Electron Transfer

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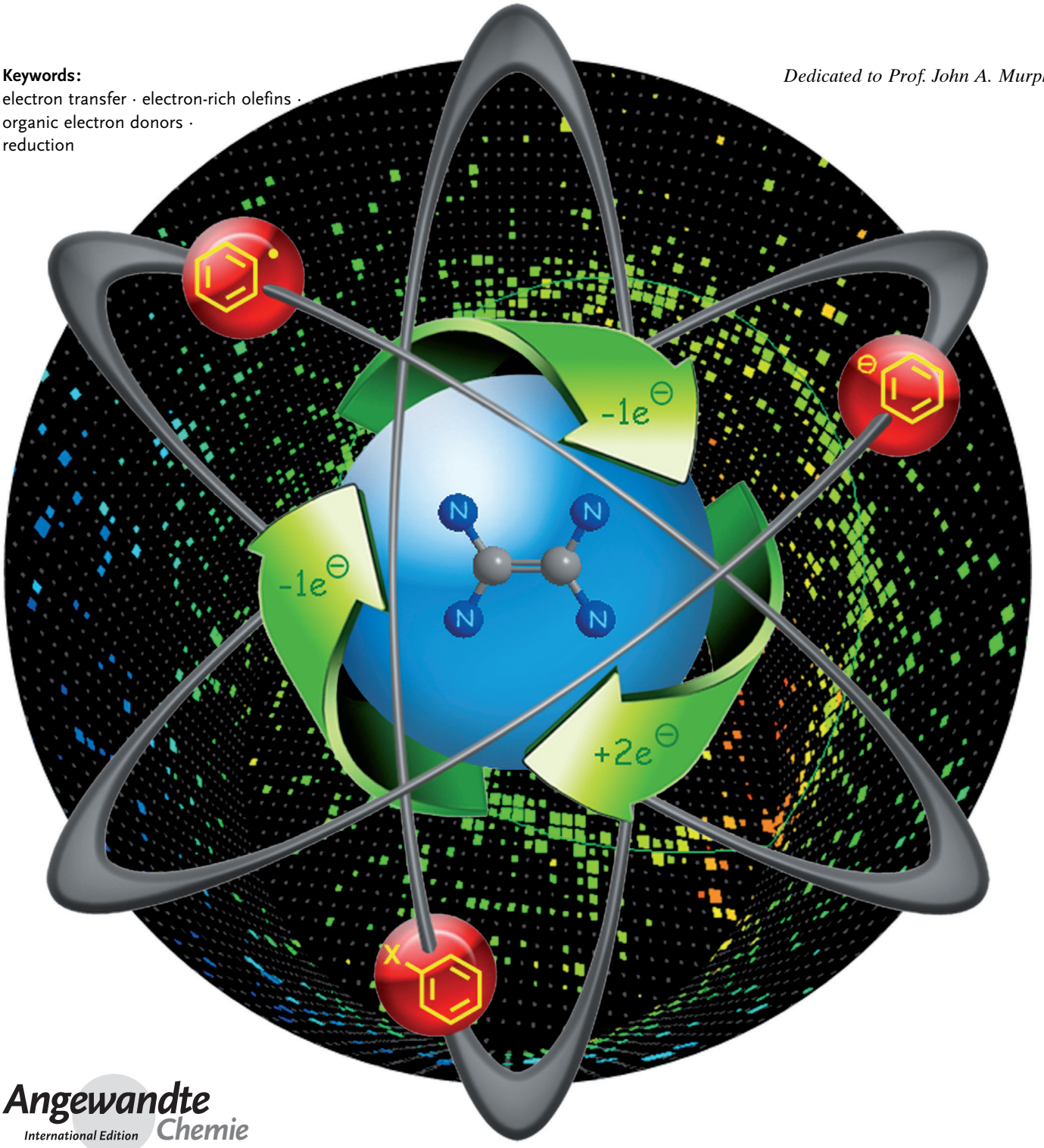
# Organic Electron Donors as Powerful Single-Electron Reducing Agents in Organic Synthesis

*Julie Broggi,* Thierry Terme,* and Patrice Vanelle**

**Keywords:**
electron transfer · electron-rich olefins · organic electron donors · reduction

*Dedicated to Prof. John A. Murphy*



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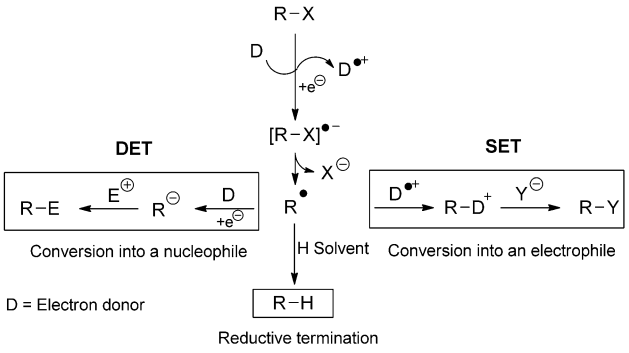
*One-electron reduction is commonly used in organic chemistry for the formation of radicals by the stepwise transfer of one or two electrons from a donor to an organic substrate. Besides metallic reagents, single-electron reducers based on neutral organic molecules have emerged as an attractive novel source of reducing electrons. The past 20 years have seen the blossoming of a particular class of organic reducing agents, the electron-rich olefins, and their application in organic synthesis. This Review gives an overview of the different types of organic donors and their specific characteristics in organic transformations.*

**From the Contents**



## 1. Introduction

The investigation of chemical reactivity is the hobbyhorse of organic chemistry and has long been the realm of electron-pair transfer reactions. First considered uncontrollable, single-electron transfer processes have attracted increasing attention over the past 40 years.[1] Molecular electrochemistry has since brought its share of discoveries, recognition (Nobel Prizes in Chemistry 1983, Taube and 1992, Marcus), and pharmaceutical and industrial applications. New synthetic methods involving radical intermediates have built up the chemist's repertoire with reactions such as substitutions, additions, cyclizations, polymerizations, and cascade processes that lead to the polycyclic carbon skeletons of natural products.[2,3] Radical reactions frequently appear to be a mild, selective, and predictable alternative method where classic polar reactions fail. Among the different ways to effect radical formation,[3] one-electron reduction in organic chemistry involves the stepwise transfer of one or two electron(s) from a donor to an organic substrate (Scheme 1). The electron




***Scheme 1.*** Radical substitutions by single- (SET) or double-electron transfer (DET).

transfer (ET) and the bond dissociation can take place either simultaneously or in two successive steps. Reductive ET-initiated bond cleavage leads to the dissociation of a large variety of chemical bonds including C–C as well as C–, N–, O–, and S–heteroatom bonds.[2] The most thoroughly investigated reduction is probably that of organic halides. The first intermediate of a single-electron-transfer (SET) reduction is often a radical anion $[RX]^{\bullet-}$ which spontaneously dissociates into a free radical R•. The reactivity depends on the activation barrier of the initial ET itself correlated with the stability of the radical anion. In radical substitution, R• can either be converted into an electrophile $[RD]^{+}$ by coupling with the radical cation $D^{\bullet+}$ of the donor, or abstract a hydrogen atom. A second one-electron transfer can also occur to give the anion $R^{-}$, which acts as a nucleophile (overall a double-electron transfer (DET)).

Numerous SET reducing agents[3] are used to promote the formation of carbon-centered radicals or anions: metals in low oxidation states (mainly alkali metals) dominate the field of ET reactions, particularly for thermodynamically difficult reductions, such as Birch reductions, acyloin condensations, and aryl halides reductions. Other methods include reduction by solvated electrons or by alkali metal salts of an organic radical anion, electrochemical reduction at a (usually metal) cathode, or photochemically assisted electron transfer.[2] Nowadays, the search for new processes and alternative reductants that result in clean carbon–carbon bond formation by free-radical reactions stems from the well-known problems encountered with inorganic SET reducers and the widely used toxic and troublesome tin hydrogen donors.[3] In this context, electron-donating reagents based on neutral organic molecules have emerged as an attractive novel source of reducing electrons. Organic species can behave as electron donors through spontaneous reaction with a substrate that has sufficient oxidizing power, or they can be induced to donate an electron photochemically, electrochemically, or on exposure to irradiation conditions.[4,5] This Review focuses on the first class of organic reducers that are prone to oxidation by intrinsic ET.[6]

Electron-rich olefins (EROs) are certainly the most representative class of multistage organic redox systems.[7]

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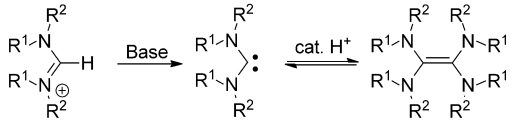
Since the 1960s, EROs have attracted considerable attention in both organic and inorganic chemistry, as a result of their unique properties as versatile and highly reactive reagents or reaction intermediates.[8] Notably, tetraaminoethylene derivatives played an important role in understanding their equilibrium, so called Wanzlick equilibrium, with the corresponding diaminocarbenes (Scheme 2).[9] The dimerization of




***Scheme 2.*** Carbene/dimer equilibrium.

carbenes is most likely achieved through a proton-catalyzed mechanism, but is thermodynamically unfavorable for unsaturated and/or sterically hindered carbenes. EROs are used as reducing agents,[10] nucleophiles,[11] precursors of carbene ligands in metal complexes,[12] and organocatalysts for acyloin-type C–C coupling reactions.[13] Up to now, their reducing abilities had been mostly examined within the framework of their chemoluminescent properties and their capacity to form electrically conductive charge-transfer systems[14] or redox-active ligands on transition-metal complexes.[15] Nonetheless, the past 20 years have seen the blossoming of this particular class of organic reductants and their applications in organic synthesis. These powerful neutral ground-state organic electron donors offer several significant advantages in the SET reduction of organic substrates:

- They undergo spontaneous sequential loss of one or two electrons and thus, upon electron transfer, generate *radicals* or *anions*, including aryl anions.
- They offer a large range of redox potentials and can be finely tuned. Their reactivity can, therefore, be modulated by appropriate structural modification.
- They are highly selective and tolerant to other functional groups (nitro, carbonyl, ester, cyano …).
- They are available as pure organic liquids or solids and can be used in appropriate quantities.
- They operate under mild conditions compared to highly aggressive metal-based reducers and are soluble in organic solvents, hence shortening the induction period.
- They avoid the use of expensive metal derivatives as well as the recycling of metal residues that cause environmental and economic problems.
- They can be easily removed from the media by precipitation as their salts and can be regenerated. They can also be attached to solid supports.
- They have wider applicability than photochemically assisted reactions.
- They avoid complications encountered with electrochemical reductions, such as the fouling of electrodes, the use of specific glassware and electrolytes, the limited range of reaction temperatures, or the inability to control the concentrations of the reductant.

We review here the different types of organic SET reducing agents which do not require activation by photochemical, electrochemical, or other methods, and their specific characteristics in organic transformations. A strong focus is given to the scope and limitations of the reductive molecular reactions promoted by organic electron donors, as well as to the mechanism of these radical methods. Our aim is to provide chemists with an exhaustive guide to the properties and capabilities of organic reductants in organic chemistry. We hope it will illustrate the milder and potential alternative offered by these electron sources compared with the use of inorganic reductants and encourage other researchers to utilize them in radical reactions.

## 2. Tetrathiafulvalenes (TTFs)

### 2.1. Properties

Since the early 1970s, tetrathiafulvalene (TTF)[16] and its derivatives have been recognized as strong organic π-electron donors of great interest. The following features are characteristic: 1) TTF is a planar non-aromatic 14-π-electron system in which oxidation to the cation radical $TTF^{\bullet+}$ and dication $TTF^{2+}$ occurs sequentially and reversibly at relatively low redox potentials [$E_{1/2}(CH_3CN) = +0.32$ and $+0.71$ V versus the saturated calomel electrode (SCE); Figure 1]. 2) $TTF^{\bullet+}$ and $TTF^{2+}$ are aromatic and thermodynamically stable species. The gain in aromatization energy together with the stabilization of both the positive charge and the radical by the lone pairs of electrons on the sulfur atoms greatly assist the electron donation. Likewise, the considerable aromatic stabi-

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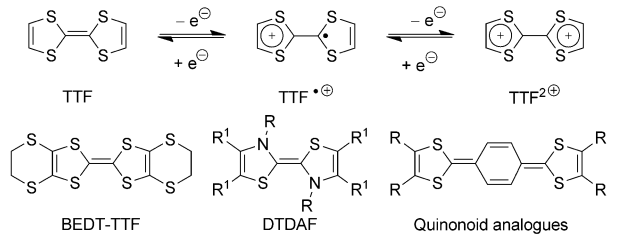


***Figure 1.*** TTF and related compounds. BEDT-TTF: bis(ethylenedithio)-tetrathiafulvalene; DTDAF: dithiadiazafulvalenes.

lization of extended quinonoid analogues enhances their reduction potentials (Figure 1: For R,R = −(CH=CH)$_2$− [$E_p$-($CH_3CN$) = −0.38 V versus SCE]), although their syntheses and characterizations have proved challenging.[17] 3) Tetrathiafulvalene can be prepared in multigram quantities, is commercially available, and relatively stable to air, unless photoactivated. Moreover, it is synthetically possible to introduce a large number of substituents at the 2-, 3-, 6-, and 7-positions of the TTF core. The oxidation potentials can, therefore, be finely tuned by attachment of electron-donating or electron-withdrawing groups. 4) TTF is stable to many synthetic transformations, although it is important to avoid strongly acidic conditions and strong oxidizing agents. 5) TTF-containing systems offer a wide range of electronic and magnetic properties. Numerous TTF-like donors have been synthesized and used extensively to form charge-transfer complexes for the development of organic conductors,[14,18] as well as building blocks in supramolecular chemistry.[19] Their synthesis, structural aspects, and properties have been widely reviewed and will not be reconsidered herein.[16]

### 2.2. Reactivity of TTF

#### 2.2.1. Concept

The use of TTF derivatives as reductants in organic chemistry has been only examined by Murphy and co-workers, despite the fact that they provide an effective and mild means to synthesize polycyclic compounds.[20] TTF acts as a reasonable single-electron donor in one-pot multistep transformations and combines radical cyclization and polar termination steps. In contrast to traditional tandem reactions induced by $SmI_2$,[21] Murphy and co-workers showed that radical cyclizations promoted by TTF were terminated by

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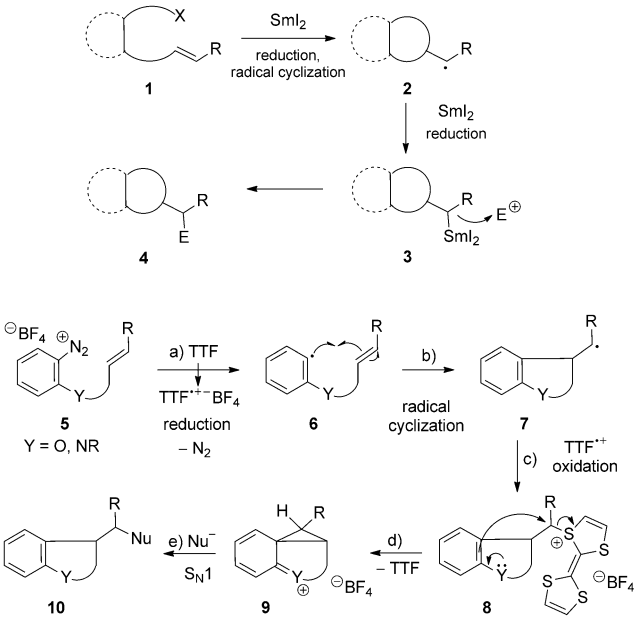


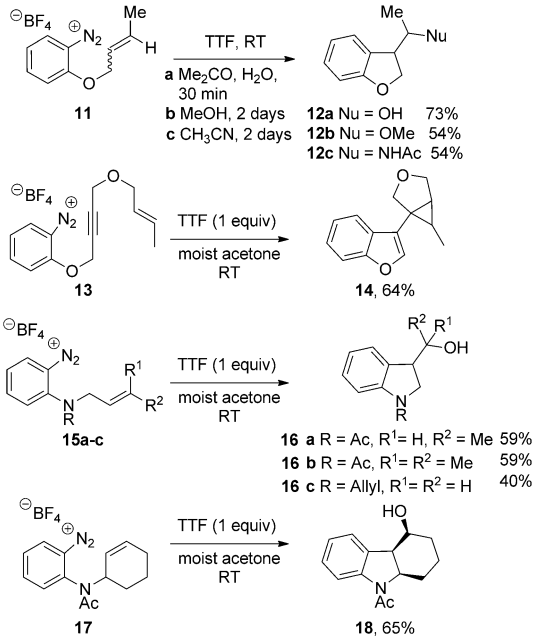

***Scheme 3.*** Comparison of a $SmI_2$- and TTF-mediated radical-polar crossover reaction.

$S_N1$-type nucleophilic substitution at the new exocyclic center instead of effecting further reduction (Scheme 3). Arene diazonium salts were chosen as partner reagents since their one-electron-reduction potential [$E_p(CH_3CN) \approx -0.2$ V versus SCE][22] is close to that of TTF.[23] The formation of C−C or C−heteroatom bonds through radical processes on arene diazonium salts generally involves the use of inorganic reductants such as copper (e.g. Sandmeyer and Meerwein reactions), tin reagents, or phosphinic acid.[24] Copper-mediated redox reactions often suffer from low yields, high catalyst loadings, and restriction to aqueous media. Heinrich and co-workers used $TiCl_3$ as a stoichiometric reductant for the generation of the aryl radical.[25] Recently, an elegant and ecofriendly approach reported by König and co-workers is the catalytic reduction of aryl diazonium salts by photoinduced electron transfer (PET) by using $[Ru(bpy)_3]Cl_2$ or organic dyes as photoredox catalysts.[26] The TTF-promoted sequence, named as a "radical-polar crossover reaction",[27] features a) the generation of an aryl radical by electron transfer from TTF to diazonium salt **5** and loss of dinitrogen, b) the cyclization of aryl radical **6** onto an alkene, c) the coupling of carbon-centered alkyl radical **7** with the radical cation $TTF^{\bullet+}$ through the sulfur atom[28] to form sulfonium salt **8**, d) an Ar-Y-assisted loss of TTF to afford cationic intermediate **9**, and e) functionalization through substitution by intra- or intermolecular nucleophiles that attack **9** and terminate the reaction.

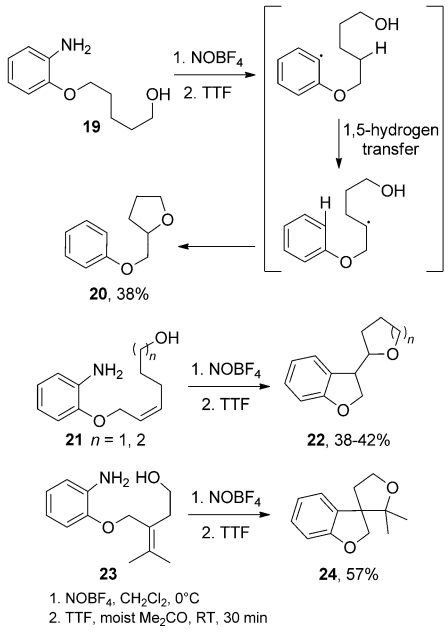
#### 2.2.2. Scope

Treatment of diazonium salt **11** in the appropriate solvent led to its conversion into alcohol **12a**, ether **12b**, or amide **12c** (the amide was formed by hydrolysis of a nitrilium cation) in moderate to good yields (Scheme 4).[29] The scope of the



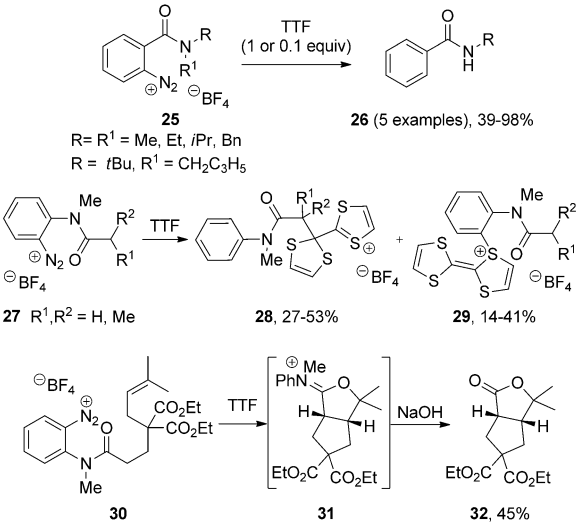

***Scheme 4.*** Scope of the TTF reactivity with diazonium salts.




***Scheme 5.*** Termination of radical-polar reactions by internal nucleophiles.

reaction was then extended to more complex oxygen and nitrogen heterocycles (Scheme 4).[30] The rapid aryl radical cyclization of **13** onto the alkyne was followed by a vinyl radical cyclization and cyclopropane formation, which led smoothly to the tetracycle **14**. The reaction of acetyl **15a**,**b** or diallyl **15c** with TTF in moist acetone at room temperature afforded indolines **16a**,**b** (59%) and **16c** (40%), respectively. Replacing the acetyl by a benzoyl group in **15b** gave a complex mixture as a result of a competing radical cyclization on the benzoyl group.[31] Lastly, the cyclization of **17** led to tricyclic alcohol **18** as a single diastereomer (65%).[30] The major drawback of this method was the competitive direct trapping of the aryl radical intermediate **6** by the sulfur atom of $TTF^{\bullet+}$, which occurred when the cyclization was slow and usually accounted for the mass balance. On the other hand, the advantage of the TTF leaving group, unlike other ET agents such as iodide, lies in its ease of displacement from **8**, which results in an astonishing selectivity for unimolecular reactions. Mechanistic studies also highlighted the crucial role of the neighboring aromatic ring in the substitution of secondary tetrathiafulvalenium salts **8** ($R \neq H$).[32] Neighboring arenes bearing at least two alkyl functions or silyloxy groups were sufficiently electron rich to undergo solvolysis of **8**, while aliphatic salts were resistant to substitution. Likewise, no substitution was observed[33] when the TTF moiety was attached to a primary carbon atom ($R = H$) unless the neighboring group was sufficiently electron donating to stabilize the primary carbocation. Hence, the *ortho*-amino group in **15c** acted through the aromatic ring to assist the departure of TTF via a cyclopropane intermediate (**9**). As TTF was regenerated during the radical-polar reaction, it also behaved catalytically (down to 5 mol%), but its turnover number was very low. Stereospecific trapping of cationic intermediate **9** by intramolecular nucleophiles was then investigated, which led to the expected poly- (**20**, **22**) and spirocyclic (**24**) compounds (Scheme 5).[34] As a result of the instability of some diazonium intermediates, the diazotization using nitrosonium tetrafluoroborate $NOBF_4$ and TTF reductions could be carried out in one pot. In the case of **19**, the aryl radical intermediate undergoes a hydrogen atom transfer (radical translocation)[35] prior to coupling with $TTF^{\bullet+}$ and trapping by the internal nucleophile.

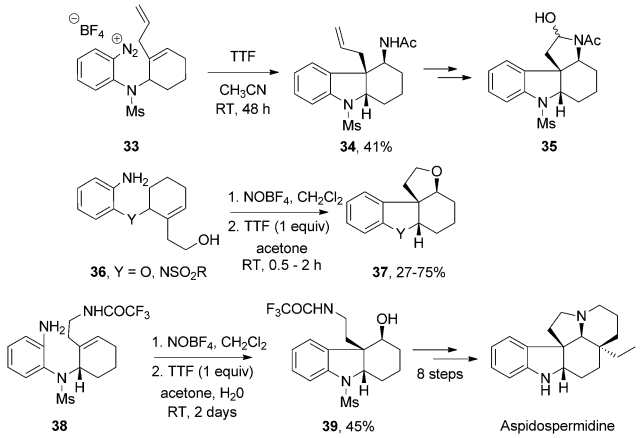
Murphy and co-workers further explored the combination of radical-polar crossover reactions with radical translocation (Scheme 6). TTF could initiate translocation reactions, but the kinetics of the hydrogen atom abstraction and the




***Scheme 6.*** Sequential radical translocation and functionalization. Bn = benzyl.

termination of the reaction were highly dependent on the substitution pattern of the translocated radical.[36] Hence, the TTF-generated aryl radicals rapidly and efficiently underwent tandem translocation/functionalization sequences, which resulted in: a) oxidized products, such as in the oxidative mono-dealkylation of *N*,*N*-disubstituted amides **25**, where the intramolecular hydrogen abstraction leads to *nucleophilic* alkyl radicals or b) an unprecedented carbon–carbon bond formation (**28**) between *electrophilic* translocated radicals and the internal carbon atom of $TTF^{\bullet+}$.[28] Unfortunately, in the latter case, direct trapping of the aryl radical prior to translocation was a major competing reaction (**29**, 14–41%). Substrates containing a less-rigid ether side chain instead of an amide also gave a mixture of translocation and recombination products. With subtrate **30**, the trapping of $TTF^{\bullet+}$ through C–C bond formation was sufficiently slow to allow its cyclization/oxidation to iminium salt **31** in moderate yield (45% after hydrolysis).

Finally, the TTF-promoted radical-polar crossover reaction was successfully applied as a key step in the synthesis of tetracyclic structures,[37] notably of aspidospermidine (Scheme 7).[38] This novel method offered a direct and mild route to these *Aspidosperma* alkaloids through a highly stereoselective cyclization of the diazonium salt.

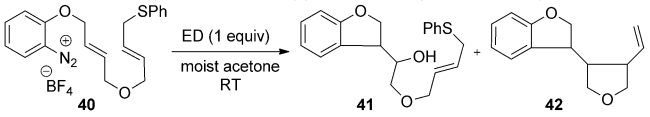



***Scheme 7.*** TTF-promoted synthesis of polycyclic heterocycles.

### 2.2.3. *Modified TTF Reagents*

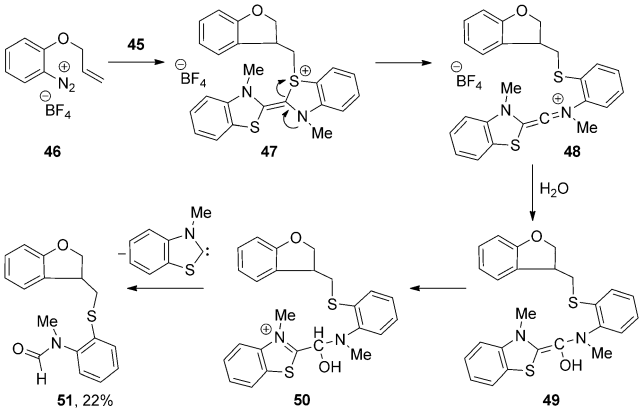
Different TTF-like donors including dithiadiazafulvalenes (DTDAFs) were compared to test if the competitive interception of $TTF^{\bullet+}$ could be avoided (Table 1).[39] In DTDAFs, two of the sulfur atoms are replaced by nitrogen, which changes the electron density of the molecule and considerably increases their donor ability.[16b] DTDAFs can reduce nitro groups such as $HNO_2$, azidinium salts, and diazonium groups.[40] However, unlike TTF derivatives, they are more difficult to isolate as a stable dimer. Whereas the radical cation of methyl-substituted **43** was a little slower than $TTF^{\bullet+}$ at trapping the carbon radical (**7**; only 8% of trapping product **41** versus 19% with TTF), DTDAFs **44** and **45** allowed predominantly bicyclization to **42** since the N substituents

***Table 1:*** Relative yields of the trapped **41** and cyclization **42** products.




| Electron donor (ED) | **41** [%] | **42** [%] |
|---|---|---|
| TTF | 19 | 48 |
| **43** | 8 | 67 |
| **44** | 0 | 72 |
| **45** | 0 | 73 |

retarded the approach to the sulfur atom. The decrease in direct trapping was, therefore, proportional to the increasing steric crowding around the sulfur atom. These results were encouraging for syntheses featuring slow radical cyclization before ionic termination. Although slow coupling rates of $DTDAFs^{\bullet+}$ were indeed observed, the reaction of DTDAFs with other diazonium salts afforded unexpected amide products, such as **51**, which results from the cleavage of the DTDAF ring system (Scheme 8). This particular pathway was attributed to the great reactivity of the nitrogen lone pair of electrons.[39]




***Scheme 8.*** Reaction of dithiadiazafulvalene **45**.

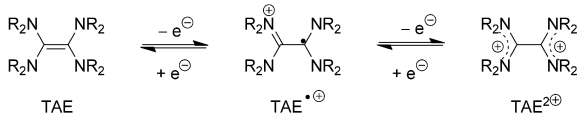
To afford an environmentally acceptable approach that avoids the use of toxic and troublesome reductants, such as tin reagents, both water-soluble[41] and polymer-supported[42] versions of TTF were prepared to facilitate the purification process. After basic regeneration, the polymer was re-used in two further cycles with a minimal decrease in activity. A slight lowering of the yield was observed compared to the corresponding solution-phase reactions.

Despite performing one-pot radical and ionic reactions under mild conditions, and providing an elegant stereoselective access to polycyclic compounds, TTF-promoted reactions were restricted to few aryl diazonium substrates and suffered from many side reactions. The premature trapping of the aryl radical was a serious handicap in reactions with a slow cyclization step. Furthermore, TTF could achieve the easier step of reducing arene diazonium salts to aryl radicals, but not the more difficult step of reducing aryl radicals to aryl anions. DTDAF donors, although more powerful, also engendered side reactions and none were strong enough to react with alkyl and aryl halides.[43] These limitations presumably explain why TTF derivatives did not receive further attention in organic synthesis.

## 3. Aliphatic Tetraaminoethylenes (TAEs)

### 3.1. Properties

Tetraaminoethylenes (TAEs)[10] are aza analogues of tetrathiafulvalenes. The presence of the more electronegative amino groups tends to decrease their oxidation potential and allows the modulation of conformational effects and thus redox properties through control of the N substituents. Moreover, the positive charges of the oxidized forms are stabilized by the unpaired electrons on the nitrogen atoms, and this is a driving force for the electron donation (Scheme 9). These differences give them very specific physicochemical properties and make TAEs considerably more powerful donors than TTF. According to the nature of the electrophile and the TAE, they can be used as a strong nucleophile, as a base able to donate π electrons, or as a reducing agent. Thus, an oxidizing agent converts the TAE into the radical cation $TAE^{\bullet+}$ and dication $TAE^{2+}$, an acid adds to the double bond or the amine, and an organic π-electron acceptor forms a colored donor–acceptor complex with the TAE.




***Scheme 9.*** Redox reaction of tetraaminoethylenes.

The first tetraaminoethylene, tetrakis(dimethylamino) ethylene (TDAE), was prepared by Pruett et al. in 1950,[44] but the systematic study of these electron-rich olefins began a decade later when Wanzlick et al. reported the synthesis of biimidazolidinylidene derivatives (Figure 2).[45] TAEs are powerful electron donors which decompose into urea derivatives upon reaction with dioxygen (Scheme 10).[46] In the case of enetetramines containing *N*-alkyl groups, this oxidation is concomitant with chemiluminescence.[47] General methods for the preparation of TAEs consist of the elimination of acids HX from aminals by heating, acid catalysis, or treatment with strong bases (Scheme 11).[10,48] Alternatively, cyclic analogues can be obtained through the reaction of diamines with ethyl orthoformate.[45] With the exception of the liquid TDAE, TAEs are usually solids.

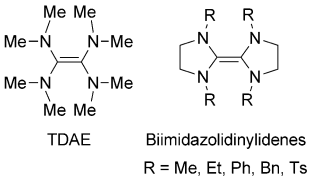
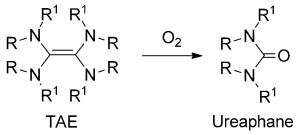
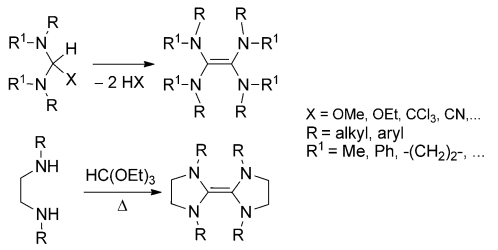



***Figure 2.*** Aliphatic tetraaminoethylenes. Ts = toluene-4-sulfonyl.




***Scheme 10.*** Reaction with $O_2$.




***Scheme 11.*** General preparation of TAEs.

### 3.2. Reactivity of Biimidazolidinylidenes

Research on enetetramines containing an imidazolidin-2-ylidene ring mainly concentrates on their reactivity through protonation, C=C bond cleavage, or as nucleophiles,[8–13,49] as well as their role in the Wanzlick equilibrium.[9] For N-heterocyclic carbenes (NHCs) with a saturated ring, the steric bulk of the N substituents determines whether the carbene is stable as a monomer or if it dimerizes to the electron-rich TAE. Imidazolidin-2-ylidenes with small *N*-alkyl groups (Me, Et, *i*Pr) readily dimerize, while benzyl groups lead to thermal instability of the enetetramine and bulky mesityl or *t*Bu to generate stable free carbenes.

In an electrochemical context, SET reduction of P–Cl bonds in phosphinous ($PClR_2$) and phosphonous ($PRCl_2$) chlorides led to the formation of P–P bonds in diphosphines ($P_2R_4$) and cyclopolyphosphines $(PR)_n$, respectively.[50] In contrast to the heterogeneous and sluggish metallic version, which needed high temperatures, the biimidazolidinylidene-promoted reduction proceeded rapidly at room temperature in high yields and under mild homogeneous conditions. Cyclic TAEs were also effective in the reduction of peroxides, thionyl chlorides, and sulfuryl chlorides.[51] Furthermore, persistent metal-centred radicals $M^{\bullet}R_3$ (M = Si, Ge, or Sn)

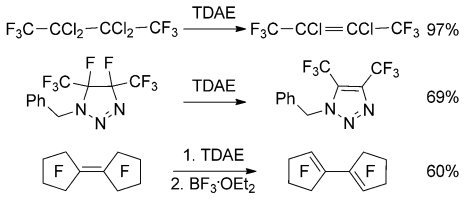
  

were prepared by electron donation to the appropriate metal chloride $MR_3Cl$ under UV irradiation.[52] However, compared to TDAE, lower donor strength was observed with biimidazolidinylidene derivatives.[10] Insertion of conjugated organic systems, such as R = Ph, instead of the methyl groups decreased the energy of the first antibonding orbital and, therefore, impeded the removal of the two reducing electrons. This no doubt explains why cyclic derivatives were not further investigated in organic synthesis.

### 3.3. Reactivity of TDAE

The electrochemical oxidation of TDAE occurs in two reversible one-electron oxidation steps [$E_{1/2}(CH_3CN) = -0.78$ and $-0.61$ V versus SCE].[53] In DMF only one two-electron reversible wave is observed at $-0.62$ V. As indicated by superpositioning of the one-electron waves, this process comes with a substantial twisting about the central C–C bond to minimize the repulsion between the two positive ends of the molecule (Scheme 9). The as-formed dication $TDAE^{2+}$ is particularly stabilized by this new conformation and by the presence of the electron-donating dimethylamino groups.[54,55] TDAE has a low ionization potential of 6.13 eV and a reducing power close to that of zinc.[10] The methoxy analogue of TDAE can also reduce sulfonyl and nitro groups.[56] As a result of its strong reducing properties, commercial availability, and convenience of use, TDAE rapidly became a very useful reagent in organic synthesis.

Since 1963, it has been shown that tetraaminoethylenes are capable of reductively cleaving carbon–halogen bonds and generating the corresponding carbanion by two sequential transfers of one electron.[57] The ease of halogen abstraction increases from fluorine to iodine and in the order $R_3CX < R_2CX_2 < RCX_3 < CX_4$. Carpenter et al. were the first to use TDAE as a SET reducing agent for selective dehalogenation in polyhalogenated hydrocarbons, thereby replacing a single halogen atom with a hydrogen atom or removing two vicinal halogen atoms to form olefins (Scheme 12).[57c,d] Reduction by a double-electron-transfer pathway




***Scheme 12.*** Reductive dehalogenations.

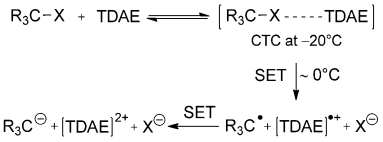
was already known. This reactivity was later applied to the synthesis of fluorinated dienes and their polymerization.[58] Nevertheless, it was only three decades later that this ability to activate C–X bonds started to be investigated intensively in organic synthesis and applied to the preparation of compounds of biological interest. Intermolecular reactions promoted by TDAE-initiated reactive species have been studied in particular.

#### 3.3.1. Difluoro- and Trifluoromethylation

In 1989, Pawelke reported that TDAE and $CF_3I$ form a deep-red charge-transfer complex (CTC) in polar solvents and at low temperature which can act as a nucleophilic trifluoromethylating agent and lead, for example, to the formation of $CF_3TMS$ from trimethylsilyl chloride [TMSCl, Eq. (1)].[59]

$$R - X + CF_3I \xrightarrow{\text{TDAE}} R - CF_3 + TDAE^{2+}X^-I^- \quad (1)$$

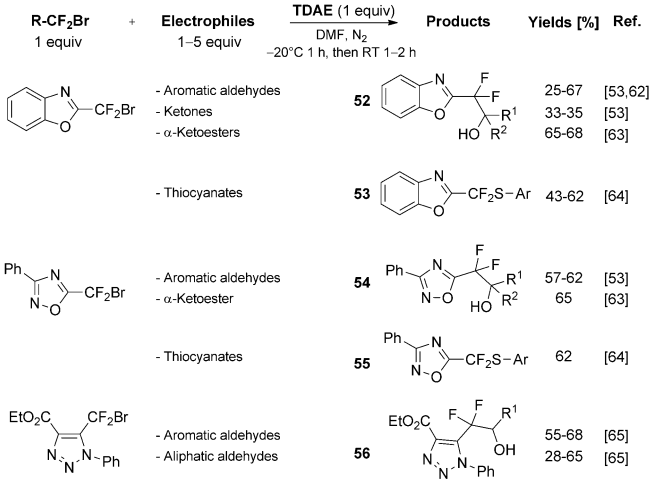
Since 1997, Médebielle and Dolbier have exploited this reactivity in several nucleophilic di- and trifluoromethylation reactions on various electrophiles.[60] Many fluorinated analogues of biological compounds exhibit a dramatic enhancement of their biological activities.[61] The TDAE strategy thus represents a convenient and efficient method for the synthesis of novel *gem*-difluorinated and trifluoromethylated systems. The mechanism of the reduction has been suggested to proceed via an initial charge-transfer complex between the halide substrate and TDAE, followed by stepwise single-electron transfers of two electrons to form $TDAE^{2+}$ and the carbanion (Scheme 13). The latter is stable enough to undergo a nucleophilic addition to carbon–heteroatom bonds. $TDAE^{2+}2X^-$ is recovered by simple filtration at the end of the reaction, thus demonstrating clearly that TDAE has been oxidized.




***Scheme 13.*** Proposed mechanism for TDAE-initiated carbon–halogen bond reductions.

A series of 2-(difluoromethyl)benzoxazole alcohols **52** were obtained by reaction of the bromodifluoromethyl substrate with aldehydes,[53,62] ketones,[53] or α-ketoesters[63] under mild conditions (Scheme 14, Figure 3). Lower yields were obtained with less-reactive electron-rich aldehydes (25%). Rather modest yields were also achieved with ketones (33–35%), probably because of steric hindrance and their enolizable character, while activated α-ketoesters reacted smoothly (65–68%). Furthermore, the $CF_2$ anion was trapped by aryl thiocyanates to form a new series of $ArSCF_2R$ derivatives **53** (43–62%).[64] Notably, attempts to generate $CF_2^-$ electrochemically, with *n*BuLi or via an organozinc intermediate, resulted in decomposition or low conversion (< 10%).

Interestingly, the benzylic anion was not formed when electron-rich dihydrofuran **61** was used as the electrophile (Scheme 15).[53] The intermediate radical **58** was trapped by **61**, thereby affording radical **59**, which triggers transfer of a bromine atom from **57** to give **60**. This radical addition confirmed the sequential transfer of the electrons in TDAE-promoted reactions. Under the same conditions, reduction of the chlorodifluoromethyl counterpart failed because of its




***Scheme 14.*** TDAE-mediated difluoromethylation.

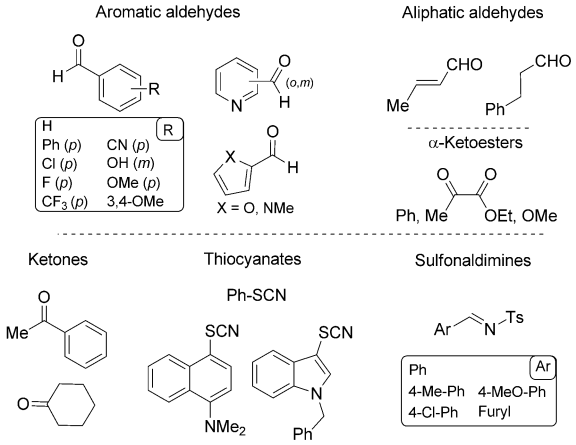
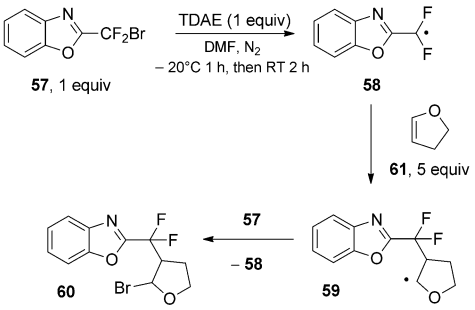



***Figure 3.*** Classes of electrophiles used in difluoromethylation reactions (see Schemes 14 and 17).

higher reduction potential [$E_p$(DMF, SCE) = −1.66 V versus −1.36 V for $BrCF_2$].

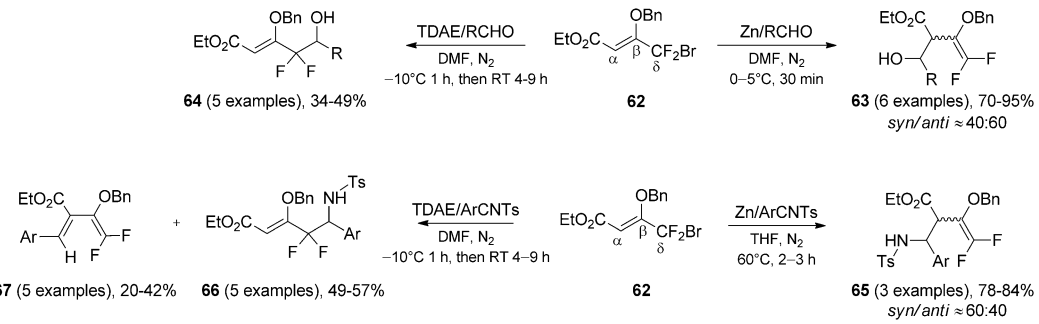
Other $CF_2Br$-substituted heterocycles such as 1,2,4-oxadiazoles[53,63,64] and 1,2,3-triazoles[65] were successfully reduced by TDAE and coupled with appropriate electrophiles to afford *gem*-difluorinated derivatives such as alcohols **54**/**56** or thioether **55** (Scheme 14, Figure 3). Cyclic voltammetry studies indicated that the reduction operated through a dissociative electron-transfer reaction in which the ET and the C−Br bond dissociation steps were concerted.[53] The formation of the hydrogenolysis products R-$CF_2H$ resulting from the protonation of the anion usually accounted for the mass balance of reactions.



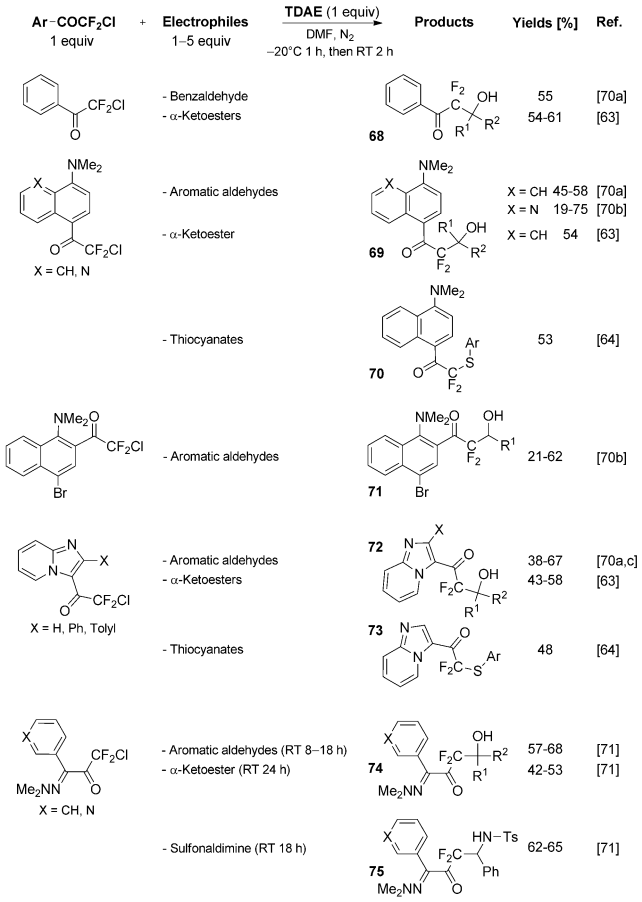

***Scheme 15.*** TDAE-promoted radical addition.

In 2004, Zhu, Peng, and co-workers reported regioselective control over the addition mode (α or γ) in the reduction of bromo-$CF_2$ benzyloxyacrylate **62** through choice of the reductant (Scheme 16).[66] At low temperature,[67] active zinc species reacted with aldehydes to give kinetically more stable α-coupled difluorovinyl β-hydroxy esters **63** with a diastereoselectivity governed by the bulkiness of the R groups. In contrast, TDAE-initiated reactions gave the γ-coupled thermodynamic products, *gem*-difluorinated δ-hydroxy esters **64**.[68] Similarly, reaction of **62** with TDAE and aldimines yielded novel γ-addition amino esters **66** (49–57%).[69] The kinetic α product **65** was also formed, but decomposed into α-difluorovinyl acrylate **67** through loss of the arene sulfonamide.

The TDAE method, which is milder than the classic Reformatsky reaction, was successfully extended to generate stable α,α-difluoroacetyl anions from chloro ketones. Their addition to aldehydes,[70] α-ketoesters,[63] and thiocyanates[64] led to hydroxy (**68**–**69**, **71**–**72**) and thioether (**70, 73**) α,α-difluoroketones, wich are biologically relevant patterns (Scheme 17, Figure 3). Moreover, these products incorporated quinoline (**69**), naphthyl (**69**–**71**), or imidazo[1,2-*a*]pyridine (**72** and **73**) units, which constitute key skeletons of numerous bioactive molecules. Furthermore, chlorohydrazones reacted with various electrophiles including an aldimine in good yields (**74** and **75**, Scheme 17).[71] As a consequence of their electron-rich character, hydrazones were poorer electron acceptors [$E_p$(DMF) = −1.50/−1.66 V versus SCE], thereby necessitating longer reaction times to reach complete consumption. Here again, the major side product was the reduced compound $ArCOCF_2H$.

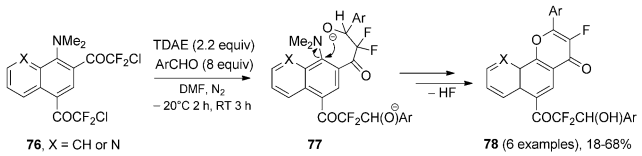



***Scheme 16.*** Comparison of TDAE- and zinc-mediated acrylate reductions.



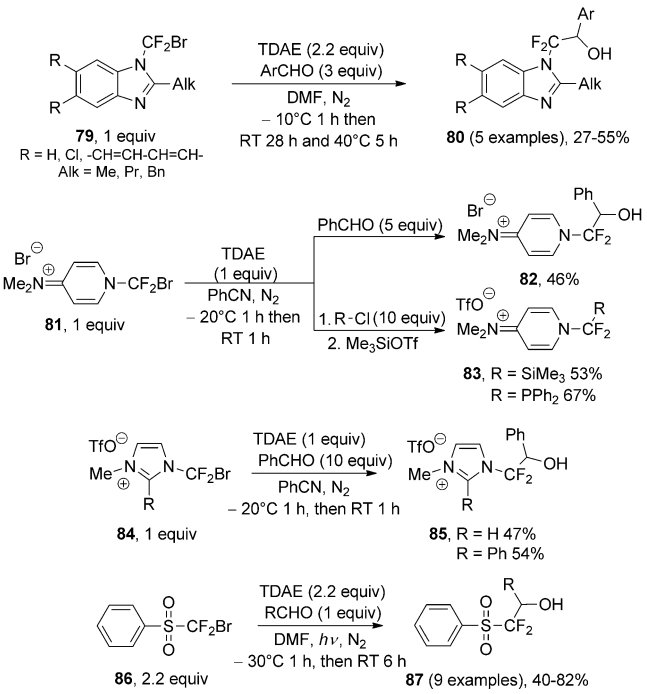

***Scheme 17.*** TDAE-initiated addition of α,α-difluoroketones. (Changes from the standard conditions are given in parenthesis.)

Surprisingly, the presence of two activating α,α-difluoroketone moieties on **76** led to a different outcome, namely the synthesis in a one-pot process of new fluorinated tricyclic naphthoflavone analogues **78** (Scheme 18).[72] The proposed mechanism consists of an initial TDAE-promoted aldolization followed by an intramolecular nucleophilic aromatic substitution ($S_NAr$) cyclization of the bis(alcoholate) intermediate **77**. The eliminated $NMe_2$ anion acts as a strong base and induces HF elimination, thereby yielding the fused derivatives **78**.




***Scheme 18.*** TDAE-initiated synthesis of tricyclic naphthoflavones.

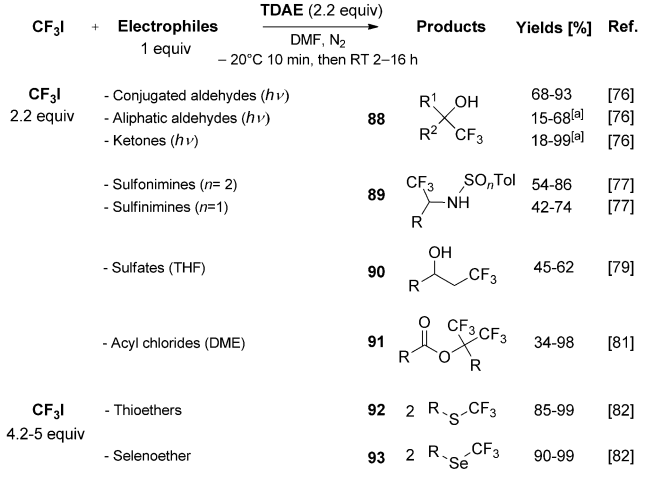
Reductions of $CF_2Br$ groups bound to heteroatoms (N or S) were also described, although more severe conditions were sometimes required (Scheme 19). Condensations of benzimidazoles **79**,[73] 4-dimethylaminopyridinium **81**,[74] 1-methylimidazolium **84**,[74] or phenyl sulfone **86**[75] with aldehydes led to the corresponding secondary alcohols in moderate yields. Chlorodiphenylphosphine and chlorotrimethylsilane were




***Scheme 19.*** TDAE-promoted reduction of $BrCF_2$ heterocycles.

also able to trap the anion intermediate of **81** to yield **83**. Photoinduction was necessary to enhance the electron transfer from the photoexcited TDAE to sulfone **86**.

Along with the generation of stable $RCF_2$ anions, Médebielle and Dolbier also reported the in situ preparation of the $CF_3$ anion and its addition to a series of electrophiles. Compared to typical trifluoromethylating agents such as $CF_3TMS$, the trifluoromethyl iodide $CF_3I$ represents a ready and inexpensive source of the unstable $CF_3^-$. The combination of TDAE and $CF_3I$ was thus an effective metal-free way to synthesize trifluoromethylated products in good to excellent yields (Scheme 20, Figure 4). Nucleophilic additions to aldehyde and ketone carbonyl groups had to be carried out




***Scheme 20.*** TDAE-mediated trifluoromethylation. (Changes from the standard conditions are given in parenthesis.) [a] NMR yield.

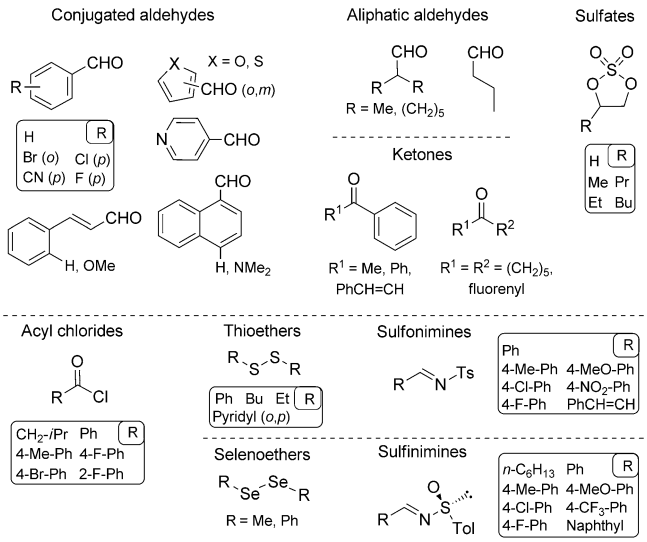
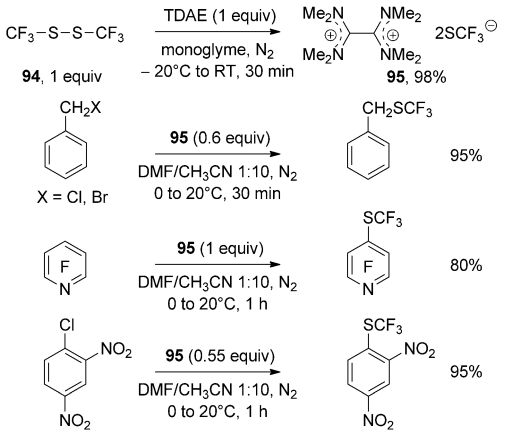



***Figure 4.*** Classes of electrophiles used in trifluoromethylation reactions (see Scheme 20).

under irradiation with light to drastically improve the yields of alcohol **88** (52–99%).[76] The yields were comparable to those obtained in analogous $CF_3TMS$ reactions, but (trifluoromethyl)trimethylsilane appeared more suitable for enolizable substrates. Indeed, the poor results observed with a linear aldehyde (15%) and methyl ketone (18%) were attributed to the kinetic acidity of their carbonyl α-H atoms when exposed to the basic nature of TDAE. It is noticable that carbanion attack on aliphatic aldehydes by using the TDAE method have rarely been reported.[65,76] The addition to sulfonimines and diastereoselective addition to enantiopure sulfinimines led to very good yields of the corresponding trifluoromethylated adducts **89**.[77] In contrast to $CF_3TMS$-promoted trifluoromethylation,[78] the reaction was limited to *N*-tosylimines with aromatic C substituents. The diastereoselectivity of the *N*-tolylsulfinimine reaction, while good (85:15), fell short of that observed by Prakash et al.[78] The TDAE/$CF_3I$ reagent was also tested in the regioselective addition of $CF_3^-$ to vicinal diol cyclic sulfates (Scheme 20).[79] The formation of trifluoroalkanols **90** (45–62%) was limited by the competitive ring-opening reaction of the sulfates with the iodide ion. The stereospecificity of the process was demonstrated by the incorporation of the $CF_3$ group on the *S* isomer of the "$R^1 = Me$" sulfate (43% yield and >99.5% *ee*). Although particularly interesting and unprecedented,[80] this reactivity could not be extended to epoxides or diols without a primary ($CH_2$) group.

In the case of acyl chlorides, the double trifluoromethylation, by using quasistoichiometric amounts of TDAE/$CF_3I$ reagent, was remarkably clean and chemoselective.[81] It was unfortunately followed by an acylation of the resultant alcoholate, which consumed half of the acyl chloride to form the ester adduct **91**. In contrast, trifluoromethyl thio- **92** and selenoethers **93** were efficiently and economically prepared by using both halves of the aryl and alkyl disulfides or diselenides.[82] It is important to underline here the productive use of $CF_3I$ in two different reactions, one through anionic attack on the initial substrate and one by an $S_{RN}1$ mechanism with the thiol-/selenoate co-product, with both leading to the same desired products **92** and **93**. Whereas competitive reduction of disulfides to thiolate anions was excluded in this latter case, because of the faster DET to $CF_3I$,[82] the reduction of bis(trifluoromethyl) disulfide **94** could still be accomplished with TDAE and allowed the quantitative formation of the $TDAE^{2+}2SCF_3^-$ salt, which is stable under an inert atmosphere (Scheme 21).[83] Trifluoromethanethiolate **95** has the same reduction potential as TDAE and was used as the anionic source in substitution reactions with activated halogeno-aromatic compounds and benzyl halides, thus generating the corresponding trifluoromethylthio derivatives in excellent yields.



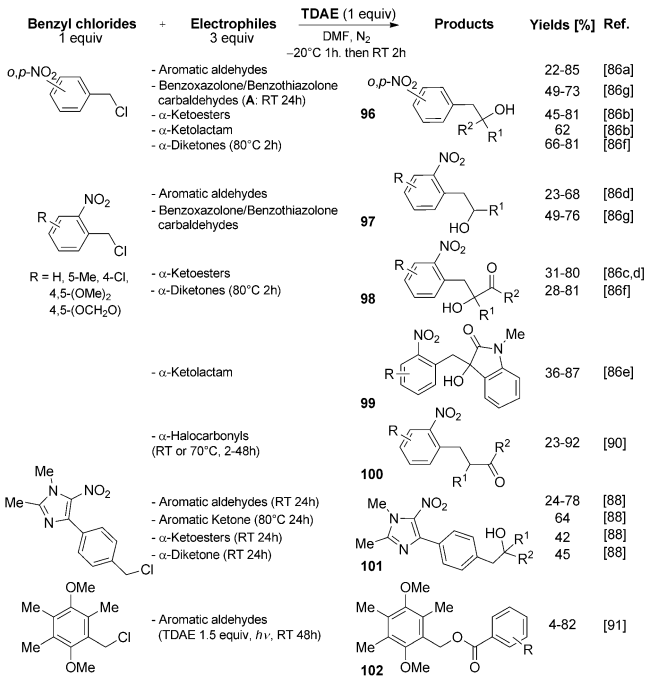

***Scheme 21.*** Preparation and reactivity of $TDAE^{2+}2SCF_3^-$ **95**.

On the basis of Petrov's earlier study,[84] this TDAE/$CF_3I$ procedure was extended under the same conditions, and with the same success for the reduction of other perfluoroalkyl iodides and their perfluoroalkylation reaction with aldehydes, ketones, imines, disulfides, and diselenides.[82b] Although the pentafluoroethylating agent generated from $C_2F_5I$ was generally almost as useful as the $CF_3$ reagent, the yields in the reaction with *n*-$C_4F_9I$ diminished, sometimes significantly.

### 3.3.2. Benzylic Addition

With the aim of developing original one- or two-electron transfer processes for medicinal chemistry applications,[85] Vanelle et al. studied TDAE-mediated intermolecular reactions with halomethyl substrates. It was demonstrated that TDAE can generate in situ stable *o*- and *p*-nitrobenzyl anions that are able to react with diverse electrophiles (Scheme 22) such as aromatic aldehydes, α-ketoesters, ketomalonates, α-ketolactams, and diketones (Figure 5).[86] The corresponding alcohol derivatives **96–99** were obtained in moderate to good yields by selective nucleophilic addition of the carbanion to carbonyl groups.[87] The standard conditions (1 equiv of TDAE in anhydrous DMF stirred at −20 °C for 1 h then at room temperature for 2 h) are convenient and mild compared to the use of highly aggressive organometallic reagents. Moreover, such metal-containing reducing agents are not selective and react with the ester moieties.




***Scheme 22.*** TDAE-promoted benzylic substitution. (Changes from the standard conditions are given in parenthesis.)

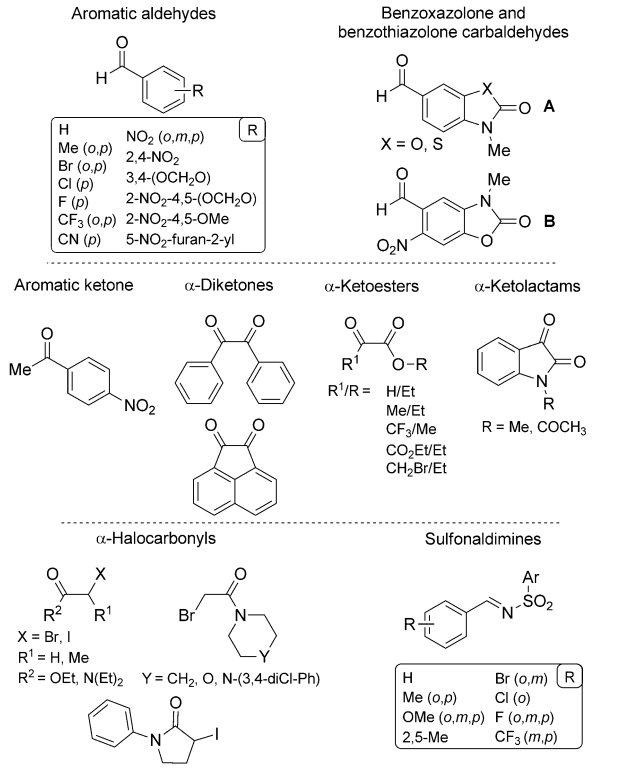
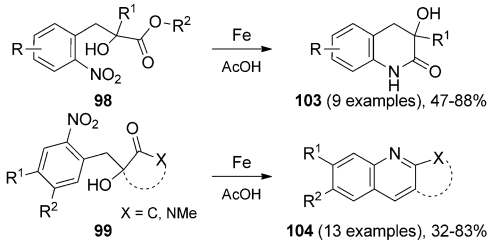



***Figure 5.*** Classes of electrophiles that react with halomethyl substrates (see Schemes 22, 24, 26, and 27).

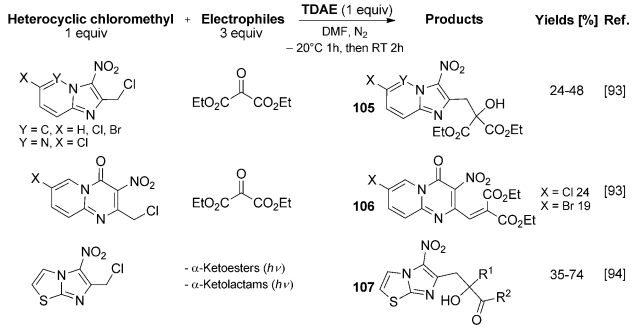
A comprehensive study of the reducing power of TDAE revealed that an electron-withdrawing group (e.g. $NO_2$) is required on the benzyl substrate to reductively cleave the halogen and stabilize the anion. This constitutes the major drawback of this strategy. Alternatively, the key nitro group can be moved away from the $C_{sp3}$–Cl bond when an imidazole is introduced at the *para* position of the benzyl chloride.[88] Highly functionalized 5-nitro-1*H*-imidazoles **101** were thus synthesized as potential anti-infection agents by applying the previously described procedure, although a longer reaction time (24 h) was needed (Scheme 22, Figure 5). The reaction yield was also influenced by the electronic and steric properties of the electrophile. *Ortho* and *para*-substituted aromatic aldehydes were more reactive than the *meta* counterpart. Moreover, aldehydes with electron-withdrawing groups were more activated than aldehydes substituted with electron-donor groups, such as methyl. The double addition diol products were obtained (43–82%) when dialdehydes were used as the electrophiles in the presence of an excess of TDAE and sodium iodide salt, which facilitated the reaction by halogen–exchange activation.[89] Nucleophilic additions to ketones were more difficult and needed longer reaction times (24 h with 4-nitroacetophenone for 40% yield)[86d] or higher temperature (80 °C with diketones).[86f] It is noteworthy that anion attack proceeded on only one of the carbonyl groups of α-diketones. The synthesized α-hydroxycarbonyl **98** or α-hydroxylactam **99** adducts were further used in the preparation of bioactive quinolinone **103** and quinoline **104** systems by one-pot reduction/cyclization and/or double dehydration reactions (Scheme 23).[86c,e,f] Nucleophile substitutions were




***Scheme 23.*** Reductive cyclization reactions.

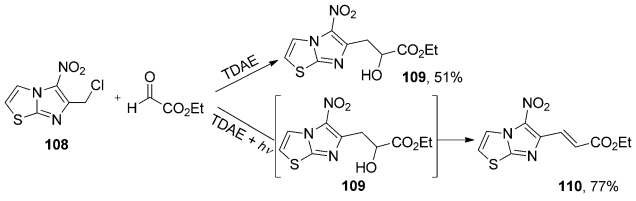
also explored by using electrophiles containing a $C_{sp3}$–halogen bond (Scheme 22, Figure 5).[90] The reaction of *o*-nitrobenzyl chlorides with various α-haloesters and α-haloamides, although less reducible than the benzyl chlorides but sufficiently electrophilic, led to the expected substitution products **100** in moderate to high yields (23–92%). The yields decreased when less-labile bromocarbonyl groups were used and as the steric hindrance of the alkyl groups was increased ($R^1$, Figure 5). No reaction was observed with chloro- (X = Cl), β-bromo- (X = $CH_2Br$), or sterically hindered ($R^1$ = Et) α-bromocarbonyl moieties. Interestingly, when dimethoxybenzyl mono- or dichlorides were used under irradiation with light, the aldehyde played the role of electron acceptor to afford the unexpected mono- (**102**) and diester adducts (Scheme 22).[91] TDAE plays here the role of PET donor.[92] It was hypothesized that the initial light-catalyzed ET from TDAE to the aldehyde led to a ketyl radical anion, which was followed by an oxidation step to yield an aromatic carboxylate anion which substituted the benzyl chloride.



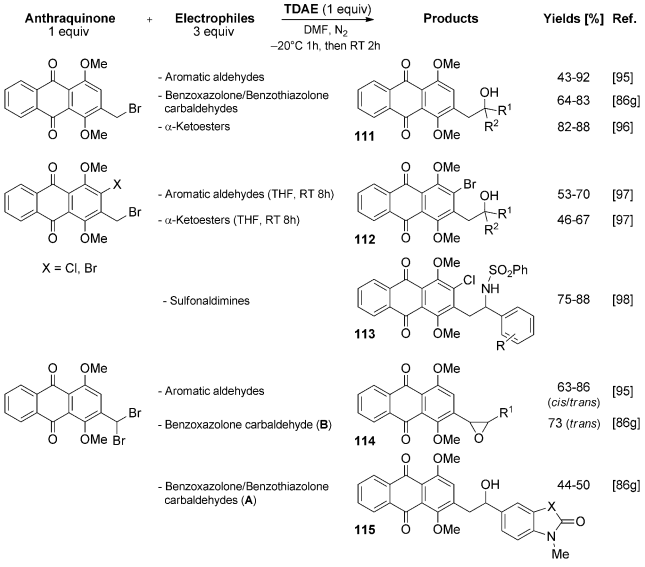

***Scheme 24.*** Reactions of TDAE with heterocyclic substrates. (Changes from the standard conditions are given in parenthesis.)

Vanelle and co-authors then extended the application of TDAE to chloromethyl heterocycles (Scheme 24, Figure 5). Hydroxymalonates **105** were obtained from imidazopyridines and -pyridazines, although the nonselectivity of the highly reactive ketomalonate resulted in moderate yields.[93] On the other hand, pyridopyrimidinones afforded methylene malonates **106** through dehydration of the unstable hydroxymalonate intermediates. This elimination was attributed to the basic properties of TDAE together with the higher acidity of the benzylic hydrogen atom in such a ring substituted with two electron-withdrawing groups. The preparation of hydroxycarbonyl 5-nitroimidazo[2,1-*b*]thiazoles **107** with antimicrobial activities against *C. tropicalis* needed irradiation with light along with TDAE to enhance the reduction and improve the yields (35–74%).[94] Nevertheless, this photoinduced ET was inadvisable in certain cases as it resulted in complex mixtures when using the highly activated ketomalonate or to dehydration of the alcohol product **109** (Scheme 25).




***Scheme 25.*** TDAE-/photoinduced acrylate synthesis.

In 2008, Vanelle, Terme, and co-workers reported the first example of quinone reduction promoted by an organic reductant.[95] The TDAE approach allowed the mild and efficient generation of a quinone anion, which cannot be formed by organometallic strategies. Their method was successfully applied to the synthesis of 1,4-dimethoxy-9,10-anthraquinones, an important pharmacophore in medicinal chemistry (Scheme 26, Figure 5). Note that the presence of a nitro group was not necessary in the quinone substrates to reduce the bromomethyl group. Regioselective addition of the anthraquinonic anion to the carbonyl group of α-ketoesters and aromatic aldehydes gave the corresponding α-hydroxyester (82–88%)[96] and alcohol adducts (43–92%)[86g,95] **111**. Adding a nitro group *ortho* to the bromomethyl group surprisingly necessitated harsher conditions and resulted in lower yields (38–63%). Exchanging the nitro group for a halogen provided hydroxyanthracenedione **112** (46–70%)[97] and *N*-benzylsulfonamides **113** (75–88%),[98] which were further cyclized by metal-catalyzed intramolecular O- and N-arylation.

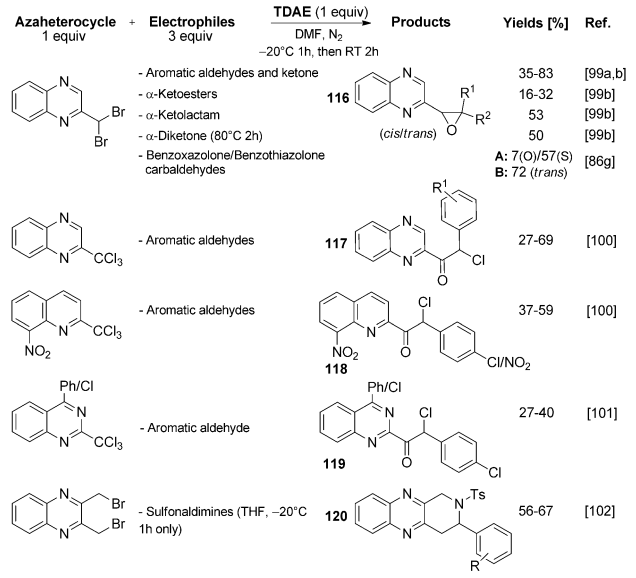



***Scheme 26.*** TDAE-promoted intermolecular reactions with anthraquinones. (Changes from the standard conditions are given in parenthesis.)

The reaction of *gem*-dibromomethyl anthraquinones with diverse aldehydes,[95] including benzoxazolone **B** (Figure 5),[86g] in the presence of 1.5 equiv of TDAE led to a mixture of *cis*/*trans* isomers of epoxides **114** in good yields (63–86%; Scheme 26). The formation of oxiranes **114** resulted from an intra-bimolecular nucleophilic substitution ($S_N2$) of the second bromine atom by the hydroxy group of the unstable bromohydroxy intermediate. The stereoselectivity of the substitution was sensitive to steric hindrance: reactions with *ortho*-substituted aldehydes were the most selective (0:100) while *para*-substituted aldehydes averaged a *cis*/*trans* ratio of 30:70 and benzaldehyde of 46:54. In the case of the less electrophile benzoxazolone and benzothiazolone **A**, reduction of the dibromomethyl substrate into its monobromomethyl counterpart was achieved prior to the formation of alcohols **115**.[86g]

Finally, the original reactivity of dihalo- and trihalomethyl quinoline derivatives was examined in greater detail (Scheme 27, Figure 5). The reaction of α-bromo carbanions, resulting from the reduction of a *gem*-dibromomethyl group, with any carbonylated electrophile led to a mixture of *cis*/*trans* epoxide isomers **116**.[86g,99] The low yields were justified by the instability of the oxiranes with two electron-withdrawing groups (e.g. α-oxyranyl ester quinoxalines: 16–32%). The *cis*/*trans* ratio with α-dicarbonyl compounds or *para*-substituted aldehydes averaged 50:50, while the ratio averaged 30:70 for bulky α-diketone and *ortho*-substituted aldehydes. Although it followed the same trend in favoring of the *trans* isomer with increasing steric hindrance, the stereoselectivity of the reaction was lower with quinoxalines

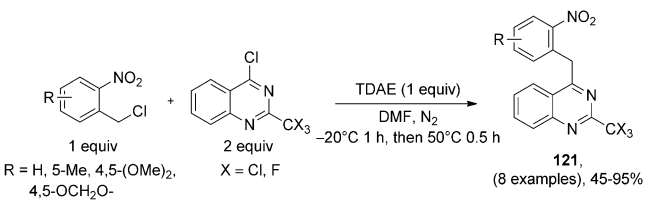
  




***Scheme 27.*** TDAE-promoted reduction of dihalo- and trihalomethylazaheterocycles. (Changes from the standard conditions are given in parenthesis.)

than with the anthraquinonic series, which benefited from the presence of methoxy substituents. The TDAE-promoted reduction of trichloromethyl quinoxalines,[100] 8-nitroquinoline,[100] and quinazolines[101] in the presence of aromatic aldehydes resulted in the synthesis of α-chloroketones **117**–**119** in moderate to good yields (Scheme 27, Figure 5). It represented a clean and simple access to highly functionalized α-chloroketones, generally prepared by photo- or acid-induced addition of chloride to ketones. The mechanism was assumed to involve an attack by a chloride anion on the chlorooxirane intermediate. Finally, reaction of 2,3-bis(bromomethyl)quinoxaline with TDAE allowed the synthesis of tetrahydropyrido quinoxalines **120** by consecutive intermolecular addition of the carbanion to *N*-(toluenesulfonyl)benzylimines and an intramolecular $S_N2$ reaction of the second bromomethyl group with the nitrogen atom.[102] The possibility of a pathway involving the formation of a biradical by cleavage of the two C–Br bonds and subsequent reaction with the imine could not be totally ruled out.

The disparities in the reducing abilities of TDAE can be used to selectively reduce one of two potential substrates. A $S_NAr$ reaction at the 4-position of 2-trihalomethylquinazolines was performed in the presence of the more reducible 2-nitrobenzyl chloride under mild and chemoselective conditions without reduction of the trihalogenated groups in **121** (Scheme 28).[101] Alternative methods to reach this benzylic

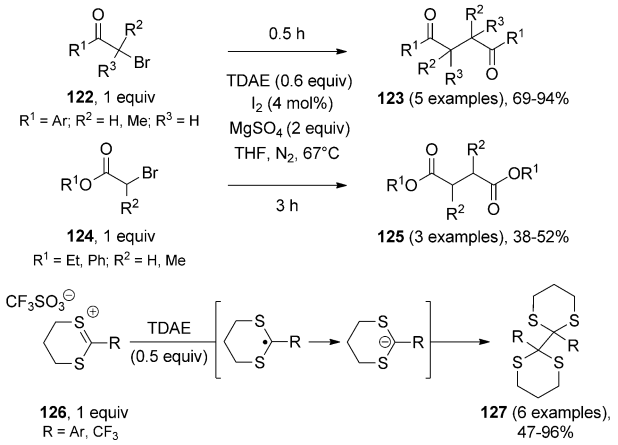



***Scheme 28.*** $S_NAr$ reaction with 2-trihalomethyl-4-chloroquinazolines.

substitution rely on the use of organomagnesium species or strong bases, and involve drastic and nonselective conditions that make them incompatible with such substrates. It is notable that no reaction was observed when the electrophilicity of the 4-position was decreased by replacing the $CX_3$ group by an ester or a methyl group.

### 3.3.3. *Miscellaneous Reactions*

Besides α,α-difluoroketone- or quinone-activated C–X bonds, α-bromo ketones **122** and esters **124** can be reduced by TDAE.[103] The preparation of 1,4-diketones **123** and, to a more limited extent, of 1,4-diesters **125** was achieved through reductive homocoupling (Scheme 29). The yields

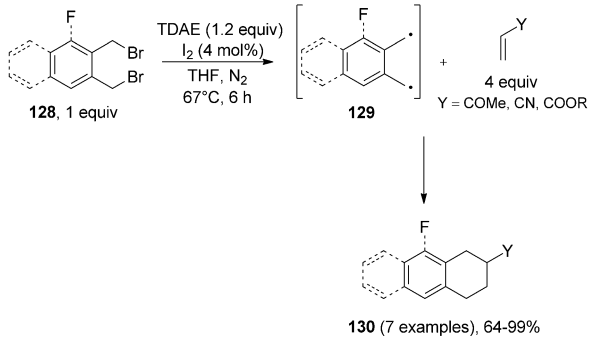



***Scheme 29.*** Reductive coupling reactions.

were drastically improved by the addition of $MgSO_4$ and a catalytic amount of iodine. This reactivity was not observed with sterically hindered ($R^2 = R^3 = Me$), dialkyl ($R^1$, $R^2$ = Alkyl), and α-chloro ketones. Likewise, reductive dimerization of aromatic and perfluoroaliphatic dithianylium ions **126** can be accomplished in higher yields (47–96%) and in a more convenient way by using TDAE instead of zinc.[104] Species **127** are important precursors of liquid-crystal building blocks. It is noteworthy that the electron transfer proceeds here between TDAE and a C=$S^+$ bond (instead of a C–X bond). The mechanism of these reductive coupling reactions via radical or anionic species could not be determined.

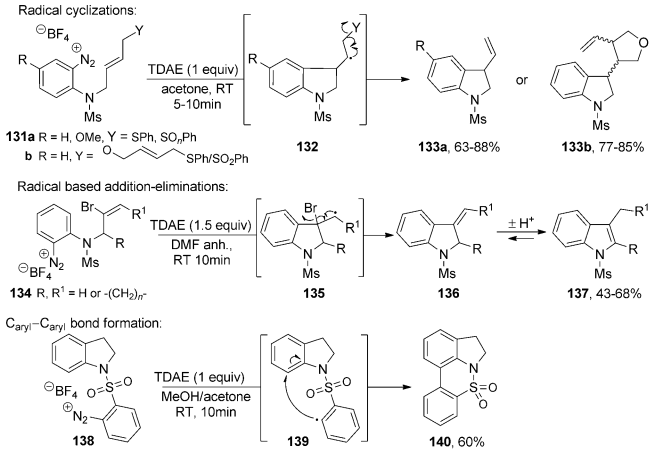
Only a few publications mention the participation of radical intermediates as the reactive species in TDAE-promoted reactions. In 2005, Nishiyama et al. published a homogeneous and metal-free method for the reductive cleavage of C–Br bonds in 1,2-bis(bromomethyl)arenes **128** (Scheme 30).[105] The biradical intermediates **129** reacted with various olefins such as acrylates, acrylonitrile, and vinyl ketone to give the 1,2,3,4-tetrahydroarenes **130** in moderate to excellent yields (64–99%). α- or β-Substituted acrylates and α,β-unsaturated diesters could also be coupled, although an excess of the olefin (10 equiv) was used and lower yields (7–51%) were obtained. It is notable that no activating function was required on the benzyl ring.




***Scheme 30.*** Radical reductive debromination.

In line with their previous studies on TTF-initiated radical-polar reactions, Murphy and co-workers showed that the reduction of arene diazonium derivatives with TDAE also led to aryl-radical intermediates (Scheme 31).[106] However, since the absence of a TDAE salt such as **8** prevented a clean termination of the radical process, a radical leaving group adjacent to the cyclized radical (**132**) was required. Treatment




***Scheme 31.*** Radical reactions with TDAE. Ms = mesyl.

of **131a** with one equivalent of TDAE gave indolines **133a** in high yields after a self-terminating *5-exo-trig* aryl radical-alkene cyclization. Likewise, facile cascade radical cyclizations afforded bicyclized products **133b** without competitive direct trapping of the alkyl radical **132** by $TDAE^{\bullet+}$. This method was then exploited in a radical-based addition/elimination route to indoles. The radical $Br^{\bullet}$ was eliminated from the cyclized radical intermediates **135** to afford unstable exocyclic alkenes **136**, which tautomerized to the corresponding indoles **137**. The method was also used for a $C_{aryl}$–$C_{aryl}$ bond-formation reaction that afforded tetracyclic sulfonamide **140** in 60% yield. These are the only reported cases where TDAE generates aryl radicals. Since the TDAE is far more powerful than TTF (by about 1.1 V for the first electron transfer), the generation of aryl anions was first expected from the reduction of aryl diazonium salts by TDAE.

Since 1999, Tanaka and co-workers have reported several examples of the use of TDAE as an electron source to reduce transition-metal catalysts in specific organometallic reactions, such as the Ni/Cr redox-catalyzed alkenylation of carbonyl groups[107] or Pd-catalyzed reductive dimerization of aryl halides.[108] In these cases, the use of mild and selective TDAE avoided excessive recourse to expensive inorganic reducers and the undesired over-reduction of other functional groups (nitro, carbonyl, ester, or cyano groups). Although this reactivity goes beyond the primary concept of organic reductants directly promoting organic synthesis, their role in the reduction of low-valent transition-metal species further illustrates the versatility of these reagents. The TDAE-Pd system was recently applied in a multistep synthesis for the homocoupling of iodoindoles or bromopyridines and the TDAE gave better results than metal reductants.[109]

In summary, tetrakis(dimethylamino)ethylene is a strong organic electron donor that is able to activate carbon–halogen bonds and thus generate electrophile radicals and stable nucleophilic anions. Hence, either radical or carbanionic reactions can be performed through the judicious choice of substrates and conditions. In terms of simplicity and mildness of the experimental procedure, including purification of the products, cost, and availability, TDAE has proved to be an attractive complement to other reducing agents. A clear illustration is the reductive dechlorination of chlorodifluoromethylated compounds, where the TDAE approach is as efficient as the Rongalite system and more practical than sodium dithionite or $n$Bu$_3$SnH/azobisisobutyronitrile (AIBN).[110] TDAE can also lead to different reactivities from those observed with zinc, despite their similar reducing power.

Unfortunately, only haloalkyl derivatives with an adequate reduction potential (electron-deficient aliphatic and benzylic systems) qualify as TDAE substrates that produce a reactive species. Chloroalkyl, unactivated alkyl halides, and aryl halides[111] are reluctant to undergo electron transfer from TDAE. Moreover, the carbanions thus generated are less reactive than those formed by an organometallic strategy because of their stabilization by the $TDAE^{2+}$ counterion, and are thus limited to reactions with activated electrophiles. Finally, the TDAE method suffers from a lack of detailed mechanistic studies, which would help elucidate certain reactivities or the effect of photoinduction.

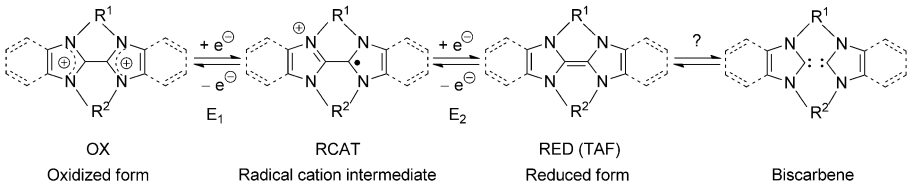
## 4. Tetraazafulvalenes (TAFs)

Tetraazafulvalenes (TAFs) hold a special place among the tetraaminoethylenes: Since their oxidized products are aromatic, the driving force for their oxidation is stronger than for alkyl-substituted tetraazaalkenes (Scheme 32). This feature makes them very attractive reducing agents, as reflected by the intensive study of this class of donors over the last decade.

### 4.1. Properties

In the early 1970s, the first TAFs[112] were already being studied in regard to their electronic properties and were described as two-step reversible redox systems.[7] Nonetheless,




***Scheme 32.*** Redox reaction sequence of tetraazafulvalenes.

it was not until the 1990s and the blossoming of carbene coordination chemistry that they started to renew interest. Unlike their saturated counterparts, N-heterocyclic carbenes based on unsaturated imidazolylidene rings rarely form enetetramines, unless to be linked through their nitrogen atoms by a double bridge.[9,113]

In this context, the research groups of Thummel and Ames undertook a thorough study of the redox and structural behavior of stable polymethylene-bridged biazolium salts: bisannulated 2,2′-bibenzimidazoles **141,**[114] 2,2′-biimidazoles **142,**[115] or mixed system **146**[116] along with monoannulated counterparts (**143**–**145**; Figure 6). The purpose was to modulate the redox properties through steric and conformational effects imposed by different nitrogen substituents.

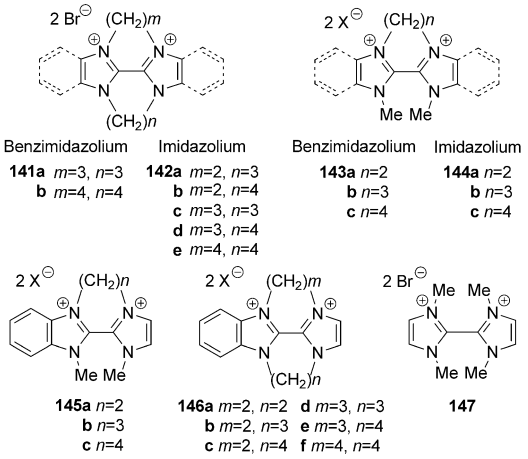



***Figure 6.*** Biazolium salts.

The ability of biazolium salts to undergo two one-electron reductions is governed by the planarity of the structure: the most planar systems, which provide an optimum resonance delocalization, are the most easily reduced and show the greatest separation between the two reduction waves. Electron uptake also depends on the stability of the radical cation RCAT and the RED species (Scheme 32), which will be favored by delocalization over the entire aromatic framework. Planarity between two ring planes (dihedral angle) can be correlated with the UV absorption energy, which diminishes (whereas the wavelength increases) as a system becomes more planar and more delocalized.

As depicted in Table 2, as the N,N′ bridge becomes longer, the wavelength decreases, thus reflecting the diminished π delocalization and the increased nonplanarity of the two aromatic rings.[117] The cyclic voltammograms of the salts (Figure 7) confirmed the shift to more negative potentials and irreversible reductions as the planarity of the systems decreased. The most highly distorted systems bearing a tetramethylene bridge,

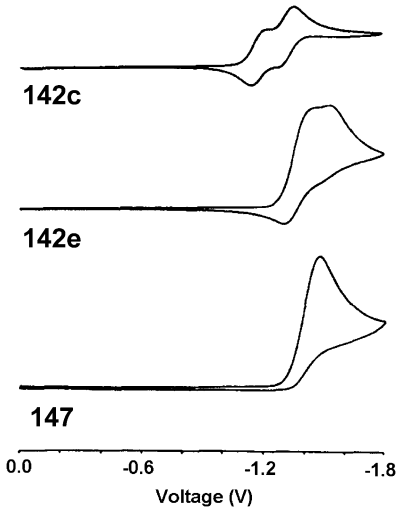



***Figure 7.*** Representative cyclic voltammograms recorded in $CH_3CN$.[115b]

for example, **142e**, **145c**, and **146f**, or four methyl groups (**147**) all showed a single irreversible wave, thus indicating that the RCAT and RED species formed upon reduction did not persist long enough to be reoxidized back to the initial OX form.

As the incorporation of a second bridge imposed added rigidity to the salt and thus increased its planarity, monoannulated salts were more difficult to reduce and had more irreversible behaviors than their bisannulated counterparts. The planarity, redox potential, and reversibility decreased in the order benzimidazolium > mixed > imidazolium. Notice that the aromaticity of the π systems prevails over the degree of annulation (a bisannulated imidazolium is more difficult to reduce than a monobridged benzimidazolium).

The geometry around the enetetraamine units was also strongly influenced by functional groups (Figure 8).[118] Electron-donating methoxy groups on dibenzoTAF **148** enhanced the pyramidalization of the N atom (C-N-C angle = 113°) and thus effectively minimized the steric interactions between opposing N substituents, thereby affording a nearly planar enetetraamine moiety (torsion = 7°). In contrast, electron-withdrawing halogen atoms (**149**, R = Br) appeared to decrease the pyramidalization of the N atom (C-N-C angle = 116°), which caused significant twisting of the two benzimidazo rings (torsion = 27°) to avoid unfavorable steric interactions. Hence, planar electron-rich enetetramines **148** [$E_{1/2}(CH_3CN) = -1.07$ V versus SCE] were more reactive than twisted electron-deficient ones [$E_{1/2}$(**149**, $CH_3CN$) =

*Table 2:* Absorption maxima and redox potentials for *N*,*N*′-bridged biazolium salts.[a]

| Compound | *m* | *n* | $\lambda_{max}$ (ROH) [nm] | $E_{1/2}$(DMF) [V] | $E_{1/2}$($CH_3CN$) [V] |
|---|---|---|---|---|---|
| **141a** | 3 | 3 | 353 | −0.55 (60), −0.87 (80)[b] | n.d. |
| **141b** | 4 | 4 | 325 | n.d. | −0.81 (100), −0.94 (110) |
| **142a** | 2 | 3 | 298→306 | −1.14 (50), −1.38 (110)[b] | −1.18 (80), −1.42 (ir) |
| **142b** | 2 | 4 | | −1.13 (110), −1.41 (105)[b] | −1.11 (80), −1.49 (ir) |
| **142c** | 3 | 3 | | −1.14 (130)[b] | −1.12 (100), −1.28 (ir) |
| **142d** | 3 | 4 | | −1.31 (ir)[b] | −1.28 (ir) |
| **142e** | 4 | 4 | 268 | −1.37 (120)[b] | −1.39 (ir) |
| **147** | | | n.d. | −1.43 (ir)[b] | −1.48 (ir) |
| **143a** | | 2 | 359 | −0.60 (ir) | −0.62 (70), −0.97 (ir) |
| **143b** | | 3 | 338 | −0.76 (90), −0.82 (80) | −0.76 (60), −0.94 (ir) |
| **143c** | | 4 | 320 | −0.87 (110) | −0.86 (60), −1.03 (70) |
| **144a** | | 2 | 304 | −1.18 (ir) | −1.21 (ir) |
| **144b** | | 3 | 283 | −1.32 (140) | −1.31 (ir) |
| **144c** | | 4 | 265 | −1.41 (ir) | −1.44 (ir) |
| **145a** | | 2 | 333 | −0.86 (90), −1.07 (ir) | −0.89 (70), −1.10 (ir) |
| **145b** | | 3 | 314 | −1.04 (ir) | −1.00 (90) |
| **145c** | | 4 | 300 | −1.12 (ir) | −1.12 (ir) |
| **146a** | 2 | 2 | 334 | −0.80 (ir) | −0.82 (ir) |
| **146b** | 2 | 3 | 330 | −0.87 (70), −1.05 (60) | −0.85 (75), −1.14 (ir) |
| **146c** | 2 | 4 | 306 | −1.08 (105), −1.22 (ir) | −1.07 (80), −1.30 (ir) |
| **146d** | 3 | 3 | 337 | −0.85 (80), −1.15 (100) | −0.86 (75), −1.26 (ir) |
| **146e** | 3 | 4 | 337 | −0.86 (70), −1.20 (ir) | −0.86 (70), −1.26 (ir) |
| **146f** | 4 | 4 | 320 | −1.03 (ir) | −1.02 (ir) |

[a] Potentials are given in volts versus SCE for saturated solutions in DMF or $CH_3CN$, 0.1 M in ammonium perchlorate recorded at 25 °C at a scan rate of 200 or 100 mV $s^{-1}$. The difference between the cathodic and anodic peak potentials (mV) is given in parenthesis. (ir) means irreversible; for these systems the potential given is the maximum of the cathodic wave. n.d. = not determined. [b] In DMSO.

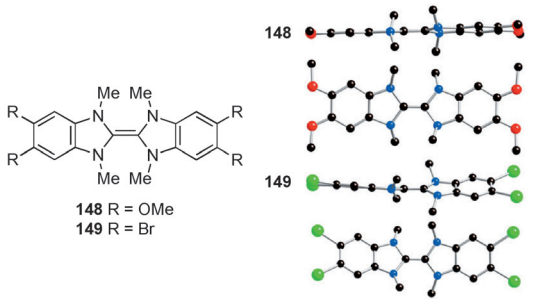
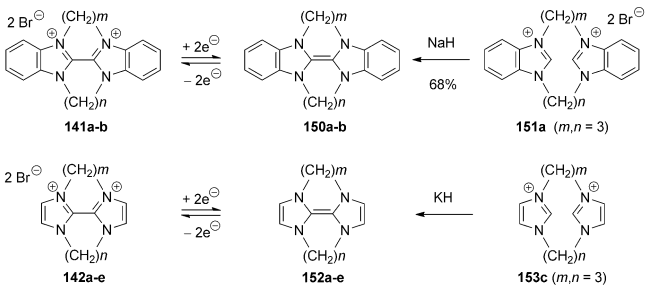



*Figure 8.* Ball-and-stick views of functionalized dibenzo-TAF.




*Scheme 33.* Preparation of dibenzo- and imidazo-tetraazafulvalenes.

−0.64 and −0.73 V versus SCE], which were more stable toward oxygen.

### 4.2. Preparation

The electrochemical generation of some neutral tetraaminoalkenes derivatives **150** and **152** (RED) was realized by bulk electrolysis of the salts **141** and **142** (OX) through two distinct reductions (Scheme 33).[114c,115] Stable **150a** and **152c** were also isolated in an inert atmosphere by double deprotonation of the bis(azolium) salts **151a** and **153c**. However, attempts to generate **152e** (*m*,*n* = 4), mono- or unbridged imidazo-TAF species, afforded biscarbenes instead.[113] Imidazocarbenes are reluctant to undergo dimerization because of the stability conferred by the aromaticity of their 6π-electron ring (bond dissociation energy (BDE) of 4 ± 3 kcal $mol^{-1}$).[113] In contrast, dibenzo-TAFs are for the most part stable at room temperature[119] (BDE of ca. 10 kcal $mol^{-1}$),[120] although significantly less stable than aliphatic tetraaminoethylenes. This underlines the extreme weakness of the central C=C π bond. The isolation of the TAF forms rather

than a pair of carbenes is highly dependent on the kinetic barrier to either dimerization or dissociation.

In summary, the reduction of biazolium salts was found to become increasingly difficult ($E_{1/2}$ more negative) and irreversible as the system becomes less planar. Diimidazolylidenes should thus be more reactive reductants in organic synthesis than dibenzimidazolinylidene derivatives. Furthermore, non-annulated (or long methylene-bridged) and electron-rich TAFs should be stronger electron donors as they are less stable and oxidize to form stabilized cations. The theoretical design (through DFT calculations) of organic donors with a wide range of ionization potentials correlated with these factors.[121] However, when it comes to the design of a powerful reducing agent, the problem is to combine sufficient stability of the generated enetetramine, rather than its conversion into a pair of carbenes, with high reactivity through rapid electron donation.

### 4.3. Reactivity

Since 2005, the Murphy research group has focused their investigation on the development of neutral organic agents that mimic the TDAE structure, but improve on their performance as electron donors: the "super-electron donors" (SEDs; Figure 9).[122] Based on the idea that both the aromatic stabilization energy of the corresponding radical cation (as in sulfur-containing reductants) and the presence of electron-donating nitrogen atoms (as in TDAE) can greatly assist electron transfers, Murphy and co-workers combined these two stabilizing factors in the same structure. This approach resulted in excellent reducing agents that could be used for organic transformations.

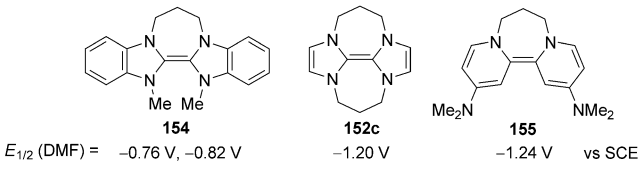
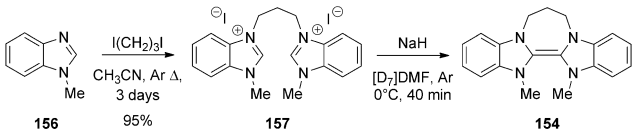



***Figure 9.*** Super-electron donors (SEDs).

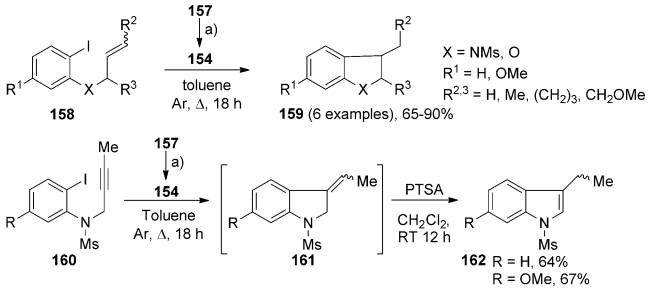
#### 4.3.1. Benzimidazole-Based Donors

Dibenzimidazolinylidene **154** was prepared by deprotonation of the stable *N*,*N*′-tethered benzimidazolium salt **157**, obtained from the reaction of benzimidazole **156** with 1,3-diiodopropane (Scheme 34).[123] Dimer **154** could not be isolated and had to be characterized in situ by low-temperature NMR spectroscopic analysis of the crude solution.

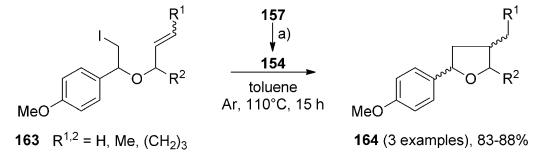



***Scheme 34.*** Formation of bibenzimidazolinylidene **154**.

*Cyclization of aromatic substrates*
Reaction conditions: a) **157** (1.2 equiv), KHMDS (2.4 equiv), DMF, toluene, Ar, RT, 1 h

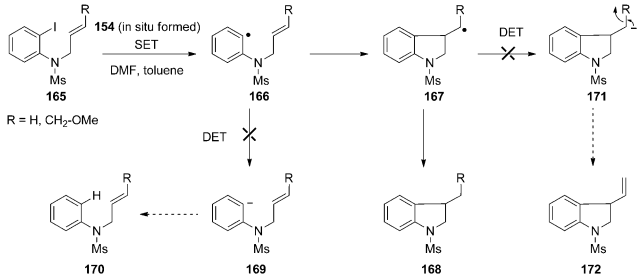



*Cyclization of aliphatic substrates*
Reaction conditions: a) **157** (4 equiv), KHMDS (7.5 equiv), THF, Ar, RT, 1 h




***Scheme 35.*** Cyclization reaction with **154**. PTSA = *p*-toluenesulfonic acid.

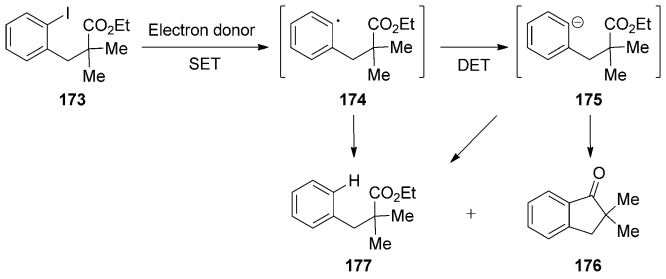
Dibenzo-TAF **154** was found to react efficiently with unactivated aryl as well as alkyl iodides through a single-electron-transfer (SET) mechanism to give the corresponding aryl and alkyl radicals (Scheme 35). Although the oxidation potential of **154** was less negative than the aryl iodides [−1.8 V], the irreversible loss of iodide assisted the reaction. Cyclization selectively afforded the indolines **159** (81-90%)[124] and tetrahydrofurans **164** (83–88%) in excellent yields. Alkyne-containing substrates **160** gave indoles **162** (64 and 67%, respectively) after acidic treatment of the exocyclic alkenes **161**. Although several observations pointed to a SET pathway, the formation of an anion intermediate (**169** or **171**) could not be totally precluded in the first study (Scheme 36).[123,125] The hydrogen atom, abstracted by radical **167** in the final reductive termination step, very likely came from the donor **154** or its oxidized form.




***Scheme 36.*** Comparison of the SET and DET mechanisms.

Shortly after, a diagnostic test irrefutably confirmed the SET pathway for donor **154**.[126] Given that, in contrast to radicals, carbanions attack esters, the reaction depicted in Scheme 37 unambiguously distinguishes aryl anions from aryl radical intermediates. Iodoester **173** was treated with donor **154** and only the reduced compound **177** was isolated (67%). The absence of indanone **176** indicated that aryl anion **175**



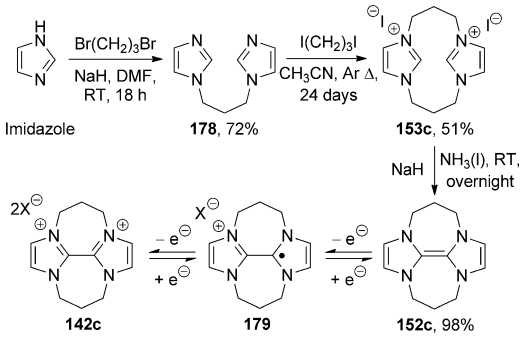

***Scheme 37.*** Diagnostic test for the formation of radical or anion intermediates.

had not been formed. It is notable that heating **173** in the presence of tris(trimethylsilyl)silane (TTMSS) and the radical initiator AIBN gave the reduced product **177** (70%) exclusively, whereas in the presence of a stannylsilane and fluoride ions (a recognized method for the formation of aryl anions), a mixture of **176** (68%) and **177** (14%) was obtained.

Thus, benzimidazole-derived donor **154** was defined as the first super-SET organic reagent. Having in hand a strong reducing agent that allows the formation of radicals from alkyl and aryl halides, the next challenge was to find organic donors able to generate stabilized carbanions through the transfer of two electrons: particularly aryl anions as they could not be obtained with the TDAE method.

#### 4.3.2. *Imidazole-Based Donors*

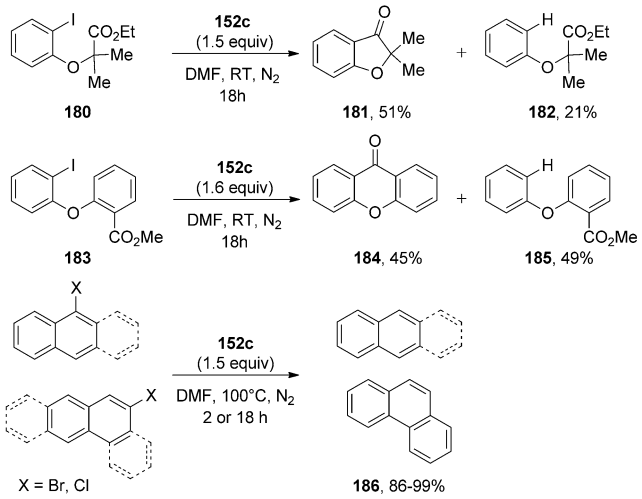
In 2007, Murphy, Tuttle et al. reported a more rigorous synthesis for bisimidazolylidene **152c**[113] by the preparation of diiodide **153c** from imidazole and dihalide propanes (Scheme 38).[126] Although improved and scaled up to 55 g,




***Scheme 38.*** Preparation of bisimidazolylidene **152c**.

the synthesis of **153c** was still restrictive as the incorporation of the second bridge to give a dimer required high dilution (4 L of $CH_3CN$) and a reaction time of several weeks (24 days), along with partial recrystallization and moderate yields (51%).[127] The (tetrakis)imidazolium macrocyclic salt was obtained as a side product.[128] The generation of **152c** then proceeded through the use of NaH in liquid ammonia to afford an air-sensitive pure yellow solid (98%).

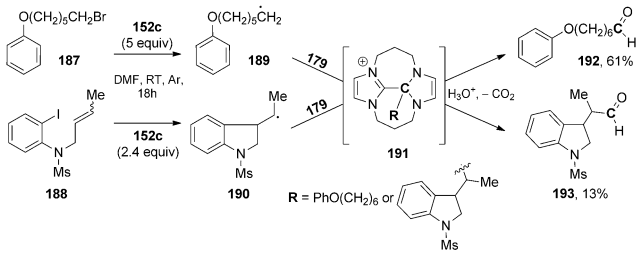
Analysis of the reaction of substrate **173** with **152c** to afford **177** (70%) and **176** (16%) proved the intermediacy of aryl anion **175** (Scheme 37). Interestingly, attempts to access ketone **176** through other reactions that should afford aryl anions, by using *t*BuLi, sodium naphthenide, or magnesium metal, gave complex mixtures. This clearly illustrated the selectivity of diimidazo-TAF **152c** compared to strong metallic reductants which reduced the resulting ketone. The significant amount of reduced product **177** can arise from hydrogen abstraction by the anion **175** and/or the aryl radical **174**. Donor **152c** shows a two-electron redox wave [$E_{1/2}$(DMF) = −1.20 V versus SCE][116] and thus represents a considerably more powerful reducing agent than TDAE [−0.62 V] or **154** [−0.76, −0.82 V]. The efficiency of the SED **152c** was further confirmed with ester substrates **180** and **183**, which are more prone to a rapid cyclization of the anion intermediate and thus give a more accurate estimation of the percentage of aryl anions formed by ET in these reactions (that is, a minimum of 51 and 45%, respectively; Scheme 39).




***Scheme 39.*** Reductions of aryl halides with donor **152c**.

**152c** was also able to reduce bromo- and chloro-substituted polycyclic aromatic hydrocarbons in high yields (**186**) (Scheme 39), in contrast to **154** which resulted in very poor conversions in the same reactions. Donor **152c** was thus the first neutral organic electron transfer agent able to selectively convert haloarenes into aryl anions by DET and in the absence of photochemical activation.

As predicted by the studies of Thummel and Ames (see Scection 4.1), diimidazolylidene **152c** exhibited better reducing ability than dibenzo-TAF **154**. However, the greater reactivity of enetetramine **152c** is also due to the greater aromatic stabilization energy gained from the formation of the more-planar[129] **142c**, whereas the overall structure of **154** becomes less and less planar upon electron removal. Indeed, the oxidation of **152c** to **142c** creates aromatic rings from completely non-aromatic precursors, thus providing an even stronger driving force than for the oxidation of **154** bearing benzene rings.

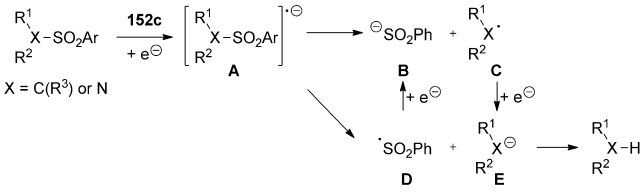


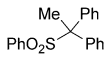
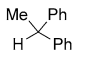
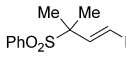
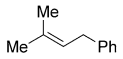
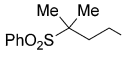
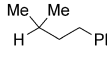
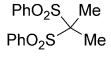
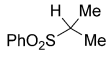
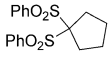
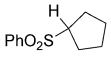
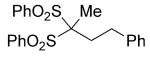
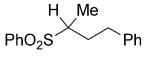
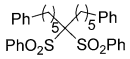
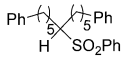
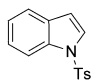
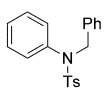
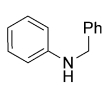
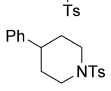
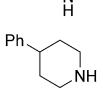
***Scheme 40.*** Formation of aldehydes.

A side reaction can occur with SED and alkyl or some aryl halides when an acidic workup is used. This reaction consists of the formation of aliphatic aldehydes by extrusion of a carbon atom from the azolium **191** (Scheme 40).[130] Trapping of the SED-initiated alkyl radical **189** (or **190**) by coupling with the radical cation **179** of donor **152c** generates intermediate **191**, which releases the aldehyde **192** (or **193**) after acid hydrolysis and decarboxylation.[131]

The scope of **152c** was then extended with success to the mild and selective reductive cleavage of sulfones and sulfonamides by DET (Table 3).[132] ET to the arenesulfonyl group affords radical anion **A**, which can fragment to give either [anion **B** + radical **C**] or [radical **D** + anion **E**], depending on the susbtrate. Transfer of a further electron leads to the pair of anions **B** + **E**. With their typical reduction potentials of −2.3 V, removal of these popular protecting groups is usually mediated by metallic or electrochemical mediators under harsh reaction conditions.[133] In the presence of **152c**, benzyl and allyl sulfones (entries 1 and 2) were efficiently reduced, whereas a less-activated alkyl sulfone (entry 3) was unreactive. Geminal disulfones gave the corresponding monosulfones in excellent yields (94–98%; entries 4–7). In contrast to piperidine (entry 10), amine structures favoring the aromatic stabilization of the anion intermediate **E**, such as indole and aniline species (entries 8 and 9), gave very good yields of the reduced product. The inactivity of the alkyl sulfone and piperidine derivative was explained by the large activation energy required for the initial electron transfer, because of the instability of their radical anion **A**. The lack of dissociation of **A** was attributed to the poor orbital overlap between the LUMO of the acceptor and the σ* orbital of the scissile X–S bonds.[132]

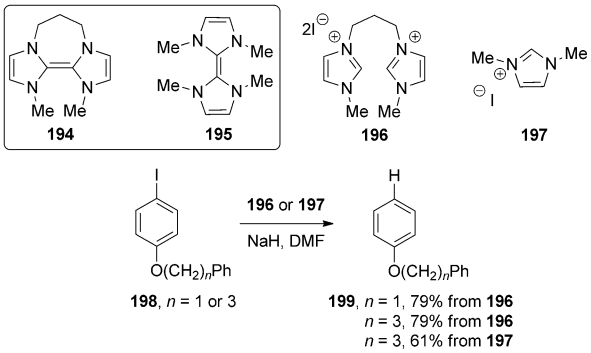
***Table 3:*** Reductive cleavage of sulfones and sulfonamides.[a]



| Entry | Substrate | Product | Yield [%] |
|---|---|---|---|
| 1 |  |  | 97 |
| 2 |  |  | 79 |
| 3 |  |  | <1 |
| 4 |  |  | 97 |
| 5 |  |  | 96 |
| 6 |  |  | 98 |
| 7 |  |  | 94 |
| 8[b,c] |  |  | 91 |
| 9[b] |  |  | 74 |
| 10[b] |  |  | <1 |

[a] Reaction conditions: Substrate (1 equiv), **152c** (3 equiv), DMF, 110°C, Ar, 18 h. [b] **152c** (6 equiv). [c] 4 h.

Recently, an interesting approach was described by Jolly et al. to overcome the difficulties related to the synthesis of tetraazaalkenes and thus enhance their potential as powerful reducing agents in organic synthesis.[134] Their concept was to target simpler TAFs by producing them in situ and to prove their presence through ET to iodoarenes. Hence, salts **196** and **197** were treated with excess NaH in DMF and reacted with **198** (Scheme 41). Reduced arenes **199** were obtained in good yields, consistent with the in situ formation of **194** and **195**.



***Scheme 41.*** In situ reduction of iodoarenes.

NMR experiments showed that these highly reactive TAFs were rapidly converted into carbenes with a half-life of a few hours for **194** and a few minutes for **195**. The equilibrium of the NHC and TAF suggested that ET reactions could be possible in ionic liquids.[135]

Following this success, the development of more powerful imidazo-TAFs related to **152c** was envisaged. However, as a result of the high molecular weight of this organic electron donor (216.3 g mol$^{-1}$), large quantities of material were required to perform the reaction scope with an excess of **152**. The fastidious preparation along with the limited choice of precursors[136] encouraged the exploration of alternative SED structures.

## 5. Bispyridinylidenes

In parallel to tetraazafulvalenes, bispyridinylidenes and the associated radical cations have long been studied in regard to their electrochemical properties. Notably, viologen and quinone derivatives have been intensively investigated as electrochromic materials[137] and components of supramolecular systems (Figure 10).[138] In the case of viologens,[139] only

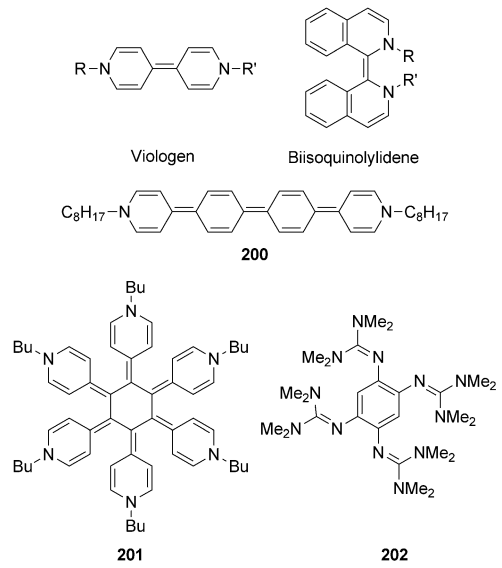
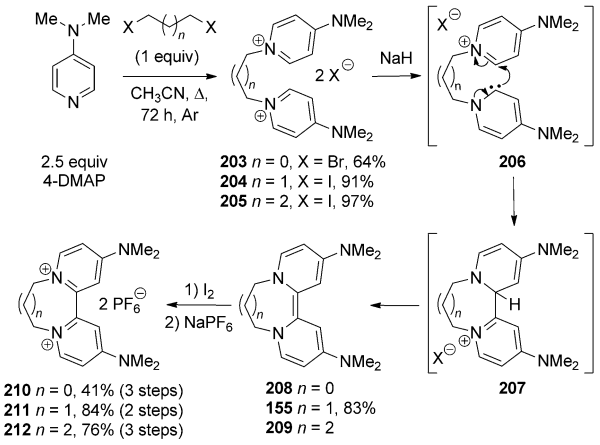



*Figure 10.* Viologen derivatives.

a few neutral 4,4′-bipyridyl forms have been isolated (R = methyl[140] or phenyl).[141] The extended viologen **200** is the strongest reducing agent of this series [$E_{1/2}$(THF) = −1.03 V versus SCE; calibrated with Fc/Fc$^+$], presumably because of the driving force provided by the aromaticity of the four quinoid rings formed upon electron donation.[142] Recently, cyclic voltammetry of six-electron redox system **201** showed that **201**$^{6+}$ is reversibly reduced to **201**$^{2+}$ in one four-electron transfer and **201**$^{2+}$ is reversibly reduced to **201**$^0$ in one two-electron transfer [$E_{1/2}$(THF) = −0.58 and −0.69 V versus SCE; calibrated using Fc/Fc$^+$].[143] Cyclic voltammetry of **202** showed a two-electron wave [$E_{1/2}$(CH$_3$CN) = −0.32 V versus SCE], although computational studies suggested that **202** could be a stronger two-electron reducing agent than **152c** in nonpolar solvents.[144] In other solvents, **152c** should be superior. Despite the numbers of nitrogen atoms and/or the aromaticity of the oxidized products, the redox potentials of these structures, lower than that of **152c**, indicate that other factors (not yet determined) influence the reducing power. To the best of our knowledge, these pyridyl derivatives have not been investigated for the reduction[145] of organic substrates.

Diquarternary salts of 2,2′-bipyridine (e.g. **210**–**212**, Scheme 42) were primarily studied for their role as electron-deficient acceptors in charge-transfer complexes[146] and for their potent herbicide properties.[147] Similar to imidazolium salts, the study of their redox and spectroscopic properties showed that oxidation steps from the bispyridinylidenes




*Scheme 42.* Formation of bispyridinylidenes.

to the aromatic oxidized forms were favored by resonance delocalization between the two coplanar rings. Lengthening the 1,1′-bridge to a tri- or tetramethylene unit increased the reduction potential ($E_{1/2}$ more negative), and electron-withdrawing groups shifted the first reduction to a more negative potential.[148]

### 5.1. Reactivity of Bispyridinylidenes

Since 2008, Murphy et al. have developed a new series of organic SEDs based on pyridine structures.[149,150] Dihalide precursors **203**–**205** with different chain lengths were easily prepared from the reaction of commercially available 4-dimethylaminopyridine with 1,*n*-dihaloalkanes (Scheme 42). Deprotonation of the bispyridinium salts afforded bispyridinylidenes **155**, **208**, and **209** via carbene **206**, which undergoes nucleophilic attack on the adjacent pyridinium ring.[151] Diverse amino groups were also incorporated at the 4-position of the pyridine rings to enhance the electron density of the π system (Figure 11). All the cyclic voltammograms

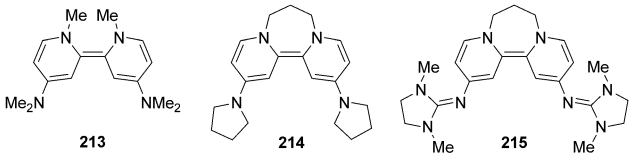



*Figure 11.* 4-Amino-substituted bispyridinylidenes.

showed reversible two-electron redox chemistry (Table 4). Apart from **208** and **214**, which show two one-electron waves, the other bipyridinium salts exhibited a single two-electron wave, thus indicating that the loss of the second electron occurred at essentially the same potential as the first. As expected, restricting the bridge length to two carbon atoms resulted in a less effective reducing agent (**208**), while increasing the flexibility with a long bridge (**209**), free rotation (**213**), or altering the nature of the 4-substituents (**214** and **215**) did not radically enhance the donor properties

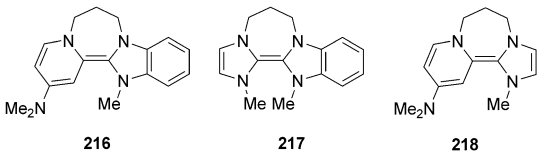
***Table 4:*** Redox potentials of selected donors.[a]

| Donor | $E_{1/2}$(DMF) [V] |
|---|---|
| **155** | −1.24 |
| **208** | −1.21, −0.98 |
| **209** | −1.23 |
| **213** | −1.27 |
| **214** | −1.33, −1.24 |
| **215** | −1.24 |
| **216** | −1.09, −0.97 |
| **218** | −1.30, −1.18 |

[a] Potentials have been converted for comparison with SCE (calibrated using $Fc/Fc^+$).

compared to **155**. Unlike the quasiplanar **142c**, which is constrained by its two trimethylene straps (dihedral angle of 1.5°),[126] the X-ray structure of **211** confirmed the nonplanarity, with the two rings twisted to avoid interaction (53°), and correlated with the greater driving force of **155** for loss of a second electron.[150]

Hybrid systems were also prepared (Figure 12).[152] Single-electron donors **216** and **217** incorporate a "stronger" and a "weaker" donor component and exhibit redox potentials

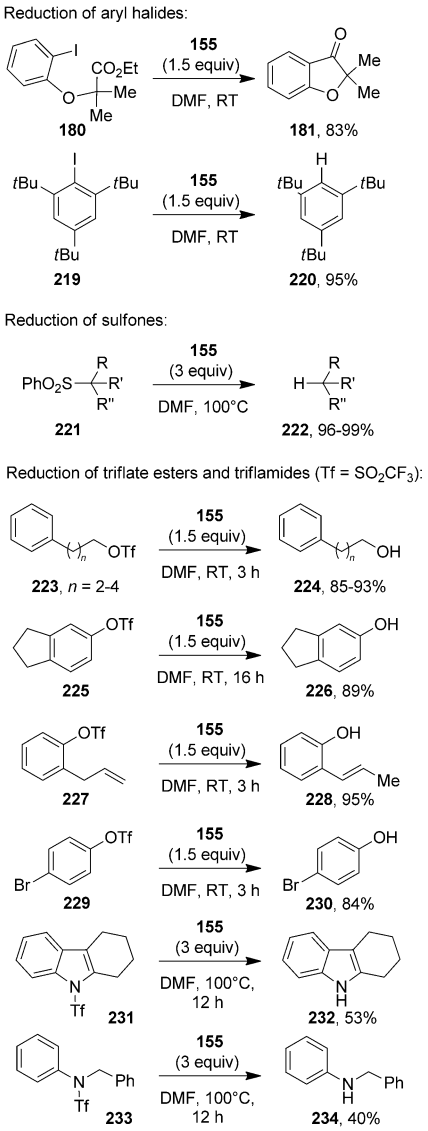



**216** **217** **218**

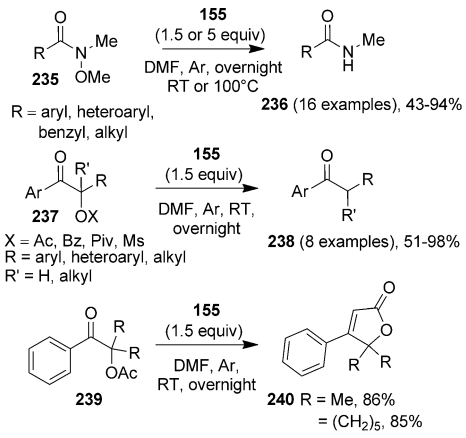
***Figure 12.*** Hybrid super-electron donors.

intermediate between those of the corresponding nonmixed systems (Table 4). Unlike the SET with **154**, which was performed at 110 °C, **216** and **217** could reduce aryl iodides to aryl radicals at room temperature. The two-electron donor **218** is a stable imidazole-derived species. The study also revealed that an excess of sodium hydride in the reaction mixture can help unstable donors, such as mono-bridged **194**, to complete the reduction reaction.[152] NaH prevents the electron donor from acting as a base itself. An excess of base can inhibit the protonation of the donor by competing for protons and, therefore, avoids the decrease in the concentration of the donor. As a consequence of their structural features, some donors such as **152c** and **218** are not affected by the absence of base.

The very powerful and easily synthesized two-electron donor **155** was evaluated in various organic reactions, including dehalogenation and desulfonylation reactions (Scheme 43). In situ generated **155** was able to reduce aryl iodides (**219**) and bromides to aryl anions at room temperature, as well as to reductively cleave phenylalkylsulfones (**221**) in excellent yields (96–99 %).[149] Deuterium-labeling studies revealed that the α-CH protons of the pyridinium ring are a major source of proton abstraction and strongly contributes to the quenching of aryl anions.[153] Bispyridinylidene **155** was also able to cleave the N–O bond of Weinreb amides **235**[154] or the C–O σ bond of acyloin derivatives **237**[155] by DET (Schemes 44 and 45). Although an electron-

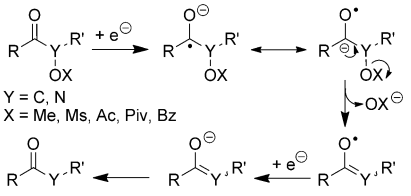



***Scheme 43.*** Reductive electron transfer promoted by **155**.




***Scheme 44.*** Reductive cleavage of N–O and C–O σ bonds. Piv = pivaloyl, Bz = benzoyl.



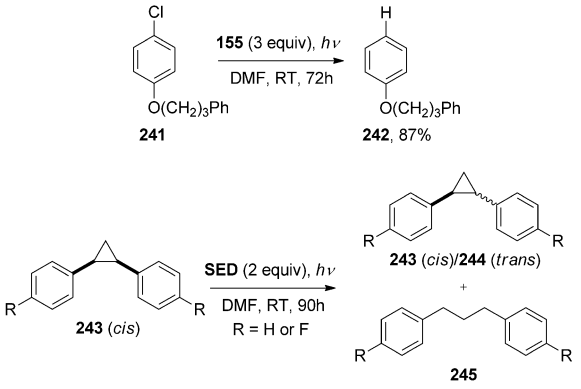

***Scheme 45.*** Proposed mechanism for the reduction of Weinreb amides and acyloins.

rich carbonyl group necessitated more forcing conditions (100 °C), the arene ring in **235** facilitated the reductive cleavage at room temperature. The α-ester acyloins **237** were successfully reduced to generate deoxy products **238** in good to excellent yields (51–98 %). Surprisingly, the acetate acyloin derivative **239** afforded the butenolide **240** instead, presumably because of the basic nature of **155** (protonation of the central C=C bond). A two-electron transfer was recently exploited for the cleavage of S–O and S–N bonds in triflate esters and triflamides to afford the corresponding alcohols and amines (Scheme 43).[156]

Unlike some reducing systems, such as $NiCl_2{\cdot}2H_2O$-Li-arene(cat.),[157] **155** selectively cleaved the S–O bond of aliphatic **223** and aryl triflates **225**, **227**, and **229** in excellent yields, with no evidence of C–O bond cleavage observed.[158] The reduction of triflamides **231** and **233**, usually done by means of $LiAlH_4$ or Red-Al, needed more vigorous reaction conditions.[156] The isomerization of the alkene in **227** was attributed to the basicity of **155**. Interestingly, selective cleavage of the triflate over the bromide group was observed for substrate **229**.

Following the same concept applied to diimidazolylidenes,[134] **155** and slow-forming *N*-methylbipyridinylidene **213** could also be produced in situ from the appropriate 4-DMAP salt. As soon as they were formed, they effected the reduction of aryl iodide **198** ($n = 3$) in a one-pot.[153] More recently, the combination of SEDs with photoexcitation allowed the reduction of more challenging arenes that were previously impossible with organic reducing agents.[159] Photoactivated SEDs **152c** and **155** were capable of reductive dechlorination (**241**→**242**) and, above all, of ET to ground-state benzene analogues (Scheme 46). Electron transfer to either the *cis* or the *trans* isomer of 1,2-diphenylcyclopropane **243** led to a mixture of *cis* (**243**) and *trans* (**244**) isomers,[160] as well as the ring-opened 1,3-diarylpropane **245**.[161] Donor **152c** was more effective in promoting the formation of **245** (35 % versus 6 % with **155**). Same experiments carried out on 4-chlorophenyl analogues (R = Cl) of **243** showed dechlorination to be a competitive reaction.

In summary, the efficient preparation of donor **155** in two steps and its excellent results in the reduction of various substrates under mild conditions makes it the most convenient SED prepared to date. Moreover, the recently developed one-pot procedure that avoids the isolation of very reactive organic electron donors and allows the use of unstable or slow-forming donors represents an attractive alternative.

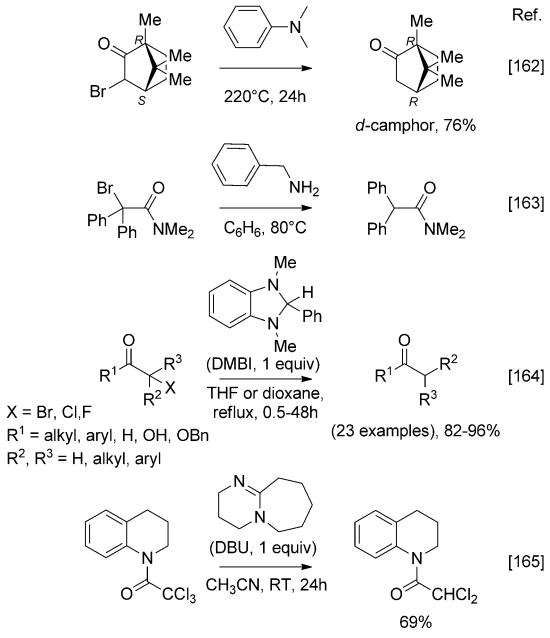



***Scheme 46.*** UV/SED-promoted electron transfer to benzene derivatives.

## 6. Amines

Although heteroatom-substituted alkenes are very important reducing agents, other molecules with nonbonding electrons are also capable of one-electron transfers. Organic amines are known to work as electron donors in SET reactions, but they usually require photochemical activation.[5] Few studies mention single-electron transfers from amines to partner substrates without photochemical assistance.

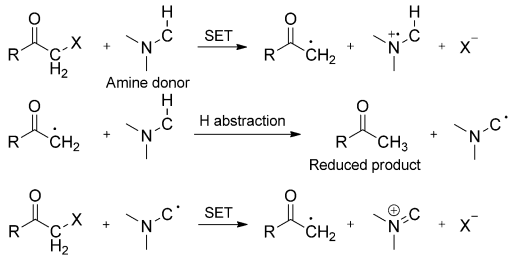
Early examples describe the reductive dehalogenation of α-halo carbonyl compounds by using *N*,*N*-dimethylaniline,[162] benzylamine,[163] 1,3-dimethyl-2-phenylbenzimidazoline (DMBI),[164] or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[165] as the reducing agents (Scheme 47). Light- and air-stable DMBI [$E_{1/2}(CH_3CN) = +0.33$ V versus SCE][166] led to the mild and chemoselective reduction of carbon–halogen bonds to carbon–hydrogen bonds without affecting the carbonyl groups.[164a] Acyclic or alicyclic α-halo ketones, aldehydes,




***Scheme 47.*** Amine-initiated reductive dehalogenation reactions.

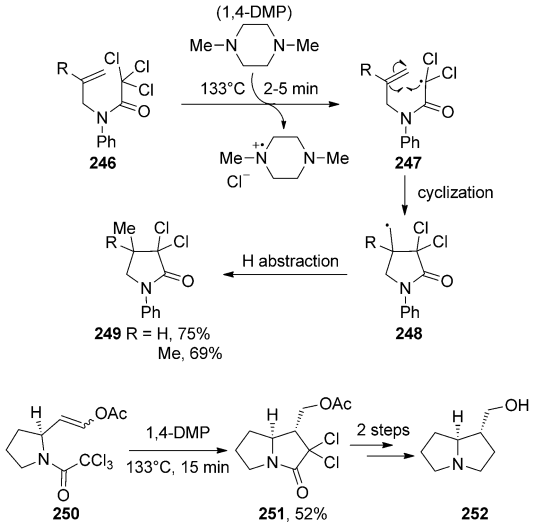
esters, lactones, and carboxylic acids were dehalogenated in almost quantitative yields at reflux temperature (Scheme 47). The reactivity decreases in the order Br > Cl > F (for the halide) and primary > secondary > tertiary (for substitution at the halogenated carbon atom).

At the end of the reaction, the imidazolium salt $DMBI^+X^-$ was recovered by simple filtration and could be reconverted into DMBI.[167] First postulated to be a direct $S_N2$ hydride transfer, the mechanism of the DMBI reduction was later shown to proceed through a radical chain process involving SET and hydrogen atom abstraction (Scheme 48).[164b]



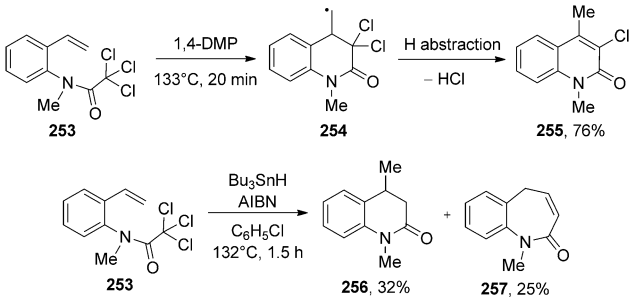

***Scheme 48.*** Reduction by a SET/hydrogen atom abstraction chain mechanism.

Ishibashi et al. demonstrated that the radical cyclization of various *N*-allyl and *N*-vinyl α,α,α-trichloroacetamides with olefins upon heating in 1,4-dimethylpiperazine (1,4-DMP) gave the corresponding γ-lactams in good yields (Scheme 49).[168] This amine reducing agent [$E_p$(30% v/v MeOH/$H_2O$) = + 0.89 V versus SCE][169] was an alternative to transition-metal catalysis[170] and was applied to the synthesis of (−)-trachelanthamidine (**252**), a pyrrolizidine alkaloid (Scheme 49).[171] The mechanism is proposed to proceed by a SET from the nitrogen atom of 1,4-DMP to the substrate **246**, followed by elimination of a chloride anion to give the dichloro-substituted radical **247**. A 5-*exo-trig* cyclization of **247** to the olefinic bond and a successive addition reaction of




***Scheme 49.*** Radical cyclization of *N*-allylic α,α,α-trichloroacetamides.

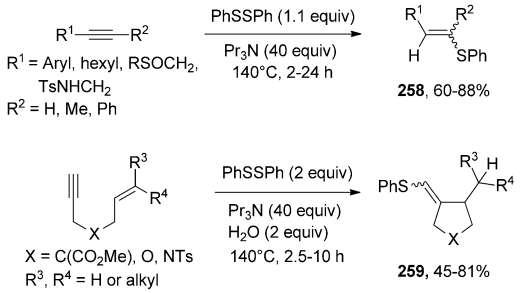
a hydrogen atom at the resulting terminal radical intermediates **248** give γ-lactam **249**. In the case of *o*-ethenyltrichloroacetanilides **253**, hydrogen abstraction by **254** was followed by elimination of hydrogen chloride to afford 6-*exo* cyclization product **255** (Scheme 50).[172] On the other hand, treatment of **253** under AIBN/$Bu_3SnH$ conditions gave a mixture of 6-*exo*




***Scheme 50.*** Radical cyclization of *o*-ethenyltrichloroacetanilides.

**256** and neophyl rearrangement products **257**. This difference in reactivity was explained by a higher concentration of the hydrogen atom source when using 1,4-DMP, thereby allowing the rapid reduction of radical **254** instead of further rearrangement. An activated trichloroacetamide group was necessary as the electron acceptor, as confirmed by the sluggish cyclization of α,α-dichloroacetamides ($NC(O)CHCl_2$) only affording 12–13% of the desired product.[168a]

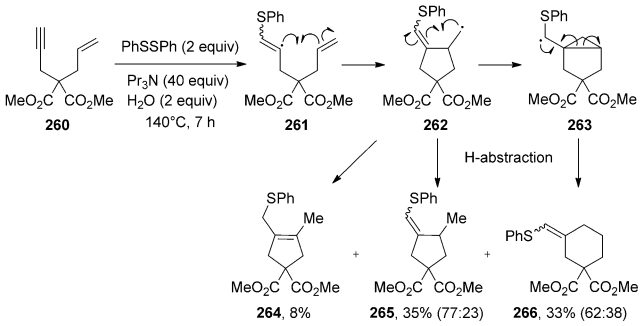
Amine-mediated SET to diphenyl disulfide could also be performed and allowed the hydrothiolation of alkynes (Scheme 51).[173] Tripropylamine [$E_p$(DMF) = + 0.95 V versus SCE][174] was used as the electron donor to cleave the




***Scheme 51.*** Reductive addition of a benzenethiyl radical to alkynes.

sulfur–sulfur bond.[175] The addition of the generated benzenethiyl radical PhS˙ to the terminal or internal alkynes and subsequent hydrogen abstraction gave the desired vinyl sulfides **258** as a mixture of *E* and *Z* isomers. The method was extended to the radical cyclization of eneyne derivatives, which yielded 5-*exo* products **259** (Scheme 51). Depending on the alkene substituents, rearrangement of the radical intermediate **262** can occur to afford the 6-*endo* product **266** through ring expansion of the cyclopropylcarbinyl radical **263** (Scheme 52). The addition of two equivalents of water




***Scheme 52.*** Mechanism of the amine-mediated radical cyclization of eneynes.

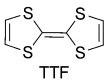
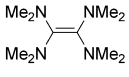
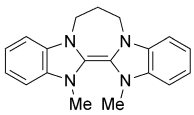
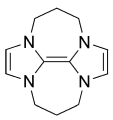
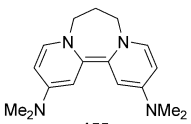
improved the yields of the 5-*exo* products **264** and **265**. Presumably, water accelerates the donation of the hydrogen atom to radical **262** and avoids its rearrangement.[168b,173]

In summary, single-electron transfer reactions initiated by organic amines lead to smooth radical cyclizations and reductive additions. Neither heavy metals nor photochemical conditions are required, although thermal activation is necessary. So far, this method has been limited to activated electron acceptors such as α-halo carbonyl compounds and diphenyl disulfide.

## 7. Conclusion and Outlook

The diversity of the chemistry and the astonishing recent advances suggest a great future for organic electron donors. As summarized in Table 5, two categories of neutral ground-state organic electron donors dominate the field: sulfur- and nitrogen-containing electron-rich olefins. These totally organic reducing agents are capable of spontaneous one- or two-electron transfer under mild and homogeneous conditions and promote effective carbon–carbon bond-formation reactions. By simple modulation of their structure and the reaction parameters, different ranges of redox potentials are obtained that allow a large choice of reactivity and selectivity

***Table 5:*** Principal characteristics of organic electron donors.

| Electron donor | ET | Redox potential (*vs* SCE) | Reduced bond | Promoted reaction |
|---|---|---|---|---|
|  TTF | 1 $e^-$ | +0.32 V, +0.71 V ($CH_3CN$) | Ar-$N_2^+$ $BF_4^-$ | radical cyclization/oxidative functionalization<br>radical translocation/oxidative functionalization |
|  TDAE | 1 or 2 $e^-$ | −0.78 V, −0.61 V ($CH_3CN$)<br>−0.62 V (DMF) | Ar-$N_2^+$ $BF_4^-$<br>$ArCH_2$-Cl<br>$ArCH_2$-Br<br>$ArCHBr_2$<br>$ArCCl_3$<br>C(O)CHR-Br<br>$CF_2$-Br<br>$CF_3$-I<br>$C(O)CF_2$-Cl | radical cyclization<br>radical addition-elimination<br>reductive coupling<br>di-/trifluoromethylation<br>benzylic substitution<br>$S_NAr$ |
|  **154** | 1 $e^-$ | −0.76 V, −0.82 V (DMF) | Ar-I | radical cyclization |
|  **152c** | 2 $e^-$ | −1.20 V (DMF) | Ar-I<br>Ar-Br<br>Ar-Cl<br>C-$SO_2$Ph<br>N-Ts | anionic cyclization<br>reduction of haloarenes and benzenes<br>reductive cleavage of sulfones and sulfonamides |
|  **155** | 2 $e^-$ | −1.24 V (DMF) | Ar-I<br>Ar-Cl<br>C-$SO_2$Ph<br>O-Tf<br>N-Ts<br>N-Tf<br>C(O)N-OMe<br>C(O)C-OX | anionic cyclization<br>reduction of haloarenes<br>reductive cleavage of sulfones, sulfonamides, triflate esters, triflamides, Weinreb amides, and acyloin derivatives |
| DMBI<br>1,4-DMP<br>$Pr_3N$ | 1 $e^-$ | +0.33 ($CH_3CN$)<br>+0.89 (30% v/v MeOH/$H_2O$)<br>+0.95 (DMF) | C(O)C-X<br>$NC(O)CCl_3$<br>PhS-SPh | reduction of α-halo carbonyl compounds<br>radical cyclization<br>hydrothiolation of alkynes |

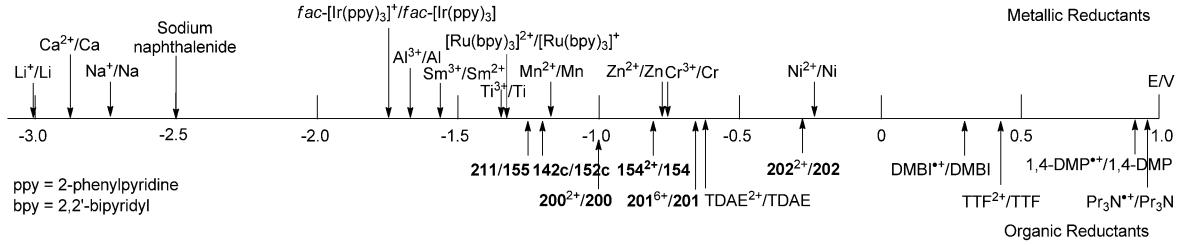



***Figure 13.*** Standard reduction potentials.

in the reduction of diverse organic substrates. Hence, according to the need, one can reduce diazonium, alkyl/aryl halides, or sulfones; generate radicals or anions as reactive species; and initiate nucleophile additions or oxidative cyclizations. As a result of limitations in terms of reactivity, tetrathiafulvalene derivatives have been neglected in favor of tetraazaalkenes. Difficult reductions, usually achieved by the means of metallic reductants, can be carried out by simple but powerful super-electron donors. Moreover, carbanions are intermediates of importance in many organic reactions. Donors such as TDAE or SED, which have the capacity for two-stage ET and that do not reduce ketones, represent a useful alternative to metallic and organometallic reagents (Figure 13). SEDs can even be generated in situ from the stable salt without any need to isolate the highly reactive enetetramine. Their final oxidized form is a water-soluble salt that can be easily removed from the reaction media. Thus, organic electron sources contribute to the development of sustainable reactions to help satisfy the ever-growing need for environmentally friendly processes.[176]

This Review underlines the fact that these organic reducing agents are not being sufficiently exploited, despite their synthetic potential and their tunability. There is great scope for the development of alternative and better reagents. Novel libraries of neutral organic reductants able to overcome current boundaries would be of great interest to organic and inorganic chemists working with electron donors. As highlighted in Figure 13, organic electron donors are currently concentrated in one region of redox potentials. Their reducing abilities limit the choice of reducible substrates. As a consequence of this restricted structural diversity, they are currently mainly used in intramolecular additions of aryl radicals to alkenes or intermolecular additions of carbanions to carbonyl derivatives. Broadening the scope of reduction potentials would enable chemists to choose one specifically tuned donor to target a particular reaction and react with a wider range of substrates. The generation of more stable and reactive nucleophiles (radical or anion) would allow additions to a larger variety of electrophiles, such as Michael acceptors, unactivated alkenes, or alkynes, or substitution reactions. Greater selectivity would be possible, thereby decreasing the need for protecting groups. Challenging these organic donors with other reducing systems under the same experimental conditions would allow a better view of their prowess. Modulation of the kinetics of electron transfer would permit new reactions, including intermolecular ones. In terms of the mechanism, a broader diversity of structures should also help elucidate the factors governing single- or double-electron transfer, as well as their reducing powers and reactivities. Finally, these reductants have high molecular weights, which mean that significant quantities are required to perform SET reductions. Catalytic versions with high turnover numbers would be of great interest and would extend their usefulness. Organic donors able to control the diastereoselectivity of the reaction or to induce enantioselectivity should also be considered. In this context, the recent development of organic dyes as visible-light photoredox catalysts and their combination to asymmetric organocatalysis is an area of great inspiration and promise.[26,177]

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