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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 electro-chemical reduction at a (usually metal) cathode,6,7 reduction by solvated electrons,8 reduction by lithium naphthalide9 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

2. Early organic electron-transfer reagents

2.1 Tetrathiafulvalene (TTF)

In developing organic electron transfer reagents, tetrathiafulvalene (TTF) can be taken as a model system. TTF 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 \( \pi \)-system and thereby TTF can act as an electron-rich donor. TTF was first synthesised by Wudl13 in 1970 and, subsequently, semiconducting properties of its salts, e.g. [TTF]Cl\(^{2-}\), were studied in 1972.14 TTF 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 was not exploited in organic synthesis before our research group began investigations.16 We started using TTF 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 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),\(^{22b}\) and the authors claimed that these donors can behave as “organic metals”.\(^{22c}\) 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,23 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 synthesised23 by replacing two sulfur atoms in TTF 1 with nitrogen. The first oxidation potential of 23 is -0.3 V vs. SCE in DMF24 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 unactivated aryl halides.26

![Fig. 1 Diazadithiafulvalene donor 23.](image)

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 Médébielle 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 MeCN30 and this manifests the higher reducing power of 24 over TTF 1 and diazadithiafulvalenes 23.

![Scheme 5 Electron donation from TDAE.](image)

TDAA can reduce electron-deficient iodotrifluoromethane 27 to trifluoromethyl anion and this is illustrated in the reaction of 27 and benzoyl chloride 28 with TDAE 24.27b 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.](image)

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 3712 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 \( 42^{+}\rightarrow42^{2+} \) at -1.14 V (translating to -
0.69 V vs. SCE) and 2-electron reduction (42^{2-}\rightarrow41^0) at -1.33 V vs. Fe/Fe^2+ (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. 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. Fe/Fe^2+ (THF) [translates to +0.19 V vs. SCE] (Scheme 7).

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 deprotonation38 (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 13C 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.

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 DMF39 and this establishes the higher reducing power of 50 over TTF 1, diazadithiafulvalenes 23 and TDAE 24.

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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. However, the reduction of aryl bromide 61 was not as successful as aryl iodides and provided a lower yield of cyclised product 62 under extended reaction times (Scheme 10).

Scheme 10 Reduction of aryl and alkyt 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 (d₆-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). 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).

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). Donor 81 had previously been prepared by Taton and Chen 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, making it a
more powerful donor than 50. The donor 81 was thought to be more powerful than benzoimidazole-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](image)

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). As seen in the reaction with donor 50, cyclisation of aryl radicals tends to occur at much faster rates than hydrogen abstraction, 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](image)

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. Reaction of 87 using (Me₃Si)₂SiH and AIBN, well known reagents used to generate purely radical species, afforded exclusively uncyclised product 88. Substrate 87 was then reacted with Bu₃Sn-SiMe₃ and CsF, standard conditions for the generation of aryl anions from iodoarenes. 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 (Me₃Si)₂SiH 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 Bu₃Sn-SiMe₃ 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).

![Scheme 14](image)

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). 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 arenesulfonamides with activated nitrogen leaving groups e.g. 101 and 102 (Scheme 15). Deprotection of these groups, generally, is carried out by highly reactive metal-containing reducing agents like alkali metals under Birch conditions or using SmI₂ with HMPA. This was the first report of such cleavages using organic super-electron-donors. No reaction was observed with aryl alkyl sulfone 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. In the proposed mechanism (Scheme 15), 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.

Murphy et al. 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 1H-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 (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). 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. 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
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 $\delta = 116$ 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.

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. 50–51

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$_2$O 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°C using 3 equiv of donor 126 (Scheme 18).

The reactivity of donor 126 was further tested with Weinreb amides and afforded the reductive cleavage of N-O bonds. 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

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

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

Cutulic et al. 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).

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. 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. 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.

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

Scheme 20 Cleavage of C-O σ-bond in acyloin derivatives.
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⁻) furnishing the corresponding alcohol 158 upon work-up (Scheme 21).

Jolly et al. 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 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 O¹⁸-DMF labelled experiments. Bromo-aryl trflate 170 reacted selectively at the trflate 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. 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 peroxydes) or pyrophoric (trialkylboranes) compounds. So, there has been a lot of interest in further developing photoactivated electron-transfer reactions. Reduction of ground-state benzene (E⁰ = -3.42 V vs. SCE) 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. Very recently, Hilmersson et al. have also seen Birch type reduction of 4-methoxybenzyl alcohol 179 using their SmI₂/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. This enhanced reactivity of the photoactivated donor 126 encouraged these researchers to test even more challenging non-halogenated benzenes.

Newcomb and Ingold had used phenylcyclopropyl-carbiny 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 open. Similar to the Newcomb and Ingold 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 closed. If the cyclopropane ring-opening is reversible, it will generate again the radical-anion of the arene 187 ra open, 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).

Very recently, Doni et al. successfully applied the enhanced reactivity of the photoactivated donor 126 to effect the first metal-free reductive cleavage of C-O 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).

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<td>46.8 : 19.6</td>
<td>188a (6.1)</td>
</tr>
<tr>
<td>cis-187b</td>
<td>2 : 98</td>
<td>28.3 : 31.3</td>
<td>188b (2.8)</td>
</tr>
<tr>
<td>trans-187a</td>
<td>99.5 : 0.5</td>
<td>54.2 : 7.0</td>
<td>188a (13.7)</td>
</tr>
<tr>
<td>trans-187b</td>
<td>99 : 1</td>
<td>41.8 : 5.3</td>
<td>188b (5.6)</td>
</tr>
</tbody>
</table>

Scheme 23 Reactivity of photoactivated donor 126.

Scheme 24 Proposed mechanism for the reduction of arenes via cyclopropane ring-opening.
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. NH₃ allowed these differences between esters and ethers to be observed.

To probe the mechanism of the above C-O bond fragmentations, cyclopropane substrates 201 and 205 were treated with the photoactivated donor 126. 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, which can be trapped by the radical-cation of the donor, 126, 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., tested the reactivity of the photoactivated donor 126 against reductive cleavage of C-N and S-N bonds (Scheme 27).

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 219 and sulfonyl radical 220. Generation of amine 215...
from the reduction of the cyclopropyl-containing 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. 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\textsubscript{2}Me) 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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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](image)

Scheme 29  Reductive benzyl-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 benzyl 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.\textsuperscript{68}
reported that cyanoesters e.g. 253 underwent clean decyanation upon reaction with SmI\textsubscript{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 overtaken 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,\textsuperscript{69} 4-DMAPP\textsuperscript{51,70} and N-methylisatin.\textsuperscript{71}

![Scheme 30](image)

Scheme 30 Other powerful neutral organic electron donors.

Isolation of tetraazafulvalenes 256 had proved elusive,\textsuperscript{37,39} with the exception of the earlier synthesis of doubly bridged donor 81 by Taton and Chen.\textsuperscript{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.\textsuperscript{65} managed to synthesise and characterise a series of tetraazafulvalenes 257a-d with extreme care under very dry reaction conditions. Garnier et al.\textsuperscript{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.\textsuperscript{70c} 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.\textsuperscript{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](image)

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 tetraethylvalene (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, aromatic 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 amines and unactivated dialkyl aminesulfonamides 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.

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References

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