Chemical Methods for Ether-Bond Cleavage by Electron-Transfer Reagents

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Keywords: Alkali metals / Cleavage reactions / Electron transfer / Radical ions / Synthetic methods

Ethers can easily be cleaved with various electron-transfer reagents. New data concerning the chemical methods of the regioselective opening of the ether bond with alkali metals (M^0), alkali metal aromatic radical anions ($Ar^{\cdot-}$, M^+), alkalides (M^-, M^+C; C denotes a ligand) and low-valent transition-metal compounds are presented.

1. Introduction

In general, there are three kinds of methods based on electron-transfer processes that have been used for reductive ether-bond cleavage — chemical,[1−17] electrochemical,[18−22] and photochemical.[23−26] The first one involves the use of alkali metals or low-valent transition-metal compounds.[27−32] Alkali metals are applied in the form of a dispersion (as M^0)[1−9] or in the ionic form as alkali metal aromatic radical anions ($Ar^{\cdot-}$, M^+)[10−13] or alkalides (M^-, M^+C), i.e. salts possessing alkali metal anions and cations complexed by a ligand.[14,15,33]

Ether radical anions are the initial reaction products formed after single-electron transfer to the ether molecule.[11,12,14,15] These charged species are usually unstable and undergo unimolecular fragmentation giving radicals and anions by mesolytic cleavage of the ether bond.[21,22] This is an elementary step of many electron-transfer processes of chemical and biochemical interest.[34−37] The reactions occur significantly faster than those observed for the homolytic cleavage of the same bonds in neutral substrates.[38−40]

This paper presents a review of data concerning the regioselectivity of the ether-bond scission under the influence of different electron-transfer reagents. The application of radicals and their further reaction products in organic synthesis is also described.

2. Linear Ether-Bond Cleavage with M^0 and $Ar^{\cdot-}$, M^+

The regioselectivity of the ether-bond cleavage by single-electron transfer is strongly influenced by the structure of the ether, the nature of the metal, and the polarity of the solvent. Alkali metals are known to induce the cleavage of the carbon−oxygen bond of alkyl aryl ethers under aprotic conditions in various solvents.[1−6] The first reaction step leads to radical anions, $ROAr^{\cdot-}$, which have been detected by ESR spectroscopy).[41]

The cleavage of the alkyl−oxygen bond with the formation of phenols (dealkylation) is observed most frequently. Cleavage of the aryl−oxygen bond (dealkoxylation) occurs

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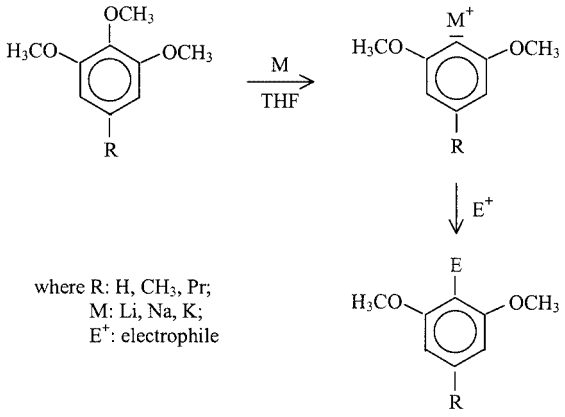
MICROREVIEWS: This feature introduces the readers to the author's research through a concise overview of the selected topic. Reference to important work from others in the field is included.

 DOI: 10.1002/ejoc.200400004

only in particular cases,[6] especially in the presence of potassium and in solvents with a low[7] or very low polarity.[8] The study of the reduction of different aryl methyl ethers by Li, Na, K and Cs in tetrahydrofuran or 1,2-dimethoxyethane confirms that the radical anions obtained undergo unimolecular fragmentation which can take place both by Ar−O or CH_3−O bond scission.[42] In the case of 1,2,3-trimethoxybenzene the methoxy group in the 2-position can be regioselectively removed by electron transfer from alkali metals and replaced with a variety of electrophiles in a one-pot procedure, affording 2-substituted resorcinol dimethyl ethers.[7] The usefulness of this synthetic method is illustrated by numerous examples, one of which is presented in Scheme 1.[7]



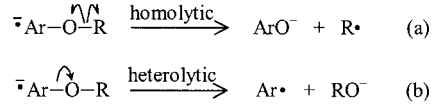
Scheme 1

Angelo[10] has investigated the reaction of some linear ethers with sodium naphthalenide as a typical $Ar^{\cdot -}$, M^+ reagent. The most likely mechanism for benzyl phenyl ether assumes the formation of a radical anion in which the added electron is localised on the benzyl substituent. Ejection of the phenoxide anion would produce the benzyl radical, which is converted into toluene upon reduction and protonation. The traces of bibenzyl observed might derive from radical coupling. Biallyl ether forms 50% biallyl and 30% allyl alcohol. In view of the facile reduction of allyl radicals by sodium naphthalenide a 50% yield of a dimer by radical coupling seems to be much too high; it is perhaps the product of a displacement reaction between the allyl carbanion and the ether.

Radical anions of appropriate ethers are formed by treatment of nitro-substituted benzyl phenyl ethers with potassium 2,4,6-tri-*tert*-butylnitrobenzenide.[11] The radical anions of 4-nitrobenzyl phenyl ethers undergo the cleavage at least 10^4 times faster than the radical anions of the corresponding 4-nitrophenyl benzyl ethers despite a perceived thermodynamic advantage for the latter set of reactions. It is possible that these results reflect a kinetic advantage for the cleavage reaction, which takes place with the regioconservation of the spin density. Similarly, naphthylmethyl phenyl ethers and naphthyl benzyl ethers are found to undergo the scission of the CH_2−O bond when treated with potassium anthracenide or fluoranthenide. The ethers of the naphthylmethyl series react 10^4 times faster than those of the naphthyl benzyl series. The radical anions of nitro-substituted phenyl alkyl ethers are inert towards any fragmentation.[20,43,44]

From a practical point of view the synthesis of organolithium compounds by the cleavage of ethers[6] is limited to the reaction of lithium metal with allylic or benzylic ethers, thereby generating allyl- or benzyllithium derivatives and avoiding Würtz-type side reactions.[45,46] However, when the lithiation reaction is applied to normal dialkyl ethers, they are generally found to be inactive. Indeed, some of them, for example diethyl ether or tetrahydrofuran, are widely used as solvents in lithiation reactions.[46] The reaction of primary alkyl or vinyl phenyl ethers with an excess of lithium powder and a catalytic amount of 4,4′-di-*tert*-butylbiphenylide (DTBB) in tetrahydrofuran at room temperature leads to the corresponding alkyl or vinyllithium intermediates. The latter afford the expected derivatives upon treatment with different electrophiles [H_2O, Me_3SiCl, *t*BuCHO, PhCHO, Me_2CO, Et_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$, PhCOMe] and subsequent hydrolysis.[47]

A new view of the mechanism of alkyl aryl ether cleavage under electron-transfer conditions has been published recently.[21,22] It is assumed that a radical anion of the ether is formed in the first step of the process (Scheme 2).[21,22] The ether-bond fragmentation then requires the transfer of the unpaired electron from the π*-orbital of the aryl ring into the region between two atoms of the scissile bond.

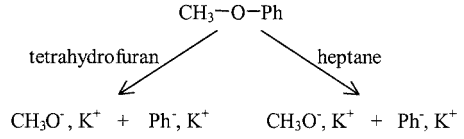


Scheme 2

Considering the electron distribution of the fragments, two modes of mesolytic scission are possible — alkyl−oxygen or aryl−oxygen. These have to involve an intramolecular π* → σ* electron transfer in a transition state. The alkyl−oxygen bond cleavage corresponds to a homolytic cleavage (path a) where the charge density is largely localised on the same set of atoms before and after the scission. It does not conserve the local spin density and should therefore show an intrinsic kinetic barrier (it is a thermodynamically favoured but kinetically forbidden process). On the other hand, the less favourable (from a thermodynamic point of view) aryl−oxygen cleavage corresponds to a heterolytic cleavage (path b), where the local spin density is conserved, and therefore no extra kinetic barrier should exist. In this case electron redistrubution can occur with the transfer of charge across the scissile bond (intramolecular dissociative electron-transfer).[21,22] It is worth noting that less likely mechanistic pathways, such as the cleavage of an aryl−oxygen bond to form Ar^- and $RO^{\cdot}$ or to $ArO^{\cdot}$ and R^-, have been discarded since similar modes of cleavage

were not observed in recent electrochemical work on diaryl ethers.[2,8]

The heterolytic scission depends on the electrophilic assistance from the counterion and is observed only in contact ion pairs. Homolytic scission takes place in solvent-separated ion pairs. For example, the reductive cleavage of 2,6-diphenylanisole with lithium in tetrahydrofuran is completely regioselective (dealkoxylation) resulting in *m*-terphenyl.[21] A significant amount of 2,6-diphenylphenol (dealkylation) is obtained when a more solvating solvent, such as dimethoxyethane, is used as it favours the formation of solvent-separated ion pairs. This trend is confirmed by the reaction conducted in the presence of 12-crown-4, which led to 43% of dealkylation and 57% of dealkoxylation products. In polar aprotic solvents such as hexamethylphosphoric acid triamide (HMPA) only dealkylation occurs in the case of several alkyl aryl ethers under the influence of alkali metals.[48] It has also been observed that the solvent can completely change the direction of the ether-bond cleavage in anisole from pure aryl−oxygen in heptane to almost 100% alkyl−oxygen in tetrahydrofuran by NaK alloy (Scheme 3).[49]



Scheme 3

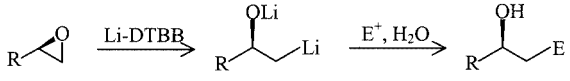
3. Ring Opening of Oxiranes and Oxetanes

The mechanism of the reduction of three-membered cyclic ethers (oxiranes) by electron transfer is less understood than that of nucleophilic ring opening by means of the hydride ion.[50] Kaiser et al.[51] have demonstrated for the reaction of phenyloxirane with lithium in liquid ammonia that a short-lived dianion picks up a proton from ammonia to yield an anion. The same experiment in HMPA or diethyl ether revealed a stable dianion. The reaction of oxiranes with alkali metals in tetrahydrofuran yields a variety of products, their nature depending on the metal and the structure of the oxirane molecule.[52] Deoxygenation to olefins is the major pathway in the case of lithium whereas rearrangement to carbonyl compounds, reduction to alcohols, and formation of dimeric products occur when oxiranes are treated with sodium.

The reduction of tetraaryloxiranes with Li, Na, K or Cs has been examined in polar aprotic solvents by Franco et al.[53] A stepwise reduction mechanism was established. The transfer of the electron produces C−O bond scission in the oxirane ring yielding a short-lived radical anion. This intermediate can either eliminate metal oxide (MO, $1/2M_2O_2$) and produce tetraarylethylene or can be further reduced to a dianion. A large proportion of the dianions undergo the C−C bond scission, which leads eventually to the corresponding ketone and diarylmethane.

Bartmann[13] has successfully reduced substituted oxiranes with lithium naphthalenide or potassium biphenylide and obtained many β-metallated alkoxides at low temperatures. For example, cyclohexene oxide is smoothly converted into β-lithiated cyclohexanolate in tetrahydrofuran at −80 to −90 °C.

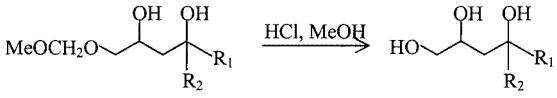
Very interesting reactions of oxiranes as well as many other classes of organic compounds with lithium and a catalytic amount of DTBB have been presented by Yus in several review articles.[54−57] For instance, the reaction of chiral oxiranes in tetrahydrofuran at −78 °C leads to the corresponding β-functionalised organolithium intermediates. The latter gave the expected chiral products in a regioselective manner upon treatment with different electrophiles at temperatures ranging between −78 °C and room temperature, followed by hydrolysis (Scheme 4).[58]



where R: Me, *iso*-Pr, CH_2OCH_2OMe

Scheme 4

The hydrolysis of compounds resulting from the reaction of a methoxymethyl-substituted oxirane and a carbonyl compound as an electrophile with hydrochloric acid in methanol gives differently substituted triols (Scheme 5).[57,59]

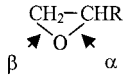


Scheme 5

The methodology shown in Schemes 4 and 5 has been applied to the synthesis of so-called functionalised branched carbohydrates, which are glycosidic components of many antibiotics.[57,60,61]

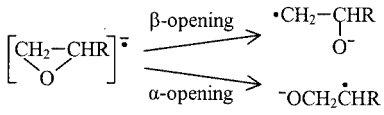
Cohen et al.[62] have observed that oxiranes are easily cleaved by lithium 4,4′-di-*tert*-butylbiphenylide (Li-DTBB) at −78 °C. Oxiranes with one or two geminal saturated substituents are opened mainly between the oxygen atom and the least substituted carbon atom. The ring opening in the other direction leads to an unstable β-lithioalkoxide, which very rapidly forms an olefin. 1,2-Disubstituted oxiranes with acyclic substituents yield only the appropriate olefins. Cyclohexene oxide gives a 3:1 ratio mixture of cyclohexanol and cyclohexene after protonation; cyclooctene oxide produces cyclooctanol and cyclooctene in 3:7 ratio. On the other hand, vinyloxiranes open at the most substituted C−O bond to produce an allylic anion associated with an alkoxide. Many of these dianions were treated with aldehydes and ketones in order to maximize the synthetic flexibility of the products. Thus, the three-membered oxacyclic

ring in monosubstituted oxiranes can be opened in two ways, since its two carbon−oxygen bonds are different: CH−O bond scission is usually determined as the ring opening in the α-position and the CH_2−O one as in the β-position (Scheme 6).



Scheme 6

A nucleophile usually attacks the more-substituted carbon in acid-catalysed cleavage (α-opening), and the less substituted in base-catalysed cleavage (β-opening).[63] The reaction of monosubstituted oxiranes with alkali metals or alkali metal aromatic radical anions involves an initial electron transfer to the oxirane molecule. This leads to the formation of a cyclic radical anion (Scheme 7).[12] The oxirane ring is then opened in the α- or the β-position. The regioselectivity of the reaction depends on the nature of the substituent R.

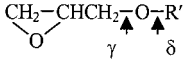


Scheme 7

α-Opening takes place if the reaction is thermodynamically controlled, because the secondary radical is more stable than the primary one. The radical is an electron-deficient species, therefore it is stabilised by an electron-donating group, such as when R is an alkyl substituent. The alkyl group also stabilises the carbon−oxygen bond and increases the energy of the appropriate σ*-orbital. Therefore, the electron is in fact transferred into the antibonding σ*-orbital of the less-substituted C−O bond, thus the reaction is kinetically controlled and the less-stable primary radical anion is formed by the oxirane ring opening in the β-position.

On the other hand, if R is an electron acceptor (Ph, $CO_2C_2H_5$,[13] CH=CH_2,[62] C≡CH[64]) then the electron is transferred into the antibonding π*-orbital of the substituent and the ring opening occurs in the α-position. This indicates a stabilising effect of the substituent even during the formation of the carbanion.

The situation is more complex when an oxygen atom is also present in the substituent R, for example in glycidyl ethers. Theoretically there is a possibility of opening both the cyclic and the linear ether bond. The latter might also be cleaved in two positions — between the glycidyl group and oxygen or between R′ and oxygen. The first type of cleavage is called a γ-opening and the second one a δ-opening (Scheme 8).

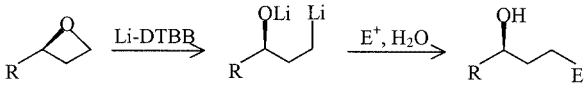


Scheme 8

Oxirane ring opening in the presence of $Ar^{\cdot -}$, M^+ has, for example, been observed in (phenoxymethyl)oxirane.[65] The linear ether bond scission in this and in other glycidyl ethers was not taken into account. The latter is already stated when alkalides are used as the electron-transfer reagents. This phenomenon is discussed in the next section of this paper.

The reductive lithiation of oxetanes in tetrahydrofuran by Li-DTBB at 0 °C efficiently generates γ-lithioalkoxides.[66] They are considerably more stable than the corresponding species derived from oxiranes.[67,68] In unsymmetrical oxetanes the direction of opening is analogous to that observed in the reduction of oxiranes. An alkyl substituent at the 2-position leads to the less-substituted carbanion. This regiochemistry in the case of oxiranes can be explained by the greater stability of the more-substituted alkoxide, which outweighs the lower stability of the less-substituted radical that is formed by the rupture of the intermediate oxirane radical anion.[12] On the other hand, a phenyl group at the 2-position leads to the more-substituted benzylic anion as in the reductive lithiation of styrene oxide.[13] γ-Lithioalkoxides can provide 2-substituted tetrahydrofurans upon trapping with aldehydes and ketones followed by acid cyclisation of the resulting 1,4-diols; the cuprates of these dianions undergo conjugate addition and nucleophilic substitution reactions.[66]

The lithiation of chiral oxetanes in the presence of a catalytic amount of DTBB in tetrahydrofuran at −78 °C leads to γ-lithioalkoxides which, in the reaction with different electrophiles (E^+), afford the expected functionalised alcohols after hydrolysis with water (Scheme 9).[69]



where R: CH_2OTHP (THP: tetrahydropyranyl)

Scheme 9

The above-mentioned type of reaction has also been applied to the cleavage of five-membered substituted cyclic ethers, for example 2,3-dihydrobenzofuran, which, under the same reaction conditions, yield the corresponding functionalised organolithium intermediate by the scission of the CH_2−O bond.[47] A similar phenomenon has previously been observed by Angelo[10] in the reaction of 2,5-dihydrofuran and 2-methylbenzofuran with other alkali metal aromatic radical anions.

4. Use of Alkalides

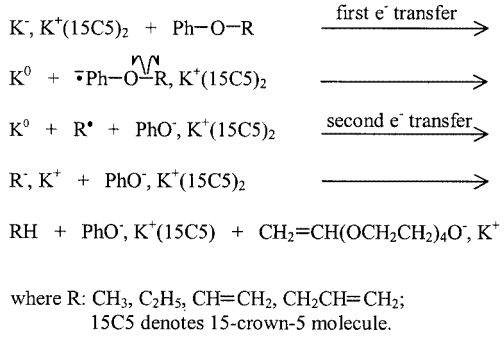
The first report on the reaction of ethers with alkalides concerned the regioselectivity of the C−O bond cleavage by the alkalide K^-, K^+(18-crown-6).[70] This study involved aromatic ethers; their relative reactivities were as follows: diphenyl ether > dibenzyl ether > 2-methoxyphenyl phenyl

ether > benzyl phenyl ether > phenethyl phenyl ether > 4-hydroxyphenyl phenyl ether. A methoxy group has no apparent effect on the relative rates of the aromatic C−O bond cleavage, while a hydroxy group dramatically decreases the rate of reaction. The regiochemistry of the C−O bond cleavage in benzyl phenyl ether shows a preference for the benzyl−oxygen bond. The addition of either a hydroxy or a methoxy group in the 4-position of diphenyl ether gives cleavage of the substituted aryl groups. However, the introduction of a methoxy group in diphenyl ether in the 2-position changed the regiochemistry to cleavage in the unsubstituted aryl group. These results imply that the theory of conservation of local spin density may also operate for the C−O bonds of aromatic ethers.

K^-, $K^+(15\text{-crown-}5)_2$ in tetrahydrofuran solution has mainly been used in other studies concerning reactions of linear and cyclic ethers with alkalides as this system has been found to be much more stable than K^-, K^+(18-crown-6), especially at room temperature.[71,72] Table 1 shows the mechanism of the C−O bond cleavage in several linear ethers by radical anions formed after the electron transfer from potassium anions of K^-, $K^+(15\text{-crown-}5)_2$.

The reaction course of phenyl ethers with alkalide is presented in Scheme 10.[73−75] K^0 and the appropriate radical anion are formed after the transfer of the first electron from K^- to the ether molecule. The radical anion of the ether is unstable and undergoes regioselective decomposition to the radical $R^\cdot$ and the phenoxide anion by homolytic cleavage of the alkyl−oxygen bond. In the next step K^0 transfers the second electron to $R^\cdot$, giving the organopotassium compound R^-, K^+, which reacts then with the crown ether causing its ring opening.

The mechanism of the reaction of alkalides with vinyl ethers is determined by the formation of a resonance-stabilized enolate anion or the phenoxide anion as well as, in some cases, by the strong tendency of the oxygen atom or atoms present in the substituent to interact with the counterion.[74]



Scheme 10

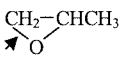
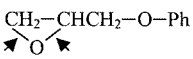
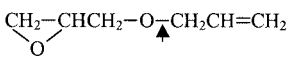
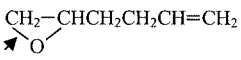
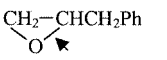
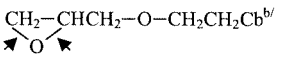
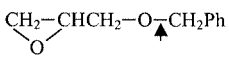
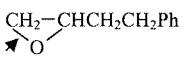
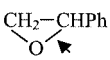
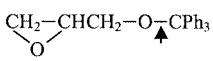
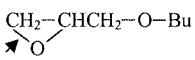
The direction of the cyclic ether bond cleavage in some monosubstituted oxiranes is presented in Table 2. It seems that the first electron transfer from K^- occurs to the σ*-orbital of the less-substituted C−O bond for oxiranes with R groups such as CH_3,[78] $CH_2CH_2CH{=}CH_2$,[79] CH_2CH_2Ph,[80] and CH_2OBu.[75] This results in the ring opening of the ether radical anion exclusively in the β-position. The same phenomenon has been observed for methyloxirane (R = CH_3) in the presence of K^-, K^+(18-crown-6).[83] These findings are in good agreement with the results found in the ring-opening reaction of methyloxirane and ethyloxirane by lithium biphenylide.[13]

On the other hand, it can be expected that the first electron is transferred from K^- to the π*-orbital of the substituent if R is $CH{=}CH_2$,[79] CH_2Ph or Ph.[80] The oxirane ring of the ether radical anion is then opened exclusively in the α-position. Such opening has been observed in the reaction of phenyloxirane with metallic sodium,[52] as well as with lithium naphthalenide or potassium biphenylide,[13] i.e. with single-electron-transfer reagents. It has been suggested that this reaction can be rationalised by a mechanism involving an initial electron transfer leading to the formation of an intermediate radical anion. In contrast to these findings, it has also been reported[83] that the oxirane ring of

Table 1. Mesolytic cleavage of linear ether radical anions generated by alkalide K^-, $K^+(15\text{-crown-}5)_2$ in tetrahydrofuran solution

Homolytic cleavage	Ref.	Heterolytic cleavage	Ref.	Homolytic or heterolytic cleavage	Ref.
$^{\cdot}Ph-O-CH_3$	[73]	$^{\cdot}PhCH_2-O-Ph$	[76]	$^{\cdot}CH_2{=}CH-O-CH_2CH_2-O-Bu$	[74]
$^{\cdot}Ph-O-C_2H_5$	[73]	$^{\cdot}PhCH_2-O-CH_2CH{=}CH_2$	[77]	$^{\cdot}CH_2{=}CH-O-CH_2CH_2-O-Bu$	[74]
$^{\cdot}Ph-O-CH{=}CH_2$	[74]	$PhCH_2-O-CH_2CH{=}CH_2{}^{\cdot}$	[77]	$^{\cdot}CH_2{=}CH-O-CH_2CH_2-O-(CH_2CH_2O)_2-CH_3$	[74]
$^{\cdot}Ph-O-CH_2CH{=}CH_2$	[75]			$^{\cdot}CH_2{=}CH-O-CH_2CH_2-O-(CH_2CH_2O)_2-CH_3$	[74]
$^{\cdot}CH_2{=}CH-O-Bu$	[74]				

Table 2. Direction of the ether bond cleavage in monosubstituted oxiranes by alkalide $[K^-][K^+(15\text{-crown-5})]_2$ [75,76,78–82]

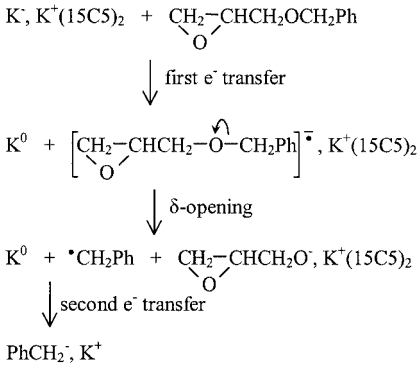
Oxirane ring opening in the β-position	Oxirane ring opening in the α-position	Oxirane ring opening in the β- or α-position [a]	Cleavage of the linear ether bond in the δ-position
			
			
			
			

[a] Opening in the β-position prevails. [b] Cb: carbazolyl group.

phenyloxirane can be cleaved by K^-, K^+(18-crown-6) both in the β-position (70%) and in the α-position (30%), similar to the reaction in the presence of potassium methoxide[84,85] or sodium methoxide.[86] However, such a result might be due to the method of substrate delivery. Phenyloxirane was introduced gradually into blue alkalide solution until its discolouration and this could cause side reactions between potassium anions and primary reaction products.[75,80] Experiments performed with an excess of phenyloxirane using the method presented in ref.,[80] showed that only the α-opening occurs in the presence of K^-, K^+(18-crown-6);[77] the final reaction products were the same as in the system containing K^-, $K^+(15\text{-crown-5})_2$.

(Phenoxymethyl)oxirane (R: CH_2OPh) possesses an aromatic ring connected to the oxygen atom of the substituent. This oxygen atom has an electron-donating character and it therefore increases the electron density of the aromatic ring, which is possibly why the electron transfer occurs from the potassium anion to the oxirane ring.[76,81] This results in both β- and α-opening of the ether radical anion, although the β-opening prevails. A similar phenomenon has been observed for (carbazolylethoxymethyl)oxirane (R: $CH_2OCH_2CH_2Cb$).[82]

The situation changes dramatically in the case of oxiranes with R groups such as $CH_2OCH_2CH{=}CH_2$,[75] CH_2OCH_2Ph, or CH_2OCPh_3;[76] electron transfer from K^- to the aliphatic double bond or to the aromatic ring is then preferred. Unexpectedly, the highly strained oxirane ring remains undisturbed. The cleavage of the linear ether bond of the substituent in the ether radical anion results in the glycidoxide anion and the appropriate resonance-stabilized radical (allyl, benzyl or triphenylmethyl, respectively). The scission of the ether bond occurs only between oxygen and the group possessing the double bond or the aromatic ring, which means that δ-opening takes place exclusively in these systems. After the second electron-transfer from K^0 to the radical, the latter becomes a resonance-stabilized carbanion. An example for (benzyloxymethyl)oxirane is shown in Scheme 11.[76]



Scheme 11

It is worth noting that all the oxirane radical anions mentioned above decompose by heterolytic cleavage of the cyclic or linear ether bond.

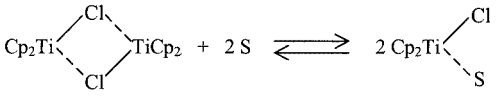
Alkalides also cleave the C–O bond of higher cyclic ethers, such as oxetane[14,87,88] and tetrahydrofuran.[71,89] The latter is usually applied as the solvent in the preparation of alkalides.[90–92] Moreover, crown ethers, which are necessary to prepare concentrated alkalide solutions,[93] also take part in the self-decomposition of the system. For example, the oxacyclic rings of 15-crown-5[89] and 18-crown-6,[71] as well as their mono- and dicyclohexano derivatives,[94] are opened by K^- of the alkalide. The potassium anion behaves in all these processes as a two-electron-transfer reagent and the transfer occurs in two steps.[95] K^+ is observed at the end of the reaction of K^- with ethers, which serve in this case as electron acceptors.

Organopotassium compounds, which are the intermediate products of the ether-bond cleavage, are generally unstable: they react with the crown ether or eliminate ethylene.[14,74,89] However, in a system containing oxiranes they can react not only with the crown ether but also with the oxirane molecule, or they undergo β- or γ-elimination.[15,81] One exception is triphenylmethylpotassium, formed by the linear ether-bond cleavage of (triphenylmethoxymethyl)oxirane,[76] which does not take part in any further processes.

5. Use of Low-Valent Transition-Metal Compounds

The carbanions obtained in the reduction of oxiranes by alkali metals can react with electrophiles, although several serious limitations of this approach have been observed. These include the non-compatibility of the highly reducing conditions with a number of common organic functional groups, the instability of such carbanionic species toward elimination or other reactions, and the narrow range of electrophiles that can be used in this sequence.[29] The use of paramagnetic low-valent transition-metal compounds is more promising due to the utilisation of the intermediate radicals for organic synthesis.[30,96] A precedent for this approach exists in the mechanistic proposal by Kochi et al.,[97] who suggested that the deoxygenation of oxiranes with chromium(II) compounds, for example $CrCl_2$, proceeds by discrete one-electron steps via the carbon-centred radical. Formation of the latter from a transition-metal-centred radical and its subsequent reactions are ubiquitous in living systems.[98] However, the application of this type of transformation in organic synthesis is largely limited to redox reactions.[29]

Important steps toward reagent-controlled oxirane ring opening were achieved between 1988 and 1994 when Nugent and RajanBabu[27−29] discovered that titanocene(III) chloride {bis(cyclopentadienyl)titanium(III) chloride, $TiCp_2Cl$} is a useful stoichiometric reagent for the reductive opening of oxiranes with or without deoxygenation and intra- or intermolecular C−C bond-forming reactions. It is easily generated and is compatible with many organic functional groups.[99] Titanocene(III) chloride was first reported by Green et al.[100] by the reduction of titanocene(IV) dichloride $TiCp_2Cl_2$ with either Zn[100] or Al[101] metal. In the solid state the complex exists as a chloride-bridged dimer (Scheme 12).[29] In donor solvents such as tetrahydrofuran, the dimer dissociates to afford the monomeric species, which may be regarded as a loosely solvated transition-metal-centred radical.

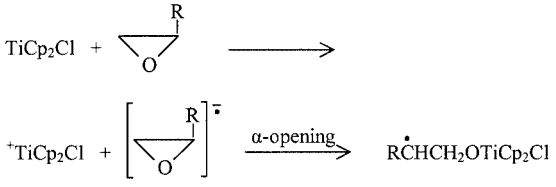


where S denotes the solvent molecule

Scheme 12

Nugent and RajanBabu[29] have suggested that the oxirane ring opening in the presence of this reagent proceeds in discrete one-electron step. The σ-complex of the oxirane with the paramagnetic Ti^{III}, which has a half-filled d-orbital, is formed as the intermediate product. The release of the ring strain might be expected to drive the homolytic C−O bond cleavage.

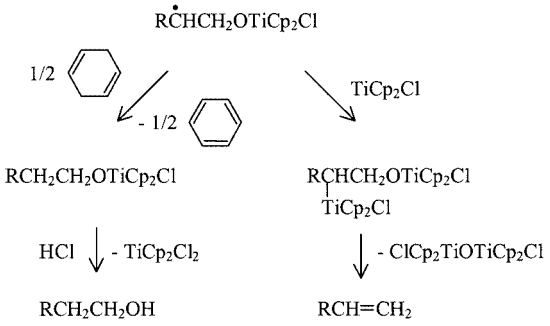
Gansäuer and Bluhm[30] subsequently defined some low-valent transition-metal compounds as electron-transfer reagents and they also proposed another mechanism for the oxirane ring opening. They suggested that after the complexation of the oxirane by the Ti^{III} reagent, the resulting adduct, presumably the radical anion of the oxirane bound to a Ti^{IV} species, was formed, thereby avoiding unfavourable steric interactions between the metal complex and the bulky substituent on the oxirane. The authors suggested that the mechanism of this transformation is similar to that postulated by Dorigo et al.[12] for the formation of an oxirane radical anion by transfer of one electron from lithium to the oxirane molecule. However, the appropriate scheme presented in the cited work[30] does not explain clearly the mechanism of the oxirane ring opening. It seems that the heterolytic cleavage of the C−O bond would be more likely in this case (Scheme 13).



Scheme 13

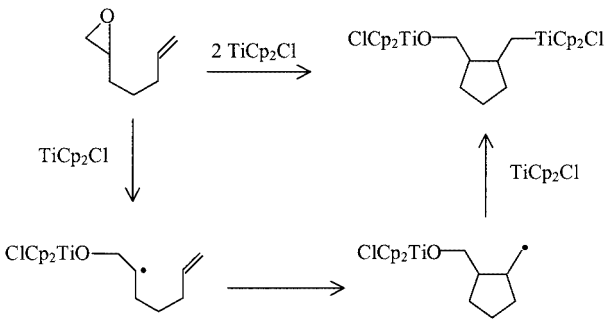
The cyclopentadienyl ligands of titanium determine the chemoselectivity of the reaction by tuning the redox properties and the steric demand of the metal complex. Ketones, tosylates and halides are not reduced and it is applicable in the synthesis of complex and sensitive molecules. Reagent control is also exercised in the formation of the more-substituted radical, i.e. the regioselectivity of the oxirane opening. The radical formed can be trapped by H-atom donors such as 1,4-cyclohexadiene or *tert*-butyl thiol, resulting in an overall reduction of the oxirane to an alcohol. In the absence of H-atom donors, this radical undergoes electron-transfer reduction by $TiCp_2Cl$ giving the β-oxide−Ti organometallic species, followed by elimination to give an olefin (Scheme 14).[28]

Several papers have been published for the deoxygenation of simple oxiranes to alkenes. An example of this reaction is the synthesis of enantiomerically pure allylic alcohols.[102] Nugent and RajanBabu,[27] and Schobert,[103] have provided independent evidence that β-metaloxy radicals are indeed intermediates in these reactions. Both *cis*- and *trans*-5,6-epoxydecane yield the same 27:73 mixture of (*E*)- and (*Z*)-5-decene as the products. This very mild deoxygenation procedure has been applied in the synthesis of deoxy sugar derivatives and a number of highly acid-sensitive products that are not readily accessible by different methods.[30]

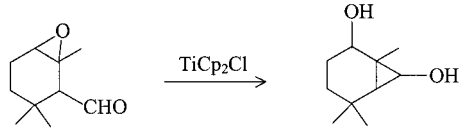


Scheme 14

One of the synthetically most important applications of the radicals is the 5-*exo*-cyclisation reaction of epoxy olefins (Scheme 15),[27,29] aldehydes (Scheme 16) or ketones.[104] After the reductive oxirane opening the resulting radical readily adds to esters of acrylic and methacrylic acid. The resulting compounds — δ-hydroxy esters — can be lactonized, thus allowing a convenient entry to the synthesis of δ-lactones from oxiranes in one-step.[105] Acryl- and methacrylnitrile are also useful radical traps in these reactions.[30]



Scheme 15



Scheme 16

Recently, Gansäuer and Rinker[31] have divided low-valent transition-metal compounds into single-electron-transfer [$CrCl_2$, SmI_2, $TiCp_2Cl$, $VCl_3(THF)_3$, VCl_3/Zn, $VCl_3(THF)_3Zn$] and two-electron-transfer reagents $\{[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]\}$. In the case of the latter, due to its dimeric nature, the second electron could be transferred to the radical formed initially. SmI_2 is not suitable for the reductive opening of oxiranes as the high Lewis acidity of this metal, combined with the high nucleophilicity of the iodine ion, leads to the formation of iodohydrins. In the case of $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$ no products other than those of oxirane deoxygenation could be observed. $CrCl_2$ is unfortunately severely limited by its low reactivity.

These findings suggest that the reason for the superiority of $TiCp_2Cl$ stems from its unique combination of low Lewis acidity, thus preventing the oxirane opening via an S_N2 or S_N1 mechanism, and low reducing power towards the β-metaloxy radical. Obviously the reduced redox potential of $TiCp_2Cl$ compared to SmI_2, combined with the higher steric demand of the cyclopentadienyl ligands, can, if desired, prevent trapping of the β-metaloxy radicals with the titanium reagent under properly chosen conditions.[30] $TiCp_2Cl$ is an exceptionally mild and selective electron-transfer reagent for the reduction of oxiranes in comparison to other low-valent transition-metal compounds.

6. Conclusions

This paper summarises results concerning the cleavage of ethers by the use of single- or two-electron-transfer reagents, such as alkali metals, alkali metal aromatic radical anions, alkalides and low-valent transition-metal compounds.

The direction of mesolytic C−O bond scission in the ether radical anion formed by single-electron-transfer depends strongly on the kind of ether and the solvent and does not depend on the kind of electron-transfer reagent. Different systems based on alkali metals lead to a variety of organometallic compounds, which are generally stable at low temperatures. These products, which are carbanions, appear to be excellent precursors of many organic compounds formed in the reaction with electrophiles. Particularly interesting is the reductive ether bond cleavage with the Li-DTBB system because of its rather wide applicability and relative ease of handling.

The reaction with potassium alkalides, which are two-electron-transfer reagents, results in the formation of organopotassium compounds, which then react extremely rapidly at room temperature with crown ether or with a substrate. The regioselectivity of the C−O bond cleavage by potassium anions is observed in this case in various linear and cyclic ethers under mild reaction conditions.

The use of titanocene-based complexes, especially $TiCp_2Cl$, is also very attractive with respect to the application of the intermediate radicals in organic synthesis. This reagent is compatible with many functional groups. The formation of radicals in this manner allows the development of unique transformations of oxiranes.

Acknowledgments

The author is greatly indebted to Prof. Andrzej Stolarzewicz for helpful exchange of information and to Prof. Adalbert Maercker for useful discussions.

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Received January 4, 2004
Early View Article
Published Online May 18, 2004

