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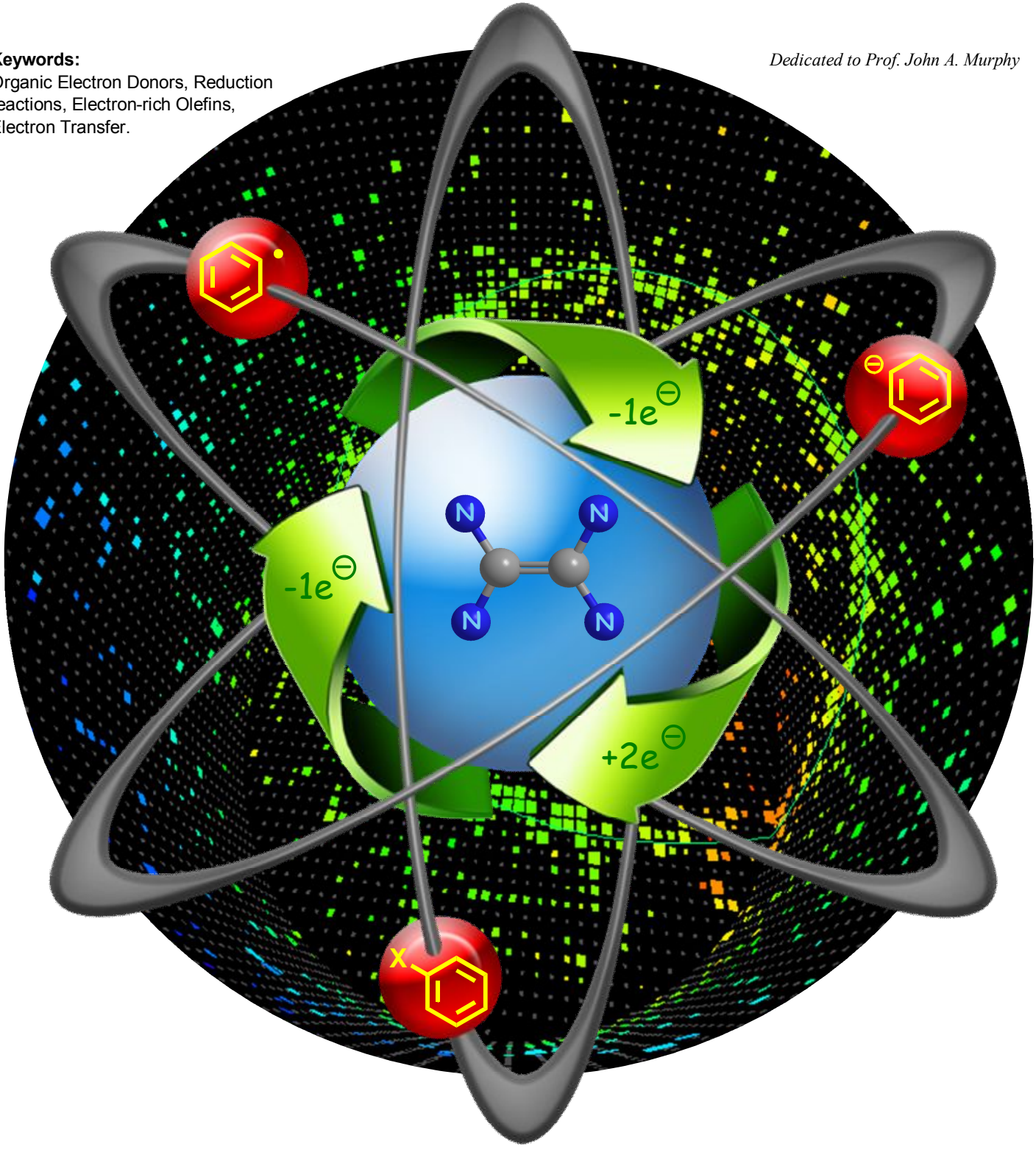
Keywords:
Organic Electron Donors, Reduction reactions, Electron-rich Olefins, Electron Transfer.

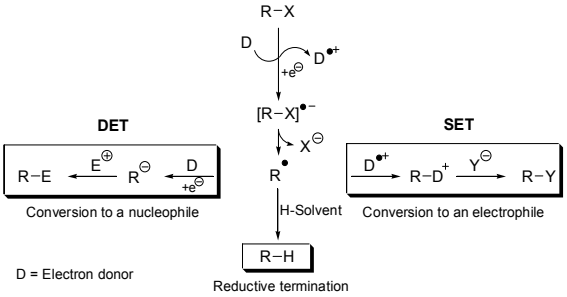
Dedicated to Prof. John A. Murphy



One-electron reduction is commonly used in organic chemistry to achieve radical formation via the stepwise transfer of one or two electrons from a donor to an organic substrate. Beyond metallic reagents, Single-Electron Transfer reducers based on neutral organic molecules have emerged as an attractive novel source of reducing electrons. The past twenty years have thus seen the blossom of a particular class of organic reducing agents, the electron-rich olefins, and the multiplication of their applications in organic synthesis. These powerful neutral ground-state organic electron donors have since showed several significant advantages in the reduction of numerous organic substrates. This review gives an overview of the different types of organic donors and of their specific characteristics in organic transformations.

1. Introduction

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 forty years.[1] Molecular electrochemistry has since brought its share of discoveries, recognition (Nobel Prizes in Chemistry 1983, Taube and 1992, Marcus) and pharmaceutical or industrial applications. New synthetic methodologies involving radical intermediates have built up the chemist's toolbox with reactions such as substitutions, additions, cyclizations, polymerizations or cascade processes leading to 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 transfer (ET) and the bond dissociation can take place either simultaneously or as two successive steps. Reductive ET-initiated bond cleavage leads to the dissociation of a large variety of chemical bonds including C-C, 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 $R^{\bullet}$. Reactivity depends on the activation barrier of the initial ET, itself correlated with the stability of the radical anion. In radical-substitution, $R^{\bullet}$ 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 giving the anion R^{-} which acts as a nucleophile (generated overall by double-electron transfer (DET)).



Scheme 1. Radical substitutions *via* single- (SET) or 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 or 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 reducers providing clean carbon-carbon bond formation by free radical chemistry stems from the well-known problems encountered with inorganic SET reducers and with 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 under 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 (ERO) are certainly the most representative class of multistage organic redox systems.[7] Since the sixties, ERO 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 the understanding of their equilibrium, so called Wanzlick equilibrium, with the corresponding diaminocarbenes (Scheme 2).[9] Dimerization of carbenes is most likely achieved *via* a proton-catalyzed mechanism but is thermodynamically unfavourable for unsaturated and/or sterically hindered carbenes. ERO are used as reducing agents,[10] nucleophiles,[11] precursors of carbene-ligands in metal complexes[12] or 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 twenty years have seen the blossom of this particular class of organic reducers with the multiplication of attracting applications in organic synthesis. These powerful *neutral ground-state organic* electron donors offer several

significant advantages in the SET reduction of organic substrates, as they:

- Undergo spontaneous sequential loss of one or two electrons and thus upon electron transfer, generate *radicals* or *anions* including aryl anions.
- Present a large range of redox potentials and can be finely tuned. Their reactivity can therefore be modulated by the appropriate structural modification.
- Are highly selective and tolerant to other functional groups (nitro, carbonyl, ester, cyano…).
- Are available as pure organic liquid or solid and can be used in appropriate quantities.
- Operate under mild conditions compared to highly aggressive metal-based reducers and are soluble in organic solvents, hence shortening the induction period.
- Avoid the use of expensive metal derivatives as well as the recycling of metal residues causing environmental and economic problems.
- Can be easily removed from the media *via* precipitation of their salt form and can be regenerated. They can also be attached to solid supports.
- Have wider applicability than photochemically-assisted reactions.
- 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 reducer's concentrations.

We review here the different types of organic single-electron transfer 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 methodologies. Our aim is to provide chemists with an exhaustive guide to the properties and capabilities of organic reducers in organic chemistry. We hope it will emphasize the milder and resourceful alternative offered by these electron sources to the use of inorganic reductants and encourage other researchers to utilize them in radical chemistry.

Julie Broggi obtained her Ph.D. in nucleoside chemistry in 2009 in the group of Prof. L.A. Agrofoglio at the University of Orléans. After a postdoctoral position in the group of Prof. S.P. Nolan at St Andrews University, she joined the "Laboratoire de Pharmacochimie Radicalaire" at the "Institut de Chimie Radicalaire - ICR" of Marseille as Assistant Professor. Her research interests focus on the applications of electron donors in the synthesis of pharmacologically interesting molecules.

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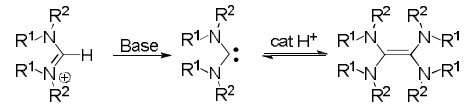
Patrice Vanelle is Professor of Organic Chemistry and Dean of the Faculty of Pharmacy of Marseille, University of Aix-Marseille. He is the Director of the "Laboratoire de Pharmacochimie Radicalaire" at the "Institut de Chimie Radicalaire - ICR". His research interests focus on electron transfer reactions in heterocyclic and quinonic series that can lead to new potentially bioactive compounds.



Scheme 2. Carbene/Dimer equilibrium.

2. Tetrathiafulvalenes TTF

2.1. Properties

Since the early 1970s, tetrathiafulvalene (TTF)[16] and its derivatives are recognized as strong π-electron organic donors of great interest, certainly owing to the following features: (1) TTF is a planar nonaromatic 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 *vs* 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 positive charge and radical by the lone pairs of sulfur atoms, greatly assist the electron donation. Likewise, the considerable aromatic stabilization of extended quinonoid analogues enhances their reduction potentials (Figure 1: For R,R = –(CH=CH)$_2$– [E_p (CH_3CN) = - 0.38 V *vs* 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 in 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 present a wide range of electronic and magnetic properties. Numerous TTF-like donors have been synthesized and extensively used to form charge-transfer complexes in the development of organic conductors,[14,18] as well as building blocks in supramolecular chemistry.[19] In this regard, their synthesis, structural aspects and properties have been widely reviewed and will not be reconsidered herein.[16]

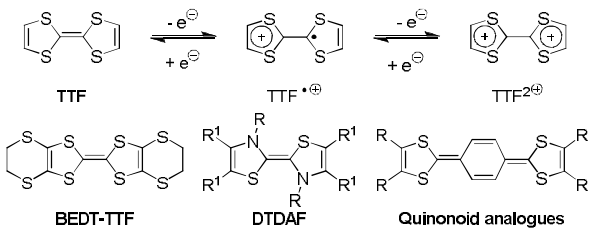
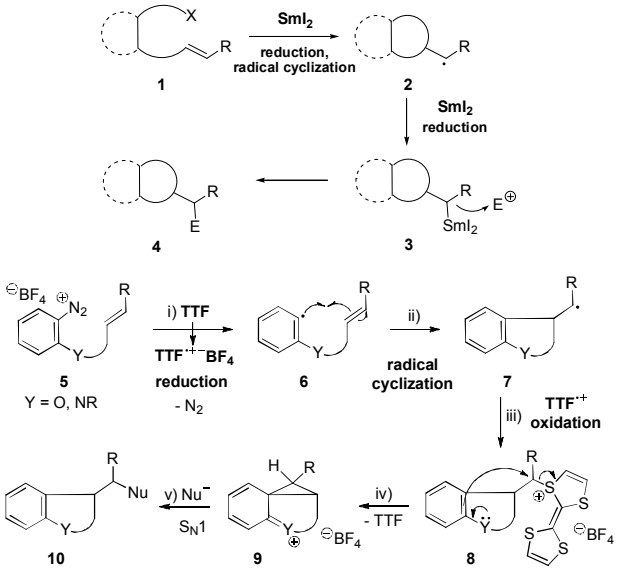


Figure 1. TTF and related compounds.
(BEDT-TTF: Bis(ethylenedithio)tetrathiafulvalene; DTDAF: Dithiadiazafulvalenes)

2.2. Reactivity of TTF

2.2.1. Concept

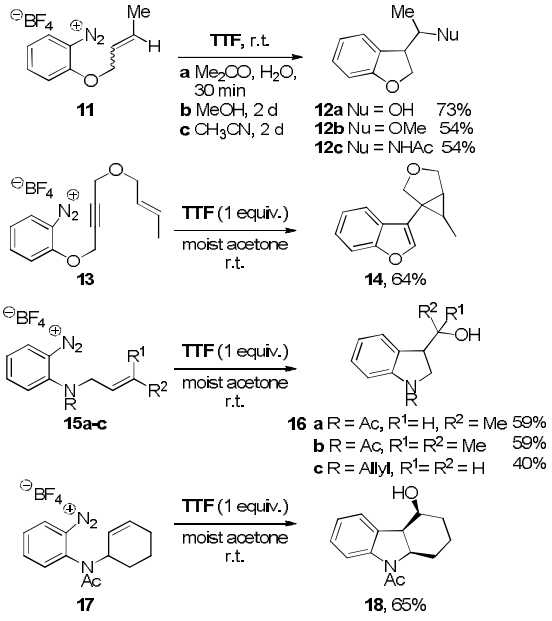
The use of TTF derivatives as reducers in organic chemistry has been only examined by Murphy and co-workers, despite the fact that they provide an effective and mild means to synthesize polycyclic compounds.[20] TTF acts as a reasonable single-electron donating agent in one-pot multi-step transformations linking radical cyclization and polar termination steps. In contrast to traditional tandem reactions induced by samarium iodide SmI_2,[21] Murphy showed that radical cyclizations promoted by TTF were terminated by S_N1-type nucleophilic substitution at the new exocyclic center instead of further reduction (Scheme 3). Arenediazonium salts were chosen as partner reagents since their one-electron reduction potential [E_p (CH_3CN) ≈ - 0.2 V *vs* SCE][22] is close to that of TTF.[23] C-C or C-heteroatom bond formation *via* radical processes on arenediazonium salts generally involves the use of inorganic reducers such as copper (*e.g.* Sandmeyer, 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, is the catalytic reduction of aryl diazonium salts by photoinduced-electron transfer (PET) using $[Ru(bpy)_3]Cl_2$ or organic dyes as photoredox catalysts.[26] The TTF-promoted sequence, named as "radical-polar crossover reaction",[27] features (i) aryl radical generation *via* electron transfer from TTF to diazonium salt **5** and loss of dinitrogen, (ii) cyclization of aryl radical **6** onto an alkene, (iii) coupling of carbon-centered alkyl radical **7** with the radical-cation $TTF^{\bullet+}$ through sulfur[28] to form sulfonium salt **8**, (iv) Ar-Y-assisted loss of TTF to afford cationic intermediate **9**, and (v) functionalization through substitution by intra- or intermolecular nucleophiles that attack **9** and terminate the reaction.



Scheme 3. SmI_2 *vs* TTF-mediated radical-polar crossover reaction.

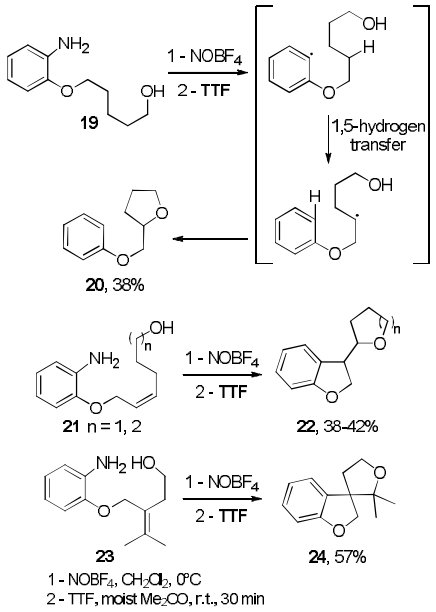
2.2.2. Scope

Upon treatment in the appropriate solvent, diazonium salt **11** was converted 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 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, leading smoothly to the tetracycle **14**. 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 in **15b** gave a complex mixture due to competing radical cyclization onto the benzoyl group.[31] Lastly, cyclization of **17** led to tricyclic alcohol **18** as a single diastereomer (65%).[30] The major drawback of this methodology was the competitive direct trapping of the aryl radical intermediate **6** by the sulfur of $TTF^{\bullet+}$ that occurred in the case of slow cyclization 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**, resulting in an astonishing selectivity for unimolecular reactions. Mechanistic study also evidenced 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, when the TTF moiety was attached to a primary carbon (R = H) no substitution was observed[33] unless the neighboring group was sufficiently electron-donor to stabilize the primary carbocation. Hence, in **15c** the *ortho*-amino group 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 trappings of cationic intermediate **9** by intramolecular nucleophiles were then investigated, leading to expected poly- (**20**, **22**) and spiro-cyclic (**24**) compounds (Scheme 5).[34] Due to the instability of some diazonium intermediates, 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 an hydrogen atom transfer (radical translocation)[35] prior to coupling with $TTF^{\bullet+}$ and trapping by the internal nucleophile.

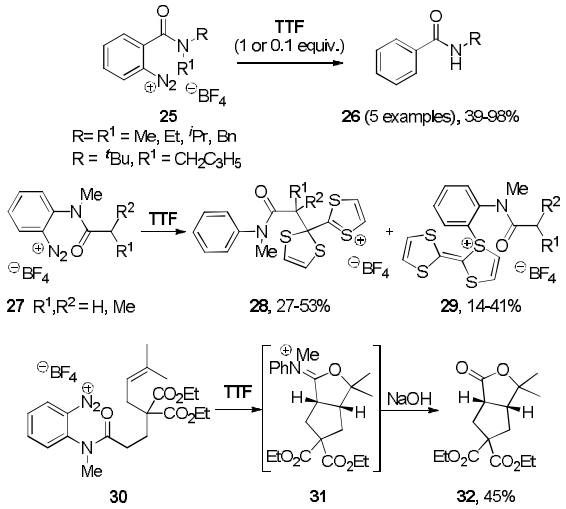


Scheme 4. Scope of TTF reactivity with diazonium salts.

Murphy further explored the combination of radical-polar crossover chemistry with radical translocation (Scheme 6). TTF could initiate translocation reactions but the kinetic of hydrogen atom abstraction and the termination of the reaction were highly dependent on the substitution pattern of the translocated radical.[36] Hence, TTF-generated aryl radicals rapidly and efficiently underwent tandem translocation/functionalization sequences, resulting in: (a) oxidized products, like in the oxidative monodealkylation of *N*,*N*-disubstituted amides **25**, when the intramolecular H-abstraction leads to *nucleophilic* alkyl radicals or (b) an unprecedented carbon-carbon bond formation (**28**) between *electrophilic* translocated radicals and the internal carbon 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 recombined products. With subtrate **30**, the $TTF^{\bullet+}$ trapping by C-C bond formation was sufficiently slow to allow its cyclization/oxidation to iminium salt **31** in moderate yield (45% after hydrolysis).

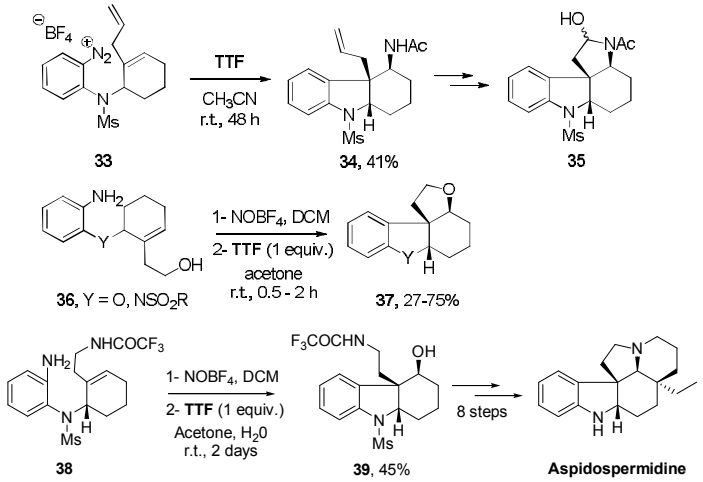


Scheme 5. Termination of radical-polar reactions by internal nucleophiles.



Scheme 6. Sequential radical translocation and functionalization.

Finally, the TTF-promoted radical-polar crossover chemistry was successfully applied as key step in the synthesis of tetracyclic structures,[37] notably the 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

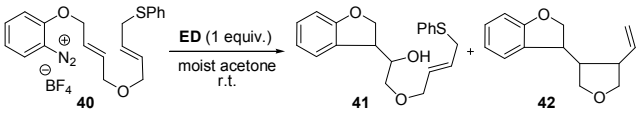
Different TTF-like donors including dithiadiazafulvalenes (DTDAF) were compared to test if the competitive interception of $TTF^{\bullet+}$ could be avoided (Table 1).[39] In DTDAF, two of the sulfur atoms are replaced by nitrogen which changes the electron density of the molecule and considerably increases their donor ability.[16b] DTDAF can reduce nitro groups like 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 at trapping the carbon radical (**7**) than $TTF^{\bullet+}$ (only 8% of trapping product **41** *vs* 19% with TTF), DTDAF **44** and **45** allowed predominant bicyclization to **42** since the *N*-substituents retarded the approach to sulfur. The decrease in direct trapping was therefore proportional to the increasing steric crowding around the sulfur. These results were encouraging for syntheses featuring slow radical cyclization before ionic termination. Although slow coupling rates of $DTDAF^{\bullet+}$ were indeed observed, the reaction of DTDAF with other diazonium salts afforded unexpected amide products, as **51**, resulting from the cleavage of the DTDAF ring system (Scheme 8). This particular pathway was attributed to the great reactivity of the nitrogen lone-pair.[39]

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

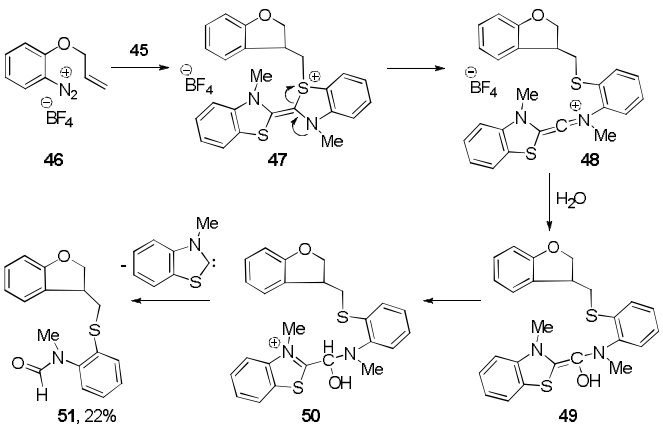
Despite performing one-pot radical and ionic chemistry under mild conditions, and providing an elegant stereoselective access to polycyclic compounds, TTF-promoted chemistry was restricted to few aryl diazonium substrates and suffered from many side-reactions. The premature trapping of the aryl radical was a serious

handicap in reactions with a slow cyclization step. Furthermore, TTF could achieve the easier step of reducing arenediazonium salts to aryl radicals, but not the more difficult step of reducing aryl radicals to aryl anions. DTDAF donors, though 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.

Table 1. Relative yields of trapping **41** and cyclization **42** products.



Electron Donor (ED)	41	42
TTF	19%	48%
43	8%	67%
44	0%	72%
45	0%	73%

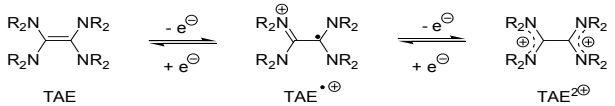


Scheme 8. Reaction of dithiadiazafulvalene **45**.

3. Aliphatic Tetraaminoethylenes TAE

3.1. Properties

Tetraaminoethylenes (TAE)[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 of the nitrogens which is a driving force for the electron donation (Scheme 9). These differences give them very specific physicochemical properties and make TAE considerably more powerful donors than TTF. According to the nature of the electrophile and the TAE, they can be used as strong nucleophile, as base able to donate π-electrons, or as 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, the 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 reported the synthesis of biimidazolidinylidene derivatives (Figure 2).[45] TAE 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 TAE consist in the elimination of acids HX from aminals by heating, acid catalysis or treatment with strong bases (Scheme 11).[10, 48] Alternatively, cyclic analogs can be obtained through the reaction of diamines with ethyl orthoformate.[45] With the exception of the liquid TDAE, TAE are usually solids.

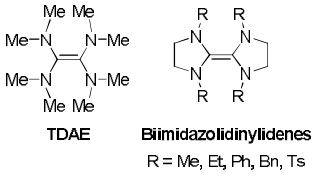


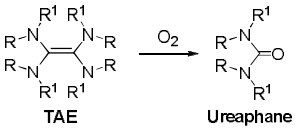
Figure 2. Aliphatic tetraaminoethylenes.

3.2. Reactivity of biimidazolidinylidenes

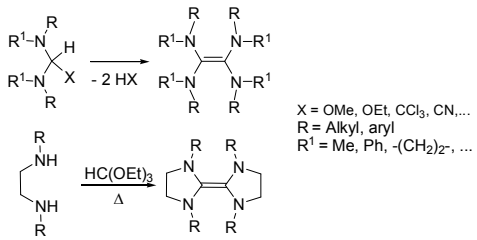
Research on enetetramines containing an imidazolidin-2-ylidene ring mainly refers to their reactivity through protonation, C=C-bond cleavage or as nucleophile,[8-13,49] as well as their role in the Wanzlick equilibrium.[9] For *N*-heterocyclic carbenes (NHC) with a saturated ring, the steric bulk of 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*-alkyls (Me, Et, iPr) readily dimerize, while benzyl groups lead to thermal instability of the enetetramine and bulky mesityl or *t*Bu to 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 r.t., in high yields and under mild homogeneous conditions. Cyclic TAE were also effective in the reduction of peroxides, thionyl chlorides or sulfuryl chlorides.[51] As well, persistent metal-centred radicals $M^{\bullet}R_3$ (M = Si, Ge or Sn) were

prepared from 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.



Scheme 10. Reaction with O_2.

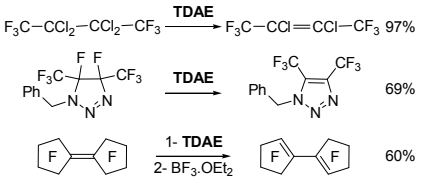


Scheme 11. General preparation of TAE.

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 *vs* SCE].[53] In DMF, only one two-electron reversible wave is observed at -0.62 V. As pointed out by the superposition 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-analog of TDAE can also reduce sulfonyl and nitro groups.[56] Due to its strong reduction 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 the reductive cleavage of carbon-halogen bonds and the generation of the corresponding carbanion *via* 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 was the first to use TDAE as SET reducing agent for selective dehalogenations in polyhalogenated hydrocarbons, conducting to the replacement of a single halogen atom with a hydrogen atom or the removal of two vicinal halogens to form olefins (Scheme 12).[57c,d] Double-electron transfer pathway of the reduction was already evidenced. This reactivity was later applied to the synthesis of fluorinated dienes or to their polymerization.[58] Nevertheless, it is only three decades later that this ability to activate C-X bonds started to be attentively investigated in organic synthesis and applied to prepare compounds of biological interest. Intermolecular reactions promoted by TDAE-initiated reactive species have been particularly studied.



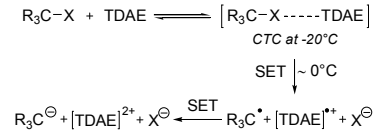
Scheme 12. Reductive dehalogenations.

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 leading, for instance, to the formation of CF_3TMS from trimethylsilyl chloride TMSCl (Eq. (1)).[59]

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

Since 1997, Médebielle and Dolbier have exploited this reactivity in several nucleophilic di- and tri-fluoromethylation reactions on various electrophiles.[60] Many fluorinated analogs of biological compounds exhibit 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, demonstrating clearly that TDAE has been oxidized.

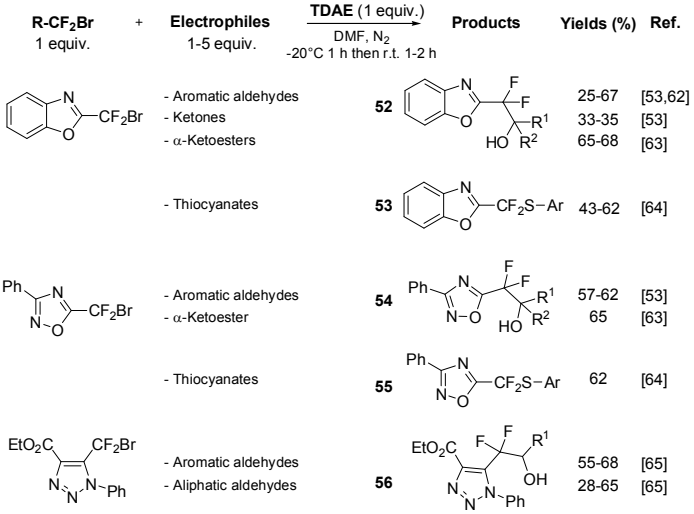


Scheme 13. Proposed mechanism for TDAE-initiated carbon-halogen bond reductions.

Hence, series of 2-(difluoromethyl)benzoxazole alcohols **52** were obtained by reaction of 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 reached with ketones (33-35%), probably due to steric hindrance and their enolizable character, while activated α-ketoester reacted smoothly (65-68%). Additionally, the CF_2 anion was trapped by aryl thiocyanates forming new series of $ArSCF_2R$ derivatives **53** (43-62%).[64] Of note, 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 using electron-rich dihydrofuran **61** as electrophile (Scheme 15).[53] The intermediate radical **58** was trapped by **61** affording radical **59** that triggers bromine atom-transfer 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 chloro-difluoromethyl counterpart failed due to its higher reduction potential [E_p (DMF, SCE) = -1.66 V *vs* -1.36 V for Br-CF_2].



Scheme 14. TDAE-mediated difluoromethylation.

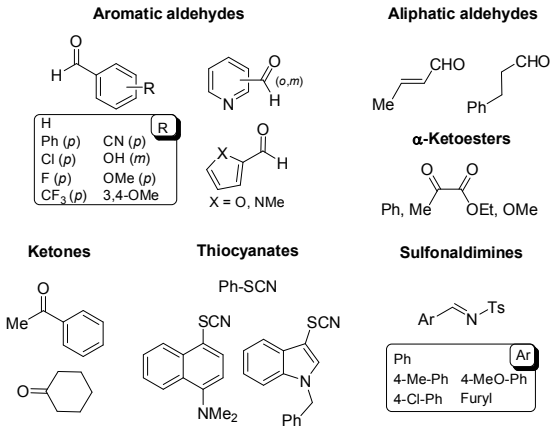
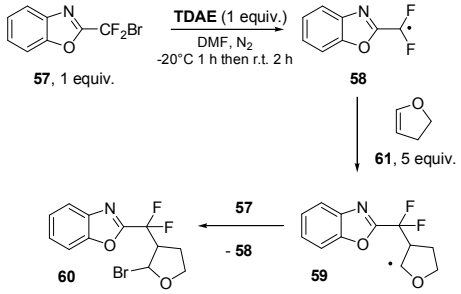


Figure 3. Classes of electrophiles used in difluoromethylation reactions (Schemes 14 and 17).

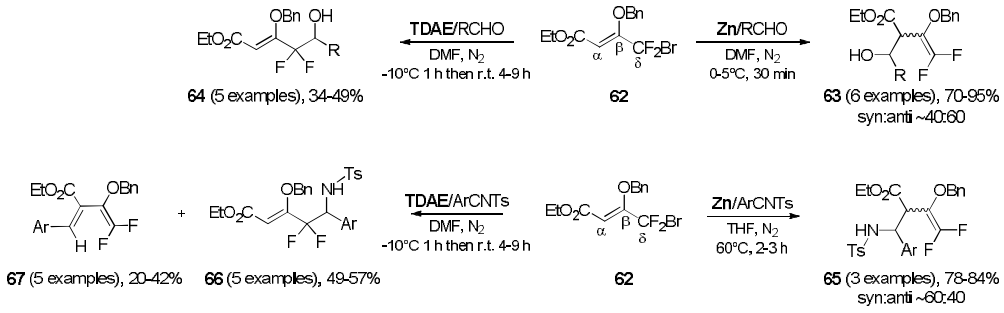
Other bromo-heterocycles such as 1,2,4-oxadiazoles[53,63,64] or 1,2,3-triazoles[65] were successfully reduced by TDAE, leading to the synthesis of alcohols **54**/**56** or thioether **55** *gem*-difluorinated derivatives upon coupling with the appropriate electrophiles (Scheme 14, Figure 3). Cyclic 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 mass balance of reactions usually accounted for the formation of the hydrogenolysis products R-CF_2H resulting from the protonation of the anion.



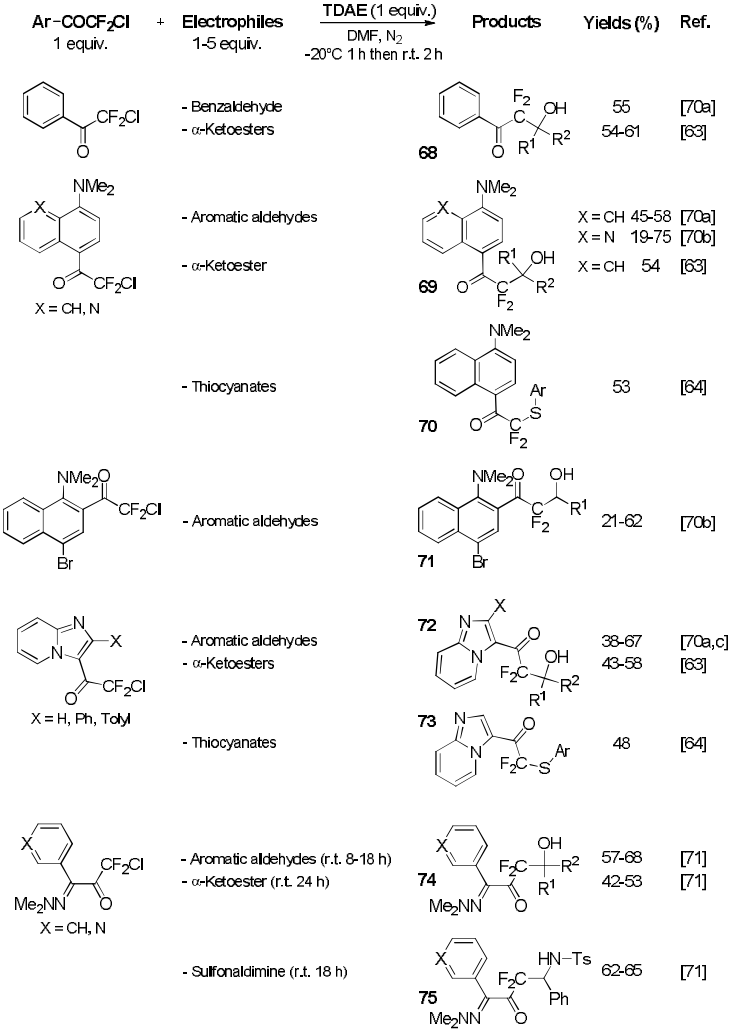
Scheme 15. TDAE-promoted radical addition.

In 2004, Zhu and Peng reported the regioselective control of the addition mode (α or γ) through the choice of reducer in the reduction of bromo-CF_2 benzyloxyacrylate **62** (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, while 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] Kinetic α-product **65** was also formed but decomposed into α-difluorovinyl acrylate **67** via loss of the arenesulfonamide.

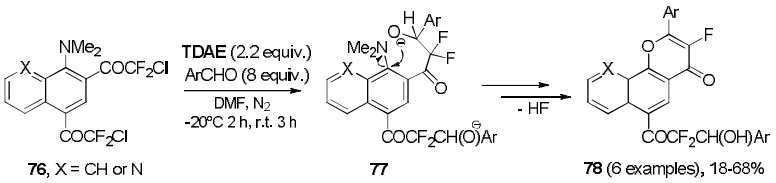
The TDAE-methodology, milder than the classic Reformatsky reaction, was successfully extended to generate stable α,α-difluoroacetyl anions from chloro-ketones. Addition to aldehydes, [70] α-ketoesters[63] and thiocyanates[64] led to hydroxy- (**68-69**, **71-72**) and thioether (**70, 73**) α,α-difluoroketones,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



Scheme 16. TDAE *vs* Zinc-mediated acrylate reductions.



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



Scheme 18. TDAE-initiated synthesis of tricyclic naphthoflavones.

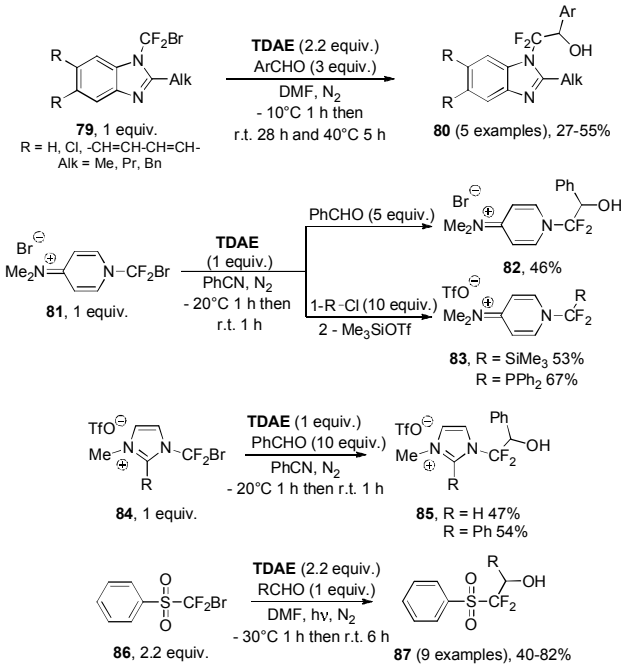
Surprisingly, the presence of two activating α,α-difluoroketone moieties on **76** led to a different outcome, namely the synthesis in a one-pot process of new fluorinated tricyclic naphthoflavone analogs **78** (Scheme 18).[72] The proposed mechanism consists of a prior TDAE-promoted aldolization followed 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 a H-F elimination, yielding the fused derivatives **78**.

Reductions of CF_2Br groups bound to heteroatoms (N or S) were also described albeit more severe conditions were sometimes required (Scheme 19). Condensations of benzimidazoles **79**,[73] 4-dimethylamino pyridinium **81**,[74] 1-methyl-imidazoliums **84**[74] or phenyl sulfones **86**[75] with aldehydes led to the corresponding secondary alcohols in moderate yields. Chlorodiphenyl phosphine and chlorotrimethylsilane were also able to trap the anion intermediate of **81**, yielding **83**. Photoinduction was necessary to enhance the electron transfer from photoexcited TDAE to sulfone **86**

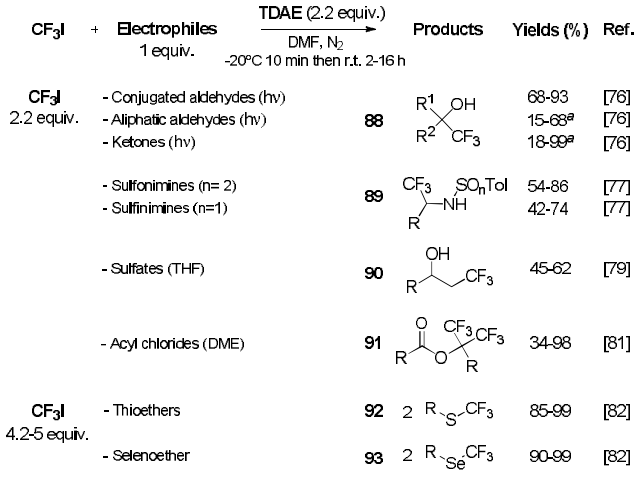
Along with the generation of stable RCF_2 anions, Médebielle and Dolbier also reported the *in situ* preparation of the CF_3 anion and its addition to series of electrophiles. Compared to typical trifluoromethylating agents such as CF_3TMS, the trifluoromethyl iodide CF_3I represents a ready and inexpensive source of the unstable CF_3^-. 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 carbonyls had to be carried out under light irradiation to radically improve alcohol **88** yields (52-99%).[76] 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 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. Notice that carbanion attacks on *aliphatic* aldehydes using the TDAE methodology have rarely been reported.[65,76] Addition to sulfonimines and diastereoselective addition to enantiopure sulfinimines conducted 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. Diastereoselectivities of the *N*-tolylsulfinimine reaction, while good (85:15), fell short of those observed by Prakash and co.[78] The TDAE/CF_3I reagent was also tested in the regioselective addition of CF_3^- to vicinal diol cyclic sulfates (Scheme 20).[79] Formation of trifluoro-alkanols **90** (45-62%) was limited by the competitive ring-opening reaction of the sulfates with the iodide ion. The stereospecificity of the process was well demonstrated with the incorporation of the CF_3 group on the (S)-isomer of the "R^1 = Me" sulfate in 43% yield and ee(S) >99.5%. Although particularly interesting as 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, using quasi-stoichiometric amounts of TDAE/CF_3I reagent, was remarkably clean and chemoselective.[81] It was unfortunately followed by an acylation of the resultant alcoholate consuming half of the acyl chloride to form the ester adduct **91**. In contrast, trifluoromethyl thio- **92** and selenoethers **93** were efficiently and economically prepared using both halves of aryl and alkyl disulfides or diselenides. [82] It is important to underline here the productive use of CF_3I in two different reactions, one *via* anionic attack on the initial substrate and one by $S_{RN}1$ mechanism with the thiol-/selenoate coproduct, both leading to the same desired products **92-93**. Whereas competitive reduction of disulfides to thiolate anions was excluded in this latter case considering the faster DET to CF_3I,[82] reduction of bis(trifluoromethyl) disulfide **94** could yet be accomplished with TDAE and allowed the quantitative formation of the $TDAE^{2+}2SCF_3^-$ salt, stable under inert atmosphere (Scheme 21).[83] Trifluoromethanethiolate **95** has the same reduction potential

as TDAE and was used as anionic source in substitution reactions with activated halogeno-aromatics and benzyl halides, generating the corresponding trifluoromethylthio derivatives in excellent yields.



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



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

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

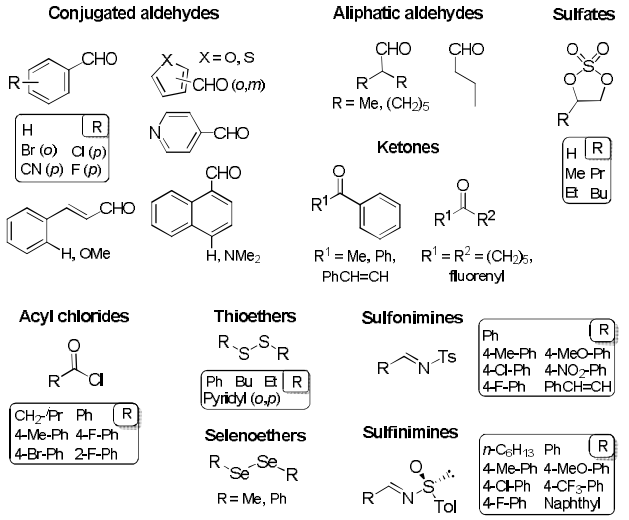
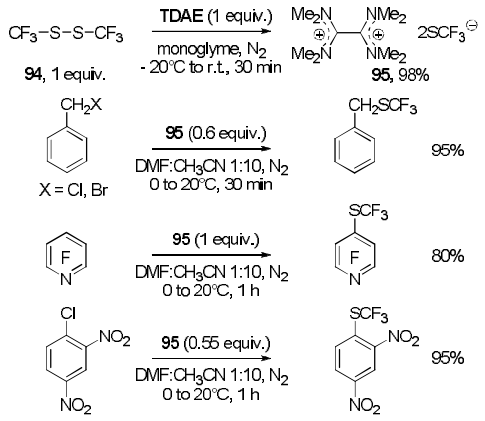


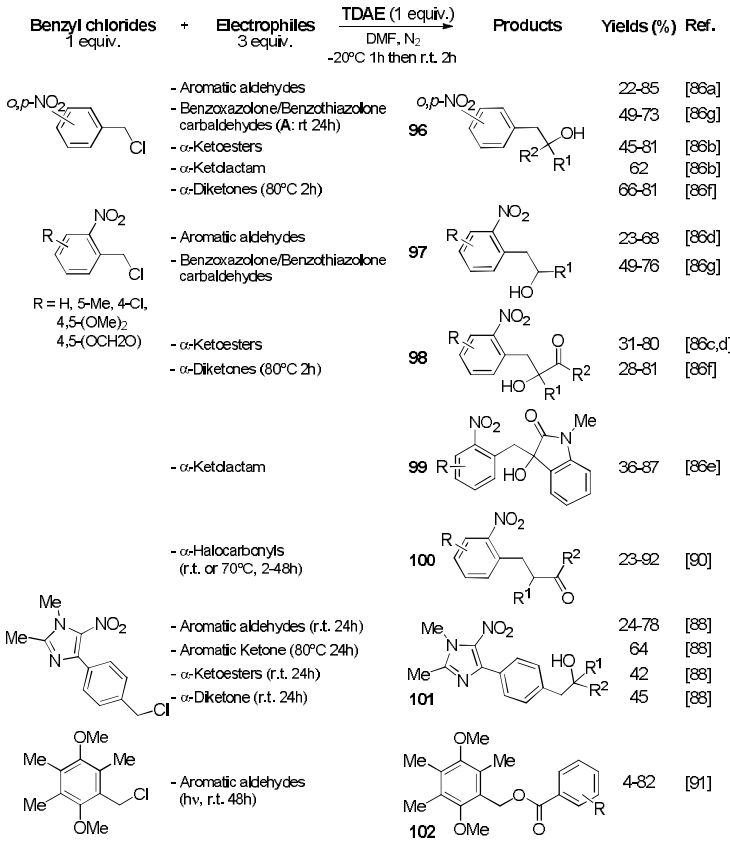
Figure 4. Classes of electrophiles used in trifluoromethylation reactions (Scheme 20).



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

3.3.2. Benzylic Addition

With the aim of developing original mono- or dielectronic transfer processes applied to medicinal chemistry,[85] Vanelle and coworkers dedicated a major part of their work to the study of TDAE-mediated intermolecular reactions with halomethyl substrates. It was demonstrated that TDAE can generate *in situ* stable *o*- and *p*-nitrobenzyl anions able to react on diverse electrophiles (Scheme 22) such as aromatic aldehydes, α-ketoesters, ketomalonates, α-ketolactams and diketones (Figure 5).[86] 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 r.t 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 on the ester moieties.



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

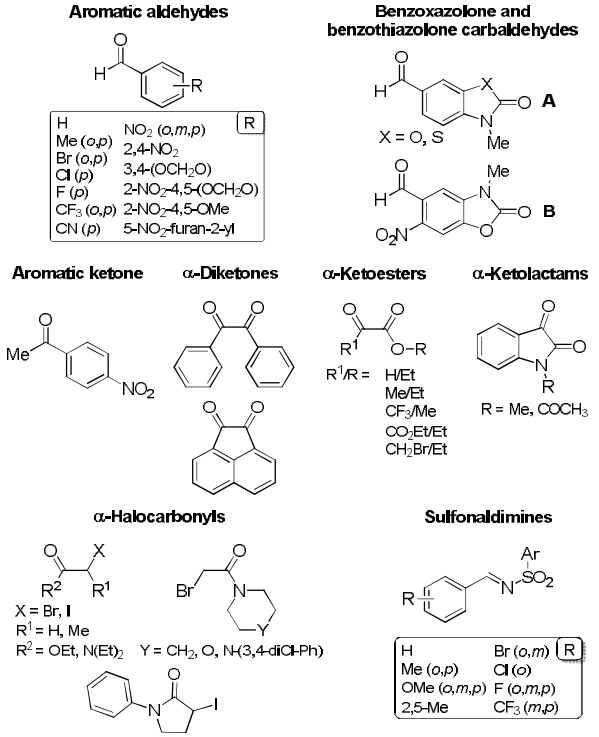
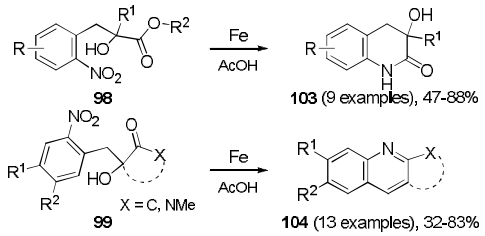


Figure 5. Classes of electrophiles reacted with halomethyl substrates (Scheme 22, 24, 26 and 27).

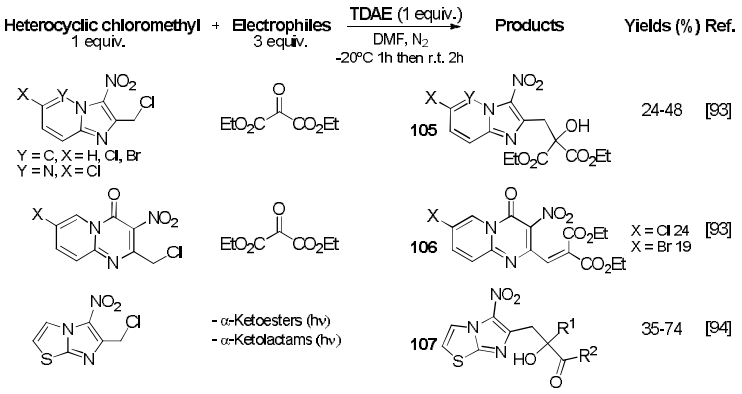
Their comprehensive study of the reducing power of TDAE revealed that an electron-withdrawing group (*e.g.* NO_2) is required on the benzyl substrate to reductively cleave the halogen and stabilize the anion, constituting the major drawback of this strategy. Alternatively, the key nitro group can be moved away from the C_{sp3}-Cl bond when introducing an imidazole on the *para*-position of benzyl chloride.[88] Highly functionalized 5-nitro-1*H*-imidazoles **101** were thus synthesized as potential anti-infectious agents by applying the previously described procedure albeit a longer reaction time (24h) 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. When dialdehydes were used as electrophiles, the double addition diol products were obtained (43-82%) 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 (24h with the 4-nitroacetophenone for 40% yield)[86d] or higher temperature (80°C with diketones).[86f] Of note, 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 *via* one-pot reduction-cyclization and/or double dehydration reactions (Scheme 23).[86c,e,f] Nucleophile substitutions were also explored using electrophiles containing a C_{sp3}-halogen bond (Scheme 22, Figure 5).[90] Reaction of *o*-nitrobenzyl chlorides with various α-haloesters and α-haloamides, less reducible than the benzyl chlorides but sufficiently electrophile, led to the expected substitution products **100** in moderate to high yields (23-92%). Yields decreased with less labile bromo-carbonyls and with the steric hindrance of the alkyl groups (R^1, Figure 5). No reaction was observed with chloro- (X = Cl), β-bromo- (X = CH_2Br) or sterically hindered (R^1 = Et) α-bromo-carbonyl moieties. Interestingly, when dimethoxybenzyl mono- or dichlorides were used under light irradiation, the aldehyde played the role of electron acceptor affording unexpected mono- **102** and diester adducts (Scheme 22).[91] TDAE plays here the role of amine PET-donor.[92] It was hypothesized that the initial light-catalyzed ET from TDAE to the aldehyde led to a ketyl radical-anion, followed by an oxidation step yielding an aromatic carboxylate anion which substituted the benzyl chloride.



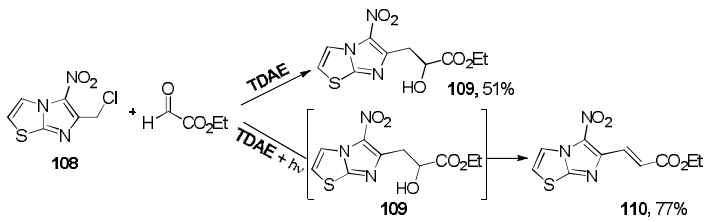
Scheme 23. Reduction-cyclization reactions.

Vanelle and co-authors then extended the reducing scope of TDAE to chloromethyl heterocycles (Scheme 24, Figure 5). In imidazo-pyridine and -pyridazine series, hydroxymalonates **105** were obtained, albeit the non-selectivity of highly reactive ketomalonate conducted to moderate yields.[93] On the other hand, in pyrido-pyrimidinone series, methylenemalonates **106** were formed 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 in such doubly electron-withdrawing group-substituted cycle. For the

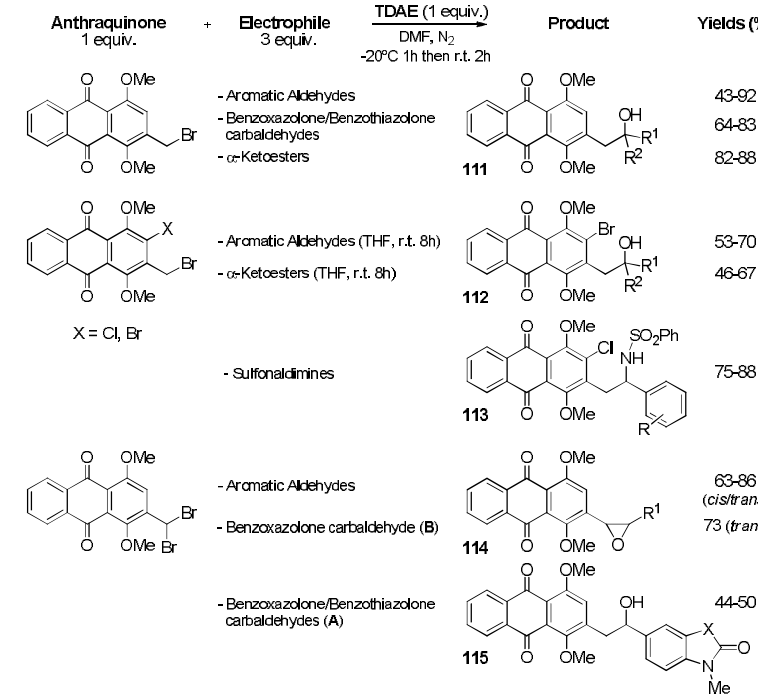
preparation of hydroxycarbonyl 5-nitroimidazo[2,1-*b*]thiazoles **107** with antimicrobial activities against *C. tropicalis*, light irradiation needed to be used along with TDAE so as to enhance reduction and improve yields (35-74%).[94] Nevertheless, this photo-induced ET was inadvisable in certain cases as it conducted to complex mixtures when using the highly activated ketomalonate or to dehydration of the alcohol product **109** (Scheme 25).



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



Scheme 25. TDAE/Photo-induced acrylate synthesis.



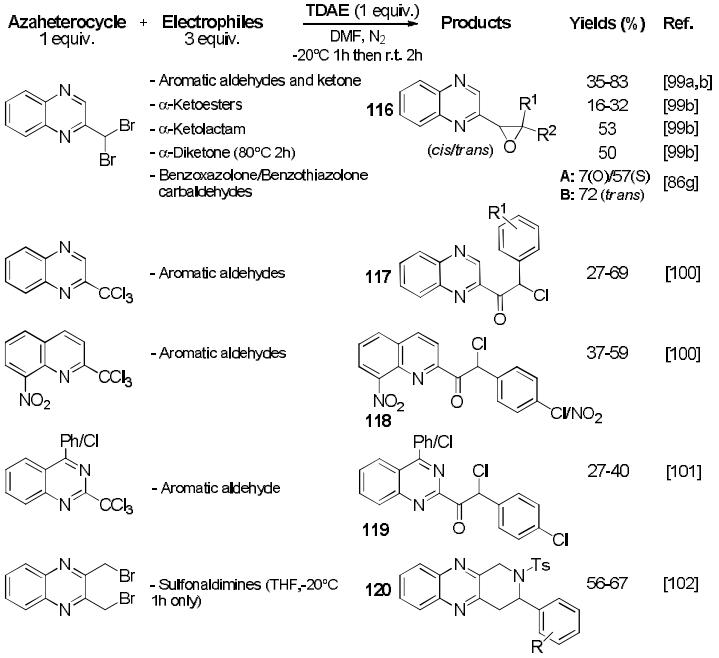
Scheme 26. TDAE-promoted intermolecular reactions with anthraquinones. (Changes from the standard conditions are given in parenthesis)

In 2008, Vanelle and Terme reported the first example of quinone reduction promoted by an organic reductant.[95] The TDAE approach allowed the mild and efficient generation of a quinonic anion, which cannot be formed *via* organometallic strategies. Their methodology 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 of α-ketoesters and aromatic aldehydes gave the corresponding α-hydroxy-ester (82-88%)[96] and alcohol adducts (43-92%)[95,86g] **111**. Adding a nitro group on *ortho* of the bromomethyl group surprisingly forced to harsher conditions and resulted in lower yields (38-63%). Exchanging the nitro group for a halogen provided hydroxy anthracenedione **112** (46-70%)[97] and *N*-benzylsulfonamides **113** (75-88%),[98] which were further cyclized by metal-catalyzed intramolecular *O*- and *N*-arylation.

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

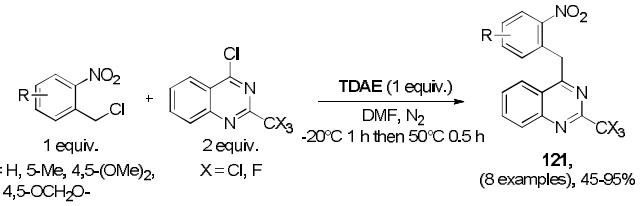
Finally, the original reactivity of dihalo- and trihalomethyl heterocyclic derivatives was examined in greater detail in quinoxaline series (Scheme 27, Figure 5). Reaction of α-bromo-carbanions, resulting from the reduction of a *gem*-dibromomethyl group, on any carbonylated electrophile led to a mixture of *cis*/*trans* epoxide isomers **116**.[99,86g] The low yields were justified by the instability of the oxiranes possessing two electron-withdrawing groups (*e.g.* α-oxyranyl-ester quinoxalines: 16-32%). *Cis*/*trans* ratio with α-dicarbonyls or p*ara*-substituted aldehydes averaged 50:50, while for bulky α-diketone and *ortho*-substituted aldehydes, the ratio averaged 30:70. Although it followed the same trend in favour of the *trans*-isomer with increasing hindrance, the stereoselectivity of the reaction was lower with quinoxalines than with anthraquinonic series which benefited from the presence of methoxy substituents. TDAE-promoted reduction of trichloromethyl quinoxalines,[100] 8-nitroquinoline[100] and quinazolines[101] in the presence of aromatic aldehydes conducted to 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 chloro-oxirane intermediate. At last, reaction of 2,3-bis(bromomethyl)quinoxaline with TDAE allowed the synthesis of tetrahydro-pyrido quinoxalines **120** *via* consecutive intermolecular addition of the carbanion to *N*-(toluenesulfonyl)benzylimines and intramolecular S_N2 of the second bromomethyl group by the nitrogen.[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.

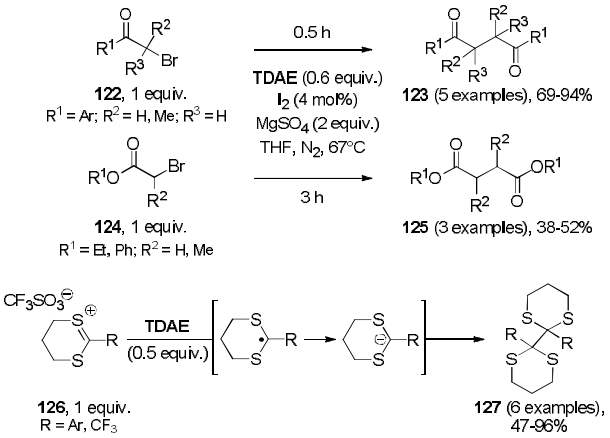


Scheme 27. TDAE-promoted reduction of dihalo- and trihalomethyl azaheterocycles. (Changes from the standard conditions are given in parenthesis)

Additionally, the disparities in the reducing abilities of TDAE can be used to selectively reduce one of two potential substrates. In the presence of the more reducible 2-nitrobenzyl chloride, S_NAr on the 4-position of 2-trihalomethylquinazolines was performed under mild and chemoselective conditions without reduction of the trihalogenated groups in **121** (Scheme 28).[101] Alternative methods to reach this benzylic substitution rely on the use of organomagnesium species or strong bases, and impose drastic and nonselective conditions making them incompatible with such substrates. Of note, 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.



Scheme 28. S_NAr on 2-trihalomethyl-4-chloroquinazolines.

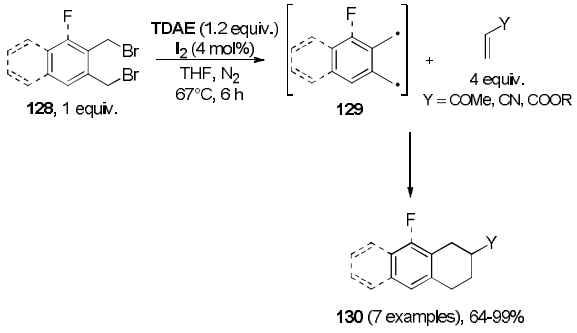


Scheme 29. Reductive couplings.

3.3.3. Miscellaneous

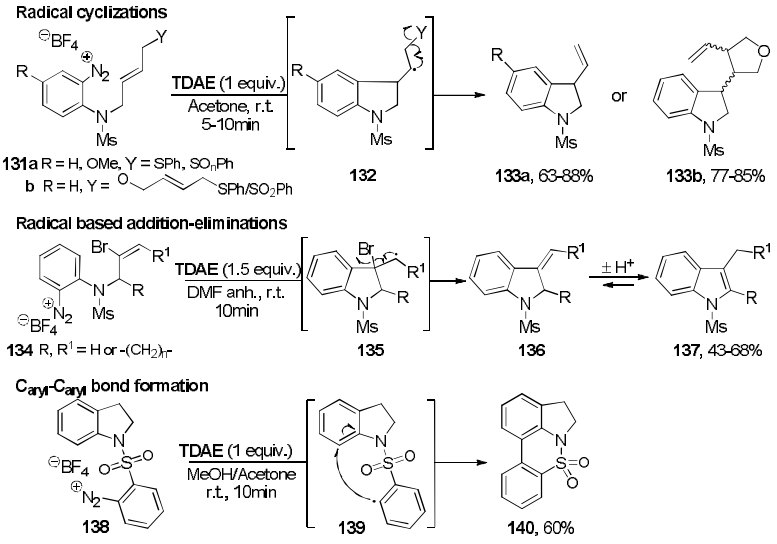
Besides α,α-difluoroketone- or quinone-activated C-X bonds, α-bromo ketones **122** and esters **124** can be reduced by TDAE.[103] Preparation of 1,4-diketones **123** and, to a more limited extent, of 1,4-diesters **125** was achieved through reductive homo-coupling (Scheme 29). Yields were drastically improved by 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 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 $C=S^+$ double bond (instead of C-X bond). The mechanism of these reductive couplings *via* radical or anionic species could not be determined.

Only few publications mention the participation of radical intermediates as the reactive species in TDAE-promoted reaction. In 2005, Nishiyama and Sonoda published a new 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 or vinyl ketone, giving 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, even though excess of olefin (10 equiv.) was used and lower yields (7-51%) were obtained. Note that no activating function was required on the benzyl ring.



Scheme 30. Radical reductive debromination.

In line with his previous work on TTF-initiated radical-polar reactions, Murphy showed that reduction of arenediazoniums using TDAE also led to aryl radical intermediates (Scheme 31). [106] However, since the absence of a TDAE-substrate salt like **8** prevented a clean termination of the radical process, a radical leaving group adjacent to the cyclized radical (**132**) was required. Treatment of **131a** with one equivalent of TDAE gave indolines **133a** in high yields after 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 methodology was then exploited in (i) a radical-based addition-elimination route to indoles. The radical Br$^{\bullet}$ was eliminated from the cyclized radical intermediates **135** affording unstable exocyclic alkenes **136** which tautomerized to the corresponding indoles **137**; (ii) an aryl-aryl C-C bond formation reaction leading to tetracyclic sulfonamide **140** with 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..



Scheme 31. Radical reactions by TDAE.

Since 1999, Tanaka and coworkers have reported several examples of TDAE employed as an electron source to reduce transition-metal catalysts in specific organometallic reactions, such as Ni/Cr redox-catalyzed alkenylation of carbonyls[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 multi-step synthesis for the homocoupling of iodoindoles or bromopyridines and the TDAE gave better results than metal reducers.[109]

In summary, tetrakis(dimethylamino)ethylene is a strong organic electron donor 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, cheapness and availability, TDAE proved to be an attractive complement to other reducing agents. A clear illustration is the reductive dechlorinations of chlorodifluoromethylated compounds, where the TDAE approach was as efficient as the Rongalite® system and more practical than sodium dithionite or *n*-Bu_3SnH/Azobisisobutyronitrile (AIBN).[110] TDAE can also lead to different reactivities from those observed with zinc, despite their similar reducing power.

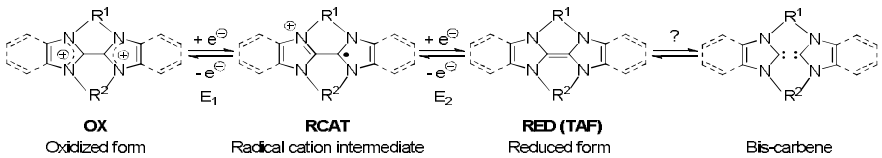
Unfortunately, only haloalkyl derivatives presenting an adequate reduction potential (electron-deficient aliphatic and benzylic systems) qualify for TDAE substrates that produce a reactive species. Chloroalkyl, unactivated alkyl and aryl halides[111] are reluctant to undergo electron transfer from TDAE.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

4. Tetraazafulvalenes TAF

Among the tetraaminoethylenes, tetraazafulvalenes (TAF) hold a special place. 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 important focus devoted to this class of donors over the last decade.

4.1. Properties

In the early seventies, the first TAF[112] were already studied for their electronic properties and described as two-step reversible redox systems.[7] Nonetheless, it was not until the 1990s and the blossom of the carbene coordination chemistry that they started to renew interest. Unlike their saturated counterparts, *N*-heterocyclic carbenes based on unsaturated imidazolylidene ring rarely form enetetramines, unless to be linked through their nitrogen atoms by a double bridge.[9,113]



Scheme 32. Redox reaction sequence of tetraazafulvalenes.

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

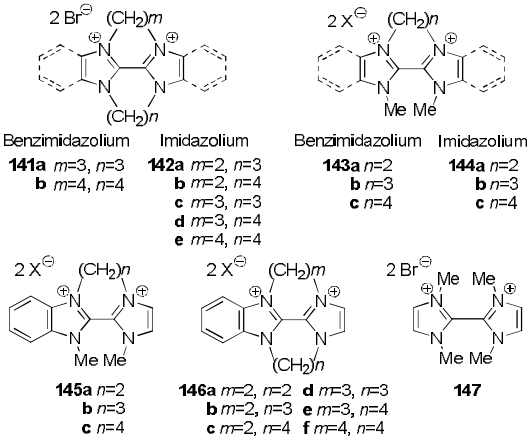


Figure 6. Biazolium salts.

The ability of biazolium salts to undergo two one-electron reductions is governed by the planarity of the structure: the most planar systems, providing 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 favoured 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 reflecting the diminished π-delocalization and the increased non-planarity of the two aromatic rings.[117] Cyclic voltammograms of the salts (Figure 7) confirmed the shift to more negative potentials and irreversible reductions with the decreasing planarity of the systems. The most highly distorted systems bearing a tetramethylene bridge, *e.g.* **142e**, **145c**, and **146f**, or four methyl groups (**147**) all showed a single irreversible wave, indicating that the RCAT and RED species formed upon reduction did not persist long enough to be reoxidized back to the initial OX form.

Table 2. Absorption maxima and redox potentials for *N,N'*-Bridged biazolium salts.[a]

Compound	m	n	λ_{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.
b	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)
b	2	4		-1.13 (110), -1.41 (105)[b]	-1.11 (80), -1.49 (ir)
c	3	3		-1.14 (130)[b]	-1.12 (100), -1.28 (ir)
d	3	4		-1.31 (ir)[b]	-1.28 (ir)
e	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)
b		3	338	-0.76 (90), -0.82 (80)	-0.76 (60), -0.94 (ir)
c		4	320	-0.87 (110)	-0.86 (60), -1.03 (70)
144a		2	304	-1.18 (ir)	-1.21 (ir)
b		3	283	-1.32 (140)	-1.31 (ir)
c		4	265	-1.41 (ir)	-1.44 (ir)
145a		2	333	-0.86 (90), -1.07 (ir)	-0.89 (70), -1.10 (ir)
b		3	314	-1.04 (ir)	-1.00 (90)
c		4	300	-1.12 (ir)	-1.12 (ir)
146a	2	2	334	-0.80 (ir)	-0.82 (ir)
b	2	3	330	-0.87 (70), -1.05 (60)	-0.85 (75), -1.14 (ir)
c	2	4	306	-1.08 (105), -1.22 (ir)	-1.07 (80), -1.30 (ir)
d	3	3	337	-0.85 (80), -1.15 (100)	-0.86 (75), -1.26 (ir)
e	3	4	337	-0.86 (70), -1.20 (ir)	-0.86 (70), -1.26 (ir)
f	4	4	320	-1.03 (ir)	-1.02 (ir)

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

As incorporation of a second bridge imposed added rigidity to the salt and thus increased its planarity, mono-annulated salts were more difficult to reduce and had more irreversible behaviors than their bis-annulated counterparts. Their 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 bis-annulated imidazolium is more difficult to reduce than a mono-bridged benzimidazolium).

The geometries about enetetraamine units were also strongly influenced by functional groups (Figure 8).[118] Electron-donating methoxy groups on dibenzoTAF **148** enhanced *N*-pyramidalization (C-N-C angle = 113°) and thus effectively minimized steric interactions between opposing *N*-substituents affording a nearly planar enetetraamine moiety (torsion = 7°). In contrast, electron-withdrawing halogen atoms (**149** R = Br) appeared to decrease the *N*-pyramidalization (C-N-C angle = 116°), which caused significant twisting of the two benzimidazo-rings (torsion = 27°) to avoid unfavourable steric interactions. Hence, planar electron-rich enetetramines **148** [$E_{1/2}$(CH_3CN) = -1.07 V *vs* SCE] were more reactive than twisted electron-deficient ones [$E_{1/2}$(**149**, CH_3CN) = -0.64 and -0.73 V *vs* SCE], which were more robust toward oxygen.

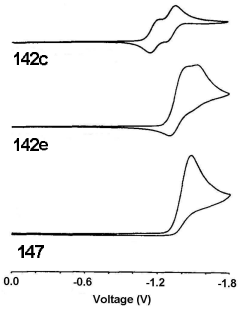


Figure 7. Representative cyclic voltammograms recorded in CH_3CN.[115b]

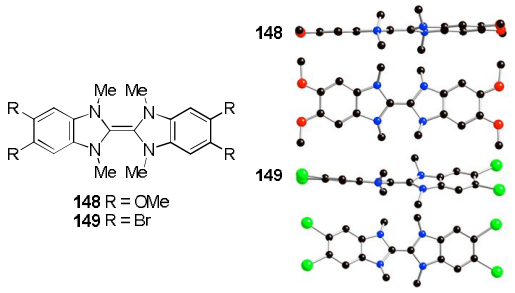
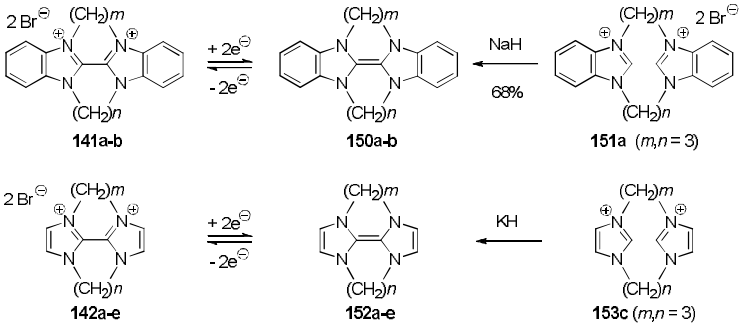


Figure 8. Ball-and-stick views of functionalized dibenzoTAF.

4.2. Preparation

Electrochemical generation of some neutral tetraaminoalkenes derivatives **150** and **152** (RED) was realized by bulk electrolysis of the salts **141** and **142** (OX) *via* two distinct reductions (Scheme 33).[114c,115] Under inert conditions, stable **150a** and **152c** were also isolated *via* 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 bis-carbenes instead.[113] Imidazo-carbenes are reluctant toward dimerization due to the stability conferred by the aromaticity of their 6π-electron ring (Bond-dissociation energy (BDE) of 4 ± 3 kcal/mol).[113] In contrast, dibenzo-TAF are for the most part stable at r.t.[119] (BDE of *ca.* 10 kcal/mol[120]), albeit significantly less than aliphatic tetraaminoethylenes. This underlines the extreme weakness of the central C=C π-bond. The isolation of the TAF form rather than a pair of carbenes is highly dependent on the kinetic barrier to either dimerization or dissociation.

In summary, reductions of biazolium salts were found to become increasingly difficult ($E_{1/2}$ more negative) and irreversible as the system becomes less planar. Diimidazolylidenes should thus provide more reactive reducers in organic synthesis than dibenzimidazolinylidene derivatives. As well, non-annulated (or long-methylene-bridged) and electron-rich TAF should be stronger electron donors as they are less stable and oxidize in stabilized cations. The theoretical design of organic donors with a wide range of ionization potentials using DFT calculations correlated these factors. [121] However, when it comes to design a powerful reducing agent, the whole problematic 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. The reactivity of few TAF structures was recently evaluated in organic synthesis.



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

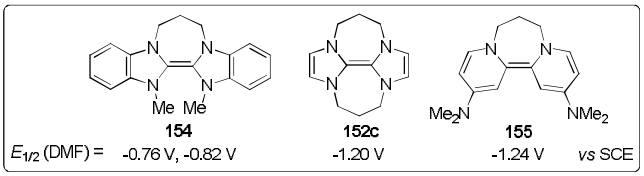
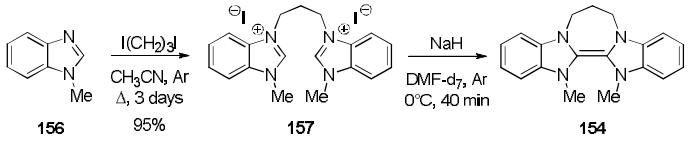


Figure 9. Super-Electron Donors (SED).



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

4.3. Reactivity of tetraazafulvalenes (TAF)

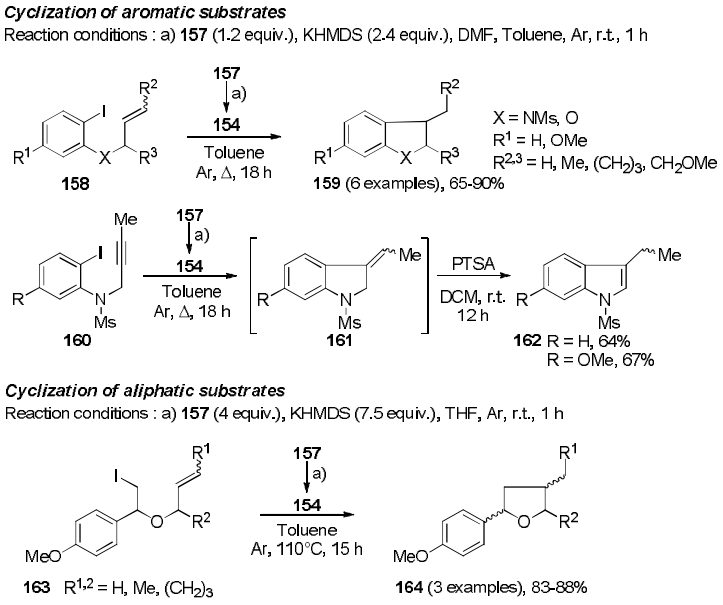
Since 2005, John A. Murphy has successfully focused his research on the development of neutral organic agents mimicking the TDAE structure but improving on their performance as electron-donors, the "Super-Electron Donors" (SED) (Figure 9). [122] Based on the idea that both the aromatic stabilization energy of the corresponding radical cation (as in sulfur-containing reducers) and the presence of electron-donating nitrogen (as in TDAE) can greatly assist electron transfers, Murphy and coworkers combined these two stabilizing factors in the same structure to afford excellent reducing agents and apply them in organic transformations.

4.3.1. Benzimidazole-based donors

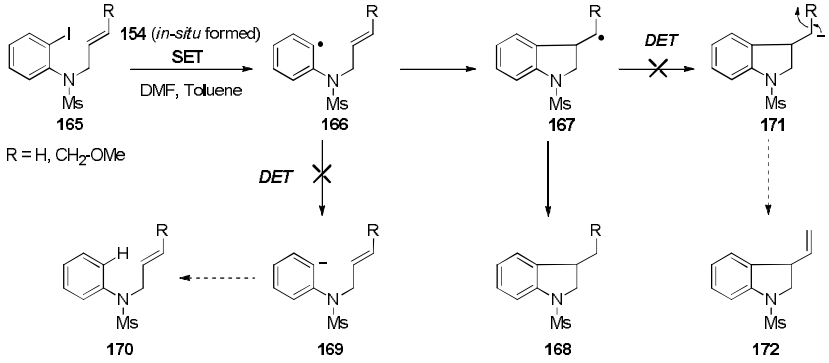
Thence, dibenzimidazolinylidene **154** was prepared by deprotonation of stable *N*,*N'*-tethered benzimidazolium salt **157**, obtained from the reaction of benzimidazole **156** with 1,3-diiodopropane (Scheme 34).[123] Dimer **154** could not be isolated and had to be characterized upon formation *in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

Dibenzo-TAF **154** was found to react efficiently with series of unactivated aryl as well as alkyl iodides leading to the corresponding aryl and alkyl radicals *via* single-electron transfer (SET) mechanism (Scheme 35). Although the oxidation potential of **154** was less negative that 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%) after acidic treatment of exocyclic alkenes **161**. Although several evidences pointed to a SET pathway, 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 forms.

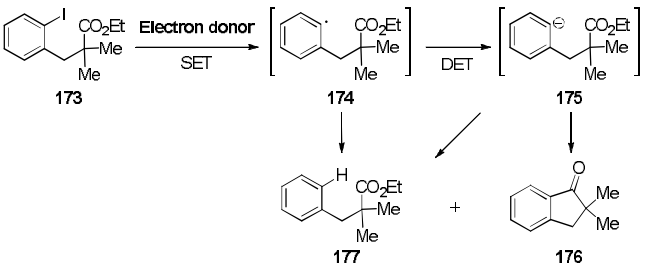
Soon after, a diagnostic test irrefutably confirmed the SET pathway for donor **154**.[126] Given that contrary to radicals, carbanions attack esters, the reaction depicted in Scheme 37 unambiguously distinguishes aryl anions from aryl radical intermediates. Iodoester **173** was reacted with donor **154** and only reduced compound **177** was isolated (67%). The absence of indanone **176** indicated that aryl anion **175** had not been formed. Of note, 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.



Scheme 35. Cyclization reaction with **154**.

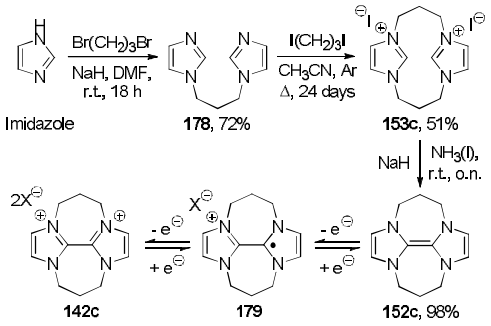


Scheme 36. SET *vs* DET mechanism pathways.



Scheme 37. Diagnostic test for radical *vs* anion intermediates formation.

Thus, benzimidazole-derived donor **154** was defined as the first Super-SET organic reagent. Having in hand a strong reducing agent allowing 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 methodology.



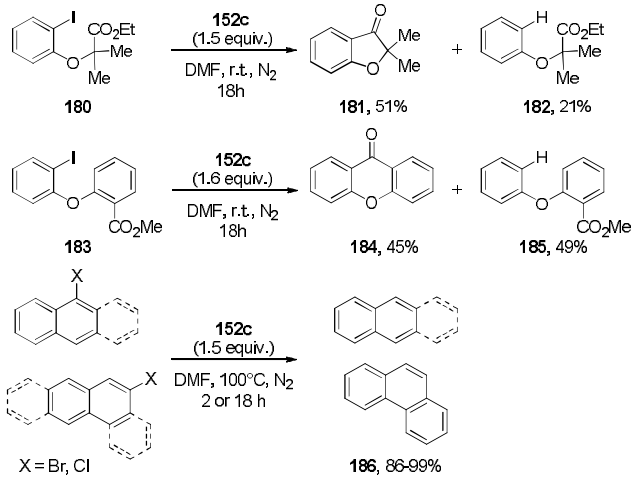
Scheme 38. Preparation of bis-imidazolylidene **152c**. o.n.: overnight

4.3.2. Imidazole-based donors

In 2007, Murphy and Tuttle reported a more rigorous synthesis for bis-imidazolylidene **152c**[113] through the preparation of diiodide

153c from imidazole and dihalide propanes (Scheme 38).[126] Although improved and scaled up to 55 g, the synthesis of **153c** was still restrictive as incorporation of the second bridge to give the dimer required high dilution (4L of CH_3CN) and weeks of reaction time (24 days), along with partial recrystallization and moderate yields (51%).[127] The (tetrakis)imidazolium macrocyclic salt was obtained as side product.[128] Generation of **152c** then proceeded using NaH in liquid ammonia to afford a air-sensitive pure yellow solid (98%). Due to the high molecular weight of the organic electron donor (216.3 g/mol), large quantities of material were required in order to perform the reaction scope with an excess of **152c**.

Diagnostic reaction of substrate **173** with **152c** afforded **177** (70%) and **176** (16%), proving the intermediacy of aryl anion **175** (Scheme 37). Interestingly, attempts to access ketone **176** through other reactions that should afford aryl anions, using ^{t}BuLi, sodium naphthenide or magnesium metal, gave complex mixtures. This clearly illustrated the selectivity of diimidazo-TAF **152c** compared to strong metallic reducers which reduced the resulting ketone. The significant amount of reduced product **177** can arise from H-abstraction by the anion **175** and/or the aryl radical **174**. Donor **152c** has a two-electron redox wave [$E_{1/2}$ (DMF) = -1.20 V *vs* 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 SED **152c** was further confirmed with ester substrates **180** and **183**, more prone to a rapid cyclization of the anion intermediate and thus giving a more accurate estimation of the percentage of aryl anions formed by ET in these reactions, *i.e.* a minimum of 51 and 45% respectively (Scheme 39). **152c** was also able to reduce bromo- and chloro-substituted polycyclic aromatic hydrocarbons in high yields (**186**) (Scheme 39), contrary to **154** which yielded very poor conversions in the same reactions. Donor **152c** was thus presented as the first neutral organic electron transfer agent able to selectively convert haloarenes to aryl anions by DET and in the absence of photochemical activation.



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

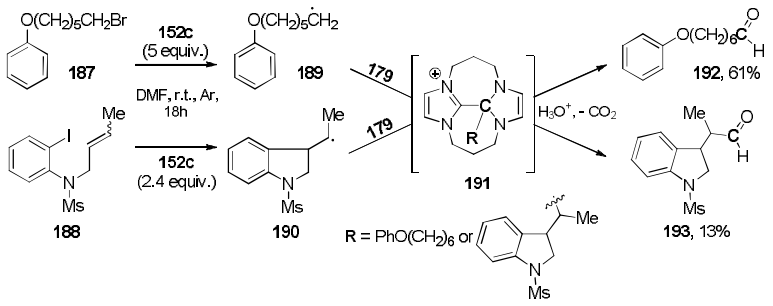
As predicted by Thummel and Ames' studies (*vide supra*), diimidazolylidene **152c** exhibited better reducing ability than dibenzo-TAF **154**. However, the greater reactivity of enetetramine **152c** is also due to the greater aromatic stabilization energy gained with the formation of more[129] planar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

A side reaction can occur with SED and alkyl or some aryl halides when an acidic workup is used. It consists in the formation of aliphatic aldehydes by extrusion of a carbon atom from the azolium **191** (Scheme 40).[130] Trapping of SED-initiated alkyl radical **189** (or **190**) by coupling with the radical-cation **179** of donor **152c** generates intermediate **191** that 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 *via* DET (Table 3).[132] ET to the arenesulfonyl group affords radical-anion **A** that 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 1-2) were efficiently reduced, whereas 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 favouring the aromatic stabilization of the anion intermediate **E**, such as indole and aniline species (Entries 8-9), 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, due to 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]

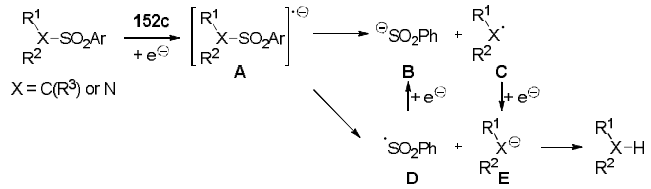
Recently, an interesting approach was described by Jolly *et al.* to overcome the difficulties related to the synthesis of tetraazaalkenes (*vide supra*) and thus enhance their potential as powerful reducing agents in organic synthesis.[134] Their concept was to target simpler TAF by producing them *in 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 *in situ* formation of **194** and **195**. NMR experiments showed that these highly reactive TAF were rapidly converted into carbenes with a half-life of few hours for **194** and few minutes for **195**. The equilibrium of NHC and TAF suggested that ET reactions could be possible in ionic liquids.[135]

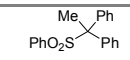
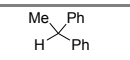
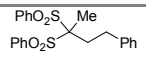
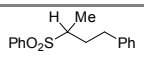
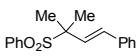
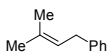
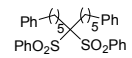
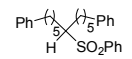
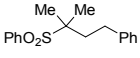
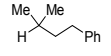
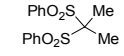
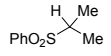
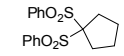
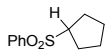
Following this success, the development of more powerful imidazo-TAFs related to **152c** was envisaged. However, due to the high molecular weight of this organic electron donor (216.3 g/mol), large quantities of material were required in order to perform the reaction scope with an excess of **152c**.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



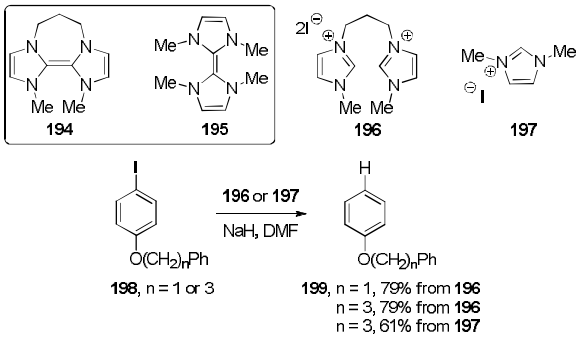
Scheme 40. Formation of aldehydes.

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



Entry	Substrate	Product	Yield (%)	Entry	Substrate	Product	Yield (%)
1			97	**6**			98
2			79	**7**			94
3			<1	**8**[b][c]			91
4			97	**9**[b]			74
5			96	**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.



Scheme 41. *In situ* reduction of iodoarenes.

5. Bis-pyridinylidenes

In parallel to tetraazafulvalenes, bis-pyridinylidenes and the associated radical cations have long been studied for their electrochemical properties. Notably, viologen and quinone derivatives have been intensely investigated as electrochromic materials[137] and components of supramolecular systems (Figure 10).[138] Among viologens,[139] only few neutral 4,4'-bipyridyl forms were 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 *vs* SCE (calibrated using 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 $\mathbf{201}^{6+}$ is reversibly reduced to $\mathbf{201}^{2+}$ in one four-electron transfer and $\mathbf{201}^{2+}$ is reversibly reduced to $\mathbf{201}^{0}$ in one two-electron transfer [$E_{1/2}$ (THF) = -0.58 and -0.69 V vs SCE (calibrated using Fc/Fc^+)].[143] Cyclic voltammetry of **202** showed a two-electron wave [$E_{1/2}$ (CH_3CN) = -0.32 V vs SCE], yet computational studies suggested that in nonpolar solvents **202** could be stronger two-electron reducing agent than **152c**.[144] In other solvents, **152c** should be superior. Despite the numbers of nitrogens and/or the aromaticity of the oxidized products, the redox potentials of these structures, lower to that of **152c**, indicate that other factors (*hitherto* not 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.

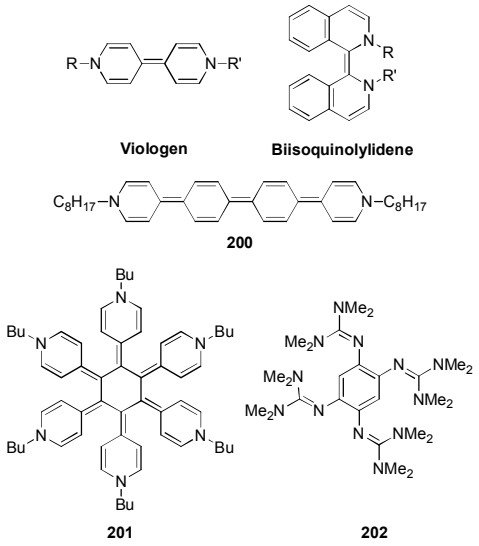
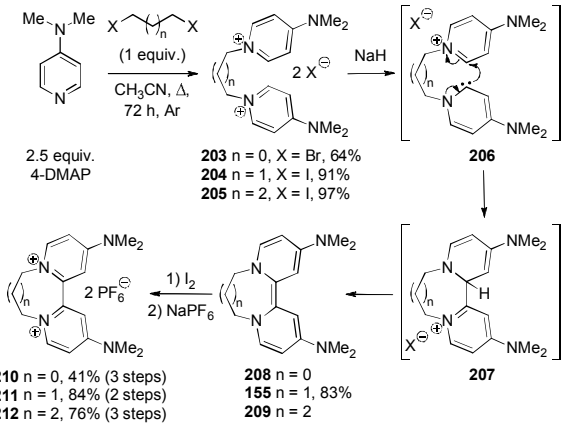


Figure 10. Viologen derivatives.

Diquarternary salts of 2,2'-bipyridine (*e.g.* **210**-**212**, Scheme 42) were primarily studied for their role of electron-deficient acceptor in charge-transfer complexes[146] and for their potent herbicide properties.[147] Like imidazolium salts, the study of their redox and spectroscopic properties showed that oxidation steps from the bis-pyridinylidenes to the aromatic oxidized forms were favoured 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), as well electron-withdrawing groups shifted the first reduction to a more negative potential.[148]

5.1. Reactivity of Bis-pyridinylidenes

Since 2008, Murphy and *co.* developed new series of organic SED based on pyridine structures.[149,150] Dihalide precursors **203**-**205** with different chain lengths were easily prepared from reaction of the commercially available 4-dimethylaminopyridine with 1,*n*-dihalide-alkanes (Scheme 42). Deprotonation of the bis-pyridinium salts afforded bis-pyridinylidenes **155**, **208** and **209** *via* carbene **206** which undergoes nucleophilic attack on the adjacent pyridinium ring.[151] Diverse amino groups were also incorporated on position 4 of the pyridine rings in order to enhance the electron density of the π-system (Figure 11). All cyclic voltammograms showed reversible two-electron redox chemistry (Table 4). Apart from **208** and **214** featuring two one-electron waves, other bipyridinium salts exhibited a single two-electron wave, 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 carbons made less effective reducing agent (**208**) while increasing the flexibility with a long bridge (**209**), permitting free rotation (**213**) or altering the nature of 4-substituents (**214**-**215**) did not radically enhance the donor properties compared to **155**. Unlike the quasi-planar **142c** constrained by its two trimethylene straps (dihedral angle at 1.5°),[126] X-ray structure of **211** confirmed the non-planarity of the two rings twisted to avoid interaction (53°) and correlated the greater driving force of **155** for loss of the second electron.[150]



Scheme 42. Formation of bis-pyridinylidenes.

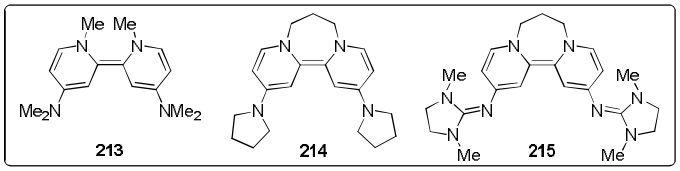


Figure 11. 4-Amino-substituted bis-pyridinylidenes.

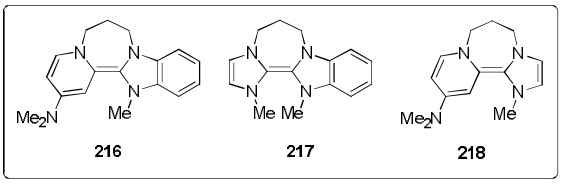


Figure 12. Hybrid Super-Electron Donors.

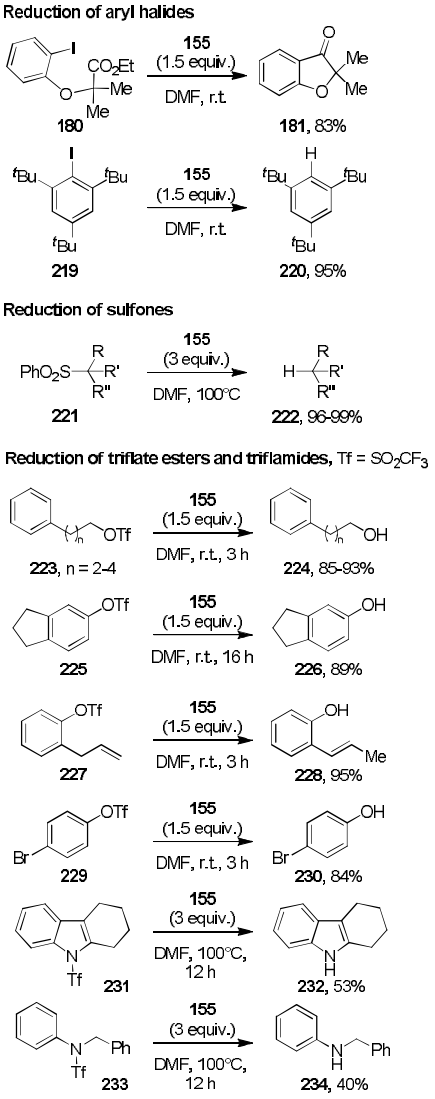
Hybrid systems were also prepared (Figure 12).[152] Single-electron donors **216** and **217** incorporate a "stronger" and a "weaker" donor components and exhibit redox potentials intermediate between those for the corresponding non-mixed systems (Table 4). Unlike SET with **154** performed at 110°C, **216** and **217** could reduce aryl iodides to aryl radicals at room temperature. Double-electron donor **218** is a stable imidazole-derived species. The study also revealed that 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 to act itself as a base. Excess of base can inhibit the protonation of the donor by competing for protons and therefore avoids the decrease of the concentration of donor. Owing to their structural features, some donors such as **152c** and **218** are not affected by the absence of base.

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

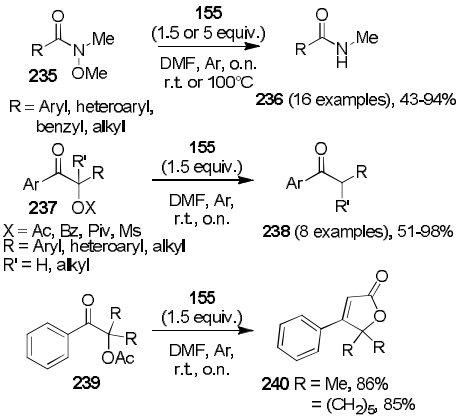
Donor	$E_{1/2}$(DMF) (V)
155	-1.24
208	-1.21, -0.98
209	-1.23
213	-1.27
214	-1.33, -1.24
215	-1.24
216	-1.09, -0.97
218	-1.30, -1.18

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

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 r.t., as well as to reductively cleave phenylalkylsulfones (**221**) in excellent yields (96-99%).[149] Deuterium-labeling studies revealed that the pyridinium ring α-CH protons are a major source of proton abstraction which strongly contributes to the quenching of aryl anions.[153] Bis-pyridinylidene **155** was also able to cleave the N-O bond on Weinreb amides **235**[154] or the C-O σ-bond on acyloin derivatives **237**[155] by DET (Scheme 44-45). While electron-rich carbonyl group imposed more forcing conditions (100°C), the arene ring close to **235** facilitated the reductive cleavage at r.t. The α-ester acyloins **237** were successfully reduced generating desoxy products **238** in good to excellent yields (51-98%). Surprisingly, the acetate acyloin derivative **239** afforded the butenolide **240** instead, supposedly due to the basic nature of **155** (protonation of the central C=C bond). Double-electron transfer was recently exploited in the cleavage of S-O and S-N bonds in triflate esters and triflamides leading to the formation of the corresponding alcohols and amines (Scheme 43).[156]

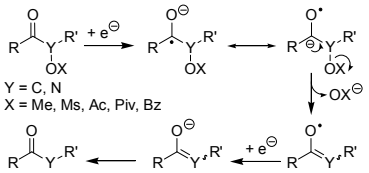


Scheme 43. Reductive electron transfer promoted by **155**.



Scheme 44. Reductive cleavage of N-O and C-O σ-bonds.

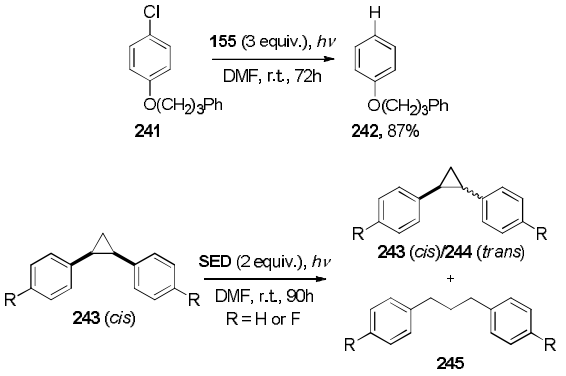
Unlike some reducing systems such as $NiCl_2 \cdot 2H_2O$–Li–arene(cat.),[157] **155** selectively cleaved the S-O bond of aliphatic **223** and aryl triflates **225**, **227** and **229** in excellent yields and no evidence of C-O bond cleavage was observed.[158] Reduction on triflamides **231** and **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 triflate over bromide functional group was observed for substrate **229**.



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

Following the same concept applied to diimidazolylidenes,[134] **155** and slow-forming *N*-methyl bipyridinylidene **213** could also be produced *in situ* from the appropriate 4-DMAP salt and underwent a one-pot reduction of aryl iodide **198** (n=3) as soon as they were formed.[153] Lately, combination of SED with photoexcitation allowed the reduction of more challenging arenes, *hitherto* impossible with organic reducing agents.[159] Photoactivated SED **152c** and **155** were capable of reductive dechlorination (**241**→**242**) and, above all, of ET to ground-state benzene analogs (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] and the ring-opened 1,3-diarylpropane **245**.[161] Donor **152c** was more effective in promoting the formation of **245** (35% *vs* 6% with **155**). Same experiments carried out on 4-chlorophenyl analogs (R = Cl) of **243** showed dechlorination as 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 avoiding the isolation of very reactive organic electron donors and allowing the use of unstable or slow-forming donors represent an attractive alternative.

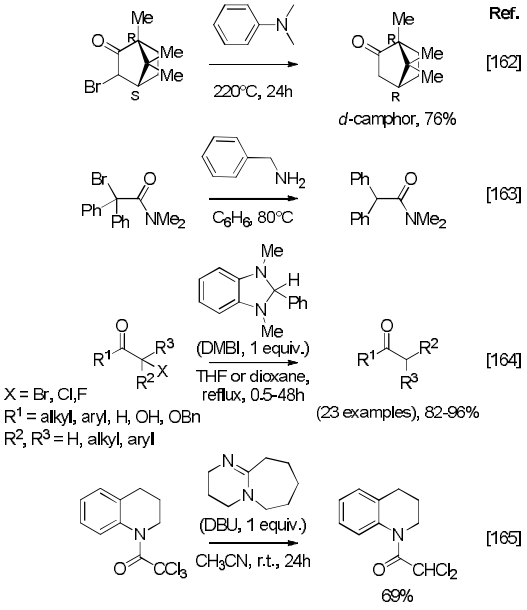


Scheme 46. UV/SED-promoted electron transfers to benzenes.

6. Amines

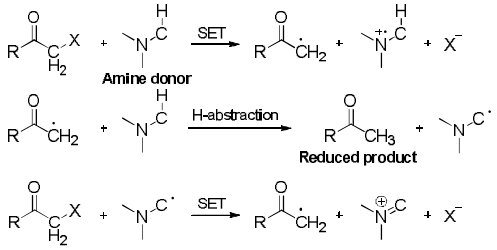
Although heteroatom-substituted alkenes are predominant reducing agents, other molecules with nonbonding electrons are also capable of one-electron transfers. Organic amines are known to work as electron donors in SET reactions, but they usually require photochemical activation.[5] Few studies mention single electron transfers from amines to partner substrates in the absence of photochemical assistance.

Early examples report the reductive dehalogenation of α-halo carbonyl compounds 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 reducing agents (Scheme 47). Light and air-stable DMBI [$E_{1/2}$ (CH_3CN) = + 0.33 V *vs* SCE][166] afforded 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, 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).



Scheme 47. Amine-initiated reductive dehalogenation reactions.

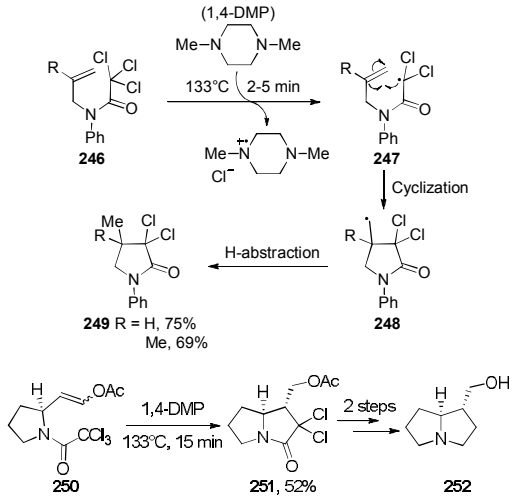
At the end of the reaction, the imidazolium salt $DMBI^+X^-$ was recovered by simple filtration and could be reconverted into DMBI.[167] First postulated to be a direct S_N2 hydride transfer, the mechanism of the DMBI reduction was later shown to proceed *via* SET and H-atom abstraction radical chain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



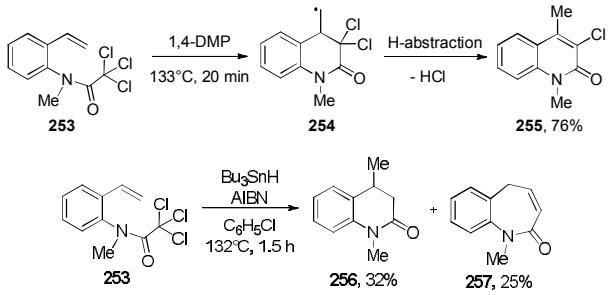
Scheme 48. Reduction by SET-Hydrogen atom abstraction chain mechanism.

Ishibashi *et al.* demonstrated the radical cyclization of various *N*-allylic and *N*-vinylic α,α,α-trichloroacetamides with olefins, upon heating in 1,4-dimethylpiperazine (1,4-DMP) used as solvent, to give 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 *vs* 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 suggested to proceed *via* a SET from the nitrogen atom of 1,4-DMP to the substrate **246**, followed by elimination of a chloride anion to give dichloro-substituted radical **247**. 5-*exo-trig* Cyclization of **247** to the olefinic bond and successive addition reaction of an H-atom at the resulting terminal radical intermediates **248** gave γ-lactam **249**. In the case of *o*-ethenyl trichloroacetanilides **253**, hydrogen abstraction by **254** was followed by elimination of hydrogen chloride affording 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* **256** and neophyl rearrangement **257** products. This difference in reactivity was explained by a higher concentration of hydrogen atom source when using 1,4-DMP, allowing the rapid reduction of radical **254** instead of further rearrangements. An activated trichloroacetamide group was necessary as electron acceptor, as confirmed by the sluggish cyclization of α,α-dichloroacetamide counterparts ($NC(O)CHCl_2$) affording only 12-13% of the desired product.[168a]

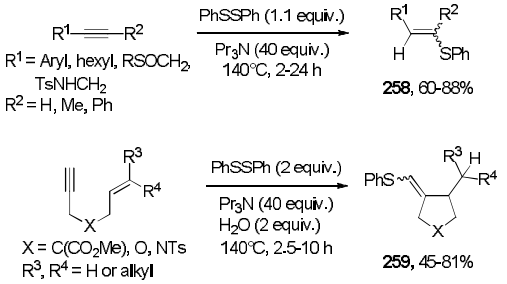
Amine-mediated SET to diphenyl disulfide could also be performed and allowed the hydrothiolation of alkynes (Scheme 51).[173] Tripropylamine [E_p (DMF) = + 0.95 V *vs* SCE][174] was used as electron donor to cleave the sulfur-sulfur bond.[175] Addition of generated benzenethiyl radical $PhS^•$ on terminal or internal alkynes and subsequent H-abstraction gave the desired vinyl sulfides **258** as a mixture of *E*- and *Z*-isomers. The method was extended to the radical cyclizations of eneyne derivatives, yielding 5-*exo* products **259** (Scheme 51). Depending on the alkene substituents, rearrangement of the radical intermediate **262** can occur giving rise to 6-*endo* product **266** *via* ring expansion of cyclopropylcarbinyl radical **263** (Scheme 52). Addition of two equivalents of water improved yields of 5-*exo* products **264** and **265**. Presumably water accelerates the H-atom donation to radical **262** and avoids its rearrangement.[168b, 173]



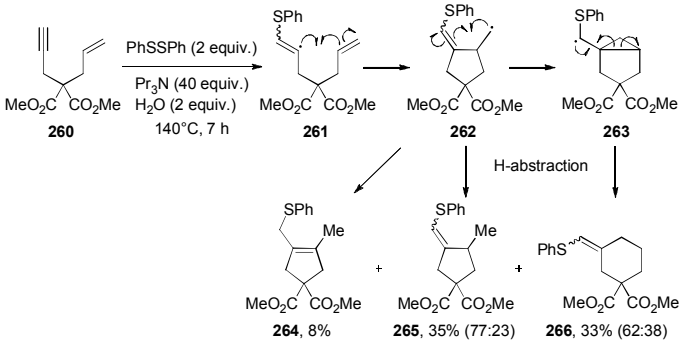
Scheme 49. Radical cyclization of *N*-allylic α,α,α-trichloroacetamides.



Scheme 50. Radical cyclization of *o*-ethenyl trichloroacetanilides.



Scheme 51. Reductive addition of benzenethiyl radical to alkynes.



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

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

7. Conclusion and Outlook

The diversity of the chemistry and the astonishing recent advances foretell great prospects for organic electron donors. As summarized in Table 5, two categories of *neutral ground-state organic* electron donors dominate the field: sulfur or nitrogen containing electron-rich olefins. These totally organic reducing agents are capable of spontaneous single- or double-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 allowing a large choice of reactivity and selectivity 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 mean of metallic reducers, were 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 that have the capacity for two-stage ET and that do not reduce ketones represent an useful substitute to metallic and organometallic reagents (Figure 13). SED 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. In that sense, organic electron sources contribute to the development of sustainable reactions with 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 reducers 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 the graph of redox potentials. Their reducing abilities limit the choice of reducible substrates. Due to this restricted structural diversity, the present reactivities mostly consist 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 mechanism, diversity of structures should also help elucidate the factors governing single- or double-electron transfer, as well as reducing powers and reactivities. Finally, these reducers are of 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 an 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]

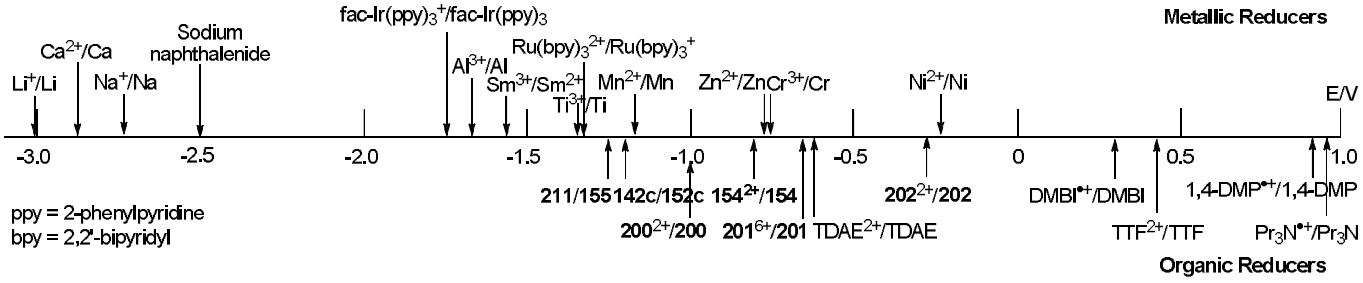
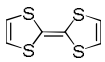
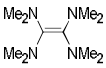
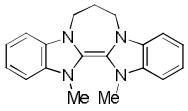
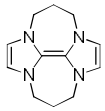
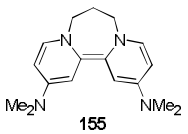


Figure 13. Standard Reduction Potentials.

Table 5. Principal characteristic of organic electron donors.

Electron Donor	E.T.	Redox potential (*vs* SCE)	Reduced bond	Promoted Reaction
 TTF	1e⁻	+ 0.32 V, + 0.71 V (CH_3CN)	Ar-N_2^+ BF_4^-	- Radical cyclization/oxidative functionalization - Radical translocation/oxidative functionalization
 TDAE	1 or 2e⁻	– 0.78 V, – 0.61 V (CH_3CN) – 0.62 V (DMF)	Ar-N_2^+ BF_4^- $ArCH_2$-Cl $ArCH_2$-Br $ArCHBr_2$ $ArCCl_3$ C(O)CHR-Br CF_2-Br CF_3-I $C(O)CF_2$-Cl	- Radical cyclization - Radical addition-elimination - Reductive coupling - Di/Trifluoromethylation - Benzylic substitution - S_NAr
 154	1e⁻	- 0.76 V, - 0.82 V (DMF)	Ar-I	- Radical cyclization
 152c	2e⁻	- 1.20 V (DMF)	Ar-I Ar-Br Ar-Cl C-SO_2Ph N-Ts	- Anionic cyclization - Reduction of haloarenes and benzenes - Reductive cleavage of sulfones and sulfonamides
 155	2e⁻	- 1.24 V (DMF)	Ar-I Ar-Cl C-SO_2Ph O-Tf N-Ts N-Tf C(O)N-OMe C(O)C-OX	- Anionic cyclization - Reduction of haloarenes - Reductive cleavage of sulfones, sulfonamides, triflate esters, triflamides, Weinreb amides and acyloin derivatives
DMBI 1,4-DMP Pr_3N	1e⁻	+ 0.33 (CH_3CN) + 0.89 (30% v/v MeOH/H_2O) + 0.95 (DMF)	C(O)C-X $NC(O)CCl_3$ PhS-SPh	- Reduction of α-halo carbonyls - Radical cyclization - Hydrothiolation of alkynes

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[**] ((General Annotations))

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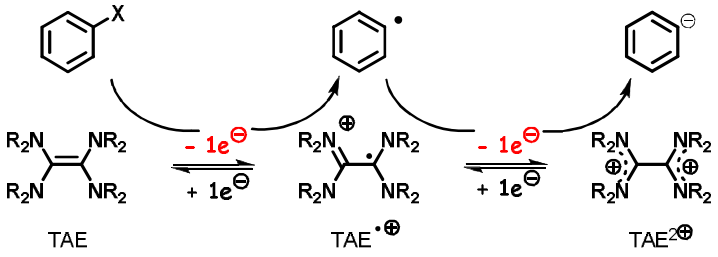
Layout 2:

Electron Transfers

Julie Broggi,* Thierry Terme,* Patrice Vanelle*_____ **Page – Page**

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



Among the different ways to effect radical formation, one-electron reduction involves the stepwise transfer of one or two electrons from a donor to an organic substrate. Apart from metallic reagents, Single-Electron Transfer reducers based on neutral organic molecules have emerged as an attractive novel source of reducing electrons. This review gives an overview of the different types of organic donors and of their specific abilities in organic synthesis.