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Reactions of δ-carbon radicals generated by 1,5-hydrogen transfer to alkoxyl radicals

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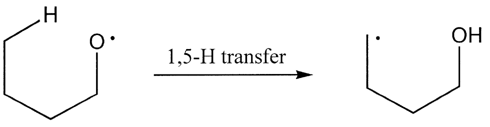
Contents

1. Introduction

Alkoxyl radicals undergo a variety of reactions such as intra- and intermolecular hydrogen abstraction,[1a–1] β-fragmentation[2a–c] and intramolecular additions.[3a,b] From the synthetic point of view, the intramolecular 1,5-hydrogen transfer from the non-activated δ-methyl, -methylene or -methine group is the most important reaction.[4–7]

Transposition of a radical center from oxygen (**1**) to the remote non-activated carbon atom (**2**) offers possibilities for the introduction of a different functional group on the non-activated carbon atom or to form a new carbon–carbon bond (Scheme 1).[8–11] The regioselective formation of a carbon radical intermediate on the non-activated carbon atom and its subsequent reactions represent a new synthetic methodology which fundamentally differs from the classical functional group introductions when particular activation of specific carbon atoms, preferentially adjacent to some functional group, is required.[1,12]

Introduction of a functional group onto a remote non-activated carbon atom is an especially prominent radical reaction which has been successfully applied in organic synthesis, particularly for functionalisation of inaccessible angular methyl groups in steroid molecules and other natural products.[1,4,5,12] The diversity of this type of reactions offers several possibilities for the introduction of different oxygen,[4–6] nitrogen,[4b,12] halogen[4c,13] and sulfur functional groups[14] as well as an olefinic bond[7] onto the non-activated carbon atoms. Recently, free radical reactions for the regioselective formation of a carbon–carbon bond on the non-activated δ-carbon atom have been discovered



1 **2**

Scheme 1.

Keywords: radicals and radical reactions; 1,5-hydrogen transfer; intramolecular functionalisation; C_δ–C bond formation.

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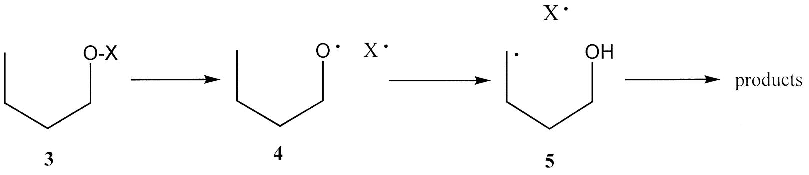
and these have not been observed in polar reactions. In this report, some newer reactions of δ-carbon radicals generated by 1,5-hydrogen transfer from alkoxyl radical intermediates are described. The scope and limitations of these reactions and their synthetic applications for carbon–carbon bond formation as well as for the functionalisation of a non-activated carbon atom will be discussed.

2. Alkoxyl radical formation: precursors and reaction conditions

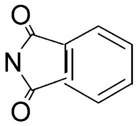
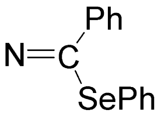
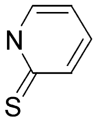
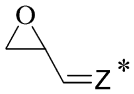
Various classes of oxygen-containing compounds can be used as appropriate precursors of alkoxyl radicals undergoing a 1,5-hydrogen rearrangement from the δ-carbon to oxygen and a variety of reagents and reaction conditions can be applied.[1,4–8,15,16] This type of rearrangement can take place only at alkoxyl radicals possessing at least one hydrogen on conformationally close carbon atoms, preferentially at the δ- (or ε-) position.

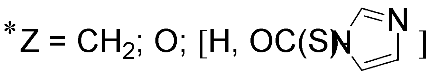
The formation of alkoxyl radicals **4** involves homolysis of a weak oxygen–heteroatom bond in **3** (RO–X, $<70\ \mathrm{kcal\ mol^{-1}}$) (Scheme 2). The alkoxyl radical **4** cannot be directly generated from alcohols, by homolysis of the O–H bond ($104\ \mathrm{kcal\ mol^{-1}}$). Numerous reagents are, however, available for the conversion of alcohols to suitable precursors **3** of alkoxyl radical intermediates (Table 1).[1,3–8] Alcohols are formally used as substrates for the oxidative formation of reactive intermediates in situ which undergo homolytic cleavage of the O–X bond. Thus, in the lead tetraacetate (LTA) oxidation of alcohols in non-polar solvents, X is $Pb(OAc)_3$ **3a**,[1,8,15,16] in the hypoiodite reaction (LTA+I_2), X is iodine **3e** (RO–I, $56\ \mathrm{kcal\ mol^{-1}}$)[1,5,11] and in the hypobromite reaction X=Br **3d** (RO–Br, $60\ \mathrm{kcal\ mol^{-1}}$).[6,17] All of these precursors of alkoxyl radicals, formed in situ from the corresponding alcohols and oxidant, are unstable and they have not been isolated. Alkyl hypochlorites **3c** (X=Cl), however, are good precursors of alkoxyl radicals, and can be prepared in a separate reaction and then subjected to photolytic



Scheme 2.

Table 1. Alkoxyl radical precursors, reagents and reaction conditions

3	Precursor of RO· X	Reagents and reaction conditions for O–X bond homolysis	Name of reaction	Ref.
a	$Pb(OAC)_3$	80°C or $h\nu$	LTA oxidation of alcohols	1a–c,j,k
b	NO	$h\nu$	Barton reaction	1d,e,g,9
c	Cl	$h\nu$ or Fe^{2+}	Photolysis of alkyl hypochlorites	4c,13,18
d	Br	Ag_2O, Ag^+, HgO	Hypobromite reaction	1f,6,17
e	I	[LTA, HgO, $Ph(OAc)_2$, $Ph_2Se(OH)OAc$]+I_2, $h\nu$	Hypoiodite reaction	1a,c,h,5
f	OH	Fe^{2+}	Ferrour ion induced decomposition of ROOH	7,20,21
g	OR	Fe^{2+}	Ferrous ion induced decomposition of ROOR	21
h	OAc	$h\nu$	Photolysis of peresters	23
I	Ce^{6+}	Δ	Ca^{6+} oxidation of alcohols	32
j	SPh(Ar)	$Bu_3Sn^{\cdot}$+$h\nu$	Photolysis of alkyl benzenesulfenates	26
k		$Bu_3Sn^{\cdot}$, 80°C	Homolysis of *N*-alkoxy phthalimides	28
l		$Bu_3Sn^{\cdot}$, 80°C	Homolysis of Se-phenyl benzoselenohydroxamates	30
m		$Bu_3Sn^{\cdot}$+$h\nu$	Homolysis of *N*-(alkoxy)-pyridine-2-(1*H*)-thiones	25
n		$Bu_3Sn^{\cdot}$	Epoxide fragmentation	31



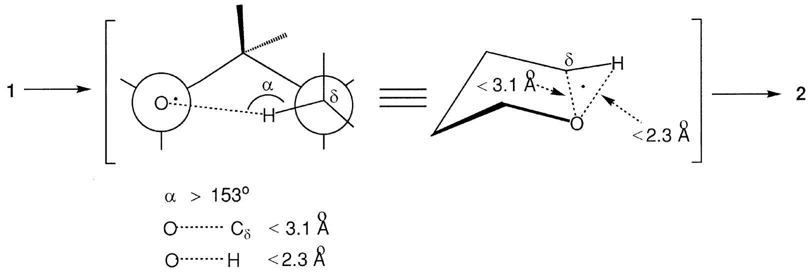


Figure 1.

decomposition.[4,10,18] Among the most convenient and easily available precursors of alkoxyl radicals are the alkyl nitrites **3b** (RO–NO, 53 kcal mol^{-1}), prepared by the esterification of alcohols with nitrous acid or nitrosyl chloride. The intramolecular reaction of alkyl nitrites is known as the Barton reaction (Scheme 2, Table 1).[4b,9,19]

Peroxy compounds (alkyl hydroperoxides **3f**, dialkyl peroxides **3g** and peroxyacetates **3h**, RO–OY, Y=H, R, Ac, >34 kcal mol^{-1}) form alkoxyl radicals by reduction with metal salts (Fe^{2+}, Co^{2+} etc), and by thermal or photolytic decomposition.[7,20–23]

Photolysis of alkyl benzenesulfenates **3j** (RO–SPh) in the presence of radical initiators generates the alkoxyl radical intermediates[24–26] (alkyl benzenesulfenates are prepared by the reaction of alcohols with benzenesulfenyl chloride in the presence of triethylamine as a base).

Several new precursors of alkoxyl radicals such as *N*-alkoxypyridine-2-(1*H*)-thiones **3m**,[27] *N*-alkoxyphthalimides **3k**[28,29] and Se-phenyl benzeneselenohydroxamates **3l**[30] were also synthesised from the alcohols and appropriate reagents. In the reactions of these compounds with the $Bu_3Sn^{\cdot}$ radical, under photolytic conditions, alkoxyl radicals are generated. Epoxides possessing potential for radical generation at the α-carbon atom **3n** were used as convenient precursors for the generation of alkoxyl radicals.[31] Irrespective of $X^{\cdot}$ transposition of the alkoxyl radical **4** takes place to produce the δ-carbon radical **5**.

3. 1,5-Hydrogen atom transfer

Alkoxyl radicals, as electrophilic species, are efficient reactive intermediates for hydrogen atom abstraction from non-activated C–H bonds.[1i,1] There are two groups of factors controlling the intramolecular hydrogen transfer: (a) energy factors which are related to energy values such as the bond dissociation energy and the enthalpy of reaction and (b) structural factors which depend on steric, conformational and polar effects. Enthalpy control is the most important, because the bond dissociation energy of RO–H is considerably higher than those of most C–H bonds and hydrogen transfer to an alkoxyl radical is an exothermic reaction ($\Delta H=-3$ kcal mol^{-1} for the formation of a primary carbon radical, -5 kcal mol^{-1} for a secondary and -9 kcal mol^{-1} for a tertiary carbon radical). Formation of the more stable carbon radical requires a smaller enthalpy of activation (ΔH^*).

In the intramolecular 1,5-hydrogen abstraction, entropy factors dominate and the rate constant is 2.7×10^7 M^{-1} s^{-1},[33] whilst the rate constant for intermolecular hydrogen abstraction is about 10^5–10^7 M^{-1} s^{-1}.[34]

Transposition of the radical center from the alkoxyl radical to the δ-carbon atom involves 1,5-hydrogen transfer, passing through a chair-like six-membered cyclic transition state (Fig. 1).[35] The six-membered transition state resembles a flattened chair arrangement with coplanar oxygen and three carbon atoms ($O–C_{\alpha}–C_{\gamma}–C_{\delta}$) in which the migrating hydrogen atom is slightly out-of-plane with the C···H···O angle over 153°.[35] All other geometries of the transition states are higher in energy. Entropy factor and proximity effects favour the intramolecular 1,5-hydrogen rearrangement. 1,5-Hydrogen transfer is mostly favoured when both reactive centers (alkoxyl radical and proactivated carbon atom) possess a fixed stereochemistry resembling a quasi-six-membered cyclic transition state.[1a–c,5,35] An intramolecular 1,5-hydrogen abstraction occurs, however, if one or both reactive centers are flexible and constitutionally remote non-activated carbon atoms are conformationally suitably oriented with respect to the attacking oxygen radical in the transition state controlling this process. Such an orientation is attained with minimal interactions and distortions when the intramolecular distance between the attacking alkoxyl radical and the proactivated carbon atom reaches the optimal distance 2.5–2.7 Å, indicating that the recognition of a particular hydrogen atom to be abstracted in the molecule possessing a more energetically similarly non-activated carbon–hydrogen bond is mainly controlled by stereochemical factors.

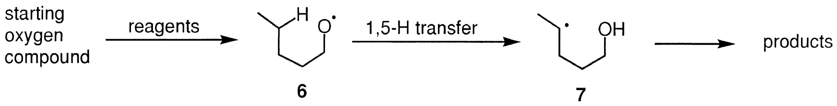
The predominance of intramolecular 1,5-hydrogen transfer over 1,6-hydrogen rearrangement comes mainly from entropy control. The ratio of rate constants for 1,5-/1,6-hydrogen transfer is 10:1. 1,6-Hydrogen migrations, involving a seven-membered cyclic transtion state, were observed as a side reaction, but this may be the main reaction only when favourable conformational factors exist or when there are no hydrogen atoms at the δ-carbon atom.[1a–e,35]

1,6-Hydrogen atom transfer involving a quasi-seven-membered ring transition state is not, however, favourable because angle strain and non-bonding interactions require more activation energy, even when the ε-hydrogen atom is energetically activated by benzylic or allylic interactions.[36,37] On the other hand, in rigid bicyclic or polycyclic systems in which, due to structural and stereochemical factors, the ε-carbon atom and oxygen radical assume the optimal distance of 2.5–2.7 Å, 1,6-hydrogen transfer is the favoured reaction.[38] 1,4-Hydrogen migration in alkoxyl radicals, involving a five-membered cyclic transtion state, is rare and was only theoretically considered.[35]

4. Reactions of intermediary δ-carbon radicals

The fate of the δ-carbon radicals generated by 1,5-hydrogen transfer to alkoxyl radical is determined by the precursors of the alkoxyl radicals, the reagents used and the reaction conditions (Scheme 3,Table 2).

In addition to the precursors of alkoxyl radicals listed in Table 2, *N*-(alkoxy)pyridine-2(1*H*)-thiones are efficient precursors of the free alkoxy radicals, but 1,5-hydrogen abstraction was not described for these systems. Intramolecular addition and β-fragmentations were only investigated.[25]



Scheme 3.

Table 2. Starting compounds, reagents and products derived from the δ-carbon radical **7** generated by 1,5-hydrogen abstraction in the alkoxy radical **6**

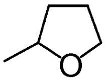
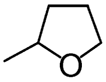
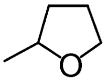
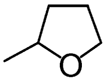
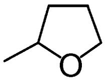
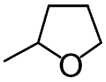
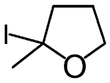
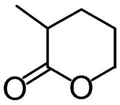
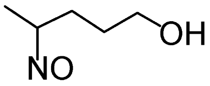
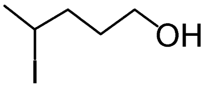
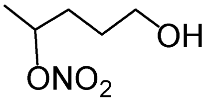
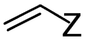
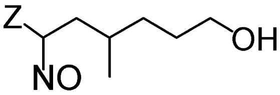
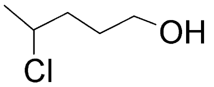
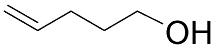
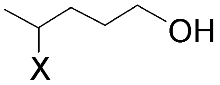
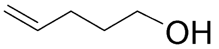
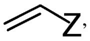
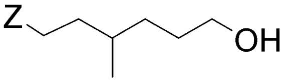
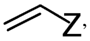
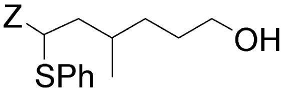
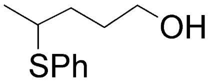
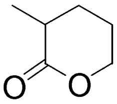
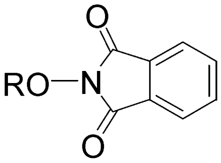
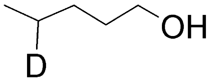
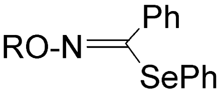
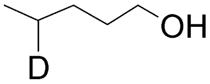
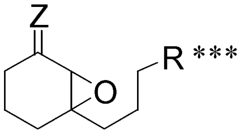
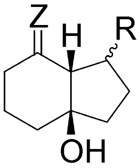
Starting oxygen compound	Reagents, solvents	Products derived from δ-carbon radical **7**	Ref.
ROH	LTA, C_6H_6		1a,b,4a,8,15
	LTA+I_2, C_6H_{12}		1a,c,h,5
	HgO+I_2, C_6H_{12}		39,40
	Ag_2O+Br_2, pentane		6,17
	PhI$(OAc)_2$+I_2		41–43
	$Ph_2Se(OH)Oac$+I_2		43,44
ROH	LTA+I_2 (excess), C_6H_{12}[a]		1a,c,5
ROH	LTA+CO, C_6H_6, 80 atm.		45
RONO	*hν*, C_6H_6		1d,e,4b,9,12
	hν, $Cu(OAc)_2$, C_6H_6		46
	I_2, *hν*, C_6H_6		47
	O_2, *hν*, C_6H_6		48
			49

Table 2 (*continued*)

Starting oxygen compound	Reagents, solvents	Products derived from δ-carbon radical **7**	Ref.
ROCl	hν, CCl_4		4c,10,13
ROOH	$FeSO_4$, $Cu(OAc)_2$, AcOH	 **	7,20,21
	$FeSO_4$, CuX_2, AcOH		22
ROOR	$FeSO_4$, $Cu(OAc)_2$, AcOH	 **	50
ROSPh(Ar)	, hν, Bu_3SnH, C_6H_6		49
	, hν, $(Bu_3Sn)_2$, C_6H_6		49,51
	hν, $(Bu_3Sn)_2$, C_6H_6		14
	CO(60 atm), hν, C_6H_6		45
	hν, Bu_3SnD, C_6H_6		28,29
	hν, Bu_3SnD, C_6H_6		30
	Bu_3SnH, C_6H_6, AIBN, Δ		31,52

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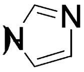
[a] Excess of iodine and prolonged reaction time is required.

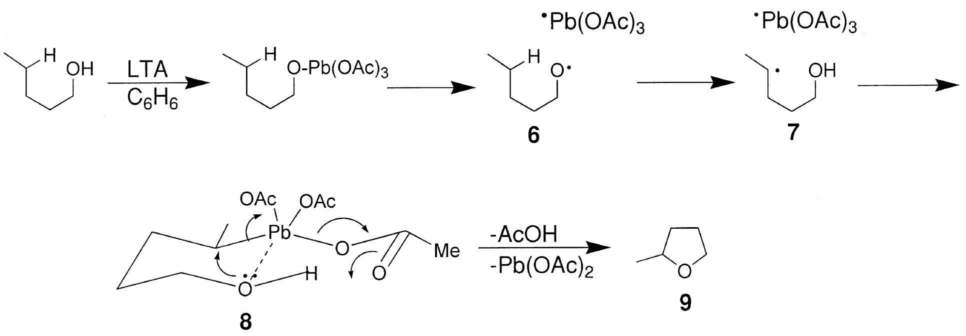
[**] ε-Unsaturated alcohols were presented in the mixture up to 12%.

[***] *Z = CH_2; O; [H, OC(S)N ].

4.1. Lead tetraacetate oxidation of alcohols

In the oxidation of saturated alcohols by means of LTA in non-polar solvents, such as benzene or cyclohexane, under thermal or photolytic conditions the intramolecular reaction occurs and the corresponding five-membered cyclic ethers are obtained in variable yields.[1a,b,h,g] Tetrahydrofuran ring closure involves the alkoxyl radical **6** and δ-carbon radical **7** as intermediates. The formation of the alkoxyl radical involves the homolytic decomposition of the intermediary lead(IV) alkoxides.[1a–c] Internal 1,5-hydrogen transfer is a characteristic reaction of the alkoxyl radical **6**, resulting in the generation of the corresponding δ-carbon radical. The carbon radical **7**, however, exists as a tight radical pair with its $^{\cdot}Pb(OAc)_3$ radical counterpart and undergoes concerted intramolecular ligand transfer oxidation. We believe that the ether ring closure involves a transition state such as **8** (Scheme 4). Since the δ-carbon radical **7** exists in a radical pair system with a Pb(III) species, oxidation of the δ-carbon radical probably occurs via the transition state **8** involving Pb–C bond formation and, in the subsequent intramolecular ligand transfer-like reaction a five-membered cyclic ether ring closure takes place, affording the final product **9**.

When an intramolecular ligand transfer reaction is not favourable, an electron transfer oxidation of the carbon radical occurs by Pb(III) or Pb(IV) salts and products derived from the carbocation intermediate are formed as



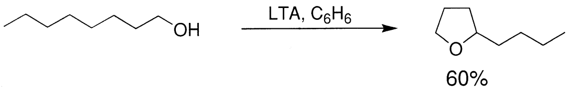
Scheme 4.

side products.[36a,53] Evidence that a partially positively charged δ-carbon intermediate is involved has been obtained from the oxidations of alcohols containing an asymmetric tertiary δ-carbon atom where a completely racemised tetrahydrofuran derivative was obtained.[54] One-electron transfer oxidation of the δ-carbon radical to the corresponding carbocation intermediate is also supported by the results obtained in the oxidation of alcohols possessing a neopentyl δ-carbon atom. Such alcohols in LTA oxidation undergo 1,2-migration of the alkyl and phenyl groups or an elimination reaction, typical for carbocation intermediates, while, when a tertiary δ-carbon radical and the subsequent carbocation are involved, unsaturated alcohols as side reaction products are obtained.[36a,53]

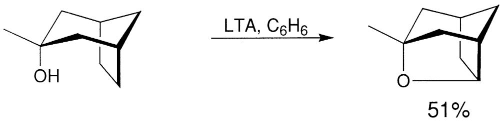
In the LTA oxidation of tertiary alcohols, β-fragmentaion of alkoxyl radicals is a serious competing reaction with the 1,5-hydrogen shift. β-Cleavage of alkoxyl radicals is favoured when effects stabilising the carbon radical or carbonyl compound, arising in the fragmentation reaction, are present.[1b,8,55]

There is no strong evidence for δ-carbocation involvement in the process of cyclic ether ring closure, since products of elimination and/or rearrangement generally were not obtained. Elimination reactions occur only when a tertiary δ-carbocation intermediate is involved. Skeletal rearrangements such as the neopentyl-type rearrangement, typical for carbocation intermediates, were not observed, but when a neophyl-type δ-carbocation is involved products of 1,2-migration of the aryl group were obtained.[36,53]

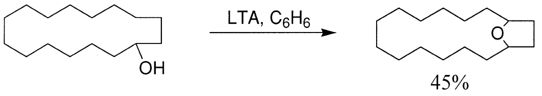
The following examples illustrate the synthetic possibilities for the introduction of an ether oxygen function at the non-activated δ-carbon atom (Eqs. (1)–(4)).[8,56–58]



(1)



(2)



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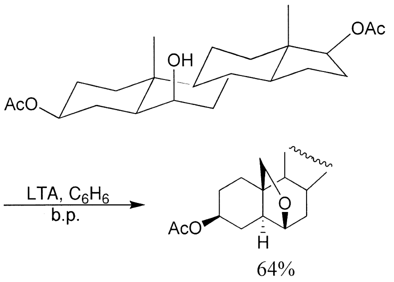
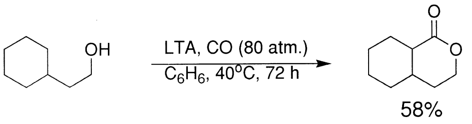


(4)

The interception of δ-carbon radicals formed in the LTA oxidation of alcohols by some other reagents was only achieved with carbon monoxide, when the oxidations were performed under a high pressure of carbon monoxide (80 atm, 72 h) and the corresponding δ-lactones are obtained (Eq. (5)).[45] Inter- and intramolecular addition or substitution reactions of the δ-carbon radical generated in the LTA oxidations of alcohols were not observed. Carbonylation of δ-carbon radicals, in the LTA oxidation of alcohols, involves the reaction of the radical with carbon monoxide to give the corresponding acyl radicals which by a subsequent oxidation reaction, lead to the δ-lactone ring closure. The formation of some lead acetate carbonyls of type $Pb(OAc)_{4-n}(CO)_n$ and carbonylation of carbon radicals by ligand transfer oxidation could be an alternative path for the carbonylation and formation of δ-lactones. Since a complementary carbonylation of the δ-carbon radical generated by photolysis of alkyl p-nitrobenzenesulfenates is a very fast reaction (1 h at 60 atm), this strongly supports the idea that the δ-carbon radical in the LTA oxidation of alcohols is in a tight radical pair with Pb(III) or Pb(IV) species coordinated to the hydroxylic group, subsequently undergoing the ligand-transfer reaction of hydroxylic oxygen or carbon monoxide onto the δ-carbon atom.



(5)

4.2. Alkyl hypohalites

Alkyl hypochlorites, hypobromites and hypoiodites are good precursors of alkoxy radicals which in a subsequent 1,5-hydrogen rearrangement give the δ-hydroxyalkyl radical.[1a–c,4] Alkyl hypohalites can easily be prepared from the corresponding alcohols. Alkyl hypochlorites are stable compounds in the absence of light at room temperature,[4,13,18] whereas alkyl hypobromites and hypoiodites are not stable at rt and they are prepared in situ as intermediates in the oxidations of alcohols with the corresponding halogen and oxidants.[1a,c,h,6] Since the formation of an intermediary alkoxy radical from these substrates takes place with different reagents and under different reaction conditions, a 1,5-hydrogen shift is involved as a common reaction step, thus forming a δ-hydroxyalkyl radical which, however, furnishes different reaction products.

4.2.1. Alkyl hypoiodites. Alkyl hypoiodites are prepared in situ from the corresponding alcohols, iodine and oxidants such as LTA,[1a,c,h,5,39,40] HgO,[39,40] $PhI(OAc)_2$[41–43] and $Ph_2Se(OH)Oac$ (Eq. (6)).[43,44] The reactions of alkyl hypoiodites are mechanistically very similar to the LTA oxidations of alcohols.

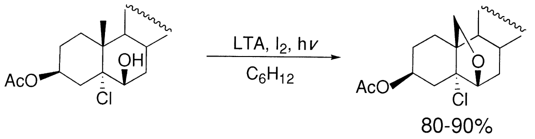
$$RCH_2OH \quad + \quad I_2 \quad + \quad \text{oxidant} \longrightarrow RCH_2O\text{-}I$$

$$\text{oxidant} = \text{LTA, HgO, } PhI(OAc)_2\text{, } Ph_2Se(OH)OAc \tag{6}$$

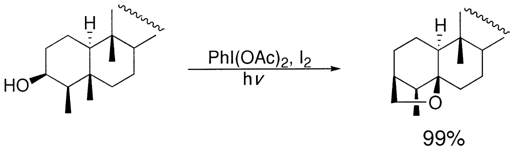
Homolysis of the O–I bond of the alkyl hypoiodite **10** is induced by photolysis to generate an alkoxyl radical **11** (Scheme 5).[1a,c] In the subsequent 1,5-hydrogen transfer, a δ-carbon radical **12** is formed which is captured by iodine or by the abstraction of iodine from alkyl hypoiodites, thus forming an intermediary 1,4-iodohydrin **13**. In the presence of an excess of metallic oxidants and a prolonged reaction time, the 1,4-iodohydrin undergoes a cyclisation reaction yielding the tetrahydrofuran derivative **14**. The formation of cyclic ethers in the hypiodite reaction was also explained by further oxidation of the hydroxylic group of iodohydrin **13** with oxidants and iodine to give a new alkyl hypoiodite **15** having an iodine at the δ-position. In the subsequent alkoxyl radical formation, a carbon radical **16** is formed by a 1,5-hydrogen shift which undergoes cyclisation to the α-iodotetrahydrofuran derivative **17**. The alkoxyl radical formed from the hypoiodite **15** may undergo intramolecular homolytic substitution to give a cyclic ether **14**.

The δ-carbon radical **12** in the hypoiodite reaction is in tight radical pair with an iodine radical or a metallic species from the oxidants and it cannot be intercepted by some other reagent so that only an ether oxygen **14** and/or iodine **17** are introduced at the non-activated δ-carbon atom.[1a,c]

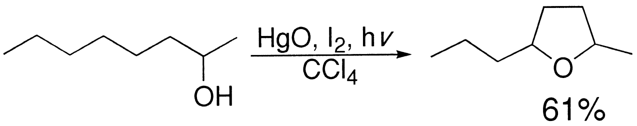
The following examples illustrate the synthetic applications of this reaction to functionalise a non-activated carbon atom (Eqs. (7)–(11)).[6,11,40,41,59]



(7)



(8)



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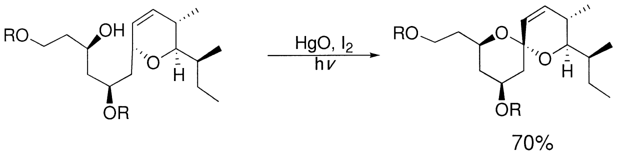
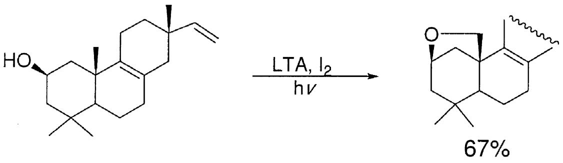
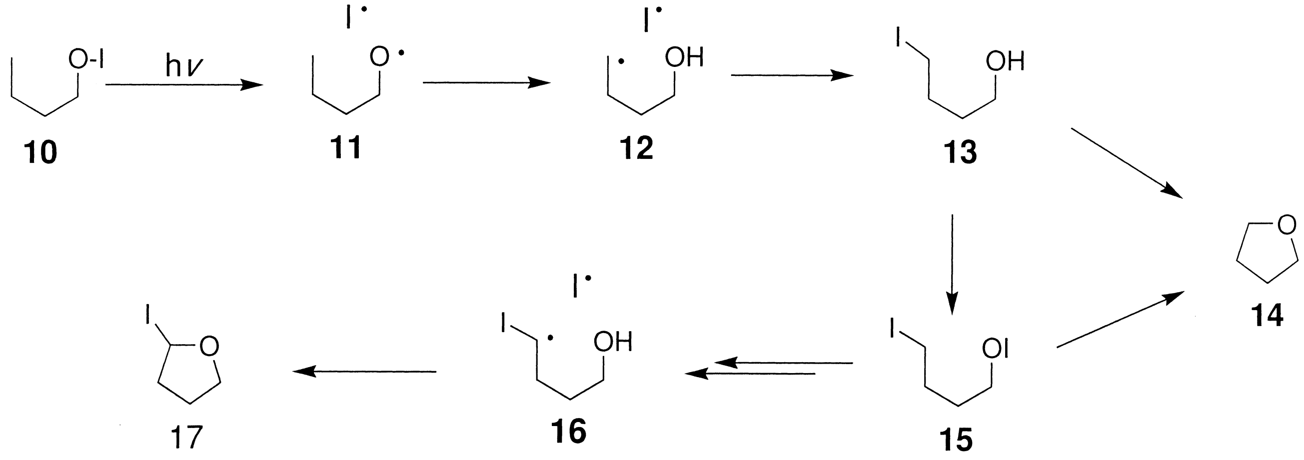


(10)

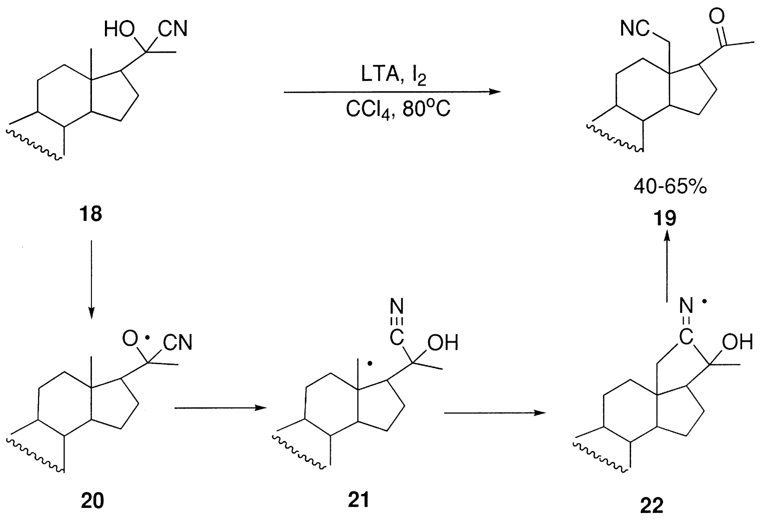


(11)

The alkoxyl radical **20** derived from the hypoiodite of the cyanohydrins **18**[1c,60] or their peresters[23] also undergoes 1,5-transposition of the radical center to give the corresponding δ-carbon radical **21**. When one or both reactive centers are fixed, the δ-carbon radical, with a cyano group in an appropriate position, undergoes intramolecular addition to the cyano group to give the intermediary imino radical **22**. In the subsequent step, C–C bond cleavage occurs and the



Scheme 5.

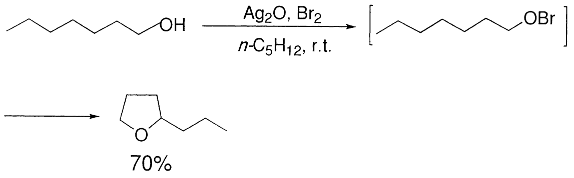


Scheme 6.

δ-cyanoketones **19** are obtained in good yields.[60] This type of 1,4-migration of a cyano group fails with flexible, open-chain cyanohydrins (Scheme 6).

1,4-Migration of a cyano group was also observed when peracetate was used as a precursor of the alkoxyl radicals.[23]

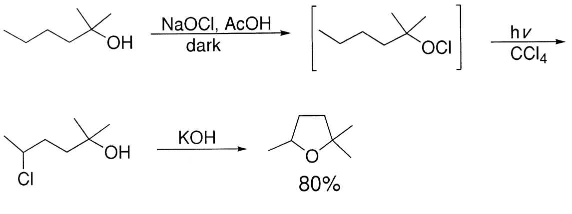
4.2.2. Alkyl hypobromites. Alkyl hypobromites appear as intermediates in the reaction of alcohols with bromine and silver oxide (or acetate) or mecury oxide.[6,17,61] Alkyl hypobromites are very unstable and their decomposition occurs in daylight, forming an alkoxyl radical. The δ-carbon radical, arising from a 1,5-hydrogen shift, may be in a tight radical pair with metal ions and there is no strong evidence for the interception of such a radical by bromine with the formation of a 1,4-bromohydrin. If bromohydrins are, however, really involved as intermediates they rapidly undergo an intramolecular cyclisation to the corresponding tetrahydrofurans (Eq. (12)).[6] The evidence indicating that the δ-carbon radical reacts with the hydroxylic group, by some concerted process, to give a THF ring is the absence of noticeable amounts of the other reaction products in the hypobromite reaction. Alkoxyl radicals, even tertiary radicals generated by alkyl hypobromite decomposition, do not undergo the β-fragmentation, a fact strongly supported by the alkoxyl and δ-alkyl radicals being in a tight radical pair with a metallic species.



(12)

4.2.3. Alkyl hypochlorites. Irradiation of alkyl hypochlorites gives 1,4-chlorohydrins as products of the intramolecular radical reaction.[4] Chlorohydrins are unstable and smoothly cyclise under basic conditions and thus the corresponding THF derivatives are obtained in the subsequent reaction (Eq. (13)). Alkyl hypochlorites were easily prepared from the corresponding alcohols and by reaction with hypochlorous acids (from sodium or calcium hypochlorite and acetic acid). Tertiary alkyl hypochlorites are prepared without special precautions at room temperature and in dim light, whilst alkyl hypochlorites derived from primary and secondary alcohols must be prepared in the dark at rt.[4,18]

In the photolysis of alkyl hypochlorites the δ-carbon radical, formed by intramolecular 1,5-hydrogen transfer, reacts with the starting hypochlorites rather than with a chlorine radical. When the concentration of the alkyl hypochlorite becomes too low, however, the coupling of the δ-carbon radical with a chlorine atom is a possible reaction. Since the O–Cl bond in hypochlorites is very weak (about 60 kcal mol^{-1}), this intermolecular chlorination by chlorine atom transfer is favoured and quenching of the δ-carbon radical by an added reagent was only observed when the radical possesses an appropriately located olefinic bond. In this case, the intramolecular cyclisation reaction competes with the chlorine atom transfer reaction.

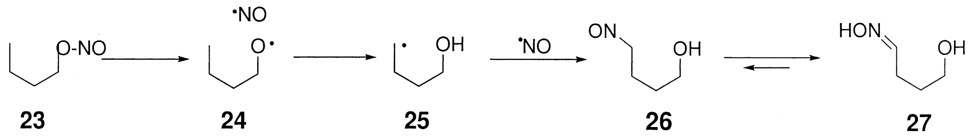


(13)

The decomposition of primary and secondary alkyl hypochlorites in the dark was carried out by ferrous salts and a mixture of 1,4-chlorohydrins and tetrahydrofuran derivatives was obtained. Treatment of the crude reaction mixture with potassium hydroxide, however, gave good yields of the tetrahydrofuran derivatives.[18]

4.3. Photolysis of alkyl nitrites (Barton reaction)

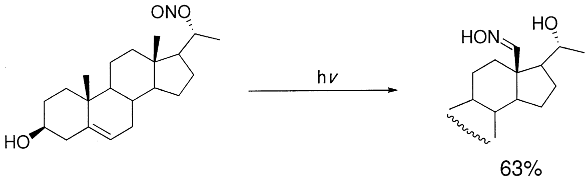
Alkyl nitrites are among the most convenient precursors of alkoxyl radicals to perform an intramolecular functionalisation of the non-activated carbon atom and to introduce a nitrogen-containing functional group at the δ-carbon atom.[1d,e,g] Photolysis of the alkyl nitrite **23** involves homolysis of the RO–NO bond (53 kcal mol^{-1}) to give an alkoxyl radical **24** and, by a subsequent 1,5-hydrogen



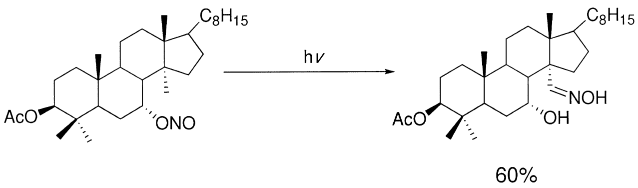
Scheme 7.

shift, the δ-carbon radical **25** is generated.[1d,e,g,3,12] Coupling of the carbon radical with the nitroso radical gave a δ-nitrosoalcohols **26** as the final product of the intramolecular reaction (Scheme 7).

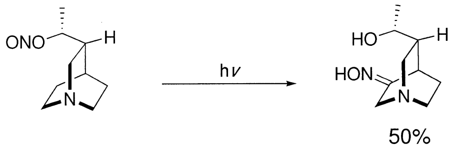
This type of reaction is known as a Barton reaction. It was successfully applied for the introduction of a nitrogen functional group onto the inaccessible non-activated δ-carbon atom such as angular methyl groups in steroid molecules.[1g,4b,12,19,62] The following examples illustrate the synthetic potential of the Barton reaction (Eqs. (14)–(17)).[39,62]



(14)



(15)



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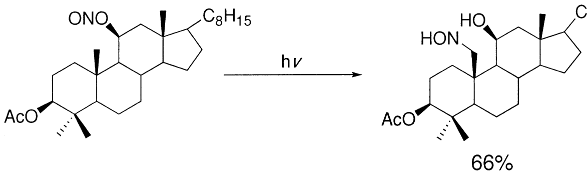
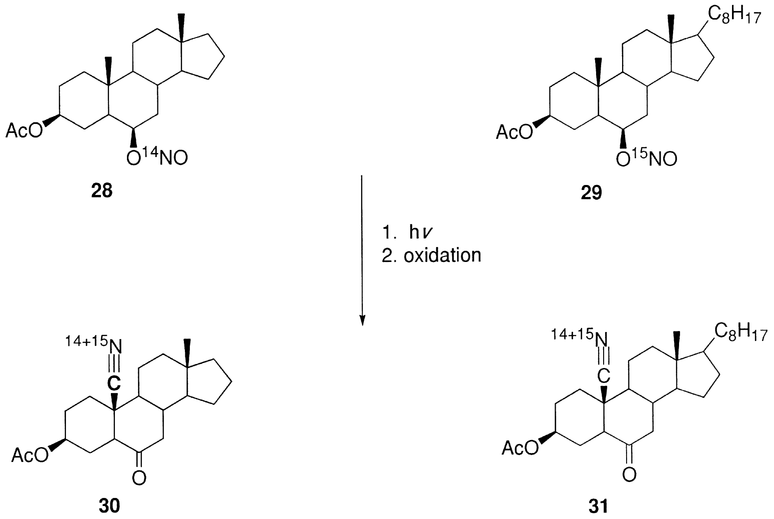


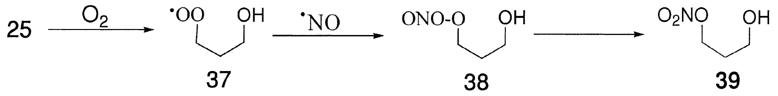
(17)

In the ‘normal’ Barton reaction, a δ-carbon radical reacts with nitroso radicals to give the δ-nitrosoalcohols which usually tautomerise to give the corresponding oxime **27**. The alkoxyl radical and the δ-carbon radical **25** are not in a tight radical pair with the nitroso radical, however, and thus the δ-carbon radical can be captured with an added reagent. Strong proof that the δ-carbon radical **25** is not in a radical pair system was obtained by photolysis of a mixture of 3β-acetoxy-androstan-6β-yl nitrite **28** and 3β-acetoxy-cholestan-6β-yl nitrite **29** labeled with the isotope ^{15}N. It was found that both steroidal oximes and the corresponding nitriles **30** and **31**, obtained after their oxidation and dehydration, contain the isotope ^{15}N in equal amounts (Scheme 8).[63]

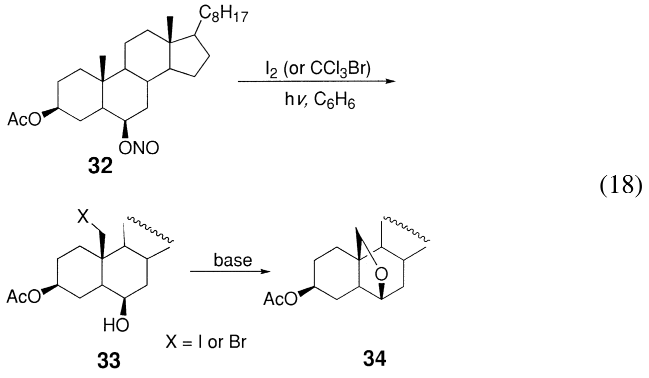
In the photolysis of the alkyl nitrite **32** in the presence of iodine, the δ-carbon radical reacts with iodine to give the corresponding δ-iodohydrin **33** which is converted by base to the 5β,19-cyclic ether **34** (Eq. (18)),[1d,47,64] while, in the reaction of the alkyl nitrite **35**, in the presence of oxygen, the δ-carbon radical is quenched by oxygen and the δ-nitrate esters **36** are obtained (Eq. (19)).[65] The formation of the δ-nitrate ester group involves a coupling of the δ-carbon radical with oxygen to give a peroxy radical **37** which reacts further with a nitroso radical, thus forming a peroxy nitrate **38**, which is isomerised to the corresponding δ-nitrate group (Scheme 9).



Scheme 8.



Scheme 9.



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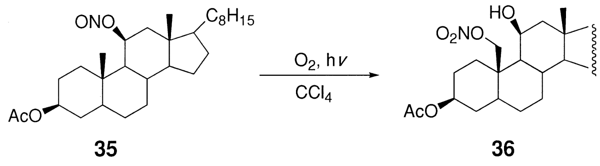
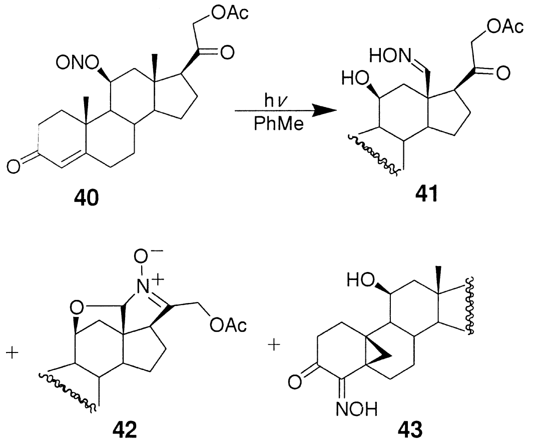


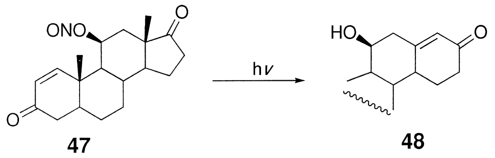
(19)

In addition to these reactions of δ-carbon radicals generated in the Barton photolysis of alkyl nitrites, under certain structural conditions other possibilities were found for the stabilisation of the δ-carbon radical. Thus, in the photolysis of steroidal nitrites such as corticosterone-11β-nitrite-21-acetate **40**, in addition to the expected products of functionalisation of the angular C-18 methyl group, **41** and **42**, the 5-oximinosteroid compounds **43** were also obtained (Eq. (20)).[66] The formation of **43** involves an intramolecular 11β-alkoxyl radical **44** hydrogen abstraction from the C-19 methyl group, thus generating the δ-carbon radical **45**, which is a 3-butenyl-type radical. The electron-deficient olefinic bond is present in the appropriate position and it undergoes a 3-*exo*-cyclisation to give a radical **46** which was quenched by the nitroso radical to give the 5-oximinosteroid compound **43** (Scheme 10).[63,66]



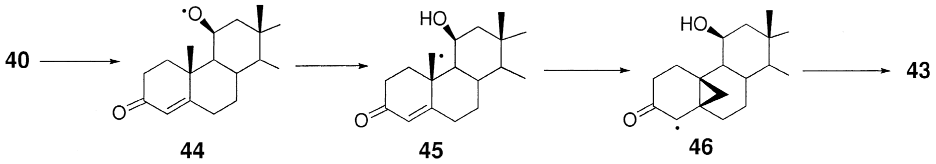
(20)

The carbon radical at the C-18 methyl group **50**, generated by 1,5-hydrogen shift of the alkoxyl radical **49** in the photolysis of Δ^1-androsten-3,17-dione-11β-nitrite **47**, undergoes a 3-*exo*-cyclisation with the adjacent carbonyl group to give a cyclopropyloxy radical **51**. From the carbon radical **52**, formed by a subsequent cyclopropane ring opening, hydrogen elimination and D-ring enlargement occurs affording the conjugated ketone **48** (Eq. (21))(Scheme 11).[67]

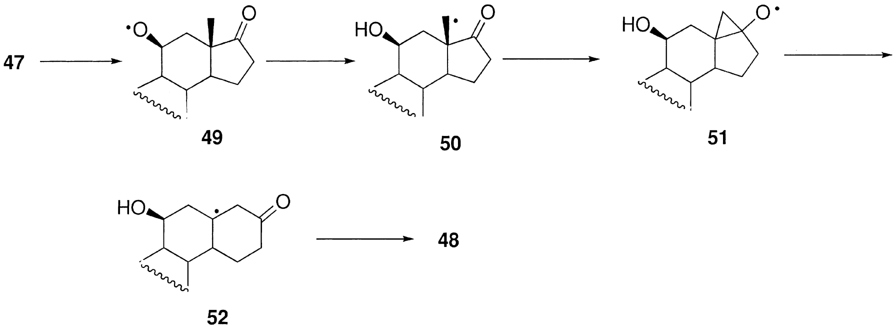


(21)

Strong evidence that the δ-carbon radical **54** generated by the photolysis of alkyl nitrites, e.g. **53**, is not in a tight radical pair with the nitroso radical was obtained when the carbon radical possesses an olefinic bond at the 5-position and it undergoes 5-*exo*-cyclisation affording a cyclic nitrosoalcohol **55**

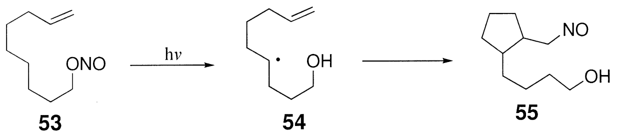


Scheme 10.



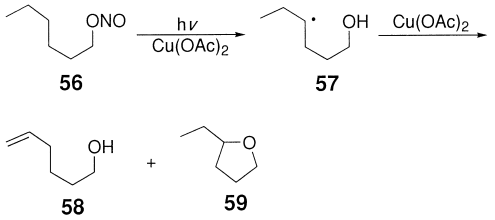
Scheme 11.

(Eq. (22)). When the same type of δ-carbon radical was generated by the LTA oxidation of a corresponding unsaturated alcohol it did not undergo a cyclisation reaction thus strongly supporting the theses that, in the LTA oxidation of alcohols, the δ-carbon radical is in a tight radical pairing with the lead species.[68]



(22)

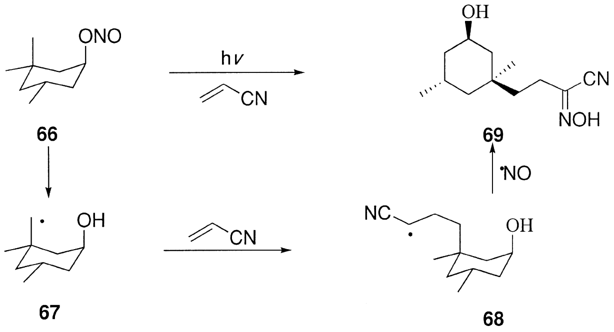
The δ-carbon radical **57** generated by photolysis of the alkyl nitrite **56** in the presence of cupric acetate was also quenched by cupric ions and one-electron transfer oxidation occurs, affording preferentially the δ-unsaturated alcohol **58** as a principal reaction product, accompanied by a small amount of the corresponding five-membered cyclic ether **59** (Eq. (23)).[46]



(23)

δ-Carbon radicals can undergo a hydrogen abstraction reaction when the stereochemical and conformational requirements are fulfilled, as in the case of the nitrite **60**. Possessing methyl groups in the *syn*-1,3-axial orientation is most convenient for 1,5-hydrogen transfer so that the δ-carbon radical **62**, arising from alkoxyl radical **61**, undergoes a second 1,5-hydrogen abstraction, generating a radical **63** ('billiard reaction'). The formation of the two oximes, **64** and **65**, is only possible when rearrangement of the free δ-carbon radical **62** is a competing reaction to the coupling with the nitric oxide (Scheme 12).[69]

The free radical addition of a carbon radical onto an electron-deficient olefinic bond is well known and is a synthetically valuable reaction. It was found that the δ-carbon radical **67** generated in the Barton photolysis of the alkyl nitrite **66** undergoes an intermolecular addition to a radicophilic olefin, thus generating a new carbon radical **68** which then reacts with a nitroso radical to give the δ-alkylated product **69**, possessing both an electron-withdrawing group and an α-oximino group in the alkylating chain (Scheme 13).[26,51]

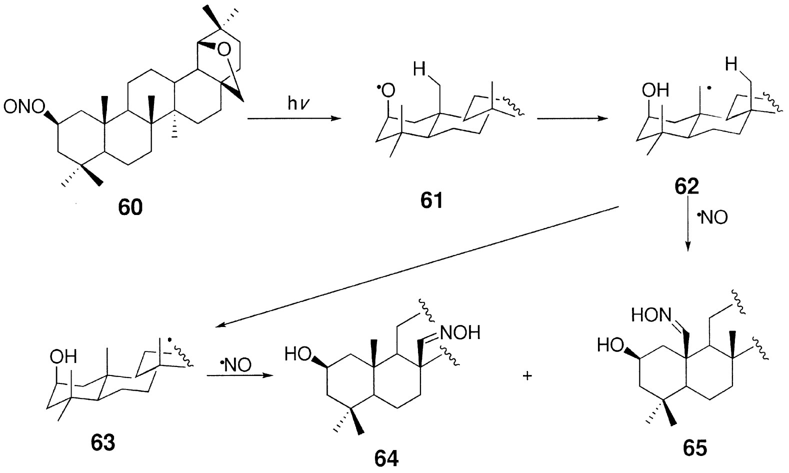


Scheme 13.

In order to suppress a normal Barton reaction and coupling of the δ-carbon radical (e.g. **67**) with the nitrosyl radical, it is necessary to use a 80 M equiv. excess of an activated olefin. By using a higher concentration of the activated olefin, its polymerisation becomes an important side reaction, while, by using a 50 M equiv. excess of a radicophilic olefin, the formation of products of a normal Barton reaction (δ-nitrosoalcohols) is a serious competing reaction to the δ-alkylation reaction. The introduction of a functionalised alkyl chain onto the inaccessible angular methyl group in steroid molecules and similar compounds, as well as in acyclic and cyclic molecules was also successfully accomplished.[51]

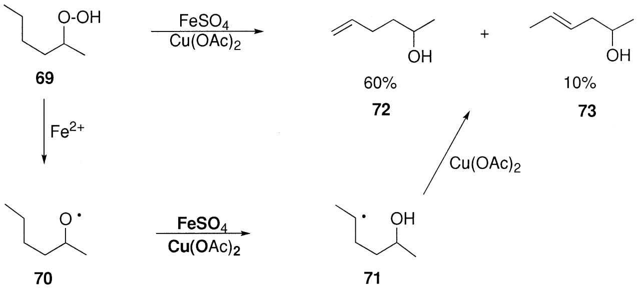
4.4. Decomposition of alkyl hydroperoxides and dialkyl peroxides

In the ferrous ion-induced decomposition of alkyl hydroperoxides, e.g. **69**,[7,20,21] and dialkyl peroxides[43] an alkoxy radical intermediate **70** is involved and they undergo an intramolecular 1,5-hydrogen shift, thus generating a δ-carbon radical **71**. Radicals formed under these conditions

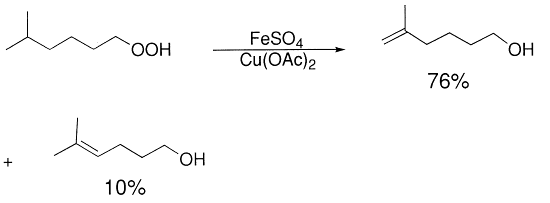


Scheme 12.

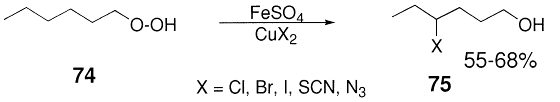
can undergo electron transfer or ligand transfer oxidations.[7,21,22] For the ferrous ion-induced decomposition of alkyl hydroperoxides such as **69** in the presence of cupric acetate, the δ-unsaturated alcohol **72** was obtained as the main reaction product, in addition to a small amount of the ε-unsaturated alcohol **73** (Scheme 14) (Eq. (24)).[7,20,21] On the other hand when the decomposition of the alkyl hydroperoxide **74** and dialkyl peroxides was carried out by ferrous ion in the presence of cupric halides or pseudohalides, a ligand transfer oxidation of the δ-carbon radical occurs and a halide atom or pseudohalide group was introduced at the δ-carbon atom **75** (Eq. (25)).[22]



Scheme 14.



(24)



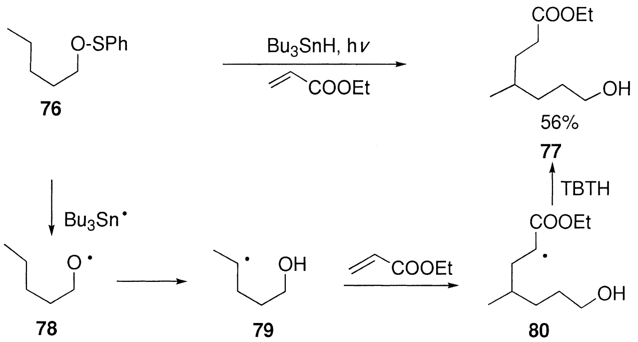
(25)

4.5. Alkyl benzene(arene)sulfenates

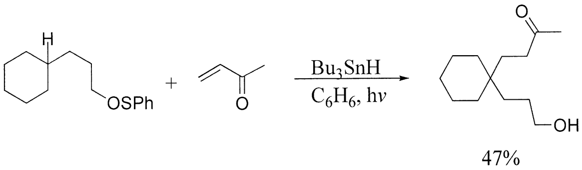
The RO–SPh bond of alkyl benzenesulfenates undergoes homolytic cleavage in a reaction with the tributyltin radical[14,24,26] or by laser flash photolysis[35] and alkoxyl radical intermediates are formed (Eq. (26)). Independently of the reaction conditions for the generation of the alkoxyl radical and irrespectivfe of whether it exists as a radical pair or as a free alkoxyl radical it undergoes 1,5-hydrogen transfer to give the δ-carbon radical.

$$\text{RO-SPh(Ar)} \xrightarrow{\text{Bu}_3\text{Sn}^\bullet} \text{RO}^\bullet + \text{Bu}_3\text{Sn-SPh(Ar)} \quad (26)$$

When an alkoxyl radical is generated by the photolysis of an alkyl benzenesulfenate, e.g. **76**, in the presence of an equal amount of tributyltin hydride (TBTH) and a 50 molar equivalent excess of a radicophilic olefin, the δ-carbon radical **79**, formed by transposition of the radical center in the alkoxyl radical **78**, by intermolecular addition to the olelfinic bond, is converted to the carbon radical **80** (Scheme 15). The final reaction product **77** is formed by the reaction of the radical **80** with TBTH. In this way, alkylation of the remote carbon atom was achieved and a functionalised alkyl chain was introduced on the non-activated δ-carbon atom (Eq. (27)).[26,49]

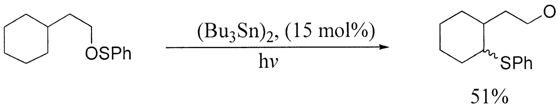


Scheme 15.

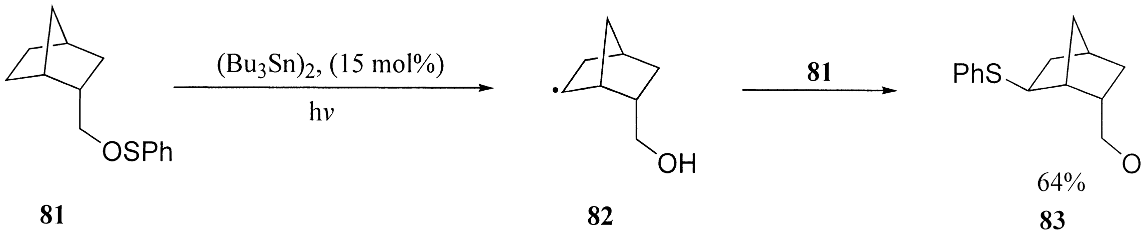


(27)

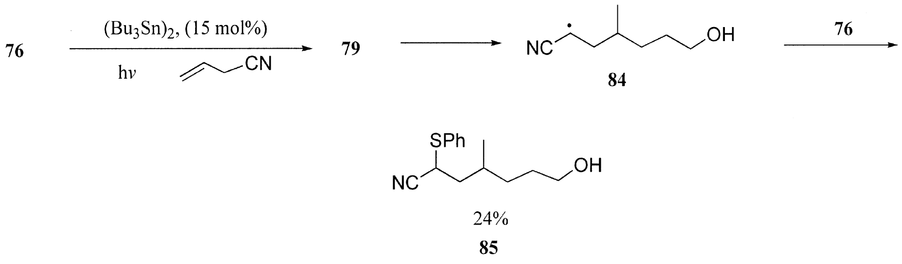
For the photolysis of alkyl benzenesulfenates, e.g. **81**, in the presence of 15 mol% of hexabutylditin and in the absence of any other reactive molecules or intermediary species, the δ-carbon radical **82** undergoes abstraction of the phenylthio group from the starting alkyl benzenesulfenate, giving the δ-phenylthio alcohol **83** and generating a new alkoxyl radical which continues the radical chain reaction (Scheme 16) (Eqs. (28) and (29)).[14]



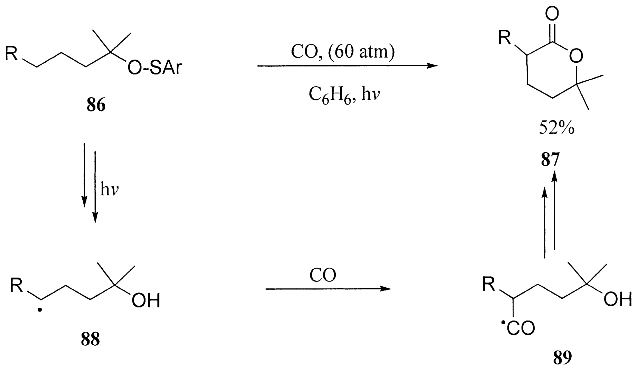
(28)



Scheme 16.

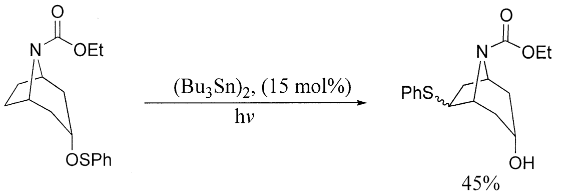


Scheme 17.



R = n-C_6H_{11}, Ar = p-nitrophenyl

Scheme 18.



(29)

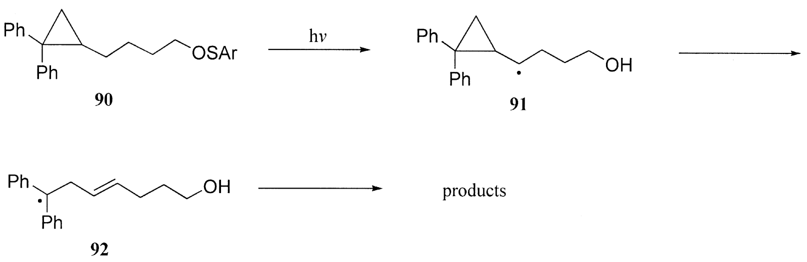
When the photolysis of alkyl benzenesulfenates such as **76** is carried out in the presence of 15 mol% of hexabutylditin and two mole equivalents of a radicophilic olefin, an alkylation of the δ-carbon atom occurs to generate a new electrophilic carbon radical **84** which reacts with the starting alkyl benzenesulfenate to give a δ-alkylated product **85** possessing a phenylthio group next to the electron-withdrawing group (Scheme 17).[49]

The δ-carbon radical **88** generated from alkyl p-nitrobenzenesulfenates, e.g. **86**, after a 1,5-hydrogen shift in the intermediary alkoxyl radical, was quenched by carbon monoxide when the reaction was performed under a high pressure (60 atm) of carbon monoxide. The intermediary acyl radical **89** reacts with the starting sulfenate esters to give arylthio esters as intermediates. In the subsequent thiophenol elimination, a good yield of the δ-lactone **87** was obtained as the final reaction product (Scheme 18).[45]

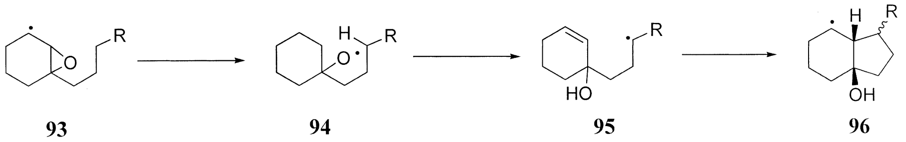
The p-nitrobenzenesulfenate esters **90**, possessing a cyclopropane ring at the 5-position, were used as the precursors of alkoxyl radicals and, after 1,5-hydrogen migration, the δ-carbon radical **91** is generated. Since this radical is of the cyclopropylcarbinyl type, it undergoes cyclopropane ring opening to give the open-chain 3-butenyl-type radical **92** (Scheme 19).[35]

4.6. Other precursors of alkoxyl radicals

Epoxides possessing a radical precursor group on the α-carbon atom are highly efficient substrates for alkoxyl radical generation since the intermediate oxiranylmethyl radical **93** undergoes rapid ring opening by homolytic cleavage of the C–O bond to produce allyloxy radical intermediates **94**.[31,35b] Irrespectieve of the nature of the original functional group attached to the α-carbon atom of the epoxide ring, these alkoxyl radicals can then undergo a 1,5-hydrogen transfer to give carbon centered radicals **95** which are suitably disposed for 5-*exo*-trig cyclisation to give bicyclic radicals **96** (Scheme 20).[31]

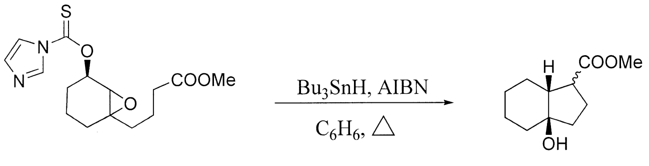


Scheme 19.



Scheme 20.

The oxiranylmethyl radical generated from the thiocarbonyl imidazlide **97** undergoes the following sequence of radical reactions: epoxide fragmentation/1,5-hydrogen migration/5-*exo*-cyclization and finally hydrogen atom capture from the stannane to give the bicyclo[4.3.0] derivative **98** (Eq. (30)).[31]

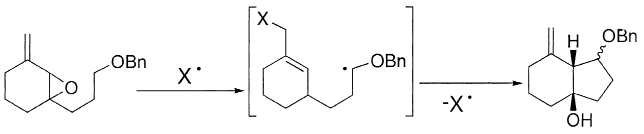


97

98 69%

(30)

In the reaction of the vinyl epoxide **99** with a tributyltin radical, an oxiranylmethyl radical is generated which, in the subsequent cascade of radical reactions, affords a bicyclic product **100** (Eq. (31)).[52]



73%

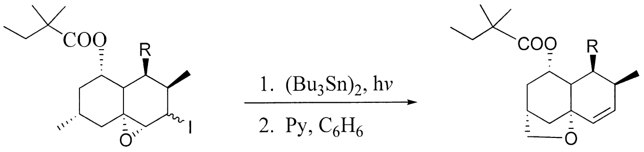
99

100

X = $Bu_3Sn^{\bullet}$, $PhS^{\bullet}$

(31)

In similar fashion, the oxiranylmethyl radical was also generated from the α-iodoepoxide **101** and the1,4-iodohydrin was formed (and converted to the tetrahydrofuran derivative **102**) by iodo transfer to a δ-carbon radical (Eq. (32)).[70]



58%

101

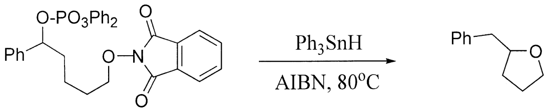
102

(32)

α-Ketoepoxides were also used as convenient precursors of oxiranylmethyl, and hence alkoxyl radicals.[71]

N-Alkoxyphthalimides, e.g. **103**, are convenient precursors of alkoxyl radicals.[28,29,72] They are readily prepared from the alkyl halides and *N*-hydroxyphthalimide in the presence of sodium hydroxide or in the reaction of alcohols with *N*-hydroxyphthalimide in the presence of triphenylphosphine and diethyl azidodicarboxylate. Homolysis of the O–N bond in *N*-alkoxyphthalimide occurs by reaction with TBTH (or TBTD) in refluxing benzene solution in the presence of AIBN as an initiator and an alkoxyl radical intermediate **104** is formed. In the subsequent 1,5-hydrogen transfer, a δ-carbon radical **105** is generated. In the reaction of the carbon radical **105** with TBTD, the δ-deuterio alcohol **106** is obtained in high yield (Scheme 21).[28]

When the δ-carbon radical, generated from *N*-alkoxyphthalimides as a precursor of the alkoxyl radical, is adjacent to a diphenylphosphatoxy group **107**, it undergoes formation of a five-membered cyclic ether **108**. Formation of the tetrahydrofuran derivatives involves a dissociative mechanism with formation of a radical-cation intermediate which undergoes the cyclic ether ring closure and subsequent hydrogen abstraction from TBTH (Eq. (33)).[29]

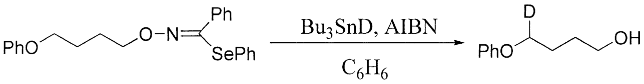


107

108

(33)

Se-phenyl benzeneselenohydroxamates such as **109** were also used as precursors of alkoxyl radicals under standard free radical conditions (TBTH, AIBN, benzene solution).[30] The alkoxyl radical formed in the reaction of **109** with Bu_3SnD undergoes an intramolecular hydrogen rearrangement and the 4-deuterio alcohol **110** is obtained (Eq. (34)).



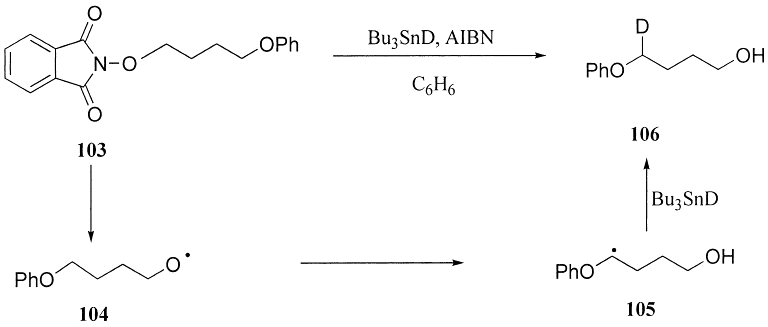
109

110

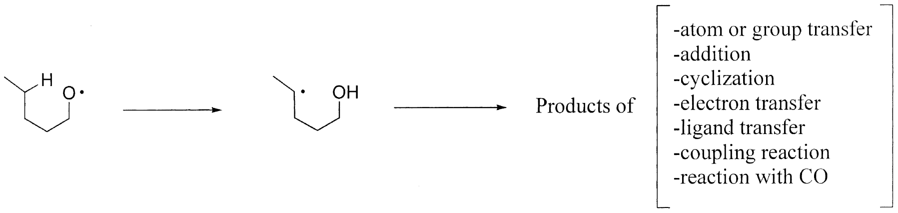
(34)

It was also observed that alkoxyl radicals generated from this type of precursor undergo an intramolecular addition to the olefinic bond and the corresponding tetrahydyrofuran derivatives are obtained.[30]

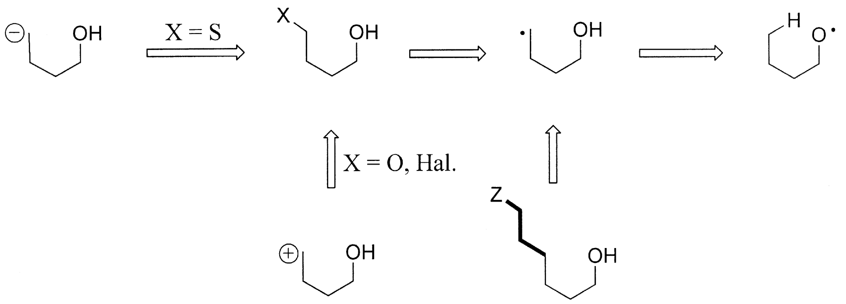
In addition to previously described precursors of alkoxyl radicals undergoing a 1,5-hydrogen transfer, *N*-(alkoxy)-pyridine-2-(1*H*)-thione **111** may also be good precursors for this type of radical transposition reaction.[25,27] Alkoxyl radicals **112** from these precursors are generated by the reaction with TBTH or by photolysis. However, it was only observed that, independently of the reaction conditions for the formation of alkoxyl radicals, then undergo the addition



Scheme 21.

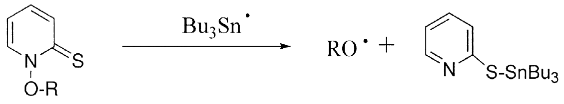


Scheme 22.



Scheme 23.

and β-fragmentation reactions (Eq. (35)). Thus, alkenyloxy radicals generated from *N*-(4-alkenyloxy)pyridine-2-(1*H*)-thione undergo the intramolecular cyclisation to the olefinic bond with preferential formation of tetrahydrofuran derivatives.[25]



(35)

111 **112**

5. Summary

The present review has attempted to highlight the fact that the introduction of new precursors and methods for alkoxyl radical generation have considerably enhanced the range of substituents and carbon–carbon bond forming reactions which can be carried out following the key 1,5-hydrogen atom abstraction step. With the exception of nitrite photolysis, these milder methods offer new opportunities which were not possible some forty years ago when reactions such as lead tetraacetate oxidation of alcohols and decomposition of alkyl hypohalites were explored. Some of the key pathways for evolution of the carbon centered radical which have therefore been developed are shown in Scheme 22.

Moreover, as indicated in Scheme 23, the introduction of appropriate functionality by 1,5-hydrogen atom abstraction then allows the rich chemistry of both carbanions and carbocations to be pursued.

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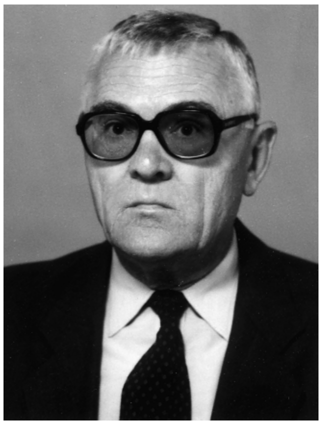
Biographical sketch



Živorad Čeković was born in Koštunići, Serbia. He recived his BSc and PhD degrees from the University of Beograde, completing his doctoral thesis in 1964 under supervision of Professor M. Lj. Mihailović. In 1965 he joined Professor C. Walling group at Columbia University, New York, as a posdoctoral fellow to work on free radical reactions. Two years later he returned to Belgrade and worked with Mihailović on the lead tetraacetate oxidation of alcohols and related intramolecular free radical functionalisation reactions. In 1970 he was appointed as an assistant professor at the University of Belgrade. In 1973 he joined Professor M. M. Green at Michigan University, Ann Arbor, USA, as a research associate, working on the intramolecular functionalisation of alkyl hydroperoxides. He received full professorship at University of Belgrade (1984). He held visiting professorship at Columbia University. His main research interest is in free radical reactions concentrating on the invention and discovery of new synthetically useful reactions such as intramolecular functionalisation, annulation, sequential and δ-alkylation reactions. He was elected president of the Serbian Chemical Society, dean of the Faculty of Science, University of Belgrade, a member of Educational council of Serbia. He is a corresponding member of the Serbian Academy of Science and Arts and is recipient of the Medal for scientific achievements of the Serbian Chemical Society, Belgrade's award for science.