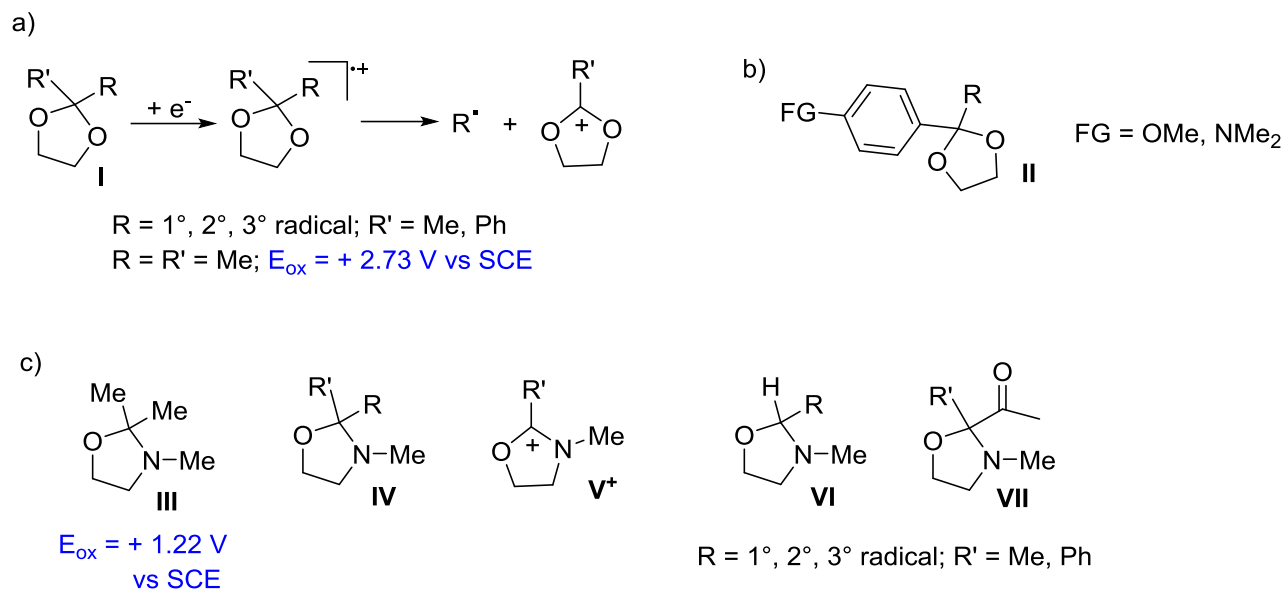# New uncharged precursors for photoredox-mediated radical generation

RESEARCH PROGRAM

With the renaissance of photocatalytic processes, radical chemistry has emerged as a powerful tool in organic synthesis. [1] This has paved the way to a more eco-sustainable tin-free radical chemistry. In fact, a lot of radical precursors were designed in order to liberate an alkyl (or a related) radical upon a single electron transfer reaction with a photoredox catalyst. The strategy is based on the fragmentation of the species formed upon oxidation/reduction of the radical precursor. [1,2] An ideal radical source should be easily reducible or oxidizable. This forces in some cases to adopt cationic species (e.g. *N*-alkylpyridinium salts [3]) or anionic species (e.g. alkyl carboxylates, [4] alkyl organoborates [5] or hypervalent bis-catecholato silicon compounds [6]), respectively. These precursors are available as salts and this limits the use of medium to polar (protic or aprotic) solvents due to solubility problems. Uncharged precursors are likewise available, but only a handful of derivatives are widely employed, including *N*-phthalimidoyl derivatives [7a,b] or recently introduced 4-alkyl-1,4-dihydropyridines. [7c,d] Accordingly, there is an urgent need to develop new neutral easily prepared and highly reactive radical precursors. [8] Some years ago, 2,2-dialkyldioxolanes [9] or 2-alkyl-2-phenyl-dioxolanes **I** [10] (Scheme 1a) were used as radical precursors, able to release an alkyl radical and a dialkoxyalkyl carbocation upon single electron transfer (SET) with excited benzene-1,2,4,5-tetracarbonitrile (TCNB). The presence of a methyl or a phenyl group in position 2- of the ring assured the exclusive fragmentation of the C–R bond at the radical cation stage since the methyl and the phenyl radicals are too unstable to be liberated. Unfortunately, the wide applicability of these derivatives is hampered by their high oxidation potential ($E_{ox} = + 2.73$ V vs SCE for the 2,2-dimethyl derivative), thus drastically limiting the number of photocatalysts that can serve for this process (Scheme 1a).

a)

R = 1°, 2°, 3° radical; R' = Me, Ph
R = R' = Me; E_{ox} = + 2.73 V vs SCE

b)

FG = OMe, NMe$_2$

c)

III

E_{ox} = + 1.22 V
vs SCE

IV

V$^+$

VI

VII

R = 1°, 2°, 3° radical; R' = Me, Ph

Scheme 1

One way to overcome this problem is to design related derivatives having a lower oxidation potential. The first approach consists in tethering an electron-donating group (OMe or NMe$_2$ in the aromatic ring of dioxolanes **II**, Scheme 1b). The dioxolanyl derivatives obtained from *p*-methoxy- or *p*-N,N-dimethylaminophenyl ketones appear as suitable candidates due to the decrease of the oxidation potential imparted by the aromatic nucleus, e.g. of anisole (*E*ox = + 1.77 V vs SCE) [11] and especially *N,N*-dimethylaniline (*E*ox = + 0.85 V vs SCE). [11]

In alternative, by substituting a nitrogen for an oxygen atom in dioxolanes as in the case of *N*-methyloxazolidine **III** (Scheme 1c), the oxidizability of the title compound is markedly improved (*E*ox = + 1.22 V vs SCE). [12] Compound **III** was used to generate (and accumulate) in solution the radical anion of cyanoarenes (used as electron acceptors), but no evidence of the fragmentation of the corresponding radical cation **III**·+ in any of the adjacent positions to the nitrogen atom was observed. [12] However, the presence of an alkyl group R in place of a methyl group (as in compound **IV**) may induce the liberation of the former upon oxidation, thanks to the great stability of the oxazolidinyl cation **V$^+$** intermediate. In principle, even compounds **VI** easily formed by reaction of an aldehyde and 2-(methylamino)ethanol are worth to be tested (Scheme 1c). Once verified the photoreactivity of oxazolidines **IV** and **VI**, the oxazolidine scaffold can be used for the generation of different radicals (e.g. acyl radicals by using compounds **VII**).

A different approach in the development of alkyl radical precursors by photoredox catalysis is represented by the adoption of silyl ethers (Scheme 2). It was reported that the photocatalyzed oxidation of compound **VIII** caused the formation of the corresponding radical cation and the following loss of an alkyl radical (a *t*Bu radical in this case). [9b] However, even in this case the E_{ox} of this class of compounds is very high (Eox $> + 2.5$ V vs SCE for EtOSiMe$_3$). [13] Nevertheless, it can be envisaged that the presence of a phenyl group in aryl silyl ethers **IX**, easily obtained from the corresponding phenols, could allow to lower the potential down to *ca.* $+ 1.8$ V vs SCE (value estimated from PhOSiMe$_3$ [14]). The E_{ox} may be further lowered when tethering suitable FG groups (mostly electron-donating) on the aromatic ring (Scheme 2). Since the silyl group is a well-known protecting group for phenols, the synthesis of silyl ethers **IX** is particularly straightforward.
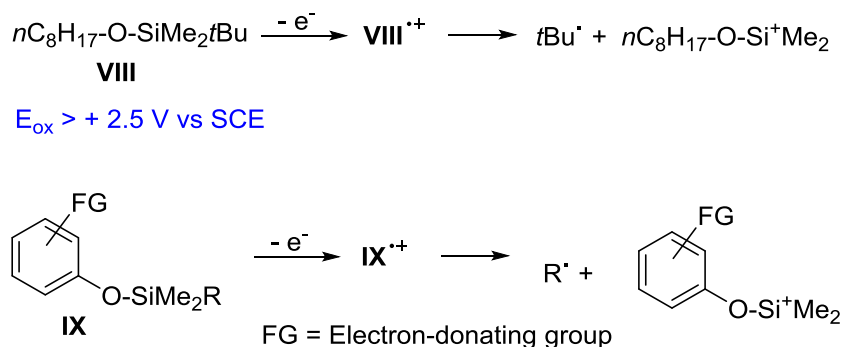
Scheme 2

The radical formed in the reaction (once demonstrated) will be used in typical chemistry including addition reactions, Minisci-like functionalizations or *ipso*-substitution on aromatic rings, along with substitution reactions mostly finalized to the synthesis of valuable compounds. [1]

The recruited ESR should initially prepare suitable novel radical precursors to be used in photoredox catalyzed alkylations of electron-poor olefins, aromatics, etc. for the preparation of valuable compounds both under batch and flow conditions in cooperation with the other partners.

For this aim known photocatalysts or innovative photocatalysts developed by the partners of the project will be tested for radicals generation.

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