry-ice condenser under a stream of argon. Liquid ammonia (approx. 500 mL) was condensed onto the reactants forming a dark purple solution. The reaction was refluxed for 4 h before the liquid ammonia was allowed to completely evaporate overnight. At room temperature, the Schlenk flask was resealed under

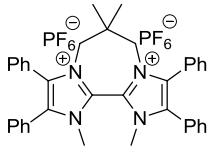
an atmosphere of argon with a septum and transferred back into the glove-box. The solid was scraped down with a spatula and the dark purple product was repeatedly extracted with diethyl ether until extracts were almost completely colourless. The combined organic extracts were concentrated under vacuum with stirring to afford 1,*2,3,6,6,9,10*,11-*octamethyl-5,6,7*,11-*tetrahydro*-1*H-diimidazo[*1,*2-a:2'*,1*'-c][*1,*4]diazepine* (1.96 g, 3.7 mmol, 91 %) **3.34** as a dark purple crystalline solid; ^{1}H-NMR (500 MHz, C_6D_6) δ 0.95 (6H, s, CH_3), 3.08 (6H, s, CH_3), 3.19 (4H, s, CH_2), 7.05-7.11 (4H, m, CH), 7.14-7.19 (8H, m, CH), 7.49 (4H, d, J = 7.3 Hz, CH) and 7.52 ppm (4H, d, J = 7.5 Hz, CH); ^{13}C-NMR (125 MHz, C_6D_6) δ 25.9 (CH_3), 34.9 (CH_3), 35.0 (C), 60.5 (CH_2), 127.0 (CH), 127.6 (C), 128.2 (CH), 129.1 (CH), 129.2 (CH), 129.4 (CH), 129.9 (C), 130.5 (CH), 132.4 (C), 132.8 (C) and 133.1 ppm (C).

Preparation of 1,6,6,11-tetramethyl-2,3,9,10-tetraphenyl-5,6,7,11-tetrahydro-1H-diimidazo[1,2-a:2',1'-c][1,4]diazepine-4,8-diium iodide, 3.35.



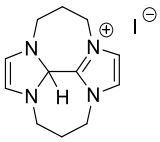
In the glove-box 1,2,3,6,6,9,10,11-octamethyl-5,6,7,11-tetrahydro-1*H*-diimidazo[1,2-a:2',1'-c][1,4]diazepine (0.268 g, 0.5 mmol, 1.0 eq.) **3.34** was dissolved diethyl ether (10 mL) with stirring, iodine (0.152 g, 0.6 mmol, 1.2 eq.) was added to the dark purple solution causing precipitation, as well as a colour change in the diethyl ether to transparent. The suspension was stoppered and removed to a fumedhood where the brown precipitate was collected at the pump, washing with diethyl ether to afford pure 1,*6,6*,11-*tetramethyl-2,3,9,10-tetraphenyl-5,6,7*,11-*tetrahydro*-1*H-diimidazo[*1,*2-a:2'*,1*'-c][*1,*4]diazepine-4,8-diium iodide*, **3.35** (0.38 g, 0.484 mmol, 97%); mp = 188-190 °C; ν_{max} (KBr)/cm^{-1} 3052, 2962, 2874, 1619, 1488, 1444, 765 and 699; [Found: (HNES^{+}) (M-I)$^{+}$ 663.1976. $C_{37}H_{36}N_4I_2$ (M-I) requires 663.1979]; ^{1}H-NMR (500 MHz, DMSO-d_6) δ = 1.01 (6H, s, CH_3), 3.97 (2H, d, J = 14.6 Hz, CH_2), 4.09 (6H, s, CH_3), 4.46 (2H, d, J = 14.6 Hz, CH_2), 7.59-7.61 (16H, m, ArH) and 7.72-7.74 ppm (4H, m, ArH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ = 25.0 (CH_3), 37.6 (CH_3), 45.1 (C), 54.1 (CH_2), 124.9 (C), 125.5 (C), 128.1 (C), 129.8 (CH), 129.9 (CH), 131.6 (CH), 131.8 (CH), 131.9 (CH), 132.4 (CH), 135.7 (C) and 138.1 ppm (C).

Preparation of 1,6,6,11-tetramethyl-2,3,9,10-tetraphenyl-5,6,7,11-tetrahydro-1H-diimidazo[1,2-a:2',1'-c][1,4]diazepine-4,8-diium hexafluorophosphate, 3.36.



1,2,3,6,6,9,10,11-octamethyl-5,6,7,11-tetrahydro-1*H*-diimidazo[1,2-a:2',1'-c][1,4]diazepine-4,8-diium iodide (0.553 g, 0.7 mmol, 1.0 eq.) **3.35** was dissolved in a minimum volume of boiling MeOH. The volume was doubled with water and heated to boiling before hexafluorophosphoric acid (0.15 mL, 1.75 mmol, 2.5 eq.) was added. 1,*6,6,*11-*tetramethyl-2,3,9,10-tetraphenyl-5,6,7,*11-*tetrahydro*-1*H-diimidazo[*1,*2-a:2',*1'*-c][1,4]diazepine-4,8-diium hexafluorophosphate* (0.64 g, 0.444 mmol, 63%) **3.36** was recrystallised from this solution, as a brown solid; mp = 248-252 °C; ν_{max} (KBr)/cm^{-1} 3060, 2962, 1619, 1489, 1464, 843, 699, and 558; [Found: (HNES$^+$) (M-PF$_6$)$^+$ 681.2572 $C_{37}H_{36}N_4P_2F_{12}$ (M-PF$_6$) requires 681.2576]; ^{1}H-NMR (500 MHz, DMSO-d$_6$) δ = 0.98 (6H, s, CH$_3$), 4.01 (2H, d, J = 14.6 Hz, CH$_2$), 4.07 (6H, s, CH$_3$), 4.31 (2H, d, J = 14.6 Hz, CH$_2$) and 7.55-7.68 ppm (20H, m, ArH); ^{13}C-NMR (125 MHz, DMSO-d$_6$) δ = 25.2 (CH$_3$), 37.4 (CH$_3$), 45.3 (C), 54.2 (CH$_2$), 125.1 (C), 125.7 (C), 128.6 (C), 130.3 (CH), 130.4 (CH), 132.0 (CH), 132.0 (CH), 132.3 (CH), 132.5 (CH), 135.9 (C) and 137.0 ppm (C).

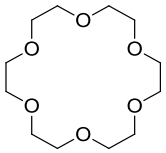
Preparation of 3,4,5,8,9,10-hexahydro-2a1H-2a,5a,7a,10a-tetraazadicyclopenta[ef,kl] heptalen-7a-ium iodide, 3.75.



In a glove-box, 3,4,5,8,9,10-hexahydro-2a,5a,7a,10a-tetraazadicyclopenta[ef,kl]heptalene-7a,10a-diium iodide **1.265** was ground to a fine powder with a pestle and mortar before weighing (472 mg, 1.0 mmol, 1.0 eq.) into a 2-dram vial. Pure sodium hydride (24 mg, 1.0 mmol, 1.0 eq.) was added and the dry reagents were thoroughly mixed. The mixed solid (47 mg) was dissolved in anhydrous deuterated dimethyl sulfoxide (1.0 mL) in an NMR tube. The tube was sealed with a cap and parafilm and then removed from the glove-box. NMR analysis revealed the *in situ* formation of *3,4,5,8,9,10-hexahydro-2a*1*H-2a,5a,7a,*10*a- tetraazadicyclopenta[ef,kl]heptalen-7a-ium iodide*, **3.75** as the sole product; ^{1}H-NMR (400 MHz, DMSO-d$_6$) δ = 2.12-2.22 (4H, m, CH$_2$), 2.72-2.75 (2H, m, CH$_2$), 3.42-3.49 (2, m, CH$_2$), 4.35-4.40 (4H, m, CH$_2$), 5.19 (1H, s, CH), 5.72 (2H, s, CH) and

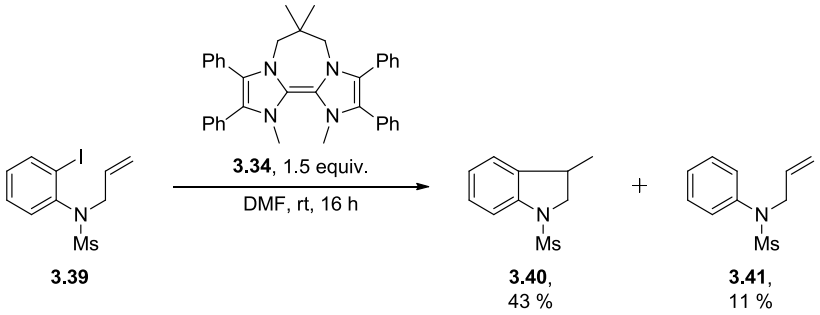
7.70 ppm (2H, s, ArH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ = 26.8 (CH_2), 49.6 (CH_2), 51.6 (CH_2), 83.7 (CH), 120.7 (CH), 123.3 (CH) and 146.3 ppm (C).

Purification of 1,4,7,10,13,16-hexaoxacyclooctadecane.[241]



1,4,7,10,13,16-hexaoxacyclooctadecane was distilled from phosphorus (V) oxide under reduced pressure. The solid was recrystallised from dry acetonitrile under inert atmosphere before freeze-thaw drying using high vacuum using liquid nitrogen. The pure dry 1,4,7,10,13,16-hexaoxacyclooctadecane was then stored in the glove-box.

Preparation of 3-methyl-1-(methylsulfonyl)indoline, 3.40[91] and *N*-allyl-*N*-phenylmethanesulfonamide, 3.41.[252]

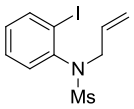


3.39 **3.40**, 43 % **3.41**, 11 %

In a glove-box, *N*-allyl-*N*-(2-iodophenyl)methanesulfonamide, **3.39** (0.101 g, 0.300 mmol, 1.0 eq.) was dissolved in anhydrous DMF (2 mL). 1,6,6,11-Tetramethyl-2,3,9,10-tetraphenyl-5,6,7,11-tetrahydro-1*H*-diimidazo[1,2-a:2',1'-c][1,4]diazepine, **3.34** (0.242 g, 0.450 mmol, 1.5 eq.) was added and stirred overnight. The reaction was removed from the glove-box and diluted with ethyl acetate (25 mL) before being worked up with water (50 mL) plus diethyl ether (25 mL). The organic layer was separated before the aqueous phase was further extracted with diethyl ether (3 x 50 mL). The combined organic phase was washed with water (3 x 50 mL) and brine (50 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a brown/yellow oil. The crude organic residue was purified on silica gel eluting with ethyl acetate/hexane (polarity gradient increasing from 20% ethyl acetate to 25% then 30%) to afford 3-methyl-1-(methylsulfonyl)indoline, **3.40** (27 mg, 0.128 mmol, 43%): ^{1}H-NMR (400 MHz) δ = 1.37 (3H, d, J = 6.6 Hz, CH_3), 2.88 (3H, s, SO_2CH_3), 3.44-3.52 (2H, m, CH_2), 4.12-4.17 (1H, m, CH), 7.06 (1H, ddd, J = 7.7, 7.7, 1.6 Hz, ArH), 7.19-7.24 (2H, m, ArH) and 7.39-741 (1H, m, ArH); ^{13}C-NMR (100 MHz) 19.8 (CH_3), 34.7 (CH), 35.1 (CH_3), 58.2

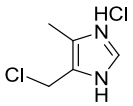
(CH_2), 113.9 (CH) 124.1 (CH), 124.6 (CH), 128.5 (CH) 136.6 (C) and 141.8 ppm (C); and *N*-allyl-*N*-phenylmethanesulfonamide, **3.41** (7 mg, 0.033 mmol, 11 %) as colourless crystalline solids: ^{1}H-NMR (400 MHz) δ = 2.9 (3H, s, SO_2CH_3), 4.31 (2H, dt, 6.2, 1.3 Hz, CH_2), 5.13-5.22 (2H, m, =CH_2), 5.80-5.90 (1H, m, =CH) and 7.31-7.43 ppm (5H, m, ArH).

Synthesis of *N*-allyl-*N*-(2-iodophenyl)methanesulfonamide, 3.39.[91]



This compound was prepared using the same procedure as for *N*-(2-bromocyclohex-2-enyl)-*N*-(2-iodophenyl) methanesulfonamide, **4.15b** with *N*-(2-iodophenyl)methanesulfonamide **4.53a** (0.89 g, 3.00 mmol, 1.1 eq.) and 2-butyn-1-ol (0.19g, 2.73 mmol, 1.0 eq.). The crude product purified by column chromatography on silica gel (20% ethyl acetate and 80% petroleum ether) to afford *N*-allyl-*N*-(2-iodophenyl)methanesulfonamide **3.39** (1.1 g, 97%) as a colourless viscous oil. ^{1}H-NMR and ^{13}C-NMR agreed with spectra previously reported within the group: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 3.1 (3H, s, SO_2CH_3), 4.03 (1H, dd, *J* = 15.1, 7.4 Hz, CH_2), 4.41 (1H, dd, *J* = 15.1, 6.2 Hz, CH_2), 5.09-5.17 (2H, m, HC=CH_2), 5.92-6.01 (1H, m, *H*C=CH_2), 7.04-7.10 (1H, m, ArH), 7.39 (2H, d, *J* = 4.0 Hz, ArH) and 7.94 ppm (1H, d, *J* = 7.9 Hz, ArH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 41.3 (CH_3), 54.3 (CH_2), 102.2 (C), 120.1 (CH_2), 129.3 (CH), 130.4 (CH), 132.4 (CH), 132.7 (CH), 140.4 (CH) and 141.2 ppm (C).

Preparation of 5-(chloromethyl)-4-methyl-1*H*-imidazole hydrochloride, 3.46.[196]



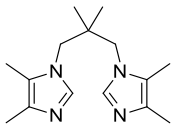
Thionyl chloride (9.1 mL, 125 mmol, 5.0 eq.) was carefully added, dropwise from a syringe, to (4-methyl-1*H*-imidazol-5-yl)methanol hydrochloride **3.45** (3.715 g, 25.0 mmol, 1.0 eq.), with stirring, allowing any gas evolved to be expelled via a bubbler. The suspension was allowed to stir for 1 h before chloroform (50 mL) was added, the white solid was filtered and washed thoroughly with chloroform (3 x 50 mL), before being dried under vacuum to afford pure 5-(chloromethyl)-4-methyl-1*H*-imidazole hydrochloride **3.46**, (3.92 g, 23.5 mmol, 94 %) as a white powder: mp 265-267 °C (lit. = 277 °C)[196]; ν_{max} (KBr)/cm^{-1} 3087, 2996, 1638, 1446, 1221, 1170, 842 and 726; [Found: (EI) (M-HCl)$^+$ 130.0292. $C_5H_8N_2Cl_2$ requires (M-HCl), 130.0292]; ^{1}H-NMR (400 MHz, DMSO-d_6) δ = 2.36 (3H, s, CH_3), 4.93 (2H, s, CH_2), 9.04

(1H, s, ArH) and 14.68 ppm (2H, br. s, NH) ^{13}C-NMR (100 MHz, DMSO-d_6) δ = 9.4 (CH_3), 34.8 (CH_2), 125.7 (C), 128.9 (C) and 134.7 ppm (CH).

Preparation of 4,5-dimethyl-1*H*-imidazole, 3.47.[196]

5-(Chloromethyl)-4-methyl-1*H*-imidazole hydrochloride **3.46** (4.009 g, 24.0 mmol, 1.0 eq.) was weighed into a glass Cook hydrogenator bottle and dissolved in ethanol (25 mL). Pd/C (0.40 g, 10 % loading) was added and the reaction mixture was shaken under an atmosphere of hydrogen gas (100 bar) for 48 h at room temperature. The catalyst was removed by filtration through celite and ethanol removed *in vacuo* to afford a crude solid. This was redissolved in saturated potassium carbonate (50 mL) before being extracted with diethyl ether (5 x 75 mL). The organic extracts were dried over sodium sulfate and filtered. The majority of the solvent was carefully removed *in vacuo*, and the remaining solvent was carefully removed from the resulting mobile phase with gentle warming under a flow of nitrogen. 4,5-dimethyl-1*H*-imidazole **3.47**, (2.13 g, 22.2 mmol, 93%) was afforded as a white crystalline solid: mp 97-100 °C (lit. = 102 °C)[196]; ν_{max} (KBr)/cm^{-1} 3024, 2919, 2868, 1869, 1615, 1484, 1465, 1266, 1240, 983, 799 and 637; [Found: (EI) (M-H)$^-$ 95.0604. $C_5H_8N_2$ requires (M-H)$^-$, 95.0604]; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 2.18 (6H, s, CH_3) and 7.42 ppm (1H, s, ArH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 10.9 (CH_3), 126.9 (C) and 132.7 (CH).

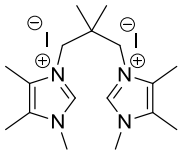
Preparation of 1,1′-(2,2-dimethylpropane-1,3-diyl)*bis*(4,5-dimethyl-1H-imidazole), 3.48.



4,5-Dimethyl-1*H*-imidazole (1.971 g, 20.5 mmol, 2.05 eq.) **3.47** was dissolved in anhydrous DMF (25mL) within a glove box. Sodium hydride (0.492g, 20.5 mmol, 2.05 eq.) was added portion-wise to the vigorously stirred reaction mixture, allowing effervescence to subside between additions. On complete addition of sodium hydride, the reaction mixture was allowed to stir for an additional 10 min before 2,2-dimethylpropane-1,3-diyl *bis*(trifluoromethanesulfonate) **3.30** (3.683g, 10.0 mmol, 1.0 eq.) was added dropwise, causing a minor exotherm. The round-bottomed flask was equipped with a condenser and heated at 105 °C overnight. The cooled reaction mixture was concentrated *in vacuo* before diluting in ethyl acetate (200 mL) and washing with 2M NaOH (3 x 75 mL), water (2 x 75 mL) and brine (50 mL). The organic layer was dried over sodium sulfate, filtered and

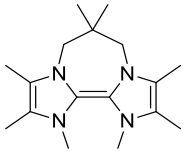
concentrated to afford 1,1'-(*2,2-dimethylpropane*-1,*3-diyl)bis*(*4,5-dimethyl*-1*H-imidazole)* **3.48**, (2.110 g, 81.0 mmol, 81%) as a viscous orange oil. ν_{max} (KBr)/cm^{-1} 2970, 2924, 1639, 1502, 1449, 1234 and 1176; [Found: (HNES)$^+$ (M+H)$^+$ 261.2077. $C_{15}H_{24}N_4$ requires (M+H), 261.2074]; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.67 (6H, s, CH_3), 1.81 (6H, s, CH_3), 1.87 (6H, s, CH_3), 3.44 (4H, s, CH_2) and 7.03 ppm (2H, s, ArH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 8.7 (CH_3), 12.6 (CH_3), 23.3 (CH_3), 37.9 (C), 52.6 (CH_2), 122.3 (C), 133.3 (C) and 135.6 (CH).

Preparation of *3,3'*-(2,2-dimethylpropane-1,3-diyl)*bis*(1,4,5-trimethyl-1H-imidazol-3-ium) iodide, 3.49.



In a flame-dried round-bottomed flask equipped with a stirrer bar and condenser, 1,1'-(2,2-dimethylpropane-1,3-diyl)*bis*(4,5-dimethyl-1*H*-imidazole) **3.48** (2.08 g, 8.0 mmol, 1.0 eq.) was dissolved in acetonitrile (20 mL) and then sealed under an inert atmosphere. Methyl iodide (1.05 mL, 16.8 mmol, 2.1 eq.) was added via a syringe and the reaction mixture was refluxed overnight. Dry diethyl ether was added to the cooled solution and the resultant precipitate was collected, rinsed with dry diethyl ether (3 x 50 mL) and dried in a desiccator. The hygroscopic pure white powder *3,3'*-(*2,2-dimethylpropane*-1,*3-diyl)bis*(1,*4,5-trimethyl*-1*H-imidazol-3-ium) iodide* **3.49**, (4.09 g, 7.52 mmol, 94%) was transferred to a glove-box for storage; mp = 198-200 °C; ν_{max} (KBr)/cm^{-1} 3459, 3415, 3057, 2968, 2870, 1635, 1564, 1446 and 1202; [Found: (HNES$^+$) (M-I)$^+$ 417.1504. $C_{17}H_{30}I_2N_4$ requires (M-I), 417.1510]; ^{1}H-NMR (500 MHz, DMSO-d_6) δ = 0.94 (6H, s, CH_3), 2.28 (6H, s, CH_3), 2.31 (6H, s, CH_3), 3.80 (6H, s, NCH_3), 4.18 (4H, s, CH_2) and 9.00 ppm (2H, s, ArH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ = 8.84 (CH_3), 9.7 (CH_3), 23.1 (CH_3), 34.4 (CH_3), 38.3 (C), 53.9 (CH_2), 128.0 (C), 128.1 (C) and 136.7 ppm (CH).

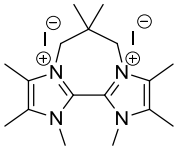
Preparation of 1,2,3,6,6,9,10,11-octamethyl-5,6,7,11-tetrahydro-1*H*-diimidazo[1,2-a:2',1'-c][1,4]di-azepine, 3.42.



3,3'-(2,2-Dimethylpropane-1,3-diyl)*bis*(1,4,5-trimethyl-1*H*-imidazol-3-ium) iodide **3.49** (2.721 g, 5.0 mmol, 1.0 eq.) and sodium hydride (0.600 g, 25.0 mmol, 5.0 eq.) were added to

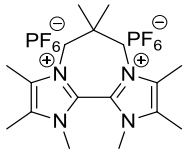
a Schlenk flask (500 mL) which was assembled with a dry-ice condenser under a stream of argon. Liquid ammonia (approx. 500 mL) was condensed onto the reactants forming a vivid yellow solution. The reaction was refluxed for 4 h before the liquid ammonia was allowed to completely evaporate overnight. At room temperature, the Schlenk flask was sealed under an atmosphere of argon with a septum and transferred to a glove-box. The solid residue was scraped down with a spatula and the highly soluble, vivid yellow product extracted several times with diethyl ether, until extracts were colourless. The combined organic extracts were concentrated under vacuum with stirring to afford 1,*2,3,6,6,9,10,*11-*octamethyl-5,6,7,*11-*tetrahydro*-1*H-diimidazo[*1,*2-a:2',*1'*-c][*1,*4]diazepine* **3.42**, as a deep yellow solid (1.39 g, 4.8 mmol, 96%); ^{1}H-NMR (500 MHz, C_6D_6) δ = 0.92 (6H, s, CH_3), 1.56 (6H, d, J = 0.7 Hz, CH_3), 1.63 (6H, d, J = 0.7 Hz, CH_3), 2.61 (4H, s, CH_2) and 2.78 ppm (6H, s, CH_3); ^{13}C-NMR (125 MHz, C_6D_6) δ = 10.5 (CH_3), 10.6 (CH_3), 25.4 (CH_3), 33.9 (CH_3), 35.0 (C), 60.7 (CH_2), 121.7 (C), 122.5 (C) and 127.8 ppm (C).

Preparation of 1,*2,3,6,6,9,10,*11-octamethyl-5,6,7,11-tetrahydro-1H-diimidazo[1,2-a:2',1'-c][1,4]diazepine-4,8-diium iodide, 3.50.



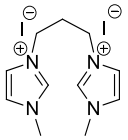
1,2,3,6,6,9,10,11-Octamethyl-5,6,7,11-tetrahydro-1*H*-diimidazo[1,2-a:2',1'-c][1,4]diazepine (0.288 g, 1.0 mmol, 1.0 eq.) **3.42** was dissolved in diethyl ether (10 mL) with stirring. Iodine (0.305 g, 1.2 mmol, 1.2 eq.) was added to the vivid, transparent yellow solution causing precipitation, as well as a colour change in diethyl ether to transparent brown. The suspension was stoppered and removed to a fumehood where the brown precipitate was collected, and washed with diethyl ether to afford 1,*2,3,6,6,9,10,*11-*octamethyl-5,6,7,*11-*tetrahydro*-1*H-diimidazo[*1,*2-a:2',*1'*-c][*1,*4]diazepine-4,8-diium iodide* **3.50** (0.537 g, 0.99 mmol, 99%) as a brown crystalline solid: mp = 180-182 °C. ν_{max} (KBr)/cm^{-1} 2957, 1612, 1450 and 1414; [Found: $(HNES)^+$ $(M\text{-}I)^+$ 415.1354. $C_{17}H_{28}I_2N_4$ requires (M-I), 415.1353]; ^{1}H-NMR (500 MHz, CD_3CN) δ = 1.22 (6H, s, CH_3), 2.42 (6H, s, CH_3), 2.43 (6H, s, CH_3), 3.75 (2H, d, J = 15.0 Hz, CH_2), 3.83 (6H, s, NCH_3) and 4.20 ppm (2H, d, J = 15.0 Hz, CH_2); ^{13}C-NMR (125 MHz, CD_3CN) δ = 9.6 (CH_3), 9.8 (CH_3), 24.2 (CH_3), 36.1 (CH_3), 45.4 (C), 54.4 (CH_2), 126.9 (C), 132.7 (C) and 133.8 ppm (C).

Preparation of 1,2,3,6,6,9,10,11-octamethyl-5,6,7,11-tetrahydro-1H-diimidazo[1,2-a:2',1'-c][1,4]diazepine-4,8-diium hexafluorophosphate, 3.51.



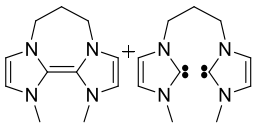
1,2,3,6,6,9,10,11-Octamethyl-5,6,7,11-tetrahydro-1*H*-diimidazo[1,2-a:2',1'-c][1,4]diazepine-4,8-diium iodide (0.380 g, 0.7 mmol, 1.0 eq.) **3.50** was dissolved in a minimum volume of boiling MeOH. The volume was doubled with water and heated to boiling before hexafluorophosphoric acid (0.15 mL, 1.75 mmol, 2.5 eq.) was added. 1,*2,3,6,6,9,10*,11-*octamethyl-5,6,7*,11-*tetrahydro*-1*H-diimidazo[*1,*2-a:2'*,1*'-c][*1,*4]diazepine-4,8-diium hexafluorophosphate* (0.28 g, 0.489 mmol, 70%) **3.51** was recrystallised from this solution, as a pale brown solid: mp = 172-174 °C; ν_{max} (KBr)/cm^{-1} 2971, 1616, 1453, 838 and 558; [Found: (HNES$^+$) (M-PF_6)$^+$ 433.1942. $C_{17}H_{28}N_4P_2F_{12}$ (M-PF_6) requires 433.1950]; ^{1}H-NMR (500 MHz, DMSO-d_6) δ = 1.16 (6H, s, CH_3), 2.44 (6H, s, CH_3), 2.45 (6H, s, CH_3), 3.86 (6H, s, NCH_3), 3.90 (2H, d, J = 14.9 Hz, CH_2) and 4.37 ppm (2H, d, J = 14.9 Hz, CH_2); ^{13}C-NMR (125 MHz, DMSO-d_6) δ = 9.3 (CH_3), 9.1 (CH_3), 24.4 (CH_3), 35.6 (CH_3), 45.0 (C), 53.3 (CH_2), 127.3 (C), 131.1 (C) and 132.5 ppm (C).

Preparation of 3,3'-(propane-1,3-diyl)*bis*(1-methyl-1*H*-imidazol-3-ium) iodide, 3.5.[253]



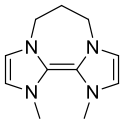
1-Methyl-1*H*-imidazole (3.42 mL, 50 mmol, 2.5 eq.) was dissolved in acetonitrile (20 mL) and sealed under inert atmosphere. 1,3-Diiodopropane (2.3 mL, 20 mmol, 1.0 eq.) was added via syringe and the reaction mixture was refluxed overnight. Dry diethyl ether was added to the cooled solution and the resultant precipitate was collected at the pump, and rinsed with dry diethyl ether (3 x 100 mL). The white crystalline residue was dried in a desiccator affording the pure hygroscopic 3,3'-(propane-1,3-diyl)*bis*(1-methyl-1*H*-imidazol-3-ium) iodide **3.5** (8.460 g, 18.4 mmol, 92 %) and stored in a glove-box: mp = 143-145 °C (lit. = 137 °C)[3]; ν_{max} (KBr)/cm^{-1}; 3075, 3020, 2988, 2834, 1568, 1557 and 1451; [Found: (HNES)$^+$ (M-I)$^+$ 333.0571. $C_{11}H_{18}I_2N_4$ requires (M-I), 333.0571]; ^{1}H-NMR (500 MHz, DMSO-d_6) δ = 2.42 (2H, quin, J = 6.7 Hz, CH_2), 3.90 (6H, s, CH_3), 4.26 (4H, t, 6.7 Hz, CH_2), 7.78-7.80 (4H, m, ArH) and 9.14 ppm (2H, s, ArH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ = 30.4 (CH_2), 36.8 (CH_2 or CH_3), 46.6 (CH_3 or CH_2), 123.1 (CH), 124.7 (CH) and 137.7 ppm (CH).

Preparation of 1,11-dimethyl-5,6,7,11-tetrahydro-1*H*-diimidazo[1,2-a:2',1'-c][1,4]diazepine, 1.309a and 3,3'-(propane-1,3-diyl)*bis*(1-methyl-4,5-deutero-1*H*-imidazol-2-ylidene), 3.8.



In a glove-box, 3,3'-(propane-1,3-diyl)*bis*(1-methyl-1*H*-imidazol-3-ium) iodide (0.920 g, 2.0 mmol, 1.0 eq.) **3.5** and sodium hydride (0.480 g, 20.0 mmol, 10 eq.) were weighed into a Schlenk flask (1 L) and sealed with a septum, before removing to a fumehood. The septum was replaced with a dry-ice condenser under a stream of argon. Liquid ammonia (1 L) was condensed into the Schlenk flask, the reaction was then refluxed for a full 24 h with the aid of cryocooler before the liquid ammonia was allowed to evaporate completely overnight. The Schlenk flask containing the dry grey solid with a yellow/green hue was sealed with a septum under argon and transferred back into a glovebox. The solid was scraped down with a spatula and extracted with diethyl ether (4 x 250 mL). Evaporation of the organic under reduced pressure afforded an yellow/orange residue containing a mixture of dimer 1,11-*dimethyl-5,6,7*,11-*tetrahydro*-1*H-diimidazo[*1,*2-a*:*2'*,1*'-c][*1,*4]diazepine* **1.309a** and *bis*-carbene *3,3'-bis*(1-*methyl*-1*H-imidazol-2-ylidene)* **3.8**. ^{1}H-NMR (C_6D_6) showed doublets at δ = 5.3-5.5 suggestive of a enetetramine and a pair of doublets about δ = 6.5 suggestive of an imidazol-2-ylidene , but the very small amount led us to investigate the successful formation of 1,11-dimethyl-5,6,7,11-tetrahydro-1*H*-diimidazo[1,2-a:2',1'-c][1,4]diazepine by Birch reduction (subsequently performed by Dr. Zhou).[2]

Preparation of 1,11-dimethyl-5,6,7,11-tetrahydro-1H-diimidazo[1,2-a:2',1'-c][1,4]diazepine, 1.309a by Birch reduction (performed by Dr. Zhou)[2]

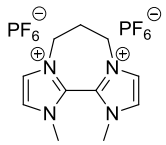


An air condenser was assembled on top of a Schlenk flask containing imidazolium salt **3.89** (X = Br) (500 mg, 1.37 mmol) in a glovebox. The flask was moved out of the glovebox and linked to an argon line, an ammonia line and a vacuum line with a three-way tap.

The gas lines were put under vacuum and refilled with argon. The operation was repeated five times to make sure there was no oxygen in the line. Then a gentle flow of argon was passed through the system with a bubbler at the end. The Schlenk flask was cooled in a dry

ice-acetone bath and ammonia gas was introduced, with liquid ammonia (~15 mL) being condensed into the flask (The ammonia had been dried under argon with sodium in another Schlenk flask and distilled at room temperature). The ammonia gas flow was stopped and the mixture was stirred in the cooling bath with a gentle argon flow passing through. Sodium (154 mg, 6.70 mmol, freshly cut in the glovebox) was added quickly from the top of the air condenser. The cooling bath was removed, the argon flow was stopped and the deep blue mixture was stirred at room temperature while the ammonia slowly evaporated. When the ammonia evaporation was complete, the reaction flask was moved into a glovebox and the mixture was extracted with diethyl ether (that had been freshly dried in the glovebox with sodium and benzophenone) [or benzene C_6D_6 (freshly dried by refluxing with molten potassium metal in a glovebox for 6 h)]. The solvent was removed affording **1.309a** as a yellow solid (228 mg, 81%). NMR spectra were taken with specially dried C_6D_6 (freshly dried by refluxing with molten potassium metal in a glovebox for 6 h). ^{1}H-NMR (C_6D_6, 400 MHz) δ = 1.31-1.37 (2H, m), 2.44-2.47 (4H, m), 2.56 (6H, s), 5.43 (2H, d, J = 2.4 Hz) and 5.54 ppm (2H, d, J = 2.4 Hz); ^{13}C-NMR (C_6D_6, 100 MHz) δ = 29.8 (CH_2), 35.7 (CH_2), 52.3 (CH_3), 119.8 (CH), 121.3 (CH) and 125.9 ppm (C).

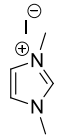
Preparation of 1,11-dimethyl-6,7-dihydro-5H-diimidazo[1,2-a:2',1'-c][1,4]diazepine-1,11-diium hexafluorophosphate, 3.90.



The above reaction was repeated and the neutral dimer **1.309a** was extracted inside a glovebox with freshly dried benzene (30 mL) (dried by refluxing with potassium metal for 5 h inside a glovebox followed by distillation). The mixture was filtered and to the solution was added solution of I_2 (1.05g, 4.11 mmol) in dry benzene (20 mL). The mixture was stirred for 10 min and was transferred out of the glovebox. Water (40 mL) was added and the mixture was stirred vigorously at room temperature for 2 h. The water layer was separated and HPF_6 (3 mL, 60%) was added. The suspension was stirred at room temperature and then neutralized with NaOH. The solid was filtered, washed with water and dried under vacuum affording *1,11-dimethyl-6,7-dihydro-5H-diimidazo[1,2-a:2',1'-c][1,4]diazepine-1,11-diium hexafluorophosphate* **3.90** as a white solid, (312 mg, 46 %). mp 259 ºC (dec.). ν_{max} (KBr)/cm^{-1} 3161, 1560, 1544, 1508, 1459, 1384, 1242, 1180, 839. [Found: (ESI) $(M\text{-}PF_6)^+$ 349.1011, $C_{11}H_{16}F_6N_4P$ (M-PF_6) requires 349.1011; Found $(M\text{-}2PF_6\text{-}H)^+$ 203.1290, $C_{11}H_{15}N_4$ (M-2PF_6-

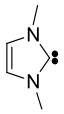
H) requires 203.1291]; 1H-NMR (DMSO-d_6, 400 MHz) δ = 2.54-2.62 (2H, m, CH_2), 4.05 (6H, s, CH_3), 4.25 (2H, ddd, J = 14.8, 9.6, 9.6 Hz, CH_2), 4.69 (2H, ddd, J = 14.8, 4.3, 4.3 Hz, CH_2), 8.17 (2H, d, J = 1.8 Hz, ArH) and 8.22 ppm (2H, d, J = 1.8 Hz, ArH); 13C-NMR (DMSO-d_6, 100 MHz) δ = 29.7 (CH_2), 37.5 (CH_3), 45.4 (CH_2), 126.2 (CH), 127.1 (CH) and 128.0 ppm (C).

Preparation of 1,3-dimethyl-1*H*-imidazol-3-ium iodide, 3.91.[254,255]



1-Methyl-1*H*-imidazole (9.853 g, 120.0 mmol, 1.0 eq.) was dissolved in acetonitrile (20 mL) In a round-bottomed flask equipped with a stirrer bar and condenser, under an inert atmosphere. Methyl iodide (8.22 mL, 132.0 mmol, 1.1 eq.) was added via a syringe and the reaction mixture was refluxed overnight. Dry diethyl ether was added to the cooled solution and the resultant precipitate was collected, and rinsed with dry diethyl ether (3 x 100 mL). The white crystalline solid residue was dried in a desiccator and the pure highly hygroscopic 1,3-dimethyl-1*H*-imidazol-3-ium iodide **3.91** (26.22 g, 117.0 mmol, 98%) was then stored in a glove-box; ν_{max} (KBr)/cm^{-1} 3155, 3100, 2951, 1622, 1575, 1174 and 620; Found: $(HNES)^+$ $(M\text{-}I)^+$ 97.0760. $C_5H_9IN_2$ requires (M-I), 97.0760]; mp = 80-82 °C; ^{1}H-NMR (500 MHz, DMSO-d_6) δ = 3.89 (6H, s, CH_3), 7.34 (2H, d, J = 1.5 Hz, ArH) and 9.11 ppm (1H, br. s, ArH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ = 36.7 (CH_3), 124.3 (CH) and 137.8 ppm (CH).

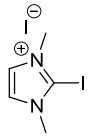
Preparation of 1,3-dimethyl-1*H*-imidazol-2-ylidene, 3.92.[255]



1,3-Dimethyl-1*H*-imidazol-3-ium iodide **3.91** (0.896 g, 4.0 mmol, 1.0 eq.) and sodium hydride (0.96 g, 40.0 mmol, 10.0 eq.) were weighed into a Schlenk flask (500 mL) under argon. The Schlenk flask was equipped with a dry-ice condenser and liquid ammonia (approx. 500 mL) was condensed onto the reactants, forming a yellow solution. The reaction was refluxed for 4 h before the liquid ammonia was allowed to evaporate to dryness overnight. At room temperature, the solid residue was scraped down with a spatula under inert atmosphere and the yellow product was repeatedly triturated with diethyl ether, until extracts were colourless. The combined organic extracts were concentrated under vacuum with stirring to afford 1,3-dimethyl-1*H*-imidazol-2-ylidene **3.92** as a yellow-green oil. ^{1}H-

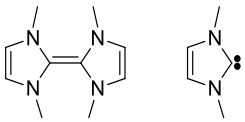
NMR (400 MHz, C_6D_6) δ = 3.38 (6H, s, CH_3) and 6.30 ppm (2H, s, ArH); ^{13}C-NMR (100 MHz, C_6D_6) δ = 38.1 (CH_3), 120.3 (CH) and 217.1 ppm (C).

Preparation of 2-iodo-1,3-dimethyl-1*H*-imidazol-3-ium iodide, 3.93.



1,3-Dimethyl-1*H*-imidazol-2-ylidene **3.92** was dissolved in diethyl ether (50 mL) with stirring under nitrogen. Iodine was added until precipitation had ceased and a colour change from yellow to brown was observed in the diethyl ether. The suspension was stoppered and removed to a fumehood where the brown precipitate was collected and washed with diethyl ether (2 x 50 mL) to afford pure 2-iodo-1,3-dimethyl-1*H*-imidazol-3-ium iodide **3.93** as grey solid (0.824 g, 3.67 mmol, 92%); mp = 135-137 °C; ν_{max} (KBr)/cm^{-1} 3124,1639, 1168, 641 and 618; [Found: $(HNES)^+$ $(M-I)^+$ 222.9722. $C_5H_8N_2I_2$ requires (M-I), 222.9727]; ^{1}H-NMR (400 MHz, CD_3CN) δ = 3.86 (6H, s, CH_3) and 7.97 ppm (2H, s, CH); ^{13}C-NMR (100 MHz, CD_3CN) δ = 40.1 (CH_3), 106.8 (C-I) and 126.5 ppm (CH).

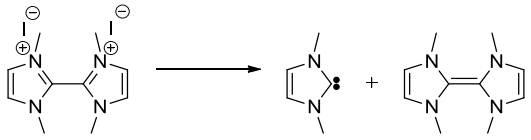
Preparation of 1,1',3,3'-tetramethyl-1,1',3,3'-tetrahydro-2,2'-biimidazolylidene 1.309b and **1,3-dimethyl-1*H*-imidazol-2-ylidene 3.92.**



Within a glove-box, 1,3-dimethyl-1*H*-imidazol-3-ium iodide **3.91** (0.672 g, 3.0 mmol, 1.5 eq.) and pre-washed sodium hydride (0.048 g, 2.0 mmol, 1.0 eq.) were weighed into a Schlenk flask (100 mL) that was then equipped with a dry-ice condenser under a stream of argon. The minimum volume of liquid ammonia required to fully dissolve the reactants was condensed into the Schlenk flask. Initially a pink colouration of the reaction mixture was observed and this gradually changed to yellow. The liquid ammonia was refluxed for 1 h and then allowed to evaporate overnight. At room temperature, the viscous yellow semi-solid was triturated and diethyl ether (50 mL) and the diethyl ether took on a yellow colour. This diethyl ether extract was concentrated to a pink residue (mass estimated at less than 50 mg) which was examined by NMR. A number of components were present but the presence of a singlet at δ = 5.3 ppm was suggestive of a enetetramine while a singlet at δ = 6.2 was suggestive of an imidazol-2-ylidene but the very small amount led us to investigate the

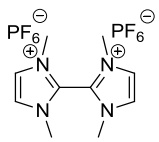
successful formation of 1,1',3,3'-tetramethyl-1,1',3,3'-tetrahydro-2,2'-biimidazolylidene by Birch reduction (subsequently performed by Dr. Zhou).[2]

Preparation of Preparation of 1,3-dimethyl-1*H*-imidazol-2-ylidene 3.92 and 1,1',3,3'-tetramethyl-1,1',3,3'-tetrahydro-2,2'-biimidazolylidene, 1.309b (Birch Reduction carried out by Dr. Zhou).[2]



In a Schlenk flask (50 mL) equipped with a dry-ice condenser, 1,1',3,3'-tetramethyl-1H,1'H-[2,2'-biimidazole]-3,3'-diium iodide **3.80** (223 mg, 0.5 mmol, 1.0 eq.) was suspended in dry degassed diethyl ether (10 mL) and placed under an argon stream before being dissolved in condensed liquid ammonia (approx. 15 mL). A specialised dropping funnel containing pure sodium (0.048g, 2.087 mmol, 4.0 eq.) was placed in between the Schlenk flask and condenser, the sodium was dissolved in condensed liquid ammonia (10 mL) before adding dropwise to the vigorously stirred bi-imidazolium solution. The blue solution of solvated electrons instantly began to change the colourless transparent imidazolium solution vivid transparent yellow, dropwise addition was continued until the reaction mixture become blue green. The dropping funnel was then removed under stream of argon and the ammonia was allowed to evaporate. During the evaporation the yellow colour faded to almost colourless and a white precipitate began to form. At room temperature the suspension was transferred to a glove-box and some yellow colouration of both diethyl ether and precipitate began to redevelop. The diethyl ether was filtered and concentrated in under vacuum. NMR analysis support the formation of dimer *1,1',3,3'-tetramethyl*-1,1'*,3,3'-tetrahydro-2,2'-biimidazolylidene*, **1.309b**; ^{1}H-NMR (C_6D_6, 400 MHz) δ = 2.53 (12H, s), 5.45 ppm (4H, s). ^{13}C-NMR (C_6D_6, 100MHz) δ = 35.7, 121.7, 126.2 ppm. The ^{1}H-NMR spectrum also contained signals at δ = 3.39 and 6.27 ppm ascribed to a trace of carbene **3.92**.

Preparation of 1,1',3,3'-tetramethyl-1H,1'H-[2,2'-biimidazole]-3,3'-diium hexafluoro-phosphate, 3.95. (Performed by Dr. Zhou)[2]

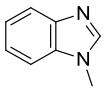


The above reaction procedure was repeated and the neutral dimer was extracted inside a glovebox with benzene (30 mL, freshly dried by refluxing with molten potassium metal for 5

h in a glovebox and distilled). The clear solution was decanted into a flask and a solution of I2 (1.05 g, 4.11 mmol) in dry benzene (20 mL) was added. The mixture was stirred for 10 min and was transferred out of the glovebox. Water (40mL) was added and the mixture was stirred vigorously at room temperature for 2 h. The water layer was separated and HPF_6 (3mL, 60%) was added. The suspension was stirred at room temperature and neutralized with NaOH. The solid was filtered, washed with water and dried under vacuum, affording *1,1',3,3'-tetramethyl-1H,1'H-[2,2'-biimidazole]-3,3'-diium hexafluorophosphate* **3.95** as a white solid, (167 mg, 31%), mp > 300ºC (dec.), ν_{max} (KBr)/cm^{-1} 3162, 1567, 1540, 1520, 1442, 1386, 1240, 832. [Found: (HNES) $(M\text{-}PF_6)^+$ 337.1011, $C_{10}H_{16}F_6N_4P$ $(M\text{-}PF_6)$ requires 337.1011; $(M\text{-}2PF_6\text{-}H)^+$ 191.1289, $C_{10}H_{15}N_4$ requires 191.1291]; ^{1}H-NMR (DMSO-d_6, 400MHz) δ = 3.87 (12H, s) and 8.27 ppm (4H, s); ^{13}C-NMR (DMSO-d_6, 100MHz) δ = 36.4 (CH_3), 124.7 (C) and 128.0 (CH) ppm.

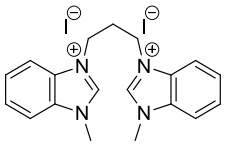
6.4 Chapter 4: Indoles Synthesis *via* Radical Cyclisation Mediated by a Super-Electron-Donor

Synthesis of 1-methyl-1*H*-benzo[d]imidazole.[256]



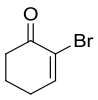
In a 500 mL round-bottomed flask, benzimidazole (30.0 g, 254 mmol, 1.0 eq.) was suspended in acetonitrile (200 mL) and cooled with an ice-bath, aqueous sodium hydroxide (25%, 19.98 g in 63 mL water) was added. Methyl iodide (15.5 mL, 279 mmol, 1.1 eq.) was added to the suspension over 5 min. The reaction was allowed to stir overnight. The orange reaction mixture was concentrated to low volume *in vacuo*, diluted with CH_2Cl_2 (100 mL) and worked up with water (2 x 100 mL) and brine (100 mL). The organic layer was dried over sodium sulfate and concentrated to a mobile oil *in vacuo*. The crude product was purified by distillation under vacuum at 190 °C furnishing 1-methyl-1*H*-benzo[d]imidazole as white crystalline solid (27.6 g, 209 mmol, 82%): mp = 57-59 °C (lit. = 57-60 °C)[256]; ^{1}H-NMR (500 MHz, DMSO-d_6) δ = 3.88 (3H, s, CH_3), 7.23-7.26 (1H, m, ArH), 7.29-7.32 (1H, m, ArH), 7.59-7.60 (1H, m, ArH) and 7.67-7.69 ppm (1H, m, ArH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ = 31.5 (CH_3), 111.0 (CH), 120.2 (CH), 122.3 (CH), 123.1 (CH), 135.5 (C), 144.2 (C) and 145.4 (CH).

Synthesis of 3,3'-(propane-1,3-diyl)*bis*(1-methyl-1*H*-benzo[d]imidazol-3-ium) iodide, 1.274.[91]



1-Methyl-1*H*-benzimidazole (27.61 g, 209 mmol, 4.0 eq.) and 1,3-diiodopropane (15.45 g, 52 mmol, 1.0 eq.) were dissolved in acetonitrile (100 mL) under argon. This solution was heated under reflux for 24 h. After cooling, diethyl ether (100 mL) was added precipitating a white solid salt from the reaction mixture. The solid was filtered and washed with diethyl ether (4 x 30 mL), after which it was dried *in vacuo* to afford the 1,3-*bis*[3-methyl-3 *H*-benzimidazolium]propane diiodide, **1.274** as a white solid (27.26 g, 48.6 mmol, 93%); mp = 280-283 °C dec. (lit. = 276-277 °C dec.)[91]; ^{1}H-NMR (400 MHz, DMSO-d_6) δ = 2.60 (2H, quintet, J = 7.0 Hz, CH_2), 4.08 (6H, s, NCH_3), 4.67 (4H, t, J = 7.0 Hz, CH_2), 7.68-7.74 (4H, m, ArH) and 8.02-8.08 ppm (4H, m, ArH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ = 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) and 143.2 ppm (CH).

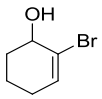
Synthesis of 2-bromocyclohex-2-enone, 4.34.[213]



2-Cyclohexen-1-one **4.33** (1.94 mL, 20 mmol, 1.0 eq.) was dissolved in dry CH_2Cl_2 (50 mL) and cooled to -78 °C under argon. Bromine (1.08 mL, 21 mmol, 1.05 eq.) in dry CH_2Cl_2 (20 mL) was added dropwise to the solution with stirring, and the reaction mixture was allowed to stir at -5 °C for 1.5 h. Triethylamine (4.65 mL, 33.4 mmol, 1.67 eq.) in dry CH_2Cl_2 (20 mL) was added dropwise into the reaction maintaining the temperature at -5 °C, a colour change from transparent orange to colourless and finally to transparent grey was observed. The reaction mixture was stirred at room temperature for 2 h before working up with 1M HCl (2 x 20 mL), water (20 mL) and brine (20 mL), the aqueous phase was back-extracted with CH_2Cl_2 (3 x 20 mL). The combined transparent green organic layer was dried over sodium sulfate and filtered, decolourised with activated charcoal, refiltered and concentrated *in vacuo* at room temperature. The colourless semi-solid was recrystallised from ethyl acetate/hexane warming to no more than 30 °C, to afford 2-bromocyclohex-2-enone **4.34**, as colourless, prisms (2.28 g, 13.027 mmol, 65%): mp = 73-75 °C (lit. = 75-76 °C)[213];]; ν_{max} (KBr)/cm^{-1} 2956, 2934, 2868, 1683, 1597, 1122 and 700; ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 2.06-2.12

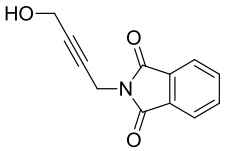
(2H, m, CH_2), 2.45-2.48 (2H, m, CH_2), 2.63-2.66 (2H, m, CH_2) and 7.44 ppm (1H, t, J = 4.5 Hz, CH=).

Synthesis of 2-bromocyclohexen-1-ol, 4.30.[213,257]



2-Bromocyclohex-2-enone **3.34**, (1.61 g, 9.20 mmol, 1.0 eq.) and cerium (III) chloride heptahydrate (3.34g, 9.20 mmol, 1.0 eq.) were dissolved in methanol (40 mL) and cooled to 0 °C. Sodium borohydride (0.35 g, 9.20 mmol, 1.0 eq.) was added to the stirred solution in portions causing effervescence. The reaction was allowed to stir for 30 min then quenched with water (30 mL) and extracted with CH_2Cl_2 (4 x 20 mL). The combined extracts were dried over sodium sulfate, filtered and concentrated to colourless oil *in vacuo*. Drying under vacuum yielded 2-bromocyclohexen-1-ol **4.30**, (1.34 g, 7.57 mmol, 82.3 %) as large colourless, regular crystals; mp = 36-39 °C (lit. = 37-39 °C)[257]; ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 1.62-1.79 (2H, m, CH_2), 1.87-1.99 (2H, m, CH_2), 2.03-2.17 (2H, m, CH_2), 2.18 (1H, s, OH), 4.21-4.23 (1H, m, C*H*OH) and 6.22 ppm (1H, t, J = 4.0 Hz, CH=); ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 17.6 (CH_2), 27.8 (CH_2), 32.0 (CH_2), 69.9 (CH), 125.8 (C) and 132.5 (CH).

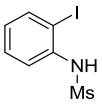
Synthesis of 4-phthalimidobut-2-yn-1-ol, 4.67.[229]



2-Butyn-1,4-diol (3.51 g, 40.8 mmol, 1.5 eq.), phthalimide (4.00 g, 27.2 mmol, 1.0 eq.) and triphenylphosphine (7.13 g, 27.2 mmol, 1.0 eq.) were dissolved in dry THF (50 mL) under argon then cooled to -20 °C in a 250 mL RB flask. Diethyl azodicarboxylate (5.50 g, 27.2 mmol, 1.0 eq.) in dry THF (50 mL) was added dropwise to the stirred reaction mixture. The reaction mixture was allowed to warm to room temperature and react overnight. The crude product was concentrated *in vacuo* and chromatographed on silica gel, eluting with ethyl acetate /hexane 40:60. The concentrated organic was recrystallised from hot CH_2Cl_2 to afford 4-phthalimidobut-2-yn-1-ol **4.67**, (3.81g, 17.7 mmol, 65%): mp = 169-171 °C (lit. = 166-167 °C); ν_{max} (KBr)/cm^{-1} 3450 (OH), 1767 and 1718 (C=O), 1427, 1397, 1345, 1126 and 724; ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 1.74 (1H, t, J = 6.0 Hz, OH), 4.25 (2H, dt, J = 6.0, 2.0 Hz, C$\underline{H_2}$OH), 4.50 (2H, t, J = 2.0 Hz, CH_2), 7.74-7.76 (2H, m, ArH) and 7.88-790 (2H, m, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 27.3 (CH_2), 51.0 (CH_2), 79.3 (C), 81.4 (C), 123.6 (CH),

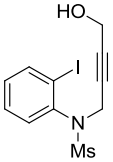
132.0 (C), 134.2 (CH) and 167.1 ppm (C); [Found: $(HNES^+)$ $(M+NH_4)^+$ 233.0926. $C_{12}H_{13}O_3N_2$ $(M+NH_4)$ requires 233.0921]; ν_{max} (KBr)/cm^{-1} 3450 (OH), 1767 and 1718 (C=O), 1427, 1397, 1345, 1126 and 724.

Synthesis of *N*-(2-iodophenyl)methanesulfonamide, 4.53a.[213]



2-Iodoaniline (5.00 g, 22.9 mmol, 1.0 eq.) and DMAP (0.28g, 2.3 mmol, 0.1 eq.) were dissolved in CH_2Cl_2 (10 mL) under an inert atmosphere. Methanesulfonyl chloride (2.13 mL, 27.9 mmol, 1.2 eq.) was diluted in CH_2Cl_2 (5 mL) under an inert atmosphere before being transferred dropwise to the 2-iodoaniline solution *via* a cannula and allowed to stir overnight. The reaction mixture was concentrated to a brown semi-solid *in vacuo*. The crude material was dissolved in CH_2Cl_2 (50 mL) and extracted with 2M HCl (2 x 20 mL) and 2M NaOH (5 x 40 mL). The combined NaOH extractions were acidified with conc. HCl, inducing a brown/cream precipitation. The precipitate was extracted with CH_2Cl_2 (4 x 40 mL), the combined organic was washed with water (50 mL) and brine (50 mL) then dried over $NaSO_4$. The filtered organic was concentrated *in vacuo* to a brown oil, which on cooling afforded *N*-(2-iodophenyl)methanesulfonamide **4.53a**, (5.56 g, 83 %) as a yellow/brown crystalline solid; mp = 89-92 °C (lit. = 94-95 °C)[213]; ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 3.02 (3H, s, SO_2CH_3), 6.65 (1H, s, NH), 6.93-9.96 (1H, m, ArH), 7.37-7.41 (1H, m, ArH), 7.66 (1H, dd, J = 8.1, 1.4 Hz, ArH) and 7.84 ppm (1H, dd, J = 8.1, 1.5 Hz, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 40.1 (CH_3), 92.1 (C), 122.4 (CH), 127.3 (CH), 129.9 (CH), 137.6 (C) and 139.4 ppm (CH); [Found: $(HNES^+)$ $(M+NH_4)^+$ 314.9666. $C_{12}H_{17}O_3NI$ $(M+NH_4)$ requires 314.9659].

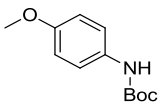
Synthesis of *N*-(4-hydroxybut-2-ynyl)-*N*-(2-iodophenyl)methanesulfonamide, 4.70.



N-(2-iodophenyl)methanesulfonamide, **4.53a** (0.93 g, 3.13 mmol, 1.0 eq.) and 2-butyne-1,4-diol (0.54 g, 6.26 mmol, 2.0 eq.) were dissolved in dry tetrahydrofuran (10 mL) under argon. The solution was cooled to -20 °C and tri-*n*-butylphosphine (1.17 mL, 4.70 mmol, 1.5 eq.) was added dropwise from a syringe. DEAD (0.82 g, 4.70 mmol, 1.5 eq.) in dry tetrahydrofuran (5 mL) was transferred to the reaction vessel dropwise *via* a cannula, the reaction was allowed to warm to ambient temperature and stir overnight. The solvent was

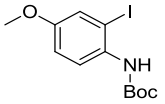
removed *in vacuo* and crude residue was dissolved in ethyl acetate (20 mL) then worked up with 2M NaOH (3 x 20 mL), 2M HCl (1 x 20 mL), water (2 x 20 mL) and brine (20 mL). The organic phase was dried over sodium sulfate and then concentrated *in vacuo*. The crude product was purified by chromatography on silica gel, elution in CH_2Cl_2/ethyl acetate (4:1) removed tri-*n*-butylphosphine, re-chromatographed in Et_2O to yield the desired product *N*-(4-hydroxybut-2-ynyl)-*N*-(2-iodophenyl)methanesulfonamide **4.70** (0.54 g, 1.48 mmol, 47%) as large irregular off-white crystals; ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 1.75 (1H, s, OH), 3.16 (1H, s, CH_3), 4.13 (1H, d, *J* = 18.0 Hz, CH_2), 4.29 (2H, s, C$\underline{H}_2$OH), 4.75 (1H, d, *J* = 18.0 Hz, CH_2), 7.13 (1H, ddd, *J* = 8.0, 7.5, 1.5 Hz, ArH), 7.44 (1H, ddd, *J* = 8.0, 7.5, 1.5 Hz, ArH), 7.62 (1H, dd, *J* = 8.0, 1.5 Hz, ArH), 7.96 (1H, dd, *J* = 8.0, 1.5 Hz, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 40.8 (CH_3), 41.4 (CH_2), 51.0 (CH_2), 80.1 (C), 84.3 (C), 101.9 (C), 129.3 (CH), 130.7 (CH), 131.5 (CH), 140.4 (CH), 140.9 (C); [Found: (ESI$^+$) $(M+NH_4)^+$ 382.9926. $C_{11}H_{16}IO_3N_2S$ requires $(M+NH_4)$ 382.9921.

Synthesis of *tert*-butyl 4-methoxyphenylcarbamate, 4.25.[216,217]



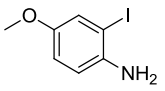
Para-anisidine (10.0 g, 81.2 mmol, 1.0 eq.) and di-*tert*-butyl dicarbonate (26.58 g, 121.8 mmol, 1.5 eq.) were dissolved in dry THF (100 mL) and stirred overnight. The reaction mixture was concentrated to a brown crystalline solid *in vacuo*. The crude organic residue was redissolved in diethyl ether (50 mL) and washed with water (3 x 50 mL) and brine (50 mL). The organic phase was dried over sodium sulfate, filtered and decolourised with activated charcoal. The charcoal was removed then by filtration through celite and the concentrated crude product was recrystallised from diethyl ether/hexane to afford *tert*-butyl(4-methoxyphenol)carbamate **4.25**, as long white needles with a purple iridescence (16.5 g, 73.9 mmol, 91 %). ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 1.52 (9H, s, *t*Bu), 3.79 (3H, s, CH_3), 6.35 (1H, s, NH), 6.83-6.86 (2H, m, ArH) and 7.27 ppm (2H, d, *J* = 8.0 Hz, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 28.4 (CH_3), 55.5 (CH_3), 80.2 (C), 114.2 (CH), 120.6 (CH), 131.4 (C), 153.2 (C) and 155.7 ppm (C); [Found: (HNES$^+$) $(M+H)^+$ 224.1284. $C_{12}H_{18}O_3N$ (M+H) requires 224.1281].

Synthesis of *tert*-butyl 2-iodo-4-methoxyphenylcarbamate, 4.26.[216,217]



In a flamed-dried round-bottomed flask *tert*-butyl(4-methoxyphenyl)carbamate **4.25** (5.51 g, 25 mmol, 1.0 eq.) was dissolved in dry diethyl ether (100 mL) under an atmosphere of argon and cooled to -20 °C with stirring. *tert*-butyllithium in pentane (41.40 mL, 62.5 mmol, 2.5 eq.) was added dropwise to the stirred solution maintaining the temperature at -20 °C. The reaction mixture was stirred for 3 h at -20 °C before cooling to -78 °C. 1,2-diiodoethane (10.57 g, 37.5 mmol, 1.5 eq.) was added dropwise under argon maintaining -78 °C, on complete addition the reaction was allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched with saturated sodium thiosulfate solution (80 mL) and extracted with diethyl ether (2 x 120 mL). The organic phase was then washed with brine (100 mL) and dried over sodium sulfate, filtered and concentrated *in vacuo*. The dark crude organic residue was purified by flash chromatography on silica gel eluting with hexane/ethyl acetate (19:1), *tert*-butyl 2-iodo-4-methoxyphenylcarbamate, **4.26** (5.12 g, 14.7 mmol, 59%) was afforded as a white crystalline solid after concentrating *in vacuo*: mp = 49-50 °C (lit. = 48-49)[216]; ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 1.53 (9H, s, *t*Bu), 3.77 (3H, s, CH_3), 6.54 (1H, s, NH), 6.90 (1H, dd, J = 9.0, 3.0 Hz, ArH), 7.30 (1H, d, J = 3.0 Hz, ArH) and 7.84 ppm (1H, d, J = 9.0 Hz, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 28.3 (CH_3), 55.7 (OCH_3), 80.7 (C), 89.8 (C), 114.9 (CH), 122.0 (CH), 123.7 (CH), 132.5 (C), 153.1 (C) and 156.0 ppm (C); [Found: (HES^+) $(M+H)^+$ 350.0254. $C_{12}H_{17}O_3NI$ (M+H) requires 350.0248].

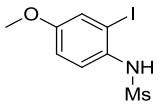
Synthesis of 2-iodo-4-methoxyaniline, 4.27b.[216,217]



tert-Butyl(2-iodo-4-methoxyphenyl)carbamate **4.26** (4.15 g, 12.0 mmol, 1.0 eq.) in dry CH_2Cl_2 (40 mL) was cooled to 0 °C under argon. TFA (11.1 mL, 144.0 mmol, 12.0 eq.) in dry CH_2Cl_2 (10 mL) was added dropwise to the stirred solution. The reaction mixture was stirred for 3 h at 0 °C then quenched with water (60 mL) and diluted with CH_2Cl_2 (20 mL). The organic was separated and the aqueous phase was basified with sodium hydroxide pellets before extracting with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine (30 mL) and dried over sodium sulfate, filtered and concentrated *in vacuo* to crude brown oil. The crude product was purified by flash chromatography on silica gel eluting with hexane/ethyl acetate (6:1 initially, switching to 5:1 once the product began to elute). After

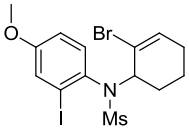
concentration *in vacuo* 2-iodo-4-methoxyaniline, **4.27b** was afforded as a colourless oil, (2.26g, 9.1 mmol, 76%): ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 3.66 (2H, s, NH_2), 3.73 (3H, s, CH_3), 6.71 (1H, d, *J*= 9.0 Hz, ArH), 6.78 (1H, dd, *J* = 3.0, 9.0 Hz, ArH) and 7.22 ppm (1H, d, *J*= 3.0, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 56.3 (CH_3), 84.6 (C), 115.7 (CH), 116.5 (CH), 123.9 (CH), 141.2 (C) and 153.1 ppm (C); [Found: ($HNES^+$) $(M+H)^+$ 249.9725. C_7H_9ONI (M+H) requires 249.9723].

3.2.9 Synthesis of *N*-(2-iodo-4-methoxyphenyl)methanesulfonamide, 2.53b.[229]



2-Iodo-4-methoxyaniline **4.27b** (2.00 g, 8.0 mmol, 1.0 eq.) and 4-dimethylaminopyridine (0.10 g, 0.8 mmol, 0.1 eq.) were dissolved in CH_2Cl_2 (15 mL) under argon and cooled in an ice-bath. Methanesulfonyl chloride (0.66 mL, 8.4 mmol, 1.05 eq.) was added to the reaction mixture over 30 min and the reaction was allowed stir at ambient temperature overnight. The reaction mixture was concentrated *in vacuo* then redissolved in CH_2Cl_2 (20 mL) and washed with 2M HCl (3 x 20 mL), $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried over magnesium sulfate, filtered and decolourised with activated charcoal. The organic was filtered through celite and concentrated *in vacuo* to afford *N*-(2-iodo-4-methoxyphenyl) methanesulfonamide **4.53b**, as small, fine off-white crystals (2.52 g, 7.7 mmol, 96%): mp = 118-120 °C (lit. = 116-117 °C)[229]; ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 2.97 (3H, s, SO_2CH_3), 3.80 (3H, s, OCH_3), 6.34 (1H, s, NH), 6.94 (1H, dd, *J* = 8.9, 2.8 Hz, ArH), 7.36 (1H, d, *J*= 2.8 Hz, ArH) and 7.55 (1H, d, *J*= 8.9 Hz, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 40.3 (CH_3), 56.1 (OCH_3), 94.9 (C), 115.8 (CH), 124.6 (CH), 126.1 (CH), 130.9 (C) and 158.7 (C); [Found: ($HNES^+$) $(M+NH_4)^+$ 344.9769, $C_8H_{14}O_3N_2I$ $(M+NH_4)$ requires 344.9764].

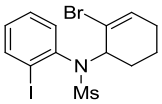
Synthesis of *N*-(2-bromocyclohex-2-enyl)-*N*-(2-iodo-4-methoxyphenyl)methanesulfonamide, 4.15b.



Under argon, *N*-(2-iodo-4-methoxyphenyl) methanesulfonamide, **4.53b** (1.00 g, 3.06 mmol, 1.1 eq.) and 2-bromo-2-cyclohexen-1-ol, **4.30** (0.49 g, 2.79 mmol, 1.0 eq.) were dissolved in dry THF (8.5 mL) with stirring and cooled to -20 °C. Tri-*n*-butylphosphine (0.93 g, 4.56 mmol, 1.5 eq.) was added to the reaction mixture before diethyl azodicarboxylate (0.80 g,

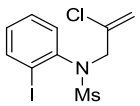
4.56 mmol, 1.5 eq.) in dry THF (5 mL) was added dropwise. The reaction mixture was allowed to stir overnight then concentrated *in vacuo*. The crude organic residue was redissolved in CH_2Cl_2 (50 mL) and washed with NaOH (2M, 2 x 25 mL), water (2 x 25 mL) and brine (25 mL). The organic layer was dried over sodium sulfate, filtered and concentrating to a mobile yellow oil *in vacuo*. The crude product was purified by flash chromatography on silica with CH_2Cl_2. *N*-(2-bromocyclohex-2-enyl)-*N*-(2-iodo-4-methoxyphenyl) methanesulfonamide **4.15b**, was afforded as a white crystalline solid (1.00 g, 2.06 mmol, 73%): ν_{max} (KBr) cm^{-1} 2953, 2935, 2912, 1644, 1585, 1478, 1336, 1151 and 761; ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 1.10-1.90 (1H, m, CH_2), 1.50-1.56 (1H, m, CH_2), 1.84-1.88 (1H, m, CH_2), 1.93-2.05 (2H, m, CH_2), 2.80-2.85 (1H, m, CH_2), 3.21 (3H, s, SO_2CH_3), 3.81 (3H, s, OCH_3), 4.96-4.97 (1H, m, NCH), 6.34 (1H, t, *J* = 4.0 Hz, =CH), 6.88 (1H, dd, *J* = 9.0, 3.0 Hz, ArH), 7.52 (1H, d, *J* = 3.0 Hz, ArH) and 7.56 ppm (1H, d, *J* = 9.0 Hz, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 17.2 (CH_2), 27.3 (CH_2), 32.4 (CH_2), 41.0 (CH_3), 55.6 (CH_3), 62.1 (CH), 106.6 (C), 114.4 (CH), 120.2 (C), 126.5 (CH), 132.5 (CH), 132.7 (C), 138.4 (CH) and 159.5 ppm (C); [Found: ($HNES^+$) $(M+NH_4)^+$ 502.9489. $C_{14}H_{21}Br_1IN_2O_3S$ $(M+NH_4)$ requires 502.9495].

Synthesis of *N*-(2-bromocyclohex-2-enyl)-*N*-(2-iodophenyl) methanesulfonamide, 4.15a.[213]



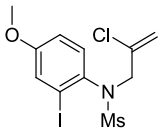
This compound was prepared using the same procedure as for *N*-(2-bromocyclohex-2-enyl)-*N*-(2-iodophenyl) methanesulfonamide, **4.15b** *N*-(2-iodophenyl)methanesulfonamide, **4.53a** (0.10 g, 0.336 mmol, 1.5 eq.) and 2-bromocyclohexen-1-ol, **4.30** (0.04 g, 0.224g mmol, 1.0 eq.) afforded *N*-(2-bromocyclohex-2-enyl)-*N*-(2-iodo-4-methoxyphenyl) methanesulfonamide as a white crystalline solid **4.15a**, (0.08g, 0.175 mmol, 78%): mp = 138-140 °C (lit. 143-144 °C)[213]; ν_{max} (KBr) cm^{-1} 2940, 2866, 1635, 1575, 1340, 1166 and 747; ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 1.04-1.13 (1H, m, CH_2), 1.51-1.59 (1H, m, CH_2), 1.82-1.85 (1H, m, CH_2), 1.92-2.05 (2H, m, CH_2), 2.83-2.86 (1H, m, CH_2), 3.24 (3H, s, SO_2CH_3), 4.99 (1H, s, NCH), 6.35 (1H, t, *J* = 4.0, =CH), 7.06 (1H, ddd, *J* = 8.0, 7.5, 1.5, ArH), 7.37 (1H, ddd, *J* = 8.0, 7.5, 1.5, ArH), 7.68 (1H, dd, *J* = 8.0, 1.5 ArH) and 8.02 (1H, dd, *J* = 7.5, 1.5 ArH); ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 17.2 (CH_2), 27.3 (CH_2), 32.4 (CH_2), 41.1 (CH_3), 62.4 (CH), 106.4 (C), 120.1 (C), 129.0 (CH), 130.2 (CH), 132.5 (CH), 138.5 (CH), 140.2 (C) and 141.4 ppm (CH); [Found: ($HNES^+$) $(M+NH_4)^+$ 472.9384. $C_{13}H_{19}BrIN_2O_2S$ $(M+NH_4)$ requires 472.9390].

Synthesis of *N*-(2-chloroallyl)-*N*-(2-iodophenyl)methanesulfonamide, 4.54a.[91]



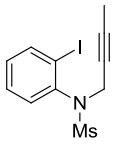
This compound was prepared using the same procedure as for *N*-(2-bromocyclohex-2-enyl)-*N*-(2-iodophenyl) methanesulfonamide, **4.15b** with *N*-(2-iodophenyl)methanesulfonamide **4.53a** (1.50 g, 5.05 mmol, 1.5 eq.) and 2-chloro-2-propen-1-ol (0.27 mL, 3.35 mmol, 1.0 eq.). The crude product was purified on silica gel eluting with CH_2Cl_2 to afford *N*-(2-chloroallyl)-*N*-(2-iodophenyl)methanesulfonamide **4.54a**, as a viscous green oil (1.01 g, 2.72 mmol, 81%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 3.16 (3H, s, SO_2CH_3), 4.25 (1H, d, *J* = 15.8 Hz, CH_2), 4.78 (1H, d, *J* = 15.8 Hz, CH_2), 5.31 (2H, m, =CH_2), 7.08-7.11 (1H, m, ArH), 7.39-7.42 (1H, m, ArH), 7.55 (1H, dd, *J* = 7.9, 1.6 Hz, ArH) and 7.95 ppm (1H, dd, *J* = 7.8, 1.5 Hz, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 42.4 (CH_3), 57.5 (CH_2), 100.7 (C), 118.2 (CH_2), 129.6 (CH), 130.8 (CH), 133.1 (CH), 137.2 (C), 140.7 (C) and 141.0 ppm (CH); [Found: (HES^+) $(M+NH_4)^+$ 388.9583. $C_{10}H_{15}ClIN_2O_2S$ $(M+NH_4)$ requires 388.9582].

Synthesis of *N*-(2-chloroallyl)-*N*-(2-iodo-4-methoxyphenyl) methanesulfonamide, 4.54b.



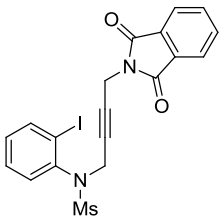
This compound was prepared using the same procedure as for *N*-(2-bromocyclohex-2-enyl)-*N*-(2-iodophenyl) methanesulfonamide, **4.15b** with *N*-(2-iodo-4-methoxyphenyl)methanesulfonamide **4.53b** (1.00 g, 3.06 mmol, 1.1 eq.) and 2-chloro-2-propen-1-ol (0.22 mL, 2.81 mmol, 1.0 eq.). The crude organic residue was purified on silica gel eluting with CH_2Cl_2 to afford *N*-(*2-chloroallyl)-N-*(*2-iodo-4-methoxyphenyl)methanesulfonamide* **4.54b** (1.12g, 2.79 mmol, 99%) as a viscous opaque oil: ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 3.14 (3H, s, SO_2CH_3), 3.81 (3H, s, OCH_3) 4.20 (1H, d, *J* = 15.7 Hz, CH_2), 4.75 (1H, d, *J* = 15.7 Hz, CH_2), 5.30-5.31 (2H, m, =CH_2), 7.91 (1H, dd, *J* = 8.8, 2.9 Hz, ArH), 7.43 (1H, d, *J* = 8.8 Hz, ArH) and 7.44 ppm (1H, d, *J*= 2.9 Hz, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 42.2 (CH_3), 56.1 (CH_3), 57.6 (CH_2), 101.2 (C), 115.1 (CH), 118.1 (CH_2), 125.9 (CH), 133.2 (CH), 137.4 (C) and 160.2 ppm (C); [Found: (HES^+) $(M+NH_4)^+$ 418.9685. $C_{11}H_{17}O_3N_2ClIS$ $(M+NH_4)$ requires 418.9688];

Synthesis of *N*-(but-2-ynyl)-*N*-(2-iodo-4-methoxyphenyl) methanesulfonamide, 4.55.[91]



This compound was prepared using the same procedure as for *N*-(2-bromocyclohex-2-enyl)-*N*-(2-iodophenyl) methanesulfonamide, **4.15b** with *N*-(2-iodophenyl)methanesulfonamide **4.53a** (0.89 g, 3.00 mmol, 1.1 eq.) and 2-butyn-1-ol (0.19g, 2.73 mmol, 1.0 eq.). The crude product was purified on silica gel eluting with CH_2Cl_2 to afford *N*-(but-2-ynyl)-*N*-(2-iodo-4-methoxyphenyl) methanesulfonamide **4.55**, as a colourless crystalline solid (0.74 g, 2.12 mmol, 78%): ν_{max} (KBr)/cm^{-1} 3064, 3024, 2927, 2301, 2229, 1467, 1437, 1334, 1219, 1154, 1066, 1054, 1023, 961, 873, 858, 771 and 728; ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 1.84 (3H, t, J = 2.4 Hz, CH_3), 3.16 (3H, s, SO_2CH_3), 4.02 (1H, d, J = 17.5 Hz, CH_2), 4.67 (1H, d, J = 17.5 Hz, CH_2), 7.11 (1H, ddd, J = 8.0, 7.9, 1.4 Hz, ArH), 7.43 (1H, ddd, J = 8.0, 7.9, 1.6 Hz, ArH), 7.60 (1H, dd, J = 7.9, 1.6 Hz, ArH) and 7.96 ppm (1H, dd, J = 8.0, 1.4 Hz, ArH); ^{13}C-NMR (500 MHz, $CDCl_3$) δ = 4.3 (CH_3), 41.9 (CH_2), 42.0 (CH_3), 74.1 (C), 83.0 (C), 103.1 (C), 129.9 (CH), 131.3 (CH), 132.0 (CH), 141.0 (CH) and 141.9 (C); [Found: (HES$^+$) $(M+NH_4)^+$ 366.9972. $C_{11}H_{16}O_2N_2IS$ requires $(M+NH_4)$ of 366.9968].

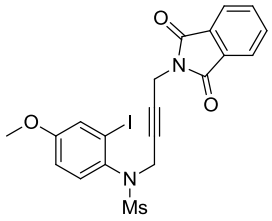
Synthesis of *N*-(4-(1,3-dioxoisoindolin-2-yl)but-2-ynyl)-*N*-(2-iodophenyl)methanesulfonamide, 4.68a.



This compound was prepared using the same procedure as for *N*-(2-bromocyclohex-2-enyl)-*N*-(2-iodophenyl) methanesulfonamide, **4.15b** with *N*-(2-iodophenyl)methanesulfonamide, **4.53a** (1.63 g, 5.50 mmol, 1.1 eq.) and 4-phthalimidobut-2-yn-1-ol, **4.67** (1.08g, 5.00 mmol, 1.0 eq.). Flash chromatography on silica gel eluting with pentane/ethyl acetate (3:2) provided a crude organic product. The crude product was dissolved in a minimum volume of ethyl acetate and pentane was added dropwise to the resultant green solution until the solution became cloudy. Sonication of the solution caused a fluffy white precipitate to form. This was collected at the pump and washed with cold pentane/ethyl acetate (4:1). The solid was dried under vacuum to provide *N*-(4-(1,3-dioxoisoindolin-2-yl)but-2-ynyl)-*N*-(2-iodophenyl)methanesulfonamide **4.68a**, as a lustrous white fluffy solid (1.80 g, 3.64 mmol,

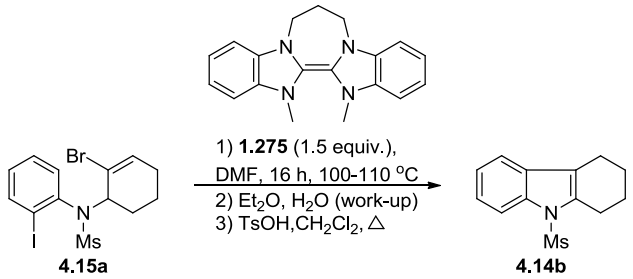
73%): ν_{max} (KBr)/cm^{-1} 2968 (CH), 1767 and 1712 (C=O), 1466, 1342 and 1150 (SO_2); ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 3.16 (3H, s, SO_2CH_3), 4.05 (1H, d, J = 18.3 Hz, CH_2), 4.47 (2H, t, J = 1.8 Hz, CH_2), 4.70 (1H, d, J= 18.3 Hz, CH_2), 7.02-7.06 (1H, m, ArH), 7.33 (1H, m, ArH), 7.59 (1H, dd, J = 7.9, 1.6 Hz, ArH), 7.77-7.78 (2H, m, ArH) and 7.89-7.91 (3H, m, ArH), [Found: (HNES$^+$) $(M+NH_4)^+$ 512.0125. $C_{19}H_{19}O_4N_3IS$ (M+H) requires 512.0135].

Synthesis of *N*-(4-(1,3-dioxoisoindolin-2-yl)but-2-ynyl)-*N*-(2-iodo-4-methoxyphenyl)-methanesulfonamide, 4.68b.[50]



This compound was prepared using the same procedure as for *N*-(2-bromocyclohex-2-enyl)-*N*-(2-iodophenyl) methanesulfonamide, **4.15b** with *N*-(2-iodo-4-methoxyphenyl)methanesulfonamide, **4.53b** (0.56 g, 1.71 mmol, 1.1 eq.) and 4-phthalimidobut-2-yn-1-ol, **4.67** (0.37g, 1.56 mmol, 1.0 eq.). The crude organic residue was dissolved in a minimum volume of CH_2Cl_2 a forming a green solution, and then pentane was added dropwise, forming a cloudy solution. The solution was then sonicated, precipitating a fluffy white solid which was collected at the pump and washed with pentane/ethyl acetate (4:1). Flash chromatography using pentane/ethyl acetate (1:1) afforded a crude product, re-chromatographed in CH_2Cl_2 and ethyl acetate (2.5%) to afford the desired *N*-(4-(1,3-dioxoisoindolin-2-yl)but-2-ynyl)-*N*-(2-iodo-4-methoxyphenyl) methanesulfonamide **4.68b**, (0.68 g, 1.30 mmol, 83%) as a white foam after concentration *in vacuo*. ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 3.13 (3H, s, SO_2CH_3), 3.77 (3H, s, OCH_3), 4.00 (1H, dt, J =18.3, 1.7 Hz, Hz, MsNCH_2), 4.47 (2H, t, J = 1.7 Hz, CH_2), 4.68 (1H, dt, J = 18.3, 1.7 Hz, MsNCH_2), 6.84 (1H, dd, J = 8.8, 2.9 Hz, ArH), 7.39 (1H, d, J= 2.9, ArH), 7.48 (1H, d, J= 8.8 Hz, ArH), 7.77-7.78 (2H, m, ArH) and 7.90-7.91 (2H, m, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 27.6 (CH_2), 41.1 (CH_2), 41.3 (CH_3), 56.0 (CH_3), 78.2 (C), 80.2 (C), 103.1 (C), 115.2 (CH), 123.9 (CH), 125.5 (CH), 131.5 (CH), 132.3 (C), 133.9 (C), 134.7 (CH), 160.3 (C) and 167.3 ppm (C); [Found: (HNES$^+$) $(M+NH_4)^+$ 524.0231. $C_{20}H_{21}O_5N_3IS$ (M+H) requires 524.0241].

Synthesis of 9-(methylsulfonyl)-2,3,4,9-tetrahydro-1*H*-carbazole, 4.14a.[213]

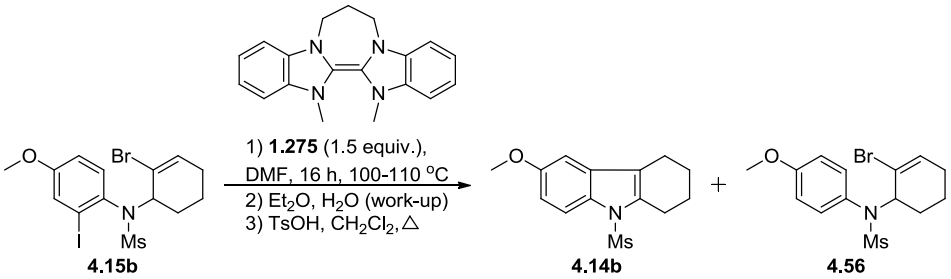


3'-(Propane-1,3-diyl)*bis*(1-methyl-1*H*-benzo[d]imidazol-3-ium) iodide **1.274**, 1.275 (0.252 g, 0.3 mmol, 1.5 eq.) was weighed into a flame-dried centrifuge tube and dried at 100 °C under high vacuum for 30 min with stirring. The cooled tube was purged with argon. Sodium hydride (60% oil dispersion) (0.180 g, 4.5 mmol, 15.0 eq.) was weighed into the tube and sealed under argon with a septum. The contents were washed with dry hexane (3 x 50 mL) and dried under an argon flow. Degassed anhydrous DMF (30 min) was transferred to the reaction vessel under argon forming a vivid yellow solution of super-electron donor 14,15-dimethyl-7,8,14,15-tetrahydro-6H-benzo[4,5]imidazo[1,2-a]benzo[4,5]imidazo[2,1-c][1,4] diazepine **1.275.** The suspension was allowed to stir for 3 h. *N*-(2-bromocyclohex-2-enyl)-*N*-(2-iodophenyl) methanesulfonamide, **4.15a** (137 mg, 0.300 mmol, 1.0 eq.), was weighed into a flamed-dried RB flask equipped with a condenser and stirrer bar then placed under vacuum for 3 h. The apparatus was purged with argon then sealed with a septum under an argon flow. The sodium hydride/super-electron-donor suspension was centrifuged and supernatant transferred to *N*-(2-bromocyclohex-2-enyl)-*N*-(2-iodophenyl) methanesulfonamide **4.15a** via a cannula. The reaction mixture was heated at 100-110 °C overnight. A colour change from vivid yellow to deep red was observed in the super-electron-donor supernatant solution on reaction with the substrate.

The cooled reaction mixture was poured water (50 mL) and extracted with diethyl ether (4 x 50 mL ether), the combined organic phase was washed with water (3 x 50 mL) and brine (1 x 50 mL) then dried over sodium sulfate, filtered and concentrated *in vacuo.* The organic residue was quickly chromatographed on silica gel to afford a mixture of indole/indolenine products which were treated with toluenesulfonic acid (0.052 g, 0.300 mmol, 0.5 eq.) in CH_2Cl_2 (5.0 mL) at reflux for 3 h. The crude organic residue was concentrated *in vacuo* and then chromatographed on silica gel with CH_2Cl_2/hexane (solvent gradient 80→90→100% CH_2Cl_2) to afford 9-(methylsulfonyl)-2,3,4,9-tetrahydro-1*H*-carbazole, **4.14a** (0.060 mg, 0.241 mmol, 80%): mp =102-103 °C (lit. 104-105 °C)[213]; ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 1.83-1.96 (4H, m, CH_2), 2.66-2.69 (2H, m, CH_2), 2.95-2.97 (2H, m, CH_2), 3.96 (3H, s, SO_2CH_3), 7.27-7.31 (2H, m, ArH), 7.42-7.45 (1H, m, ArH) and 7.98-8.01 ppm (1H, m, ArH);

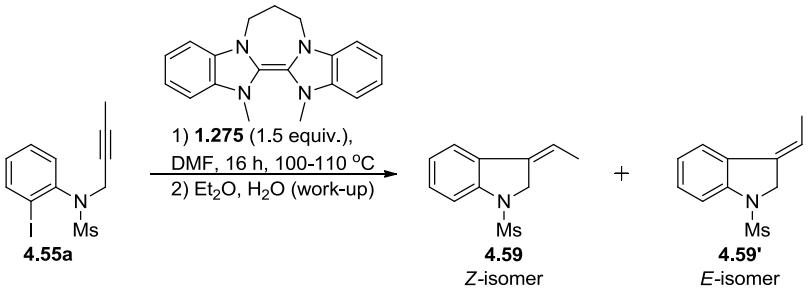
^{13}C-NMR (125 MHz, $CDCl_3$) δ = 21.4 (CH_2), 22.4 (CH_2), 23.6 (CH_2), 24.8 (CH_2), 40.6 (CH_3), 114.2 (CH), 118.5 (CH), 118.9 (C), 123.8 (CH), 124.4 (CH), 130.7 (C), 135.7 (C) and 136.4 ppm (C).

Synthesis of *6*-methoxy-9-(methylsulfonyl)-2,3,4,9-tetrahydro-1H-carbazole, 4.14b and *N*-(2-bromocyclohex-2-enyl)-*N*-(4-methoxyphenyl)methanesulfonamide, 4.56.



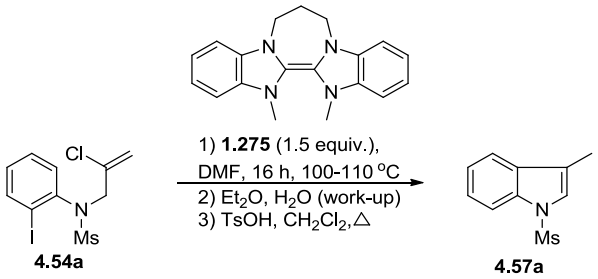
This compound was prepared using the same procedure as for 9-(methylsulfonyl)-2,3,4,9-tetrahydro-1*H*-carbazole, **4.14a** using *N*-(2-bromocyclohex-2-enyl)-*N*-(2-iodo-4-methoxyphenyl)methane-sulfonamide **4.15b** (0.146g, 0.300 mmol, 1.0 eq.). Column chromatography in CH_2Cl_2/hexane 70/30 afforded pure 6-methoxy-9-(methylsulfonyl)-2,3,4,9-tetrahydro-1*H*-carbazole, **4.14b** (45.0 mg, 0.161 mmol, 54%) as an oil that later crystallised; ν_{max} (KBr) cm^{-1} 3008, 2935, 1609, 1473, 1364, 1210, 1174, 1148, 1035, 1009, 988 and 768; ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 1.83-1.94 (4H, m, CH_2), 2.62-2.64 (2H, m, CH_2), 2.92-2.93 (5H, m, CH_2+SO_2CH_3), 3.87 (3H, s, OCH_3), 6.87-6.88 (2H, m, ArH) and 7.86-7.88 ppm (1H, m, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 20.2 (CH_2), 22.1 (CH_2), 23.2 (CH_2), 24.6 (CH_2), 39.8 (CH_3), 55.7 (CH_3), 101.1 (CH), 112.2 (CH), 114.8 (CH), 118.8 (C), 130.6 (C), 131.5 (C), 136.3 (C) and 156.7 ppm (C); [Found: (HNES$^+$) $(M+H)^+$ 280.1005. $C_{14}H_{18}NO_3S$ (M+H) requires 280.1005] and *N*-(2-bromocyclohex-2-enyl)-*N*-(4-methoxyphenyl)methanesulfonamide, **4.56** (5.0 mg, 0.014 mmol, 5%): ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 1.05-1.13 (1H, m, CH_2), 1.42-1.51 (1H, m, CH_2), 1.79-1.93 (2H, m, CH_2), 2.02-2.14 (2H, m, CH_2), 3.10 (3H, s, SO_2CH_3), 3.83 (3H, s, OCH_3), 5.05 (1H, br. s, MsNC<u>H</u>), 6.29-6.31 (1H, m, =CH), 6.90 (2H, d, *J* = 9.0, ArH) and 7.43 ppm (2H, d, *J* = 9.0, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 19.0 (CH_2), 27.4 (CH_2), 32.1 (CH_2), 40.2 (CH_3), 55.8 (CH_3), 60.2 (CH), 114.7 (CH), 123.2 (C), 128.7 (C), 133.5 (CH), 136.7 (CH) and 160.2 ppm (C).

Synthesis of (*Z*/*E*)-3-ethylidene-5-methoxy-1-(methylsulfonyl)indoline, 4.59.[91]



These compounds was prepared using the same procedure as for 9-(methylsulfonyl)-2,3,4,9-tetrahydro-1*H*-carbazole, **4.14a** with *N*-(but-2-yn-1-yl)-*N*-(2-iodophenyl)methanesulfonamide **4.55a** (105 mg, 0.300 mmol, 1.0 eq.). Column chromatography of the crude organic product on silica gel eluting with chloroform afforded 3-ethylidene-5-methoxy-1-(methylsulfonyl)indoline, **4.59** as an inseparable mixture of *Z* and *E* isomers (44 mg, 0.189 mmol 62%) as a colourless oil: ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 1.79 (2H, dt, *J* = 7.0, 2.0 Hz CH_3), 2.01-2.04 (2H, m, CH_3), 2.86 (3H, s, SO_2CH_3), 2.88 (3H, s, SO_2CH_3), 4.55-4.57 (2H, m, CH_2), 4.56-4.60 (2H, m, CH_2), 5.71 (1H, qt, *J* = 7.5, 7.0, 2.5 Hz, =CH), 5.98-6.04 (1H, m, =CH), 7.08-7.11 (1H, m, ArH), 7.01 (1H, d, *J* = 8.0 Hz, ArH), 7.22-7.26 (1H, m, ArH), 7.53 (1H, td, *J* = 7.5, 7.5, 1.0 Hz, ArH), 7.19-7.22 (1H, m, ArH), 7.39 (1H, d, *J* = 7.5 Hz, ArH), 7.47 (1H, d, *J* = 8.0 Hz, ArH) and 7.60 ppm (1H, d, *J* = 8.0 Hz, ArH); [Found: (EI$^+$) $(M-H)^+$ 222.0583. $C_{11}H_{12}NO_2S$ requires M-H of 222.0585].

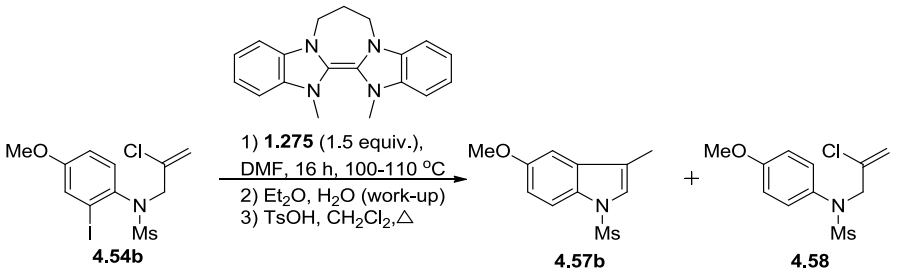
Synthesis of 3-methyl-1-(methylsulfonyl)-1*H*-indole, 57a.[35,214]



This compound was prepared using the same procedure as for 9-(methylsulfonyl)-2,3,4,9-tetrahydro-1*H*-carbazole, **4.14a** with *N*-(2-chloroallyl)-*N*-(2-iodophenyl)methanesulfonamide, **4.54a** (0.111g, 0.3 mmol, 1.0 eq.). Column chromatography of the crude organic product on silica gel eluting with pentane/ethyl acetate 4:1 afforded both 3-methylene-1-(methylsulfonyl)indoline and 3-methyl-1-(methylsulfonyl)-1*H*-indole, **4.57a** (0.047g, 0.225 mmol, 1.0 eq.) as an inseparable mixture. The crude organic product was refluxed in CH_2Cl_2 (2 mL) with *p*-toluenesulfonic acid (0.004 g, 0.023 mmol, 0.1 eq.) for 3 h. The crude organic product was concentrated *in vacuo* and then purified on silica gel eluting with pentane/ethyl

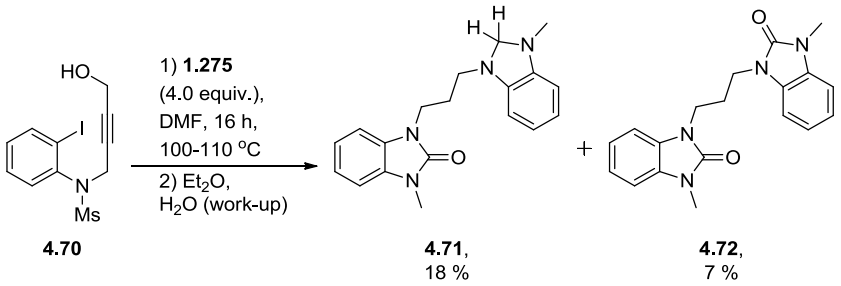
acetate 4:1 to afford 3-methyl-1-(methylsulfonyl)-1*H*-indole, **4.57a** (0.035 g, 1.67 mmol, 55.6%):[49] ν_{max} (KBr) cm^{-1} 3115, 3053, 3018, 2918, 2849, 1606, 1448, 1364, 1276, 1208, 1174, 1133, 1004, 979, 782 and 746; ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 2.31 (3H, d, J = 1.0 Hz, CH_3), 3.03 (3H, s, SO_2CH_3), 7.21 (1H, br. S, ArH), 7.32-7.40 (2H, m, ArH), 7.57 (1H, d, J = 7.6 Hz, ArH) and 7.91 ppm (1H, d, 8.2 Hz, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 9.9 (CH_3), 40.5 (CH_3), 113.5 (CH), 120.0 (C), 120.7 (CH), 123.3 (CH), 123.6 (CH), 125.2 (CH), 132.1 (C) and 135.7 ppm (C); [Found: (HNES$^+$) $(M+Na)^+$ 232.0402. $C_{10}H_{11}NNaO_2S$ requires M+Na of 232.0403].

Synthesis of 5-methoxy-3-methylene-1-(methylsulfonyl)indoline, 4.57b and *N*-(2-chloroallyl)-*N*-(4-methoxyphenyl)methanesulfonamide, 4.58.



This compound was prepared using the same procedure as for 9-(methylsulfonyl)-2,3,4,9-tetrahydro-1*H*-carbazole, **4.14a** with *N*-(2-chloroallyl)-*N*-(2-iodo-4-methoxyphenyl)-methanesulfonamide **4.54b** (120 mg, 0.300 mmol, 1.0 eq.). Column chromatography eluting with CH_2Cl_2/hexane (gradient 50:50 to 100% CH_2Cl_2) afforded 5-methoxy-3-methyl-1-(methylsulfonyl)-1*H*-indole, **4.57b** (33.0 mg, 0.138 mmol, 46%) (500 MHz, $CDCl_3$) δ 2.27 (3H, d, J = 1.15 Hz, CH_3), 3.00 (3H, s, SO_2CH_3), 3.89 (3H, s, OCH_3), 6.97-7.00 (2H, m, ArH), 7.17 (1H, d, J = 0.9 Hz, ArH) and 7.79 ppm (1H, m, ArH); (125 MHz, $CDCl_3$) 9.69 (CH_3), 39.9 (CH_3), 55.8 (CH_3), 102.3 (CH), 113.7 (CH), 114.1 (CH), 118.7 (C), 123.8 (CH), 130.0 (C), 132.8 (C) and 156.6 (C); and *N*-(*2-chloroallyl)-N-(4-methoxyphenyl)methanesulfonamide* **4.58**, (8.0 mg, 0.029 mmol, 10%) ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 3.01 (3H, s, SO_2CH_3), 3.82 (3H, s, OCH_3) 4.41 (2H, s, CH_2), 5.31 (2H, s, $=CH_2$), 6.92 (2H, d, J = 9.0 Hz, ArH) and 7.30 (2H, d, J = 9.0 Hz, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 39.4 (CH_3), 55.8 (CH_2), 57.9 (CH_3), 115.1 (CH), 116.8 ($=CH_2$), 130.7 (CH), 131.4 (=C), 137.5 (C) and 159.9 ppm (C).

Synthesis of (*E*)-2-(2-(5-methoxy-1-(methylsulfonyl)indolin-3-ylidene)ethyl)isoindoline-1,3-dione, 4.71 and 3,3'-(propane-1,3-diyl)*bis*(1-methyl-1*H*-benzo[d]imidazol-2(3H)-one), 4.72.

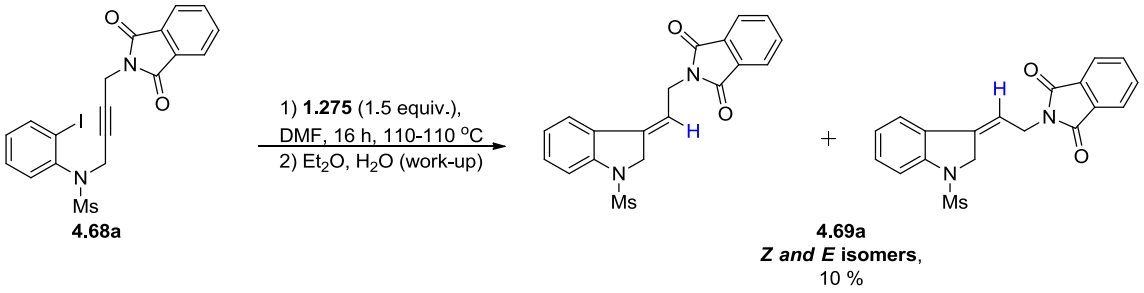


4.70 **4.71**, 18 % **4.72**, 7 %

This compound was prepared using the same procedure as for 9-(methylsulfonyl)-2,3,4,9-tetrahydro-1*H*-carbazole, **4.14a** with *N*-(4-hydroxybut-2-ynyl)-*N*-(2-iodophenyl)methanesulfonamide (0.110 g, 0.3 mmol, 1.0 eq.) and 3'-(propane-1,3-diyl)*bis*(1-methyl-1*H*-benzo[d]imidazol-3-ium) iodide, 1.275 (0.672 g, 1.2 mmol, 4.0 eq.). Column chromatography of the crude organic product on silica with ether afforded (*E*)-2-(2-(5-methoxy-1-(methylsulfonyl)indolin-3-ylidene)ethyl)isoindoline-1,3-dione, **4.71** as a yellow/brown oil (70 mg, 0.217 mmol, 18)**:** ν_{max} (thin film) cm^{-1} 3056, 2643, 2691, 1704 (C=O), 1620, 1604, 1499, 1484, 1402, 1392, 1127 and 1119 (C-N), 750 and 732; ^{1}H-NMR (500 MHz, C_6D_6) δ = 1.70 (2H, quintet, J = 6.8 Hz, CH_2), 2.29 (3H, s, CH_3), 2.71 (2H, t, J = 6.8 Hz, CH_2), 2.91 (3H, s, CH_3), 3.71 (2H, t, J = 6.8 Hz, CH_2), 3.96 (2H, s, CH_2), 6.27 (1H, d, 7.4 Hz, ArH), 6.31 (1H, d, 7.4 Hz, ArH), 6.41-6.52 (1H, m, ArH), 6.64-6.68 (1H, m, ArH), 6.73 (1H, t, J = 7.4 Hz, ArH), 6.77 (1H, t, J = 7.4 Hz, ArH) and 6.87-6.92 ppm (2H, m, ArH); ^{13}C-NMR (125 MHz, C_6D_6) δ = 27.1 (CH_3), 27.8 (CH_2), 34.7 (CH_3), 39.2 (CH_2), 46.8 (CH_2), 79.1 (CH_2), 106.9 (CH), 107.5 (CH), 107.9 (CH), 108.1 (CH), 120.0 (CH), 120.4 (CH), 121.6 (CH), 121.8 (CH), 130.6 (C), 131.2 (C), 143.6 (C), 144.4 (C) and 155.0 ppm (C); [Found: ($HNES^+$) $(M+H)^+$ 321.1709. $C_{19}H_{21}N_4O$ (M+H) requires 321.1710].

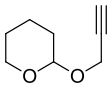
3,3'-(propane-1,3-diyl)*bis*(1-methyl-1*H*-benzo[d]imidazol-2(3H)-one), **4.72** (30.0 mg, 0.089 mmol, 7%): ν_{max} (KBr) cm^{-1} 3059, 2939, 1704 (C=O), 1620, 1499, 1435, 1403 and 750; ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 2.27 (2H, qi, J = 7.3 Hz, CH_2), 3.40 (6H, s, CH_3), 4.01 (4H, t, J = 7.3 Hz, CH_2), 6.94-6.96 (4H, m, ArH) and 7.04-7.10 (4H, m, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 27.1 (CH_3), 27.2 (CH_2), 39.0 (CH_2), 107.4 (CH), 107.5 (CH), 121.2 (CH), 121.2 (CH), 129.0 (C), 130.0 (C) and 154.3 (C); [Found: ($HNES^+$) $(M+H)^+$ 337.1663. $C_{19}H_{21}N_4O_2$ (M+H) requires 337.1659][258]

Synthesis of 2-(2-(1-(methylsulfonyl)indolin-3-ylidene)ethyl)isoindoline-1,3-dione, 4.69a.



This compound was prepared using the same procedure as for 9-(methylsulfonyl)-2,3,4,9-tetrahydro-1*H*-carbazole, **4.14a** with *N*-(4-(1,3-dioxoisoindolin-2-yl)but-2-ynyl)-*N*-(2-iodophenyl)methanesulfonamide, **4.68a** (148 mg, 0.3 mmol, 1.0 eq.).. Column chromatography of the crude organic product on silica gel eluting with CH_2Cl_2/hexane (gradient 50:50 to 100% CH_2Cl_2) afforded 2-(2-(1-(methylsulfonyl)indolin-3-ylidene)ethyl)isoindoline-1,3-dione, **4.69a** as white solid (0.011g, 0.03 mmol, 10.0%): ν_{max} (KBr)/cm^{-1} 1767 and 1709 (C=O), 1466, 1466, 1396, 1343 and 1163 (SO_2) and 720; ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 2.93 (3H, s, SO_2CH_3), 4.37 (2H, d, J = 8.0 Hz, CH_2), 4.95-4.96 (2H, m, CH_2), 5.90-5.94 (1H, m, =CH), 7.03-7.06 (1H, m, ArH), 7.25-7.29 (1H, m, ArH), 7.39 (1H, d, J = 7.4, ArH), 7.52 (1H, d, J = 8.2, ArH), 7.73-7.75 (2H, m, ArH) and 7.86-7.88 ppm (2H, m, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 35.2 (CH_3), 36.4 (CH_2), 53.3 (CH_2), 111.8 (CH), 114.7 (CH), 121.1 (CH), 123.4 (CH), 124.0 (CH), 129.1 (C), 130.5 (CH), 132.2 (C), 134.1 (CH), 137.1 (C), 144.4 (C) and 167.9 ppm (C); [Found: (HNES$^+$) $(M+Na)^+$ 391.0719. $C_{19}H_{16}O_4N_2NaS$ (M+Na) requires 391.0723].

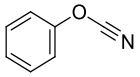
Preparation of 2-(prop-2-yn-1-yloxy)tetrahydro-2*H*-pyran, 4.79.[259]



In a round-bottomed, flask equipped with stirrer bar, condenser and thermometer, a crystal of *p*-toluenesulfonic acid monohydrate was added to dihydropyran (28.3 g, 500 mmol, 1.0 eq). The solution was warmed to 60 °C and propargyl alcohol was added from a dropping funnel over 30 min. The mildly exothermic reaction was maintained at a temperature of 60–65 °C by controlling the rate of addition of the propargyl alcohol and by occasional external cooling with an ice bath. The reaction temperature was monitored for another 30 min after complete addition (to avoid sudden exotherm caused by accumulation) and then allowed to stir for 1.5 h. Powdered sodium bicarbonate (0.2 g) was added and the mixture stirred for another 1.0 h. The mixture was gravity-filtered into a round-bottomed flask (100 mL) and distilled through a 45 cm Vigreux column under reduced pressure, 63-65 °C at 9 Torr. A small forerun was

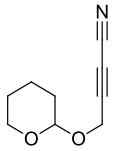
followed by the desired product 2-(prop-2-yn-1-yloxy)tetrahydro-2H-pyran **4.79** (63.14 g, 450.4 mmol, 90%). The colourless liquid product was stored over molecular sieves under argon: [Found: $(HCI)^+$ $(M+NH_4)^+$ 158.1174. $C_8H_{16}NO_2$ $(M+NH_4)$ requires 158.1176]; ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 1.52-1.68 (4H, m, CH_2), 1.72-1.89 (2H, m, CH_2), 2.42 (1H, t, J = 2.43 Hz, ≡CH), 3.53-3.57 (1H, m, CH_2), 3.83-3.87 (1H, m, CH_2), 4.23-4.32 (2H, m, CH_2) and 4.83 ppm (1H, t, J = 3.5 Hz, CH); ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 19.4 (CH_2), 25.7 (CH_2), 30.6 (CH_2), 54.4 (CH_2), 62.4 (CH_2), 74.3 (CH), 80.1 (C) and 97.2 ppm (CH).

Preparation of 1-phenyl cyanate, 4.80.[233]



A solution of cyanogen bromide (1.70 g, 16.0 mmol, 1.0 eq.) in anhydrous diethyl ether (20 mL) was cooled to -10 °C (dry ice/acetone bath) under inert atmosphere. A solution of phenol (1.50 g, 16.0 mmol, 1.0 eq.) and triethylamine (1.62g, 16.0 mmol, 1.0 eq.) in anhydrous diethyl ether (10 mL) was added dropwise to the stirred reaction mixture from an addition funnel. A white precipitate of triethylammonium bromide formed and the mixture was allowed to stir for an additional 30 min. The suspension was filtered under vacuum and the organic phase was concentrated *in vacuo* to afford the 1-phenyl cyanate **4.80** as a colourless oil. The 1-phenyl cyanate was used directly in the next step without further purification (all glassware was submerged in a bleach bath to remove cyanide contamination).

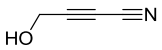
Preparation of 4-((tetrahydro-2H-pyran-2-yl)oxy)but-2-ynenitrile, 4.81.[231,232]



2-(Prop-2-yn-1-yloxy)tetrahydro-2H-pyran **4.79** (1.72 g, 12.3 mmol, 1.0 eq.) was dissolved in dry tetrahydrofuran (50 mL) under argon and cooled to -78 °C. A solution of *n*-butyllithium (8.05 mL, 1.6 M, 12.9 mmol, 1.05 eq.) in hexane was added to the stirred solution dropwise from a syringe. The reaction was allowed to warm to 0 °C and stirred for 15 min before recooling to -78 °C. Freshly prepared 1-phenyl cyanate[233] **4.80** (1.90 g, 16.0 mmol, 1.3 eq.) in dry tetrahydrofuran (20 mL) was added dropwise to the reaction mixture and allowed to warm to ambient temperature. The reaction was quenched with aqueous NaOH (6 M, 50 mL) and the organic layer separated. The aqueous was extracted with diethyl ether (50 mL) and the combined extracts were washed sequentially with NaOH (6 M, 2 x 25 mL) and saturated brine (50 mL), the dark organic was dried over $NaSO_4$ and passed through

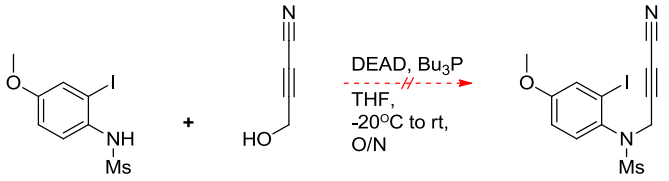
a short plug of silica gel before being concentrated *in vacuo*. The crude organic residue was chromatographed on silica gel eluting with ethyl acetate/hexane (1:9). 4-(tetrahydro-pyran-2-yloxy)-but-2-ynenitrile **4.81** (1.79 g, 10.34 mmol, 88%) was afforded as a colourless transparent oil: ν_{max} (KBr)/cm^{-1} 2946, 2873, 2304 (C≡N), 2265 (C≡C), 1345, 1121 and 1058 (C-O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 1.54-1.67 (4H, m, CH_2), 1.73-1.85 (2H, m, CH_2), 3.55-3.59 (1H, m, CH_2), 3.78-3.83 (1H, m, CH_2), 4.34-4.42 (2H, m, CH_2) and 4.77 ppm (1H, t, J = 3.1 Hz, CH); ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 18.9 (CH_2), 25.5 (CH_2), 30.3 (CH_2), 54.0 (CH_2), 60.2 (C), 62.4 (CH_2), 81.9 (C), 98.1 (CH) and 105.0 ppm (C).

Preparation of 4-hydroxybut-2-ynenitrile, 4.82.[231,232]



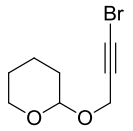
An anhydrous methanolic solution (30 mL) of 5-(tetrahydro-pyran-2-yloxy)-pent-2-ynenitrile (1.40 g, 10.0 mmol) **4.81** and Dowex 50 beads (pre-washed with anhydrous methanol) were stirred at room temperature for 1.5 h. The solution was filtered and concentrated *in vacuo* before being retreated with Dowex 50 beads for 1.5 h. Filtration and concentration of the reaction mixture afforded 4-hydroxybut-2-ynenitrile **4.82** (785 mg, 9.683 mmol, 97%) as a yellow oil: ν_{max} (KBr)/cm^{-1} 3418 (OH), 2308 (C≡N), 2247 (C≡C), 1638, 1438, 1133, 1032; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.82 (1H, t, J = 6.7 Hz) and 4.43 ppm (2H, d, J = 6.7 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 51.0 (CH_2), 60.1 (C), 83.2 (C) and 104.9 (C) ppm. (This compound is reported to be unstable to chromatography on silica gel.)[231,232]

Attempted preparation of *N*-(3-cyanoprop-2-yn-1-yl)-*N*-(2-iodo-4-methoxyphenyl)-methanesulfonamide, 4.83.



Preparation of this compound was attempted using the same procedure as for *N*-(2-bromocyclohex-2-enyl)-*N*-(2-iodophenyl) methanesulfonamide, **4.15b** with *N*-(2-iodo-4-methoxyphenyl)methanesulfonamide **4.53b** (0.540 g, 1.65 mmol. 1.1 eq.) and 4-hydroxybut-2-ynenitrile **4.82** (0.122 g, 1.500 mmol, 1.0 eq.)]. The reaction mixture was observed to undergo a colour change from yellow to black upon addition of tributylphosphine (unusual for a Mitsunobu reaction). Product formation was not observed by NMR of the crude reaction mixture.

Preparation of 2-((3-bromoprop-2-yn-1-yl)oxy)tetrahydro-2H-pyran, 4.84[260,261]



2-(Prop-2-yn-1-yloxy)tetrahydro-2H-pyran (14.018 g, 100 mmol, 1.0 eq.) was dissolved in dry THF (250 mL) under argon and cooled to -78 °C. A solution of *n*-butyllithium (62.5 mL, 1.6 M, 100 mmol, 1.05 eq.) in hexane was added to the stirred solution dropwise from a syringe, the reaction was allowed to warm to 0 °C and stirred for 15 min before recooling to -78 °C. Cyanogen bromide (10.592 g, 100 mmol, 1.0 eq.) in dry tetrahydrofuran (200 mL) was added dropwise to the reaction mixture which was allowed to warm to room temperature and stir overnight. The reaction quenched with water (500 mL) and extracted with ethyl acetate (5 x 75 mL). The combined extracts were washed sequentially with water (100 mL) and saturated brine (100 mL), the dark organic was dried over $NaSO_4$, passed through a short plug of silica gel, concentrated, and purified by column chromatography eluting with ethyl acetate/hexane (1:9) to yield 2-((3-bromoprop-2-yn-1-yl)oxy)tetrahydro-2H-pyran, **4.84** (8.25g, 37.7 mmol, 38%) as oil: ν_{max} (KBr)/cm^{-1} 2943, 2870, 2216 (C≡C), 1345, 1121 (C-O), 1058 (C-O), 1035 (C-O), 902, 871 and 750; [Found: $(GCEI)^+$ $(M)^+$ 217.1. $C_8H_{10}O_2Br$ $(M)^+$ requires 217.0; Found $(GCCIP)^+$ $(M+NH_4)^+$ 236.0. $C_8H_{11}O_2BrNH_4$ $(M+NH_4)^+$ requires 236.0]; ^{1}H-NMR (500 MHz) δ = 1.47-1.82 (m, 6H, CH_2), 3.47-3.52 (m, 1H, CH_2), 3.75-3.80 (m, 1H, CH_2), 4.22 (d, J = 15.6 Hz, 1H), 4.26 (d, J = 15.6 Hz, 1H), 4.76 (t, J = 3.4 Hz, 1H); ^{13}C-NMR δ = 18.9 (CH_2), 25.2 (CH_2), 30.1 (CH_2), 45.5 (C), 54.8 (CH_2), 61.92 (CH_2), 76.13 (C) and 96.8 ppm (CH).

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