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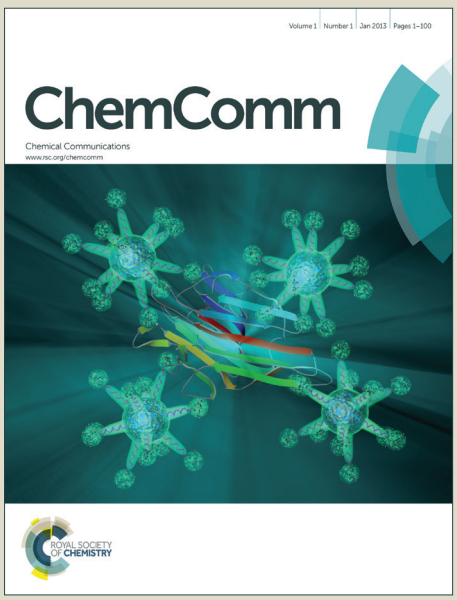

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Evolution of neutral organic super-electron-donors and their applications

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In recent times, metal-free chemistry has received significant attention due to its inherent qualities and its potential savings in the costs of (i) reagents and (ii) environmental treatments of residues. In this context, recently developed neutral organic electron-donors have shown an ability to perform challenging reductions that are traditionally the preserve of reactive metals and metal-based complexes, under mild reaction conditions. Hence, this feature article is aimed at describing the evolution of neutral organic super-electron-donors and their rapidly developing applications in electron-transfer reactions.

1. Introduction

Electron-transfer reactions are one of the major areas of organic chemistry. For many years, electron-transfer chemistry has been dominated by low valent metals and metal complexes. After the development of samarium(II) diiodide, a versatile coupling and reducing agent, by Kagan in the late 1970's,[1,2] there has been remarkable activity in finding new reactions with this reagent.[3] Several reviews have been published on the diverse reactivity of samarium(II) diiodide.[4] Many other transition metals such as Sc, Ti, V, Cr, Mn, Fe, Co, Ni, Cu and Zn are also extensively used in electron-transfer reactions.[5] Alternative methods include electrochemical reduction at a (usually metal) cathode,[6,7] reduction by solvated electrons,[8] reduction by lithium naphthalide[9] or related radical anions of organic molecules,[10] or photochemically assisted electron transfer.[11] Development of new neutral organic reagents would potentially bring altered reactivity and enhanced selectivity to the menu of reagents. Hence, we asked whether it would be possible to carry out highly challenging electron transfer reactions with purely organic molecules. Organic reducing agents are under-represented in synthetic chemistry and so this provides a rich scope for discovery of new reactions and selectivity. These reactions can be carried out in organic solvents using conventional glassware at room or elevated temperatures or under UV irradiation depending on the difficulty of the desired electron-transfer. These neutral organic electron donors are providing new selectivities and are pushing the boundaries of reactivity to improve various aspects of classical electron-transfer reactions.[12]

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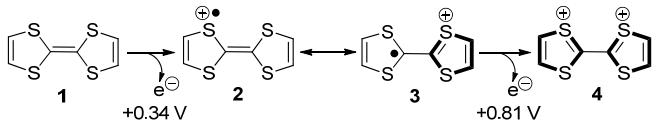
2. Early organic electron-transfer reagents

2.1 Tetrathiafulvalene (TTF)

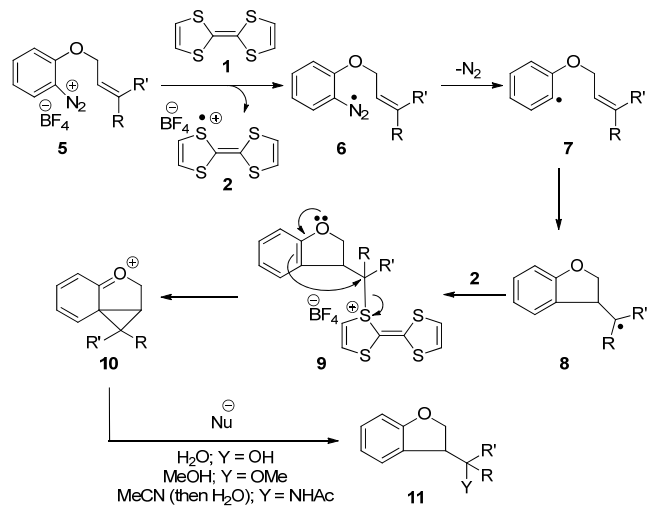
In developing organic electron transfer reagents, tetrathiafulvalene (TTF) **1** can be taken as a model system. TTF **1** is a neutral, air-stable organic compound containing four sulfur atoms attached to the central double-bond. These sulfur atoms can donate electron density to the π-system and thereby TTF **1** can act as an electron-rich donor. TTF **1** was first synthesised by Wudl[13] in 1970 and, subsequently, semiconducting properties of its salts, *e.g.* $[TTF^{\oplus}]Cl^{\ominus}$, were studied in 1972.[14] TTF **1** has been used extensively for its electron donor properties in materials chemistry, conducting polymers, photochemistry and also in the field of molecular switches and materials chemistry.[15] However, TTF **1** was not exploited in organic synthesis before our research group began investigations.[16] We started using TTF **1** as an organic electron donor in the early 90's and reported a number of radical-initiated electron transfer reactions under mild reaction conditions.[17] The driving force for electron transfer from TTF **1** is the gain in aromatic stabilisation energy upon oxidation to radical-cation **3** and dication **4** (the newly generated aromatic rings are shown in bold in Scheme 1). The

redox potential for the first electron donation is $E_{1/2}$ = +0.34 and for the second is +0.81 V *vs.* SCE in PhCN.[18]



Scheme 1 Gain in aromatic stabilisation upon oxidation of TTF **1**.

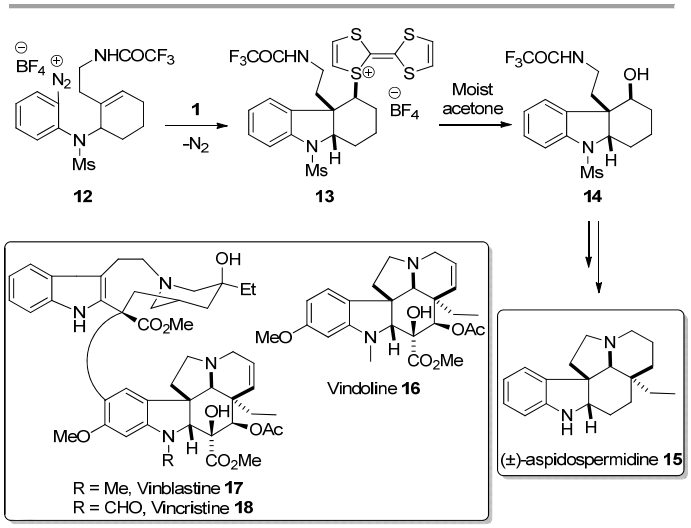
At the early stage of this research, electron-deficient diazonium salts were selected as test substrates leading to the first radical-polar crossover reactions in which radical chemistry is followed by polar/ionic displacements.[16a, 19]



Scheme 2 Radical-polar crossover reaction and mechanism.

The reaction is initiated by an electron transferred from the HOMO of TTF **1** to the LUMO of the arenediazonium salt **5** resulting in the unstable arenediazenyl radical **6**, which quickly converts to **7** by loss of nitrogen gas. Aryl radical **7** rapidly undergoes 5-*exo*-*trig* cyclisation and produces a more stable alkyl radical **8** which is trapped by the radical-cation of TTF **2** affording polar intermediate, sulfonium salt **9**, which defines the crossover from radical reactivity to polar or ionic reactivity. Expulsion of the TTF moiety from **9**, followed by nucleophilic attack by solvent afforded various substituted dihydrobenzofurans **11** (Scheme 2).[20]

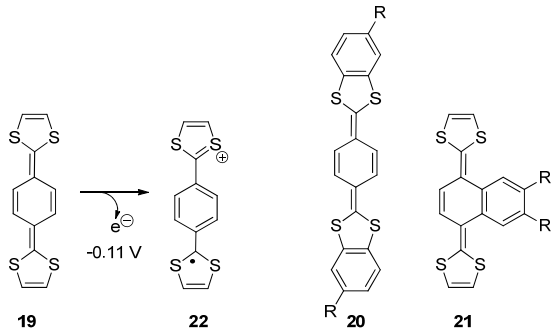
Radical-polar crossover reactions using TTF **1** as an electron donor were applied to the total synthesis of alkaloids such as (±)-aspidospermidine **15**, a close relative to vindoline **16** which is present in the potent anti-cancer drugs vinblastine **17** and vincristine **18** (Scheme 3).[19c, 21] The controlling point in this synthesis was the formation of the *cis*- ring junction in **13** upon electron transfer from TTF **1** to diazonium salt **12**, and then the isolation of alcohol **14** as a single diastereoisomer. Generation of **14** suggested that TTF radical-cation **2** trapped the radical formed after cyclisation in a stereoselective manner and then solvolysis of **13** in moist acetone formed the corresponding alcohol **14**. This alcohol **14** was then converted to (±)-aspidospermidine **15** through a series of steps in stereoselective fashion.



Scheme 3 Application of the radical-polar crossover reaction in the total synthesis of (±)-aspidospermidine **15**.

2.2 Other sulfur-containing electron donors

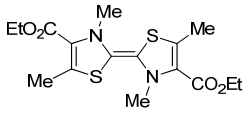
Other powerful classes of sulfur-containing electron donors such as 2,2′-bis(1,3-dithiole) derivatives **19-21** (Scheme 4) have also been developed.[22] Again, the gain in aromatic stabilisation is the key for electron donation from these donors. Donor **19** has a first oxidation potential of -0.11 V *vs*. SCE in MeCN[22a] which demonstrates that it is more powerful than the model TTF **1** (+0.28 V *vs*. SCE in MeCN),[22a] and the authors claimed that these donors can behave as "organic metals".[22a] Unfortunately, the synthesis of these donors is complicated and their use as organic electron donors is practically limited.



Scheme 4 Other sulfur-containing electron donors.

2.3 Diazadithiafulvalene

TTF **1** was successful in reducing diazonium salts but efforts to reduce more challenging aryl or alkyl halides were unsuccessful,[5] inviting the search for stronger electron donors. The limitations of TTF **1** demonstrated the need for electron-rich atoms capable of contributing strongly to the π-electron density of the molecule. So, replacing sulfur atoms with nitrogen should provide more powerful donors. Indeed, a variety of diazadithiafulvalenes such as **23** (Fig. 1) were synthesised[23] by replacing two sulfur atoms in TTF **1** with nitrogen. The first oxidation potential of **23** is -0.3 V *vs.* SCE in DMF[24] and the enhanced reducing power is associated with the strong π-electron donating nature of nitrogen atoms in **23** in comparison to sulfur atoms in TTF **1**. However, reaction of diazonium salts with diazadithiafulvalenes **23** led to undesired products,[25] limiting their use as electron donors. Although **23** is more powerful than TTF **1**, it is not powerful enough to reduce aryl halides.[26]

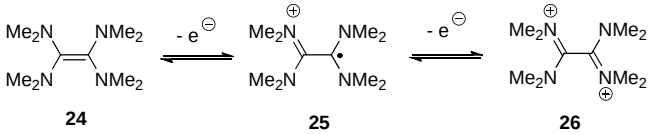


23

Fig. 1 Diazadithiafulvalene donor **23**.

2.4 [1,1,2,2-tetrakis(dimethylamino)ethylene], TDAE

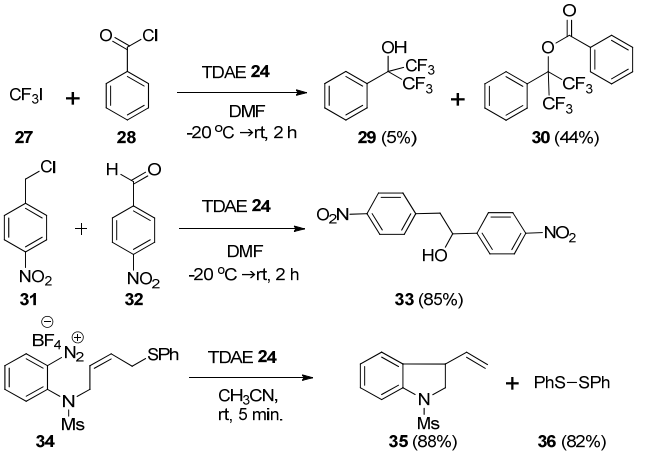
The improved reducing power of **23** highlights the importance of electron-rich atoms with greater π-electron donating nature in the donor molecule. It is also true that, compared to sulfur, nitrogen atoms would have better orbital overlap with adjacent carbon atoms due to similar size, thus leading to greater aromaticity in the oxidised forms of the analogous electron donors. Dolbier and Médebielle *et al.,*[27] Vanelle *et al.,*[28] and Nishiyama *et al*.[29] reported the use of commercially available TDAE [tetrakis(dimethylamino)ethylene] **24** as an electron donor for the reduction of various halide compounds. The first oxidation potential of **24** is -0.78 V *vs.* SCE and -0.61 V *vs.* SCE for the second in MeCN[30] and this manifests the higher reducing power of **24** over TTF **1** and diazadithiafulvalenes **23**.



24 **25** **26**

Scheme 5 Electron donation from TDAE.

TDAE can reduce electron-deficient iodotrifluoromethane **27** to trifluoromethyl anion and this is illustrated in the reaction of **27** and benzoyl chloride **28** with TDAE **24**.[27a] Similarly, in another example, *p*-nitrobenzyl chloride **31** was reduced to the corresponding benzyl anion upon treating with TDAE **24**.[27b] TDAE **24** also reduced diazonium salts *e.g.* **34** and provided the expected radical cyclisation product **35** (Scheme 6).[31] Although TDAE is more powerful than TTF **1** and diazadithiafulvalenes **23**, it is still not sufficiently powerful to reduce unactivated aryl halides.

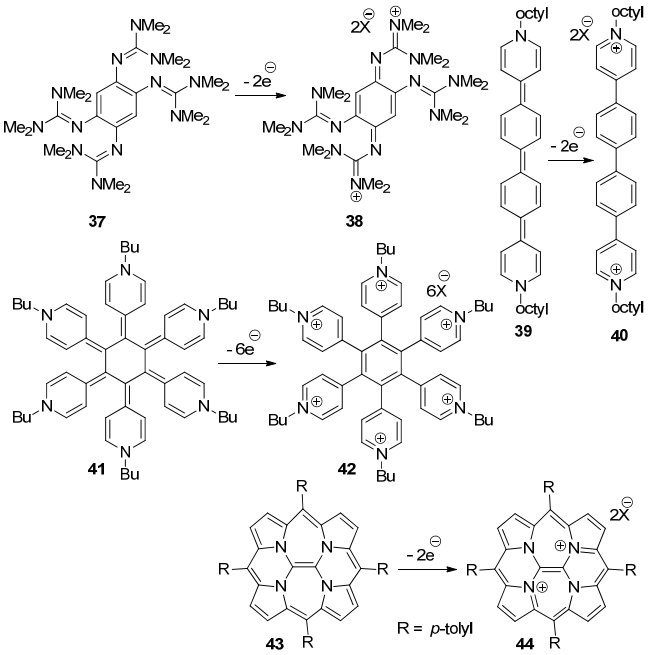


Scheme 6 Reactivity of TDAE as an electron donor.

2.5 Other electron-rich donors

As electron-rich atoms such as nitrogen in electron donors play important roles, Himmel *et al*. synthesised an interesting compound **37**[32] containing many nitrogen atoms. Compound **37** features an aromatic ring prior to oxidation and therefore there is no gain in aromatic stabilisation upon oxidation. Two-electron donation from **37** converts it into non-aromatic quinone-diiminium salt **38** and so, it is not surprising that **37** has redox potential [$E_{1/2}$ (MeCN) = -0.32 V *vs*. SCE] that shows that **37** is not as strong a reducing agent as TDAE **24**. In 2005, Vaid *et al*.[33] published the extended viologen **39** which was the most reducing neutral organic molecule known. Compound **39** showed a reversible, two-electron oxidation at $E_{1/2}$ = -1.48 V *vs*. Fc/Fc^+ (THF) [translating to -1.03 V *vs.* SCE] and the observed high reducing power is assigned to the generation of four aromatic rings in the oxidised form **40**. In 2008, the Vaid group described another fascinating molecule **41** that represents a six-electron organic redox system.[34] The molecule **41** should have enormous driving force to oxidise into molecule **42** containing seven new aromatic rings. The cyclic voltammetry of **42** was interesting and showed two redox waves representing a 4-electron reduction ($\mathbf{42}^{6+} \rightarrow \mathbf{42}^{2+}$) at -1.14 V (translating to -

0.69 V *vs.* SCE) and 2-electron reduction (**42**$^{2+}$→**41**^{0}) at -1.33 V *vs.* Fc/Fc^{+} (THF) [translating to -0.88 V *vs.* SCE]. Very recently, the Vaid group published the synthesis of another interesting porphyrin-based neutral molecule **43** and its oxidised dication **44**.[35] The molecule **43** has aromatic features in its neutral form and also in the dication **44**, and so its oxidation should not be strongly driven. And this is reflected in cyclic voltammetry where compound **43** showed reversible one-electron waves at -0.59 V (presumably oxidation to cation) [translates to -0.14 V *vs.* SCE] and -0.26 V (presumably oxidation to dication **44**) vs. Fc/Fc^{+} (THF) [translates to +0.19 V *vs.* SCE] (Scheme 7).



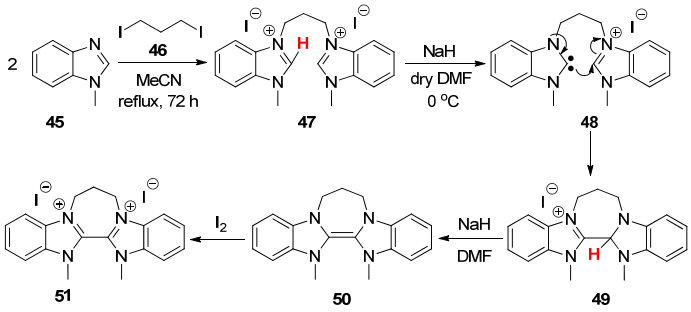
Scheme 7 Other organic electron donors.

3. Development of neutral organic super electron donors within the Murphy group

From the above discussions, it is understood that the gain in aromatic stabilisation and the presence of nitrogen atoms can provide powerful organic electron donors. So, it was proposed to combine the beneficial features of TDAE **24** (the presence of four nitrogen atoms and greatly stabilised positive charge on nitrogen) with that of TTF **1** (gain in aromatic stabilisation upon oxidation) to deliver even more powerful organic electron donors.[36]

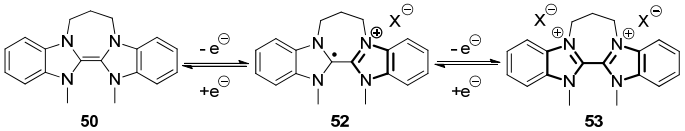
3.1 Benzimidazole-derived neutral organic super-electron-donor 50

In 2005, Murphy *et al*. published the first ever neutral super organic electron donor **50**, a compound that had been made previously but whose reactivity with organic functional groups had not previously been probed,[37] based on the *N*-methylbenzimidazole moiety **45** (Scheme 8).[26] The synthesis of the precursor salt **47** was simple and straightforward and it was prepared by the alkylation of *N*-methylbenzimidazole **45** with 1,3-diiodopropane **46** under reflux conditions in acetonitrile for 72 h.[37] Subsequent deprotonation[38] (proton highlighted in red) of the salt **47** using a strong base such as sodium hydride would generate carbene **48** which could attack onto the other benzimidazolium group in the molecule and would provide **49**. After a second deprotonation, it provided a yellow solution of the donor **50,** which was highly reactive towards air. Formation of the donor **50** was confirmed by NMR studies which showed a key signal at δ 123.1 ppm in ^{13}C NMR corresponding to the central alkene carbons. To further confirm the formation of donor **50**, the reaction mixture was treated with 1 equivalent of the mild oxidant iodine and it provided disalt **51**, which was also characterised.



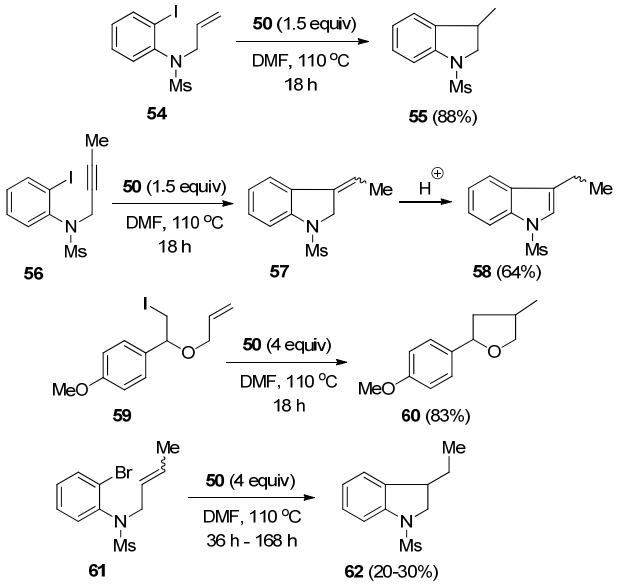
Scheme 8 Formation of benzimidazole-derived donor **50**.

Although **50** and similar compounds had appeared in the literature,[37, 39] their reductive reactivity towards organic substrates had never been studied.[26] The benzimidazole-derived donor **50** has four strong π-electron donating nitrogen atoms and it benefits from the gain of aromatic stabilisation upon oxidation to radical-cation **52** and dication **53** (the newly generated aromatic rings are shown in bold in Scheme 9). The first oxidation potential of **50** is -0.82 V *vs.* SCE and the second oxidation potential is -0.75 V *vs.* SCE in DMF[39] and this establishes the higher reducing power of **50** over TTF **1**, diazadithiafulvalenes **23** and TDAE **24**.



Scheme 9 Electron donation from benzimidazole-derived donor **50**.

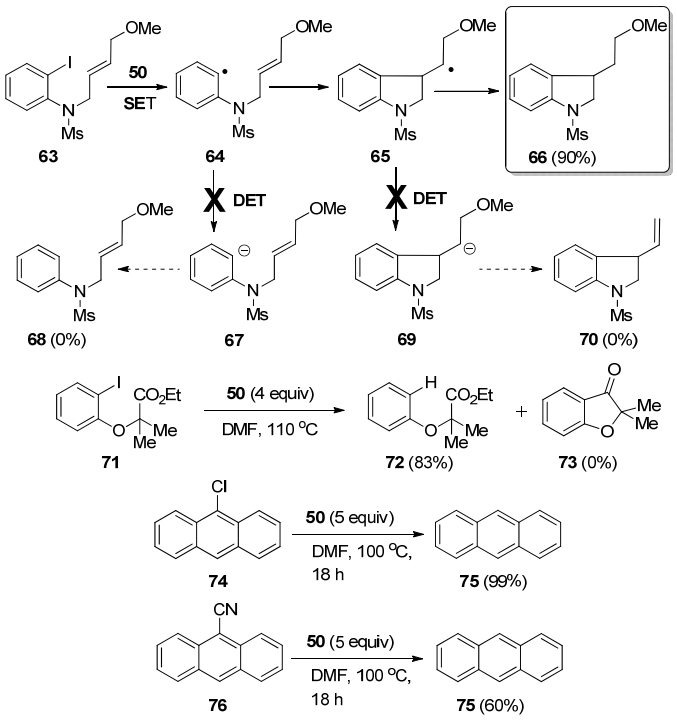
After successful synthesis of the benzimidazole-derived donor **50**, a series of reactions was undertaken to establish the reductive reactivity of this new donor. Reduction of aryl iodide **54** afforded the indoline **55** in excellent yield. The reduction of alkyne-containing aryl iodide **56** provided exocyclic alkene **57**, which was then converted to indole derivative **58** under mild acidic conditions. Additionally, an aliphatic iodide **59** was reduced to the corresponding cyclic product **60** via an alkyl radical intermediate.[26] However, the reduction of aryl bromide **61** was not as successful as aryl iodides and provided a lower yield of cyclised product **62**[40] under extended reaction times (Scheme 10).



Scheme 10 Reduction of aryl and alkyl halides with benzimidazole-derived donor **50**.

To identify the source of hydrogen atom to be abstracted by the radical intermediates, reactions were carried out in deuterated DMF (d_7-DMF) and this suggested that the source was not the solvent, as the isolated product did not show any isotopic label. So, it was suspected that the donor might be the source of these hydrogen atoms. This study of the reactivity of benzimidazole-derived electron donor **50** marked a breakthrough that provided the first successful reduction of aryl halides *and* alkyl halides, particularly iodides, by a neutral organic electron donor in excellent yields.

Substrate **63**, containing a potential anionic leaving group (methoxide) was designed to provide information on the reaction pathway *i.e.* whether single electron transfer (SET) or double electron transfer (DET) to the substrate occurred as the donor **50** could donate two electrons. However, substrate **63** exclusively afforded **66**, the expected product from SET (Scheme 11).[26] Absence of the alternative products **68** and **70,** arising from anionic intermediates **67** and **69** respectively, or more broadly from transfer of two electrons to the substrate **63**, ruled out the possibility of a DET process.



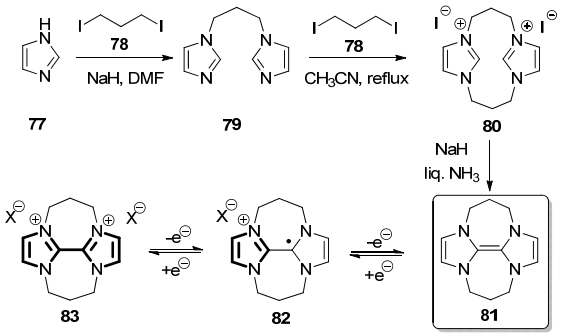
Scheme 11 Benzimidazole-derived donor **50** acting as a single electron donor.

Reaction of **71** with the donor **50** provided uncyclised product **72** and the absence of the cyclised product **73** ruled out the possibility of an aryl anion intermediate formed via a DET process and instead established that benzimidazole-derived donor **50** acted only as a single electron donor despite the promising first (-0.82 V) and second (-0.75 V *vs.* SCE in DMF) reduction potentials of donor **50**. In the next set of reactions, the donor **50** was able to reduce 9-chloroanthracene **74** in almost quantitative yield and 9-cyanoanthracene **76** in a fair yield to anthracene **75**, further extending its scope in reductive chemistry (Scheme 11).[40]

3.2 Imidazole-derived neutral organic super-electron-donor 81

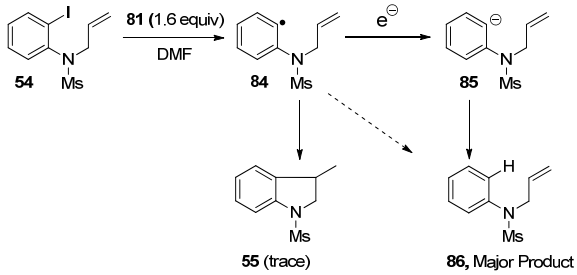
In 2007, the Murphy group reported the applications of another powerful neutral organic electron donor **81** based on imidazole moiety **77** and named it as the "doubly bridged donor" (DBD).[39, 41] Donor **81** had previously been prepared by Taton and Chen,[41b] but its reactions with organic substrates had not been explored. Electrochemistry of the DBD **81** showed that it has first and second oxidation potentials of -1.37 V vs. SCE and -1.18 V vs. SCE in MeCN,[39] making it a

more powerful donor than **50**. The donor **81** was thought to be more powerful than benzimidazole-derived donor **50** due to its greater gain in aromatisation energy upon oxidation (the newly generated aromatic rings were shown in bold in Scheme 12).



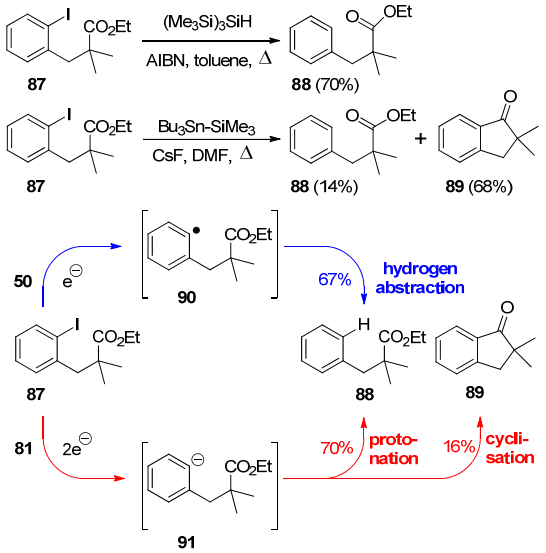
Scheme 12 Synthesis of the donor **81** and its electron donation.

The reductive chemistry of this donor was now studied. Aryl iodide **54**, which was tested earlier with donor **50**, was selected as a target and surprisingly, **86** was formed as the major product while only a trace amount of the expected cyclic product **55** was observed (Scheme 13).[42] As seen in the reaction with donor **50**, cyclisation of aryl radicals tends to occur at much faster rates than hydrogen abstraction,[43] and so **55** should be the major product, if aryl radical **84** was the intermediate. But, formation of **86** as a major product indicated that aryl anion **85** might be the intermediate, which in turn could be formed very rapidly from **84** by accepting a second electron (Scheme 13).



Scheme 13 Reactivity of the donor **81** with aryl iodide **54**.

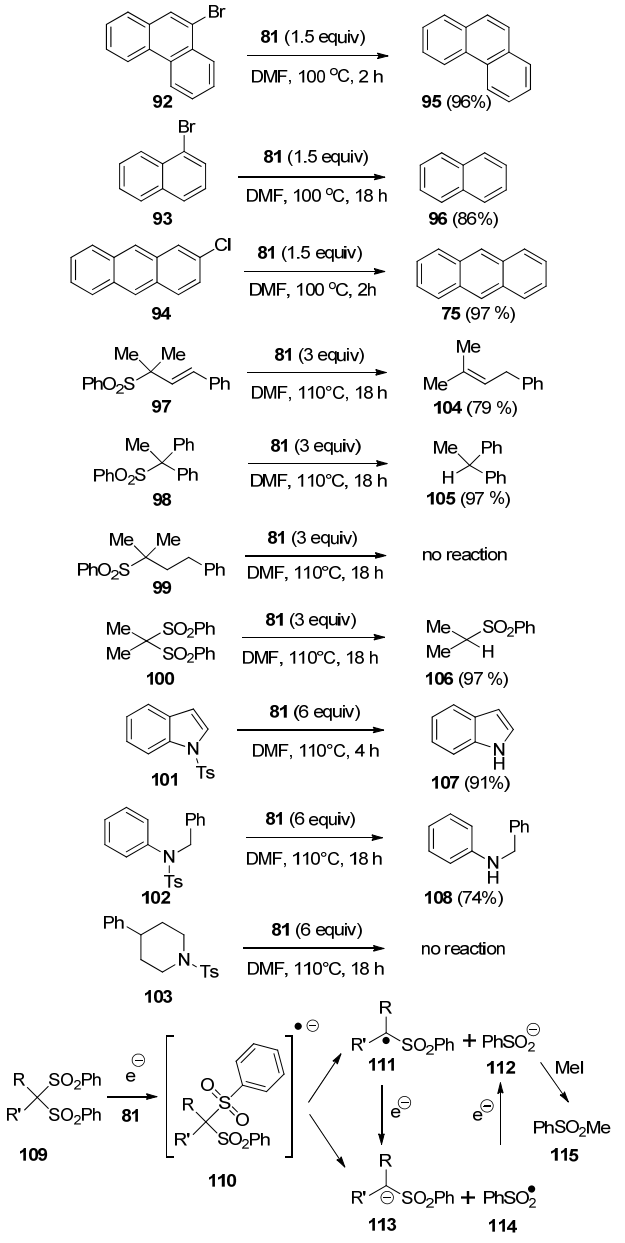
To further check the feasibility of a DET from the donor **81**, substrate **87** was selected and diagnostic test reactions for radical and anionic intermediates were carried out.[41a] Reaction of **87** using $(Me_3Si)_3SiH$ and AIBN, well known reagents used to generate purely radical species,[44] afforded exclusively uncyclised product **88**. Substrate **87** was then reacted with Bu_3Sn-$SiMe_3$ and CsF, standard conditions for the generation of aryl anions from iodoarenes.[45] This afforded uncyclised product **88** (14%) together with cyclised product **89** (68%). When the same substrate **87** was tested with the donor **50**, it provided exclusively uncyclised product **88** and replicated the result of $(Me_3Si)_3SiH$ and AIBN reaction. This confirmed that the generation of **88** purely occurred through radical intermediate **90** and, the donor **50** is acting as a single electron donor. However, the same substrate **87**, under the same reaction conditions but with the donor **81**, provided both cyclised product **89** (16%) and uncyclised product **88** (70%), reminiscent of the reactivity of Bu_3Sn-$SiMe_3$ and CsF reagents with **87**. As the formation of cyclised product **89** can only happen through an aryl anion intermediate **91**, 16% yield of cyclised product **89** reflects the minimum amount of aryl anion **91** generated in the reaction (Scheme 14).[41a]



Scheme 14 Reactivity of **87** under various reaction conditions.

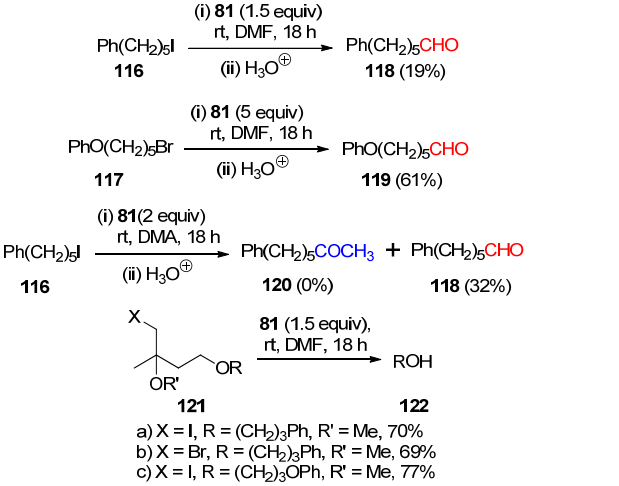
Reactivity of the DBD **81** was further explored by testing a variety of bromo and chloro aromatic substrates. The donor **81** successfully reduced the compounds **92-94** in excellent yields (Scheme 15).[41a] Previous attempts to reduce **93** with donor **50** had been unsuccessful and this suggested greater reducing power of DBD **81** over donor **50**. The DBD **81** was also found to be very successful in reductively cleaving some aryl sulfones *e.g.* **97** and **98**, disulfones *e.g.* **100** and arene-sulfonamides with activated nitrogen leaving groups *e.g.* **101** and **102** (Scheme 15).[46] Deprotection of these groups, generally, is carried out by highly reactive metal-containing reducing agents like alkali metals under Birch conditions or using SmI_2 with HMPA.[47] This was the first report of such cleavages using organic super-electron-donors. No reaction was observed with aryl alkyl sufone **99** and unactivated arenesulfonamide **103**. This might be due to the high activation energy associated with electron transfer to these

substrates along with the generation of unstabilised fragmented products and, computational studies supported these observations.[46] In the proposed mechanism (Scheme 15),[46] SET to the arenesulfonyl group affords radical-anion **110** which undergoes instantaneous scission of the C-S σ bond to form two possible radical anion pairs, either [alkyl radical **111** + sulfinate anion **112**] or [carbanion **113** + sulfonyl radical **114**]. Transfer of a second electron results in a pair of anions **112** and **113**. The anion **113** can abstract a proton to provide monosulfone product. The presence of **112** was confirmed by the addition of MeI (excess) at the end of the reaction, which provided sulfone **115** in good yield.



Scheme 15 Reactivity of the donor **81** towards aryl halides, sulfones, disulfones and sulfonamides and proposed mechanism for cleavage of disulfone **109**.

Murphy *et al.*[48] found that reaction of alkyl halides *e.g.* **116** and **117** with DBD **81** afforded traces of aldehydes **118** and **119** respectively, as observed in the ^{1}H-NMR spectra of crude material after neutral work-up. Acid work-up afforded increased yields of aldehydes suggesting that they required liberation from protection during work-up (Scheme 16).



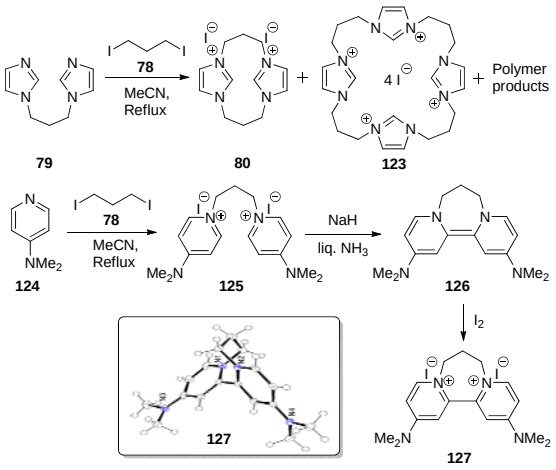
Scheme 16 Reaction of alkyl halides with DBD **81** affording aldehydes.

It was found that the isolated aldehyde products contained one carbon more than their precursor halides. Repeat reaction of **116** using dimethylacetamide (DMA) as solvent, instead of DMF, still provided the same aldehyde **118** and suggested that the donor might be the source of this extra carbon (Scheme 16). Reduction of specially designed alkyl halides **121** with the donor **81** afforded alcohols **122** and revealed that trapping of the alkyl radical intermediates by the radical-cation of donor **81** was the prime reason for the observed results[48] (see later Scheme 21 for a mechanistic proposal with an analogous donor).

3.3 4-DMAP-derived neutral organic super-electron-donor 126

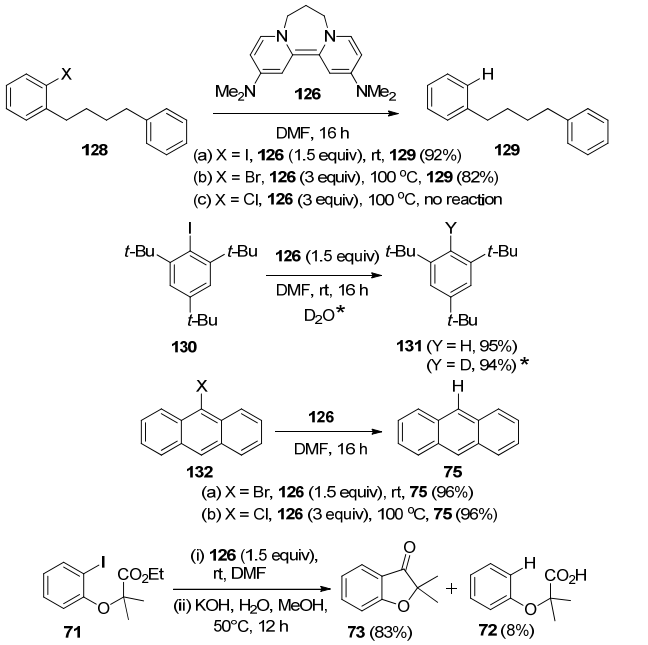
Despite the high reducing power of DBD **81**, synthesis of the precursor salt **80** is extremely laborious. Moreover, this reaction suffers from unwanted side-reactions leading to macrocyclic salts, principally **123** (Scheme 17).[49] This triggered the search for more powerful and easily accessible donors. As a result, in 2008, the Murphy group introduced a brand new donor **126** derived from 4-dimethylaminopyridine (DMAP) **124**.[50] This new donor **126** retained all the necessary features (such as the presence of electron-rich atoms and a gain in aromatic stabilisation upon oxidation) to be a powerful donor. In fact, cyclic voltammetry of donor **126**[50]

showed a single reversible two-electron peak at $E_{1/2}$ (DMF) = -1.13 V *vs.* Ag/AgCl/KCl (sat.) [translates to -1.24 V *vs.* SCE] and so, donor **126** was as strong as DBD **81**. Synthesis of the donor **126** is straightforward and it is prepared in two simple steps. Stable precursor salt **125** was easily synthesised from 4-DMAP **124** and 1,3-diiodopropane **78**. Deprotonation of **125** using a strong base like NaH in liq. NH_3 results in formation of a moisture- and air-sensitive donor **126** as a purple solid (Scheme 17). Formation of **126** was supported by the characteristic ^{13}C-NMR signal at δ = 116 ppm representing the central electron-rich alkene. Oxidation of the donor **126** with iodine afforded salt **127,** whose X-ray crystal structure (Scheme 17) was recorded subsequently and it further supported the formation of **126**.[50-51]



Scheme 17 Difficulties associated with synthesis of precursor salt of DBD, **80** and easy synthesis of 4-DMAP-derived donor **126**.

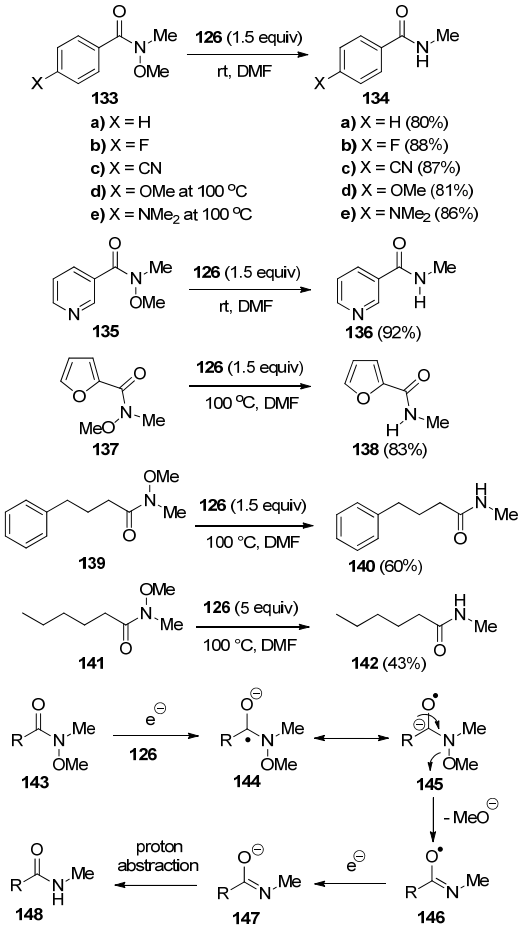
Subsequently, the reactivity of the new donor **126** was tested with a series of aryl halides and provided excellent yields of reduced products either at room temperature or at elevated temperature depending upon the difficulty of reduction.[50] Unsurprisingly, reduction of aryl bromide **128b** needed elevated temperatures and higher amounts of donor **126**, while reduction of the corresponding aryl iodide **128a** took place at room temperature. Aryl chloride **128c** did not provide any reaction even under forceful conditions. Reduction of hindered iodide **130** went cleanly and afforded an excellent yield of **131**. The regiospecific formation of the C-D bond in the reaction of **130**, upon the addition of D_2O to the reaction mixture, was consistent with the presence of an aryl anion intermediate, thereby supporting DET from DMAP-derived donor **126**. Reduction of aryl iodide **71** provided both cyclised and uncyclised products **73** and **72** respectively, further supporting the DET from the donor **126**. Reduction of 9-bromoanthracene **132a** happened at room temperature using 1.5 equiv of donor **126**, while reduction of 9-chloroanthracene **132b** took place at 100 ^{o}C using 3 equiv of donor **126** (Scheme 18).



Scheme 18 Reactivity of donor **126** with different aryl halides.

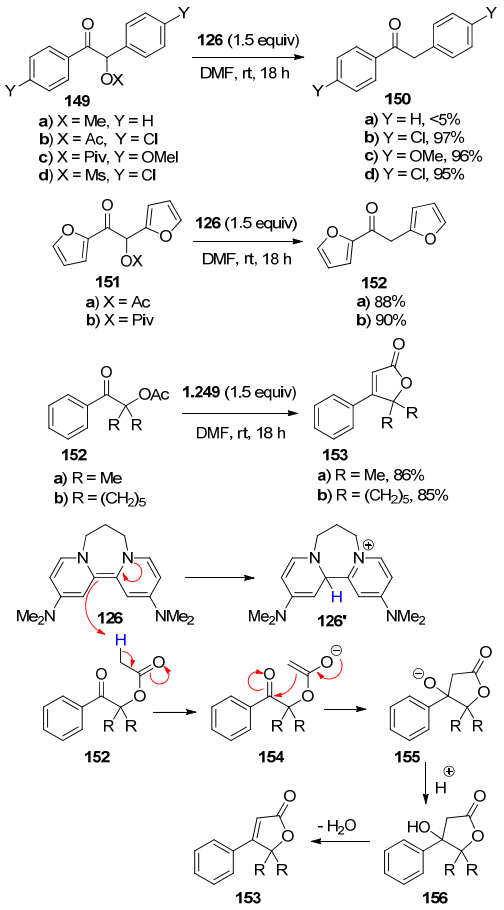
The reactivity of donor **126** was further tested with Weinreb amides and afforded the reductive cleavage of N-O bonds.[52] It was found that N-O bonds in electron-deficient Weinreb amides **133b** and **133c** were cleaved easily at room temperature in good yields while electron-rich counterparts **133d** and **133e** needed elevated temperatures. Pyridine-derived Weinreb amide **135** provided N-O bond cleavage at room temperature but electron-rich furan derivative **137** required elevated temperature for successful N-O bond scission. The observed electronic effects were in agreement with the fact that it was relatively difficult to transfer electrons into a more electron-rich system than to an electron-deficient system. A surprising fact came to light when substrates **139** and **141** were compared. Substrate **139**, containing a long alkyl chain separating the aromatic ring and the Weinreb amide group, provided a moderate yield of **140** at elevated temperature. However, cleavage of the N-O bond was even more difficult in aliphatic Weinreb amide **141** and provided a lower yield of product **142** even when more donor **126** (5 equiv) was used at elevated temperature (Scheme 19). For substrate **139** the LUMO is associated with the arene, and so it may happen that an electron transfer to the arene occurs first, facilitating the reaction; for cleavage of the Weinreb amide, this electron needs to be transferred, presumably intramolecularly, to the Weinreb amide group, generating

ketyl radical anion **144/145**. This ketyl radical anion **145** leads to the cleavage of the N-O bond and affords enolyl radical **146**. The resulting enolyl radical **146** takes another electron and forms enolate **147**, which abstracts a proton to generate amide **148** (Scheme 19). For Weinreb amide **141**, the absence of the aromatic ring means that the reaction is not facilitated.



Scheme 19 Cleavage of N-O bond in Weinreb amides.

Cutulic *et al.*[53] demonstrated that the donor **126** could cleave C-O σ-bonds in acyloin derivatives in excellent yield at room temperature (Scheme 20), dependent on the stabilisation of the anionic group that leaves upon fragmentation of the radical-anion. They observed that methylated benzoin derivative **149a** gave very little reductive C-O bond cleavage. However, when the methoxy group was replaced by electron-withdrawing groups such as acetate, pivalate or mesylate groups, benzoin derivatives **149b-d** provided excellent yields of C-O bond cleavage products **150b-d** at room temperature using 1.5 equiv of donor **126**. The same reaction was also successful on benzoin-related compounds derived from furans **151** (Scheme 20).

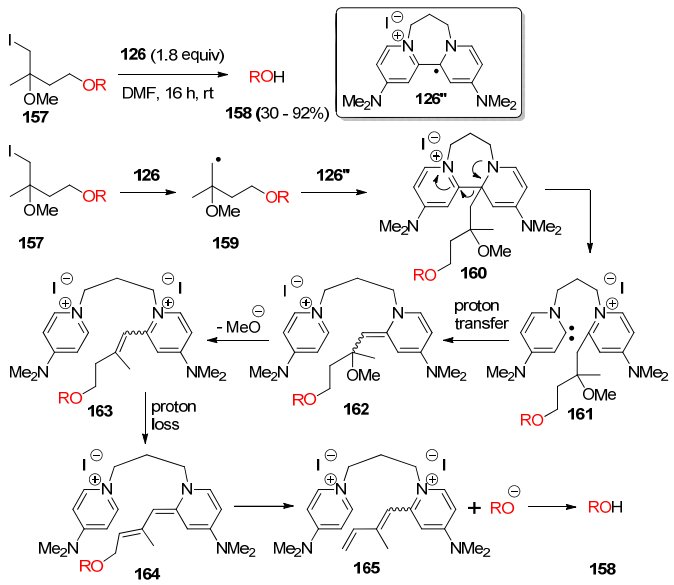


Scheme 20 Cleavage of C-O σ-bond in acyloin derivatives.

The proposed reaction mechanism is analogous to that of the cleavage of N-O bonds in Weinreb amides, and in this case, the expulsion of carboxylate anion occurred instead of methoxide of the Weinreb amides. However, when α-acetoxycarbonyl substrates **152** were reacted with the donor **126** under the same reaction conditions, they provided unsaturated lactones **153**.[53] This provides strong evidence for the basic nature of the donor **126**. During the reaction, the donor **126** deprotonates the acidic protons *α* to the ester carbonyl group to generate enolate anion **154** and this is driven by the gain in aromaticity in the pyridinium salt of the donor **126'**. The enolate anion **154** attacks the benzoyl carbonyl group to afford hydroxylactone **156**, which undergoes easy dehydration to form butenolide **153** (Scheme 20).

It was found that 4-DMAP-derived donor **126** has similar reactivity to the DBD **81**. So, a series of alkyl iodides **157** was prepared by Sword *et al.*[54] to investigate the trapping of alkyl radical intermediates by the radical cation of the donor **126**. Analogous to the previous results seen with DBD **81**, successful isolation of alcohols **158** supported the alkyl radical trapping with the radical cation of the donor, **126''**.

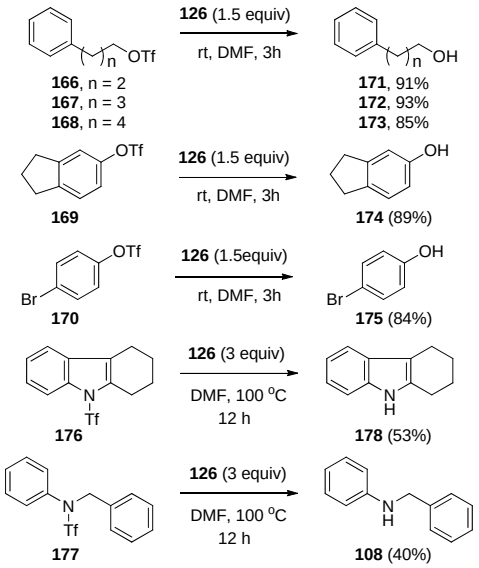
The possible mechanism for this radical trapping is shown in Scheme 21.



Scheme 21 Liberation of alcohols from the reaction of donor **126** with suitably designed alkyl iodides **157** and supporting radical trapping experiments.

SET from donor **126** to substrate **157** generates alkyl radical **159**, which can be trapped by radical-cation **126**" of the donor to form **160**. The stabilisation energy gained from aromatisation in forming the pyridinium ring is the driving force for the generation of carbene intermediate **161**. Proton transfer in **161** would lead to enamine **162**. At this point, methoxide can be expelled to generate dication **163**. This dication **163** can be deprotonated in the basic medium to afford dienamine **164**, which is in a good position to liberate the alkoxide ($RO^{\ominus}$) furnishing the corresponding alcohol **158** upon work-up (Scheme 21).

Jolly *et al.*[55] successfully reduced aliphatic and aryl triflates **166-170** via S-O bond cleavage to the corresponding alcohols and phenols cleanly and in excellent yields by reaction with the donor **126** under mild reaction conditions. Alternative C-O bond cleavage[56] of aliphatic triflates **166-168** that might arise by the nucleophilic nature of the donor **126** or DMF was not seen under these reaction conditions, which was further supported by O^{18}-DMF labelled experiments. Bromo-aryl triflate **170** reacted selectively at the triflate site. Reduction of triflamides **176** and **177**, a much more difficult task than the reduction of triflates, was also tested using the same donor **126** and pleasingly, it provided reduction at elevated temperature 100 °C (Scheme 22). The proposed reaction mechanism for these reductions is analogous to that of the reduction of arenesulfonamides.



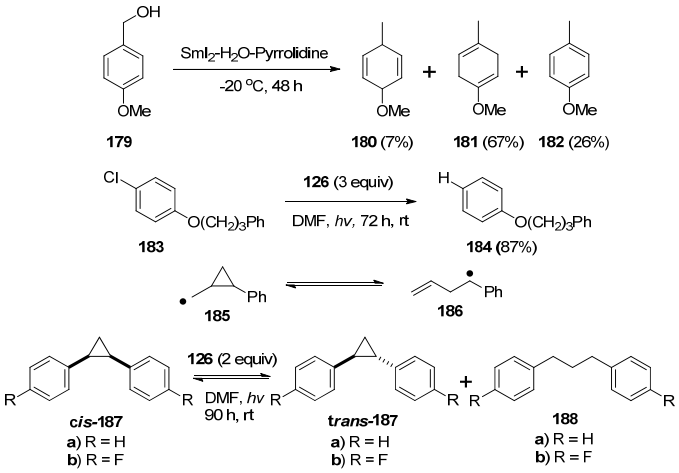
Scheme 22 Reduction of triflates and triflamides.

3.4 Photoactivated neutral organic electron donors

The discovery and development of new photochemical electron-transfer reactions has gained a lot of attention in recent times for producing new reactivities.[57] Generally, these reactions are based on the high reactivity of the excited state species. That method of generating open-shell intermediates is a welcome complement to the classical generation of radical species that often requires the use of toxic (tributyltin hydride), potentially explosive (AIBN and peroxides) or pyrophoric (trialkylboranes) compounds.[57b] So, there has been a lot of interest in further developing photoactivated electron-transfer reactions. Reduction of ground-state benzene (E^0 = -3.42 V *vs*. SCE)[58] and its close analogues is considered to be the most challenging task so far, and this was managed by using highly reactive metals including sodium, lithium and calcium in Birch and Benkeser conditions.[59] Very recently, Hilmersson *et al.*[3g] have also seen Birch type reduction of 4-methoxybenzyl alcohol **179** using their SmI_2/water/amine system (Scheme 23), but no organic donor had ever come close to reducing benzene.

Neutral organic electron donors, developed within the Murphy group, are very intense in colour (donor **126**: deep purple and, donors **81** and **50**: vibrant yellow) and therefore these donors can be excellent candidates for photoexcitation. Indeed, donor **126** showed absorption maxima at 260, 345, and 520 nm and so it is susceptible to near-UV excitation. A UV source having λ=365 nm, which is a near match to the absorption peak at 345 nm of the donor **126**, was selected for activating the donor **126**. Chlorobenzene substrate **183**, which did not react with donor **126** under thermal conditions (100

°C), was tested at room temperature with photoactivated donor **126** and this reaction provided an excellent yield of reduced product **184**.[60] This enhanced reactivity of the photoactivated donor **126** encouraged these researchers to test even more challenging non-halogenated benzenes.

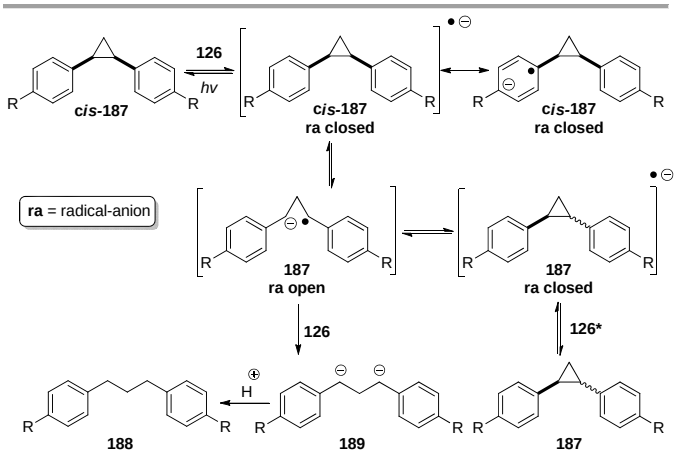


Arene	starting *trans/cis* ratio	yield (%) *trans/cis*	**188** (yield %)
***cis*-187a**	2 : 98	46.8 : 19.6	**188a** (6.1)
***cis*-187b**	2 : 98	28.3 : 31.3	**188b** (2.8)
***trans*-187a**	99.5 : 0.5	54.2 : 7.0	**188a** (13.7)
***trans*-187b**	99 : 1	41.8 : 5.3	**188b** (5.6)

Scheme 23 Reactivity of photoactivated donor **126**.

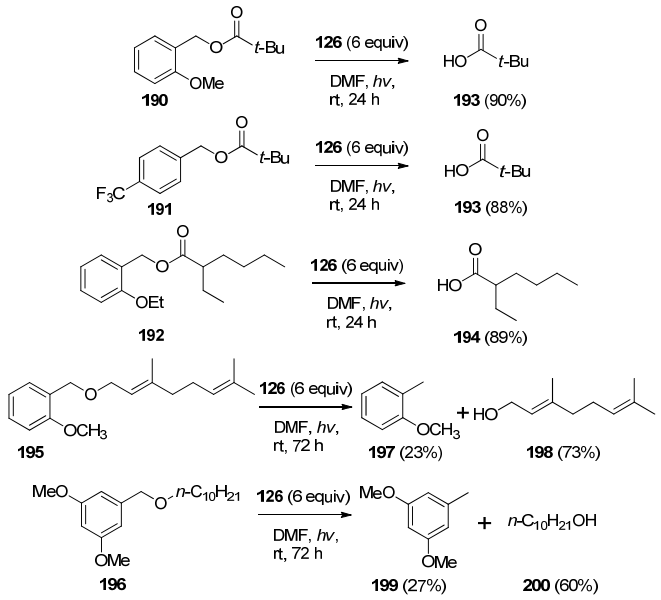
Newcomb[61] and Ingold[62] had used phenylcyclopropyl-carbinyl radicals such as **185** as probes for very fast ring-opening of cyclopropanes to phenylbutenyl radicals such as **186**. However, if cyclopropane ring-opening is reversible and if back electron transfer can occur under the photoactivated conditions, it can again generate the starting material. And so, the use of stereochemically pure diphenylcyclopropanes was proposed as a sensitive detector for electron transfer. Reversible ring-opening of the radical anions of these compounds might indeed lead to reisolation of the starting materials, but the stereochemical purity of the cyclopropanes at the end of the experiment ought to be eroded by the reversible ring-opening. Therefore, the Murphy group tested various *cis*- and *trans*-diphenylcyclopropanes **187** with photoactivated donor **126** and indeed observed the stereochemical isomerisation products along with 1,3-diarylpropanes **188**, arising from reductive trapping of the ring-opened intermediates. This represented the first successful electron-transfer from the photoactivated donor **126** to arene substrates without activating electronegative elements attached to the arene. These reactions also worked with photoactivated donor **81**.

In the proposed mechanism, SET from the photoexcited donor **126** to arene ***cis*-187** generates radical-anion ***cis*-187 ra closed**. Similar to the Newcomb[61] and Ingold[62] studies, the presence of a cyclopropane ring next to the radical site would lead to spontaneous opening of the cyclopropane ring to form **187 ra open**. If the cyclopropane ring-opening is reversible, it will generate again the radical-anion of the arene **187 ra closed**, with diminished stereochemical purity. Since back electron transfer is possible in photochemical processes, the radical-anion may finally convert to isomerised arene **187**. Alternatively, if **187 ra open** takes another electron from the donor **126**, it would form dianion **189**, which, upon protonation would convert to 1,3-diarylpropane **188** (Scheme 24).



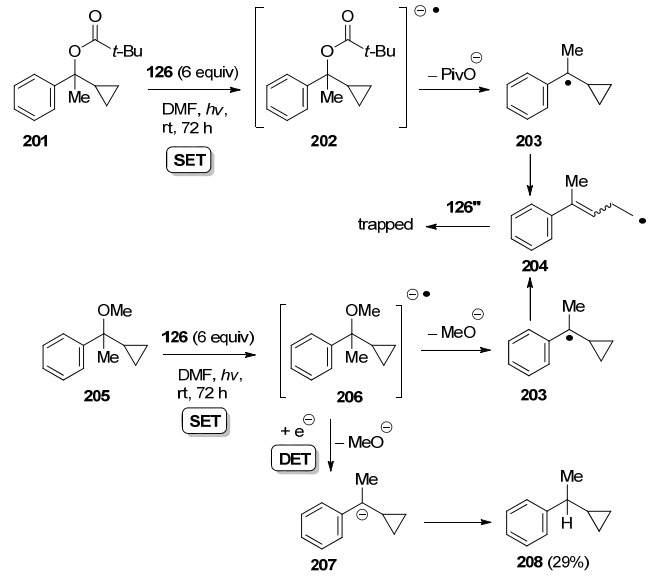
Scheme 24 Proposed mechanism for the reduction of arenes via cyclopropane ring-opening.

Very recently, Doni *et al*.[63] successfully applied the enhanced reactivity of the photoactivated donor **126** to effect the first metal-free reductive cleavage of C-O σ bonds in benzylic esters and ethers. Deprotection of the *O*-benzyl group in esters **190**-**192** went cleanly via SET from the photoactivated donor **126** and afforded the corresponding acid products **193** and **194** in excellent yields. But, in the corresponding deprotection in benzylic ethers **195** and **196**, double electron-transfer (DET) played a role and afforded both the toluene (**197** and **199**) and alcohol (**198** and **200**) products, respectively (Scheme 25).



Scheme 25 Photoactivated donor **126** mediated C-O bond cleavages in benzylic esters and ethers.

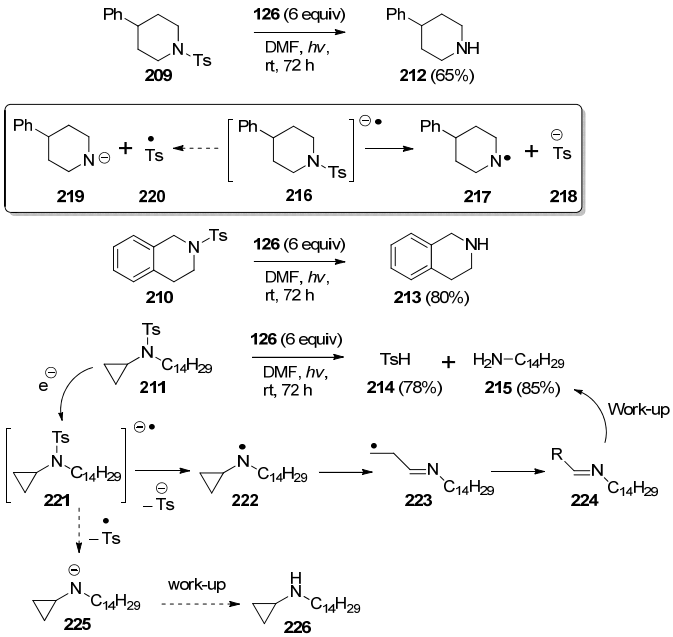
Blank reactions, carried out simultaneously with the original reaction, provided a recovery of the starting materials and further supported the need for photoactivation of donor **126** in these fragmentations. The greater selectivity of the donor **126** versus Na/liq. NH_3 allowed these differences between esters and ethers to be observed.



Scheme 26 SET *vs*. DET in C-O bond fragmentations of benzylic esters and ethers.

To probe the mechanism of the above C-O bond fragmentations, cyclopropane substrates **201** and **205** were treated with the photoactivated donor **126**.[63] Formation of benzylic radical intermediate **203** in either case, after a SET from the donor **126** and the expulsion of benzylic leaving groups, would lead to very rapid opening of cyclopropane ring to afford radical **204**,[61-62] which can be trapped by the radical-cation of the donor, **126**",[54] to form water-soluble by-products. This was indeed the fate of the benzylic esters, where only the pivalate leaving group could be isolated (as pivalic acid following workup). In the case of the benzylic ether **205**, the generation of intact cyclopropane product **208**, could only arise from the corresponding benzylic anion intermediate **207**, which was formed after a second electron-transfer to **206**, supporting the role of a DET process in C-O fragmentations of benzyl ethers (Scheme 26).

Very recently, O' Sullivan *et al*.[64] tested the reactivity of the photoactivated donor **126** against reductive cleavage of C-N and S-N bonds (Scheme 27).

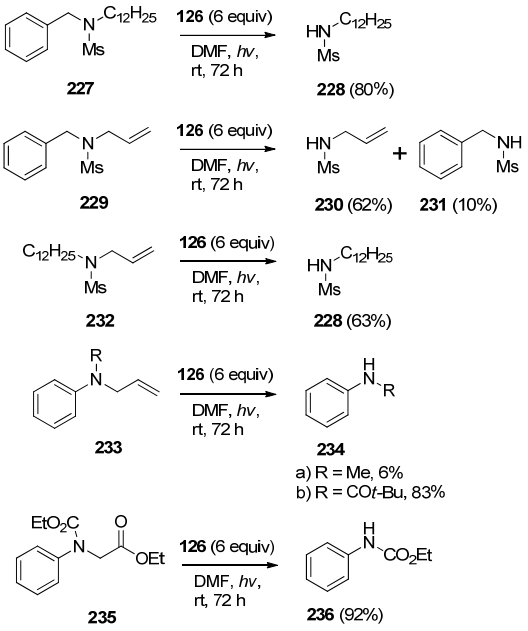


Scheme 27 Reduction of dialkylsulfonamides with photoactivated donor **126**.

Reduction of unactivated *N*,*N*-dialkyl arenesulfonamides **209** and **210**, (unactivated on nitrogen, *i.e.* upon fragmentation, the nitrogen radical leaving group is not stabilised by resonance) which did not undergo any reaction under thermal activation of the donor **126**, provided the cleavage of S-N bonds to afford parent amines **212** and **213**, respectively, in good yields and reinforced the enhanced reactivity of the photoactivated donor **126**. DFT calculations on S-N cleavage of **209** showed that fragmentation to dialkylaminyl radical **217** and sulfinate anion **218** is preferred over dialkylamide anion **219** and sulfonyl radical **220**. Generation of amine **215**

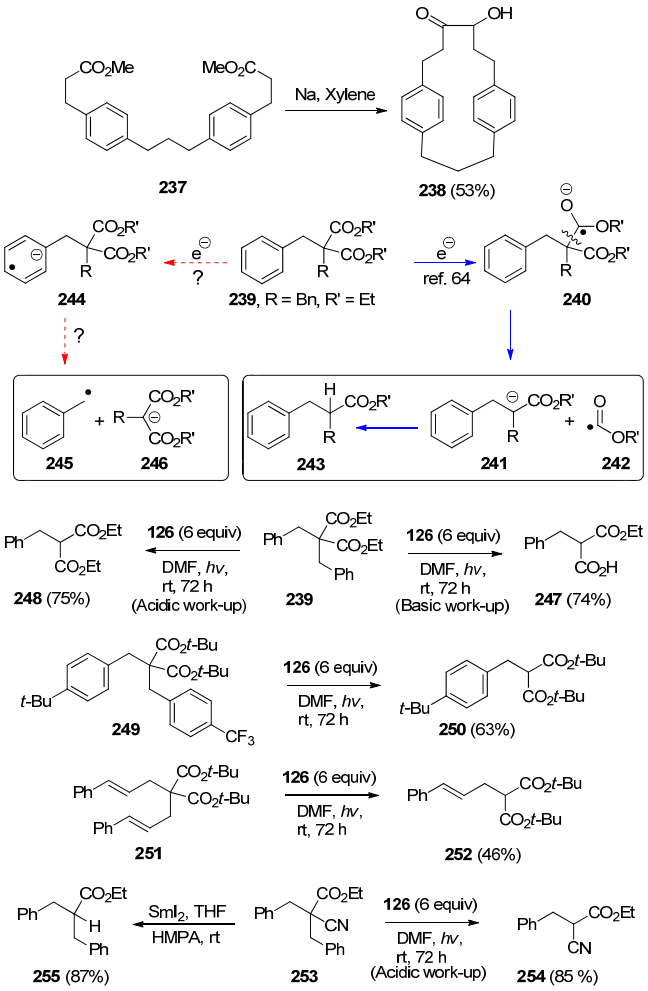
from the reduction of the cyclopropyl-contaning substrate **211** supported this argument (Scheme 27).

The same paper reported reductive deprotection of benzyl methanesulfonamides *e.g.* **227** and **229**, allyl methanesulfonamides *e.g.* **232**, allylanilines *e.g.* **233** and *N*-(acylmethyl)anilines *e.g.* **235**, using the photoactivated donor **126**.[64] All these reduction reactions went cleanly and further extended the scope of the organic electron donor **126**. In all these cases, initial electron-transfer from the donor **126** to the LUMO of the substrate occurred. Allylic groups have less extensive π-systems compared to their benzyl counterparts and so their LUMO energies are expected to be higher than for the benzyl groups. In line with this, the substrate **229** afforded **230**, arising from benzyl C-N bond cleavage, as the major product. In **233b**, the presence of an electron-withdrawing group (CO*t*-Bu) lowers the LUMO energy compared to the analogous methyl case in **233a**, providing a better reaction (Scheme 28).



Scheme 28 Photoactivated donor **126** mediated reductive deprotections.

Very recently, Doni *et al.*[65] reported the selective reduction of arenes over malonates and cyanoacetates using a photoactivated donor **126**. The reactivities observed with the non-metal based organic electron donor **126** are in direct contrast to the observed reactivities of metal-based reagents, where reactivity is expected to be greatly influenced by stabilization of transition states, intermediates and products through substrate-metal bonding. Cram *et al.*[66] had seen acyloin reaction of substrate **237** in xylene as solvent, which proceeded through selective reduction of ester groups by sodium and, this selectivity for esters over arenes is expected due to the more negative reduction potentials of benzene rings compared to ester groups. Reductive fragmentation of benzyl malonates *e.g.* **239** by sodium and potassium metals had also been described in the literature (shown in blue arrows in Scheme 29).[67] Doni suggested that in the absence of metal interactions, these substrates might provide different reactions *i.e.* selective reduction of benzene rings over ester groups (shown in red arrows in Scheme 29) and so, they tested substrate **239** with the photoactivated donor **126**.



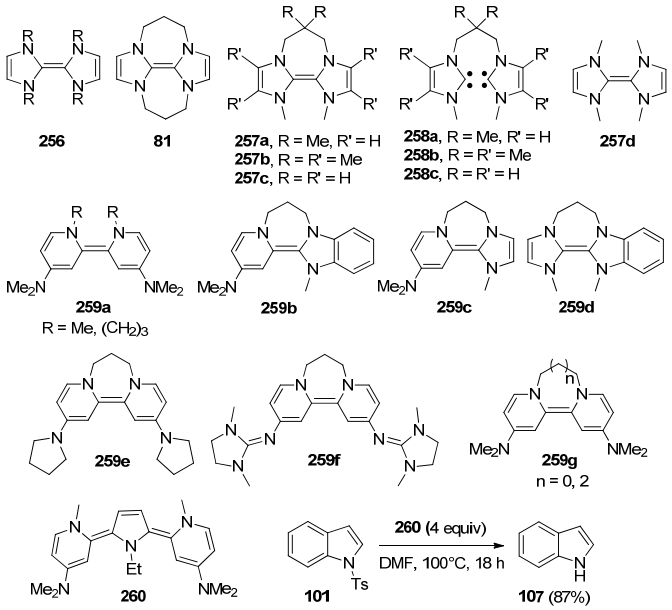
Scheme 29 Reductive benzylic C-C bond cleavages.

Indeed, this reaction provided selective reduction of the arene ring and afforded products **247** or **248**, dependent on the work-up method, and arising from the corresponding benzylic C-C bond cleavage. Mixed substrate **249** afforded selective cleavage of trifluoromethylbenzyl group, as the LUMO of the substrate is located exclusively on the relatively electron-poor trifluoromethylphenyl ring. Dicinnamyl substrate **251** provided homologous C-C bond cleavage. Kang *et al.*[68]

reported that cyanoesters *e.g.* **253** underwent clean decyanation upon reaction with SmI_2 in THF/HMPA. In contrast, the same substrate **253**, with photoactivated donor **126**, afforded exclusively benzylic C-C bond cleavage product **254** (Scheme 29), providing another example of overturned reactivity brought about by non-metal, organic electron donor **126**. In the case of the organic electron donors, selective complexation between the donor and an arene group is likely, in contrast to the association of metal ions with the heteroatom lone pairs.

3.5 Other powerful neutral organic electron donors

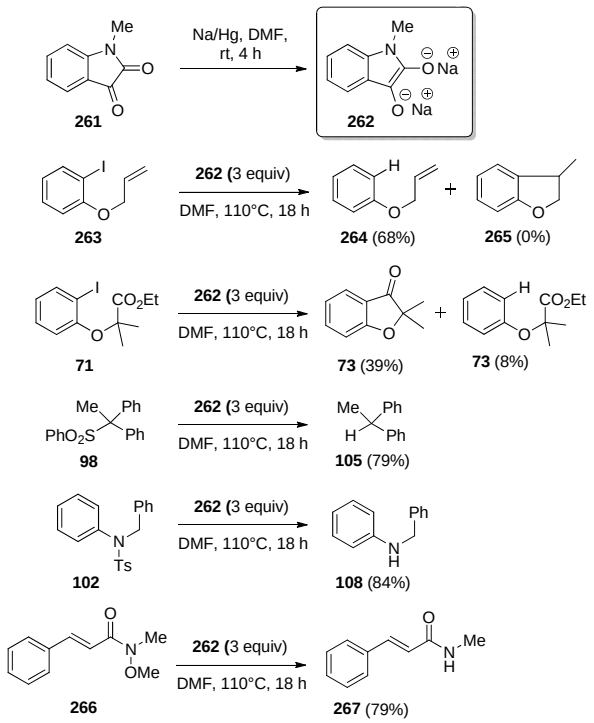
In the meantime, the Murphy group has published a number of other powerful neutral organic electron donors derived from imidazole,[69] 4-DMAP[51, 70] and *N*-methylisatin.[71]



Scheme 30 Other powerful neutral organic electron donors.

Isolation of tetraazafulvalenes **256** had proved elusive,[37, 39] with the exception of the earlier synthesis of doubly bridged donor **81** by Taton and Chen.[41b] This is partly due to the high reactivity of **256** and related tetraazafulvalenes that undergo easy conversion into the corresponding carbenes such as **258** in a reaction that is catalysed by traces of a proton source. Jolly *et al.*[69] managed to synthesise and characterise a series of tetraazafulvalenes **257a-d** with extreme care under very dry reaction conditions. Garnier *et al.*[51, 70a] synthesised a series of hybrid donors **259b-g**, derived from 4-DMAP, benzimidazole and imidazole and, successfully applied them in the reduction of aryl iodides. Farwaha *et al.*[70b] synthesised exotic, tricyclic donor **260** and cyclic voltammetry showed a record half-wave potential (-1.46 V *vs*. Ag/AgCl in DMF) [translates to -1.50 V *vs.* SCE] for this neutral organic electron donor. They also successfully applied the donor **260** in the reductive cleavage of arenesulfonamides *e.g.* **101** (Scheme 30).

Sword *et al.*[71] reported a new class of donor derived from *N*-methylisatin **261**. Active donor **262**, a green dianionic species, was readily formed by the treatment of *N*-methylisatin **261** with sodium amalgam. Cyclic voltammetry of this donor showed two quasi-reversible one-electron reductions at -0.9 and -1.9 V *vs*. Ag/AgCl. Loss of two electrons from the active donor **262**, which is aromatic, would lead back to *N*-methylisatin **261**, with loss of aromaticity in the five-membered ring, and so **262** would act as a moderate electron donor. However, they successfully applied the donor **262** in the reduction of aryl iodides *e.g.* **263** and **71**, sulfones *e.g.* **98**, sulfonamides *e.g.* **102** and Weinreb amides *e.g.* **266** (Scheme 31). Absence of cyclic product **265** in the reaction of **263** and generation of cyclic product **73** in the reaction of **71** suggested that this donor is strong enough to convert iodoarenes to aryl anions.



Scheme 31 Reactivity of the donor **262** derived from *N*-methylisatin **261**.

4. Conclusions

For many years, electron-transfer chemistry has been dominated by metals and metal complexes but now a new class of purely organic reducing molecules is pushing the

boundaries of selectivity and reactivity in electron-transfer reactions. This review highlights the sequential development of neutral organic super-electron-donors starting from the mild electron donor tetrathiafulvalene (TTF) molecule. The presence of nitrogen atoms to stabilise developing cationic species and the gain in aromatic stabilisation upon oxidation underpinned the reducing power of these donors.

The early electron donor, TTF **1**, could only reduce electron-deficient diazonium salts and the Murphy group reported first radical-polar crossover reactions using TTF **1** and successfully applied it in the total synthesis of (±)-aspidospermidine. Synthesis of other sulfur-containing electron donors **19-21** and **23** was complicated, limiting their use in reductive chemistry. Commercially available TDAE **24** is more powerful than previous donors but, it could only reduce electron-deficient alkyl and benzyl halides to the corresponding anions. For other potential electron-rich donors reported recently by the Vaid and Himmel groups, reductive chemistry towards organic molecules has not been reported. Later, the Murphy group reported even more powerful neutral organic super-electron-donors **50**, **81** and **126**. These donor molecules achieve highly challenging electron-transfer reactions including the reduction of aryl halides, anthracene derivatives, sulfones, disulfones, sulfonamides, Weinreb amides and, acyloin derivatives. It was found that benzimidazole-derived donor **50** can act as a single electron donor to iodoarenes while DBD **81** and 4-DMAP-derived donor **126** can donate two electrons. Very recently, the Murphy group successfully exploited the enhanced reactivity of the photoactivated donor **126** in achieving even more challenging reductions of arenes and unactivated dialkyl arenesulfonamides and reductive cleavage of C-O, C-N, S-N and C-C bonds. In the meantime, they also reported various hybrid donors along with a new class of donor derived from *N*-methylisatin. Finally, the recent advances with this class of neutral organic electron donors are promising even more attractive chemistry and will certainly contribute a lot more to electron-transfer chemistry.

Acknowledgements

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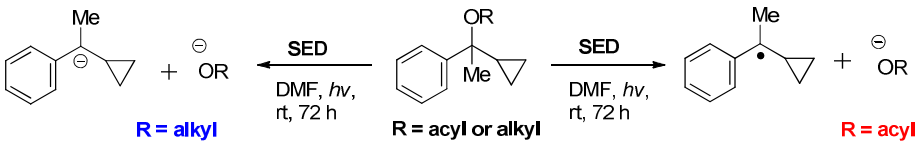
Graphical Abstract



Organic electron donors have emerged as powerful reducing reagents with unique selectivity.