DOI: 10.1002/anie.200704883

Formation of Carbanions Using Neutral Organic Molecules as Electron-Transfer Reagents: A Radical Concept

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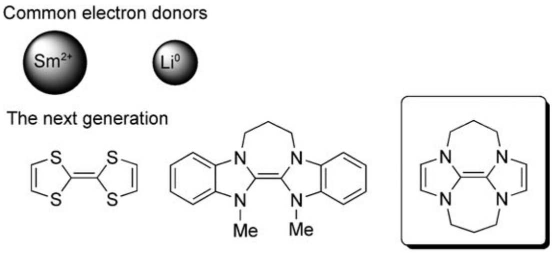
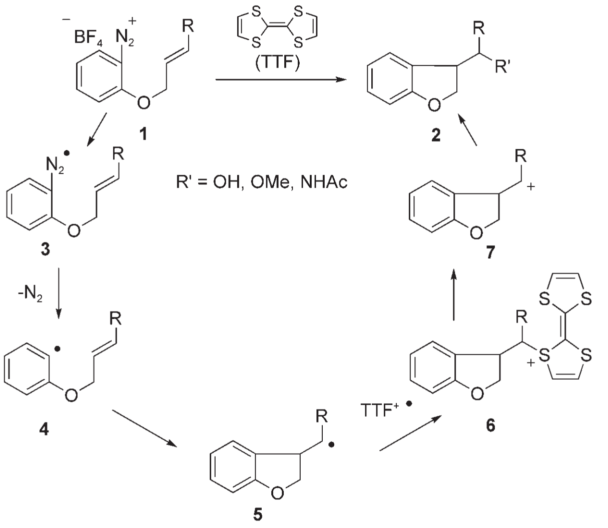
anions · electron transfer · radical reactions · reduction · synthetic methods

The reduction of organic molecules by electron transfer has been prevalent in organic synthesis for several decades.[1] Photochemical[2] and electrochemical[3] routes are occasionally used, as is reduction by solvated electrons[4] and radical anions of organic molecules.[5] However, by far the most common method for the delivery of an electron to organic substrates involves metals in low oxidation states.[6] Despite its usage, the latter method suffers from a number of drawbacks. For example, harsh conditions are often needed, and the removal of metal residues from crude reaction mixtures is a major hindrance to its use in the pharmaceutical industry. The use of organic molecules that are capable of transferring electrons (one or two) to create reactive intermediates would therefore be a very attractive prospect. A new generation of organic compounds capable of delivering radicals has now been developed. These function in processes which up until now, have been mainly carried out by metals (Scheme 1).



Scheme 1.

Some time ago Murphy and co-workers discovered that tetrathiafulvalene (TTF) could be used in radical-polar crossover reactions (Scheme 2).[1,7] The transfer of an electron from TTF to diazonium salts such as **1**, followed by loss of dinitrogen and cyclization, gives alkyl radical **5**. Coupling of this radical to TTF$^{\bullet+}$ then affords sulfonium salt **6**, and a subsequent water quench furnishes, for example, alcohol **2** (R′ = OH). The use of CH_3CN affords the corresponding amide. The initial methodology was applied to the synthesis of the complex natural product aspidospermidine, which is isolated from the alkaloid *Aspidosperma*.[8] However, the utility of this approach was hampered by the need for arenediazonium substrates. The quest for more powerful electron-transfer reagents initially only resulted in limited success.



Scheme 2.

Diazadithiafulvalene derivatives[9] are well-known powerful electron donors, but they do not react with organic halides and are susceptible to side reactions with arenediazonium salts.[10] Médebielle, Dolbier, and co-workers showed that 1,1,2,2-tetra(dimethylamino)ethane (TDAE) could be used to form strongly stabilized trifluoromethyl anions[11,12] after the transfer of two separate single electrons (Scheme 3). Benzoyl chloride underwent two nucleophilic attacks to form an alcoholate and then acylation to afford **8**. The same reagent (TDAE) was also used to afford the *p*-nitrobenzyl anion.[12] No detailed mechanistic investigation was undertaken to

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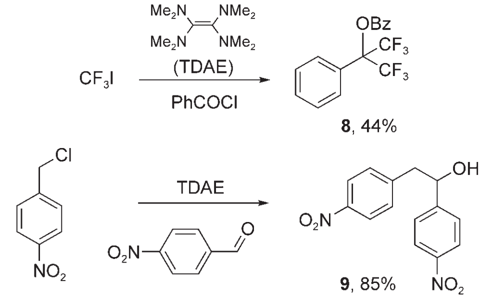
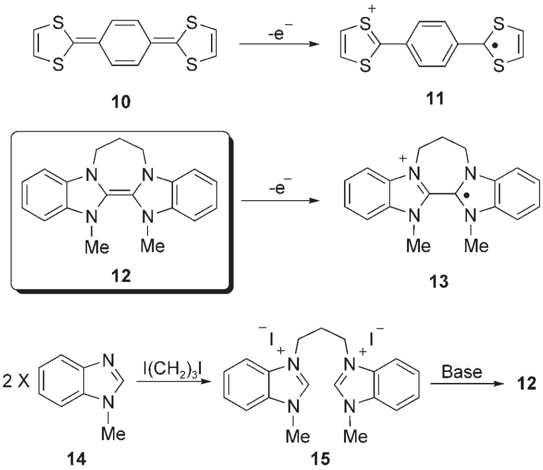


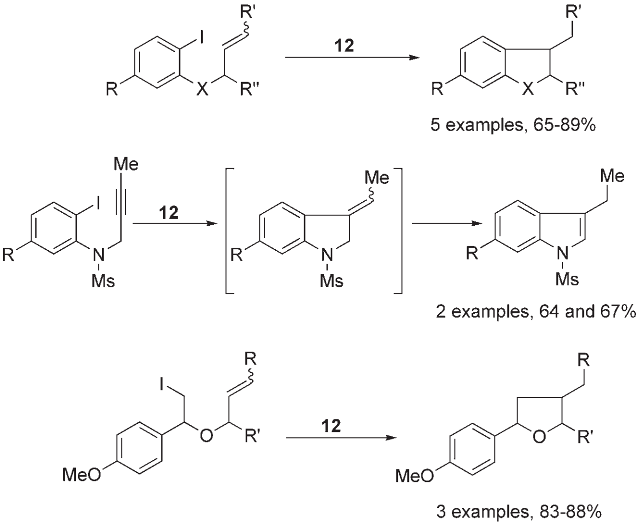
Scheme 3. Bz = benzoyl.

definitively discern if an anionic or radical pathway was in operation.

An analogue of TTF, *p*-quinobis(1,3-dithiole) (**10**), was known to readily lose an electron; however, interest in these types of molecules arose from their unusually high solid-state conductivities in charge-transfer complexes,[13] which is presumably due to the aromaticity of the corresponding radical cation **11** (Scheme 4). Murphy et al. envisaged that aromaticity factors together with a "neighboring nitrogen effect" was in operation and these provided a system capable of transferring electrons to aryl iodides.[14] Thus, **15** was prepared as a stable crystalline salt by reaction of *N*-methylbenzimidazole (**14**) with 1,3-diiodopropane. Treatment of **15** with two equivalents of base generated a yellow solution of electron donor **12**, which although air-sensitive was characterized by NMR spectroscopy in deoxygenated $[D_7]$DMF under argon. The term "super single electron transfer" (SuperSET) was coined for this reagent. No evidence of the compound having mono- or dicarbene character was observed in the NMR spectra.

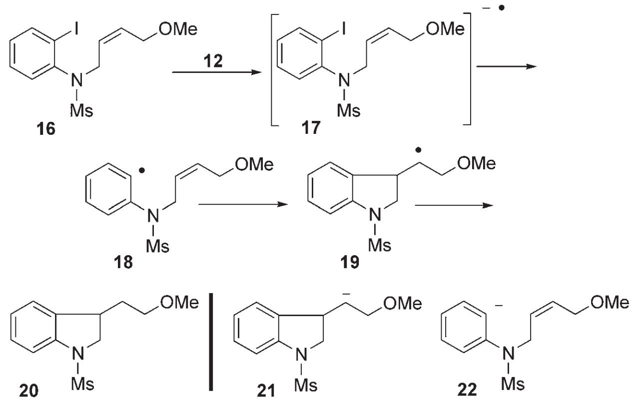


Scheme 4.



Scheme 5. Ms = mesyl = methanesulfonyl.

A series of indoline precursors and the corresponding O-tethered substrates were treated with SuperSET (**12**) in toluene/DMF at reflux. Clean cyclization of alkynyl-containing aryl iodides occurred to afford indolenines that isomerized to indoles. Aliphatic iodides also cyclized in excellent yields (Scheme 5). A possible mechanism involves an initial transfer of an electron to an aryl iodide such as **16** to afford radical anion **17** (Scheme 6).[15] Dissociation then gives aryl radical **18**, which undergoes cyclization to afford **19**.



Scheme 6.

At this stage, the possibility that **18** or **19** could accept a second electron to give anions **22** and **21**, respectively, could not be ruled out. However, no evidence of nucleophilic attack on the DMF solvent was observed. Furthermore, the presence of anions in the example shown (Scheme 6) would probably give eliminated products.[16] The formation of radical-mediated neophyl rearrangement products in certain substrates is further proof that radicals at least contribute to the overall mechanism. At this juncture, the question of the hydrogen source in the final mechanistic step arises. The use of deuterated DMF as the solvent and sodium hydride as the base gave no labeled product (a simplified substrate was used here). The hydrogen therefore most likely originates from **12** or **13**. The use of SuperSET alternatives with less available hydrogen sources would therefore be an interesting, albeit synthetically difficult, avenue to explore.

Having shown that neutral organic compounds could be used to transfer a single electron to certain substrates, the

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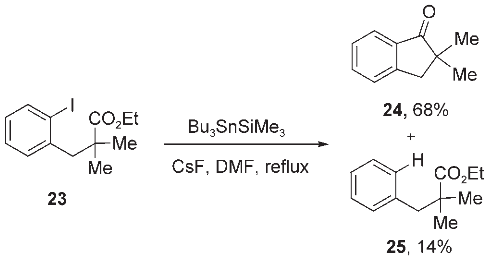
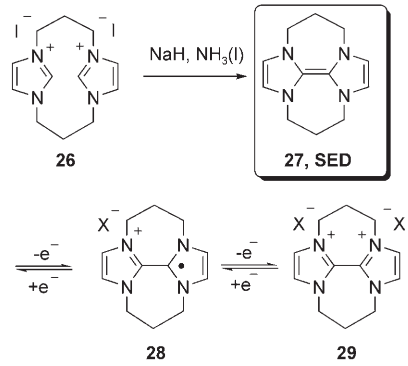
ambitious target of transferring a second electron was undertaken. Very recently the same research group, in collaboration with Tuttle and co-workers, revealed the next generation of organic molecules capable of transferring electrons.[17] These are not simply more powerful single-electron-transfer reagents, but are capable of transferring two electrons to afford aryl anions.[18] This study represents the first example of the formation of an aryl anion by using a neutral organic reagent in the absence of photochemical activation.[17]

As a control reaction, ester **23** was shown to cyclize in the presence of trimethyl(tributylstannyl)silane and CsF in refluxing DMF to give **24** and reduced product **25** (Scheme 7).



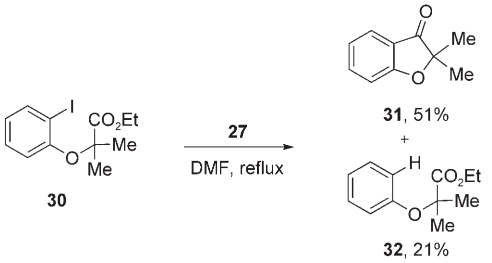
Scheme 7.

Under previously optimized conditions, SuperSET (**12**) only gave **25**, which indicated that no aryl anion had been formed. A concise and practical route to **27** was then devised with a view to assessing its ability to deliver two electrons. Diiodide **26** was prepared in two steps from imidazole. Treatment of **26** with base in liquid ammonia gave **27** (super electron donor, SED), which in theory could lose two electrons and be oxidized to **29** (Scheme 8). Treatment of ester **30** with **27** resulted in nucleophilic attack on the ester function and cyclization to give **31** in 51% yield (Scheme 9). It is noteworthy that the amount of anion created could be greater than the yields of the isolated products given the fact that some anion could leak through yielding reduced product **32**.



Scheme 8.

The increased activity of **27** compared to **12** is attributed to its added aromatic stabilization energy present in the dication after release of two electrons. In essence, the added stabilization energy is greater when going from a completely non-aromatic system (**27**) to the imidazolium rings in **28** or **29.**



Scheme 9.

A comparison of the analytical and theoretical data of dications of **12** and **27** is enlightening and intriguing (the dications are formed as their PF_6^- salts, not shown). The ^1H NMR spectrum of the dication of **27** revealed the diastereomeric nature of the NCH_2 protons (2 multiplets) present in the trimethylene bridge and is indicative of a rigid helical twist or kink in the molecule. In contrast, the NCH_2 protons in the dication of **12** are in the same magnetic environment and appear as a simple triplet in the spectrum. Computational studies also show that the bond lengths in both cations are consistent with resonance-stabilized structures. In the case of **12**, however, more pronounced structural reorganization is seen on removal of the electrons. Here the angle between the planes (τ) of the benzimidazole rings increases from 16° to 42° on formation of the dication, whereas in **27** the angle decreases from 10° to 1.5°—an almost planar structure. The internal reorganization energy was calculated by using iodobenzene as a model electron acceptor. Surprisingly the calculated sum of the component internal reorganization energies for the model reactions of iodobenzene with **12** and **27** are greater in the latter after removal of both the first and second electrons. However, the formation of the resulting positive charges in **12** is approximately 10 kcal mol^{-1} less favorable than in **27**, and is thus overall more endergonic. The activation energies were also consistent with the experimental results.

Donor **27** required $\Delta G^* = 12.3$ and 6.9 kcal mol^{-1} for the transfer of the first and second electrons, respectively, whereas **12** was calculated to require 17.4 and 12.8 kcal mol^{-1}, respectively. Furthermore, the maintenance of planarity in **27**, as opposed to the loss of planarity in **12**, may have crucial consequences. The latter compound can also engage in a π–π interaction with the approaching aryl ring of aryl ester substrates, but this is unlikely to have a significant effect.

The marked difference between the reactivities of both electron donors is beautifully exemplified in the reduction behavior of several aryl halides (Scheme 10). While the reaction of 9-bromophenanthrene (**33**) with **12** only gave reduced arene **34** in 9% yield, electron donor **27** afforded **34** in 96% yield. Similarly **27** gave excellent conversion of **35** into **36.**[17]

In a very recent study, electron donor **27** has been applied in the reductive cleavage of sulfones and sulfonamides.[19] Monosulfone **37** was cleanly reduced to its corresponding hydrocarbon **38** (Scheme 11). Alkene **39** was similarly re-

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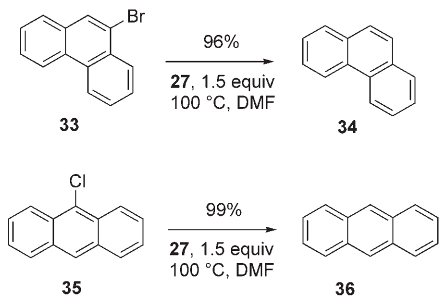
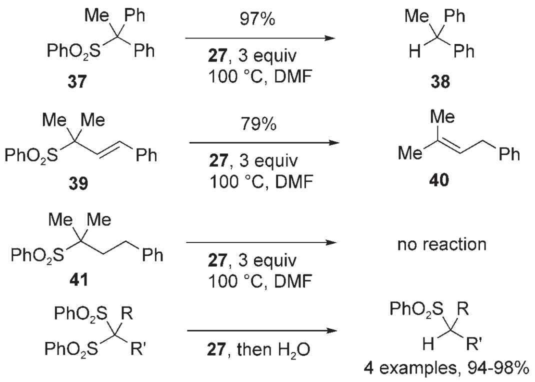


Scheme 10.



Scheme 11.

duced to **40**. Computational investigations showed that the reason for the resistance of **41** to undergo reduction is the increased activation energy required for electron transfer. In contrast, the lower activation energies of **37** and **39** are associated with their electron transfer and spontaneous dissociation into a sulfinate anion.[19] *gem*-Disulfones could also be partially reduced to monosulfones by the same method—this is a very useful transformation.

Reported reduction potentials can greatly aid a researcher in the design of a project such as this, but the authors are keen to point out[17] that thermodynamically unfavorable reactions can occur if the reduction (to a radical anion, for example) is followed by an irreversible step (loss of iodide, for example), a fact not often appreciated by synthetic chemists. Donor **27** should not be capable of reducing iodoarenes ($E_p = -2.2$ V), yet the reaction works quiet well, while indanone **24** should undergo reduction under the same conditions ($E_{1/2} = -2.02$ V versus the saturated calomel electrode (SCE)), and yet this is not observed. Furthermore, seemingly unavoidable events do not occur experimentally. For example, Andrieux and Pinson calculated that the standard potential for the reduction of an aryl radical is $+0.05$ V (E_0 versus SCE),[15b] which means that donors such as **12** ($E_{1/2} = -0.82$ V versus SCE) should give up a second electron relatively easily. So while the reaction may be thermodynamically favorable, it does not occur at an appreciable rate under the conditions used by Murphy and co-workers.

In summary, early reports on the reduction and cyclization of aryl substrates, while merited, proved of little practical use because of the need for a diazonium salt. The use of TDAE suffered from a limited substrate scope, and several mechanistic questions remained unresolved. Two recent high impact reports by Murphy and co-workers have greatly improved the possible utilization of organic molecules as single- and double-electron donors.

In time, a broad scope of practical reduction potentials will be available. One can imagine scanning a graph (Figure 1)[17,20] bearing a large number of organic electron donors and targeting one specifically tuned to a particular reaction. Thus, greater selectivity will be possible, thereby decreasing the need for protecting groups. For example, unlike sodium naphthenide and magnesium, **27** does not reduce ketones. It is likely that several important reactions involving single-electron transfer will now be targeted with a view to replacing the metallic reagents. While there remains a few inconveniences at this early stage, such as high temperatures and reactions limited to halides and sulfones, this breakthrough by Murphy and co-workers has opened up the possibility of using SuperSET, SED, and whatever future generations of neutral organic radical donors are out there in numerous other reactions. In addition to the recently revealed reduction of sulfones,[19] we can expect to see further reactions of sulfones, as well as ketones, aldehydes, and alkynes that use neutral organic molecules. The methodology could also be used to open epoxides and should be further evaluated in the direction of biological and materials chemistry. The ultimate goal of this approach would surely be a catalytic process.[21]

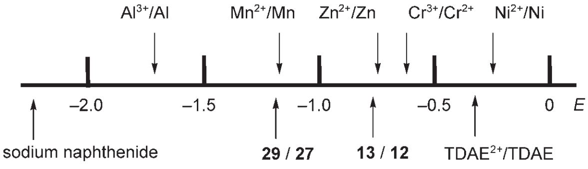


Figure 1.

Published online: January 31, 2008

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