Applications of TEMPO in Synthesis

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Abstract: This review describes the broad application of TEMPO and its derivatives in organic synthesis. Various reactions including oxidation of alcohols, sulfides and organometallic compounds are discussed. Moreover, the use of TEMPO as a stoichiometric or catalytic cooxidant in various transition-metal-mediated reactions is presented. The application of TEMPO as a carbon-radical trapping reagent in cascade reactions is discussed. Finally, the review article focuses on the application of TEMPO-derived alkoxyamines as thermal carbon-radical precursors in synthesis and in polymer chemistry.

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Key words: nitroxides, oxidations, radical chemistry, domino reactions, polymerizations

1 Nitroxides

Nitroxyl radicals, also called nitroxides, are N,N-disubstituted NO radicals with an unpaired electron delocalized between the nitrogen and the oxygen atom. The delocalization of the electron is indicated by the two resonance structures 1 and 2. The spin density is distributed between both atoms, often with a slightly higher density at the oxygen atom (Scheme 1).1,2

Scheme 1 Resonance structures of nitroxyl radicals

As early as in 1845, potassium nitroso disulfonate (3) was synthesized as the first inorganic nitroxyl radical by Fresmy.3 In 1901 Piloy and Schwerin succeeded in the synthesis and isolation of porphyrexide 4, the first organic nitroxide.4 Subsequently, Offenbächer and Wieland prepared and isolated diphenylnitroxide (5) which was until then believed to be unstable.5 However, the most prominent member of this class of compounds is the 2,2,6,6-tetramethylpiperidine-N-oxyl radical (TEMPO). This nitroxide was first synthesized by Lebedev and Kazarovskii in 1959 (Figure 1).6

Many nitroxides are stable at room temperature and belong to the class of persistent radicals.7 The delocalization energy for the unpaired electron is approximately 120 kJ/mol (three-electron N–O bond).8 The steric demand of the substituents of dialkyl nitroxides shields the nitroxide functionality and contributes to its kinetic stability. Nitroxides bearing heteroatom substituents or aryl substituents are less stable than the alkyl-substituted nitroxides. A delocalization of the radical into the aromatic ring weakens the nitrogen–oxygen bond in diaryl-substituted nitroxides.1,9

Because of their paramagnetic properties, nitroxides have gained a lot of attention in materials science. These persistent radicals have been incorporated into molecular magnets,10 organic batteries11 and other devices.12 Nitroxides can also be linked to interesting biologically active compounds. The metabolism of the nitroxide conjugate has been studied by EPR spectroscopy. This technique is called spin labeling or spin probing.13,14 The reaction of carbon radicals with nitrones or nitroso compounds leads to nitroxides which can readily be analyzed by EPR spectroscopy. Nitrones or nitroso compounds are therefore called spin traps.15 However, the use of nitroxides in materials science and their applications in the study of biological processes are not the topic of the present review article and will therefore not be further discussed herein.

This review focuses on the use of nitroxides and especially of TEMPO and its derivatives in synthesis. Alongside its application as an oxidant, TEMPO has often been used as a radical trap.
2 Oxidations

2.1 Oxidation of Alcohols

Nitroxides have been frequently applied to the oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones. A catalytic amount of the nitroxide in combination with a stoichiometric cooxidant is used in most cases. The aldehydes thus obtained can conveniently be further oxidized to the corresponding carboxylic acids in a one-pot process, for example by using sodium chlorite.

The transformations occur via the oxoammonium salt, which is readily generated either by disproportionation under acidic conditions or oxidation of TEMPO to provide salt and hydroxylamine (Scheme 2). The stability of the oxoammonium ion depends on the counter anion. The N-hydroxypiperidine can be reoxidized in the presence of oxygen under basic conditions. This pH-dependent reaction is retarded under acidic conditions.

The reaction of a primary or secondary alcohol with oxoammonium salt leads to intermediate, which undergoes fragmentation to give the desired carbonyl compound and hydroxylamine. In the presence of a stoichiometric cooxidant, is reoxidized to , thus closing the catalytic cycle (Scheme 3). It is obvious that the oxoammonium ion can also be used as a stoichiometric oxidant.

A large number of different inorganic and organic cooxidants have been used for the regeneration of the oxoammonium ion from hydroxylamine. Bisacetoxyiodobenzene has often been employed for this purpose along with the most prominent terminal oxidant sodium hypochlorite. Bromide ions have been shown to be effective cocatalysts. Regeneration of the oxoammonium ion from hydroxylamine.

Biographical Sketches

Thomas Vogler grew up in Obermaiselstein, Germany. He studied chemistry at the University of Marburg, Germany and the University of Cambridge, UK. He received his diploma under the guidance of Prof. Gerhard Hilt from the University of Marburg, Germany in 2005. He then joined the research group of Prof. Studer as a PhD student at the Westfälische Wilhelms-Universität in Münster, Germany. In the same year, he received a Kekulé stipend from the Fonds der Chemischen Industrie. He is studying the interaction of TEMPO with organometallic compounds.

Armido Studer received his diploma in 1991 and his PhD in 1995 from ETH Zürich under the direction of Prof. Dieter Seebach. He continued his scientific education as a Swiss National Science Foundation Postdoctoral Fellow at the University of Pittsburgh with Prof. Dennis P. Curran. In 1996, he started his independent career at the ETH Zürich. In 2000, he was appointed as Associate Professor of Organic Chemistry at the Philipps-Universität in Marburg, Germany and in 2004 as Full Professor of Organic Chemistry at the Westfälische Wilhelms-Universität in Münster, Germany. His current research interests focus on the development of new synthetic methods. In addition, he also works on living radical polymerizations, on the preparation of functional polymers, and on the development of methods for the chemical modification of surfaces. In 2006, he received the Novartis Young Investigator Award in Chemistry, in 2007 he was recipient of the Solvias Ligand Contest Award, and in 2008 he held a guest professorship at the University Pierre et Marie Curie in Paris.
oxoammonium salt could also be accelerated by sonication. Due to steric effects during the formation of intermediate 8, primary alcohols react more efficiently than secondary ones. Therefore, a selective transformation of a primary alcohol in the presence of a secondary alcohol can be achieved. This mild and selective oxidation has been used in natural product synthesis, in carbohydrate chemistry and in industry. Danishefsky and coworkers completed the synthesis of the unstable guanacastepene A (11) by incorporating this method. In this case, deprotection of acetonide 10 and oxidation of the primary allylic alcohol in the presence of the secondary allylic alcohol was accomplished (Scheme 4).

The workup of the reaction mixture can be simplified by the use of immobilized cooxidants. In addition, various recoverable TEMPO derivatives have been developed. To this end, nitroxides applicable in fluorous solvent extractions or in ionic liquids have been prepared. Moreover, nitroxides have been immobilized on different silicon-based materials and on a graphite felt electrode. Reiser and co-workers modified a TEMPO-derivative by click chemistry for the preparation of ‘fluorous-tagged’ nitroxide 12. The nitroxide was readily recovered by adsorption on silica after successful oxidation reactions. Sodium hypochlorite was used as terminal oxidant. Nitroxide 13 was found to be soluble in the ionic liquid [bmim][PF$_6$] and was reused three times without loss of activity. Separation was achieved by simple liquid–liquid extraction in this case (organic solvent/ionic liquid). Good yields were obtained for aldehydes and ketones with sodium hypochlorite as stoichiometric oxidant (Figure 2).

Poly(p-phenylene benzobistiazole)-immobilized nitroxide 14 was used as recoverable catalyst in oxidations. The oxoammonium salt was regenerated electrochemically. Moreover, a number of polymer–nitroxide conjugates have been successfully used as recoverable catalysts for the oxidation of alcohols. In addition, the polystyrene-bound salt 15 was applied as a stoichiometric oxidant.

In recent years, the research on aerobic metal-mediated TEMPO oxidations of alcohols has intensified. These processes have been conducted mainly with copper complexes but other transition metals have also been employed. In addition to molybdenum, iron and ruthenium catalysts, bimetallic manganese/cobalt or manganese/copper systems have been used. These reactions can proceed via the mechanism depicted in Scheme 3. The metal complex catalyzes the oxidation of the hydroxypiperidine 7 to regenerate the oxoammonium ion 6. The thus-formed reduced metal complex is reoxidized by oxygen. Aerobic oxidations with the copper-dependent enzyme laccase and TEMPO have attracted much attention. These reactions are assumed to proceed via a related mechanism was suggested for a molybdenum system. Minisci and co-workers proposed a slightly modified mechanism for a manganese/copper system by using acetic acid as a solvent: aerobic oxidation of the N-hydroxypiperidine 7 provides TEMPO and 6 is finally regenerated by disproportionation induced by acetic acid (Scheme 2).

As a mechanistic alternative, reactions where the metal complex mediates the oxidation of the alcohol have been suggested. TEMPO reacts with the metal complex as a one-electron oxidant in these cases and is itself directly reoxidized by oxygen. Sheldon and co-workers published metal-catalyzed oxidations for an aerobic ruthenium- and a copper-mediated process. The suggested mechanism for the copper-catalyzed process is shown in Scheme 5.

A copper(I) complex is oxidized by TEMPO to the corresponding copper(II)–TEMPO adduct 16. Subsequent deprotonation of alcohol 17 and ligand exchange gives complex 18 and hydroxylamine 7. Hydrogen abstraction by TEMPO finally leads to the carbonyl compound 19 and the starting copper(I) complex.

The discrepancy of the two different mechanisms discussed can be attributed to the rate of reoxidation of 7 with oxygen. This might be related to the pH-dependency of this reaction and therefore to the reaction conditions applied.
Many optically active nitroxides have been synthesized.\textsuperscript{13} These nitroxides paved the way for the development of a method for the kinetic resolution of secondary alcohols.\textsuperscript{60} As an example, Tanaka and co-workers used the chiral nitroxide \textsuperscript{23} for the resolution of benzylic alcohols, in combination with electrochemistry for the regeneration of the o xoammonium salt (Scheme 7).\textsuperscript{61}

Scheme 7 Kinetic resolution with chiral nitroxide \textsuperscript{23}

2.1 Oxidation of Sulfides and Hydrogen Abstractions

Nitroxides are also capable of oxidizing substrates other than alcohols.\textsuperscript{17,62} Selective conversions of sulfides into the corresponding sulfoxides have been carried out by TEMPO-mediated processes.\textsuperscript{63} Importantly, overoxidation to the corresponding sulfones is suppressed. N-Protected \(\beta\)-amino sulfides \textsuperscript{24} were readily transformed into the separable diastereoisomeric sulfoxides \textsuperscript{25} and \textsuperscript{26} with TEMPO and sodium hypochlorite. \(m\)-Chloroperbenzoic acid and sodium periodate as terminal oxidants gave inferior selectivities (Scheme 8).\textsuperscript{64}

The same reaction has also been conducted with the aid of transition metals. A variety of sulfides were oxidized with TEMPO-metalloporphyrin conjugates with sodium hypochlorite as cooxidant.\textsuperscript{65} A copper(II)-salen catalyst with hydrogen peroxide as terminal oxidant was used to transform various sulfides into the corresponding sulfoxides. Addition of TEMPO enhanced the conversion and suppressed the overoxidation to the corresponding sulfones. The role of TEMPO in these reactions, however, is not yet understood.\textsuperscript{66} An aerobic laccase-based oxidation in the presence of TEMPO proved not to be very effective for this process.\textsuperscript{67}

The \(\alpha\)-hydroxy \(\beta\)-lactam \textsuperscript{27} was converted into the mixed anhydride \textsuperscript{28} in excellent yield and selectivity.\textsuperscript{68,69} Impor-
tanty, no epimerization was observed for this TEMPO-mediated Baeyer–Villiger oxidation (Scheme 9).  

In addition, TEMPO was applied in the oxidation of benzylic ethers to the corresponding benzoates. Moderate to good yields were obtained with sodium hypochlorite as an oxidant. Successful aerobic conversion of a catechol derivative into the corresponding 1,2-benzochinone with TEMPO was reported. Moreover, electrochemical oxidative coupling of naphthol derivatives to the corresponding binaphthyls was demonstrated. TEMPO can react directly with activated hydrocarbons by hydrogen abstraction. As an example, the reaction of hydroxy-TEMPO with cyclohexene generates hydroxylamine and the stabilized radical. Trapping of the allylic radical with nitroxide gave alkoxyamine in a moderate yield (Scheme 10).

Hydrogen abstraction from acetonitrile or toluene by TEMPO under photoirradiation conditions was reported by Scaiano and co-workers. Moreover, oxoammonium ions were directly used for allylic oxidations. These reactions are supposed to occur via ene-type chemistry. In addition, the electrochemical allylic oxidation of alkenes to the corresponding alkenones was reported. Copper-assisted hydrogen abstractions by TEMPO in oxidation reactions have already been discussed in Scheme 5.

Chan and co-workers used TEMPO for selective abstraction of benzylic β-hydrogen atoms in some rhodium and iridium complexes. Furthermore, metal hydrides are capable of reducing TEMPO. This was shown unambiguously by Chan and co-workers for porphyrin-ligated rhodium and iridium hydrides. Sheldon and co-workers proposed that the regeneration of a catalytically active ruthenium species in an aerobic ruthenium-catalyzed oxidation reaction occurs by hydrogen abstraction of TEMPO from a Ru–H complex. Moreover, Chatgilialoglu and co-workers showed that TEMPO reacts spontaneously at 80 °C with tributyltin hydride and triphenylgermanium hydride by hydrogen atom abstraction to give the corresponding hydroxylamine and the stannyl or germyl radical, respectively. Hydrogen abstraction by TEMPO for other group 14 metal hydrides not discussed herein, and can also lead to nitrogen–oxygen bond cleavage of the nitroxide. A similar reactivity was also found for group 13 metal hydrides. Phthalimide-derived nitroxides are more reactive as hydrogen abstractors than TEMPO. This is due to the higher oxygen–hydrogen bond energies of the corresponding hydroxylamines. Less reactive substrates such as adamantane react efficiently with these nitroxides by hydrogen transfer to the nitroxide. Trapping of the thus-generated carbon-centered radical with oxygen leads to peroxyl radicals which are further transformed into the corresponding alcohols and ketones by transition-metal-mediated processes. Recently, Einhorn and co-workers succeeded in the kinetic resolution of N-acyl oxazolidines via a nitroxide-mediated oxidation (Scheme 11).

This aerobic process was conducted with a chiral C2-symmetric phthalimide-N-oxyl radical generated in situ from the corresponding hydroxylamine. The reaction is assumed to proceed via hydrogen abstraction at the benzylic position and subsequent reaction of the intermediate formed stabilized carbon-centered radical with oxygen, in analogy to the suggested mechanism for nitroxide-mediated ring openings of benzyldiene acetics. Similarly, oxidation of alcohols by phthalimide-derived nitroxides is believed to occur by hydrogen transfer to the nitroxide.

Scheme 8 Oxidation of sulfides to sulfoxides

Scheme 9 Baeyer–Villiger oxidation of β-lactam

Scheme 10 Oxidation of cyclohexene
3 TEMPO as Trapping Reagent

As already shown in Scheme 10, TEMPO has often been used as a radical scavenger. Trapping of a carbon-centered radical with TEMPO is a fast process. The rate constants are strongly influenced by the nature of the carbon radical and the solvent, and range from about $5 \cdot 10^7 \text{M}^{-1}\text{s}^{-1}$ to $2 \cdot 10^9 \text{M}^{-1}\text{s}^{-1}$ at room temperature.\(^{88,89}\) Trapping of biologically important radicals with TEMPO was successfully applied in the study of metabolisms by mass spectrometry.\(^{90}\) Nitroxides have also been used as stabilizers in polymers and in biochemical systems because of their efficient radical trapping properties.\(^9\) Moreover, nitroxide–peptide conjugates with a high affinity for mitochondrial membranes have been developed. These conjugates can react with reactive oxygen species and protect mitochondria from oxidative damage and apoptosis.\(^{91}\) The nitroxide can be regarded as an antioxidant in these processes since it is oxidized to the corresponding oxoammonium ion, by peroxyl radicals for example.\(^92\) Monitoring of these reactions by ESR spectroscopy allowed for cell membrane oxidative stress to be measured.\(^93\)

Trapping of carbon-centered radicals with nitroxides is an important method for the synthesis of alkoxyamines. Various methods for the generation of carbon-centered radicals have been employed for this purpose.\(^{94,95}\) Alkoxyamines can also be synthesized by nucleophilic substitution of an alkyl halide with the sodium salt of hydroxylamine \(^7\) readily obtained via deprotonation.\(^{96,97}\) The synthesis of alkoxyamines can also be accomplished with the oxoammonium ion \(^6\) as an electrophile.\(^{20,98}\) As an example, the stable tetrafluoroborate salt \(^34\) was treated with the lithium enolate derived from cyclohexanone to give \(^35\) in a good yield, as reported by Schäfer and Schämann (Scheme 12).\(^{20}\)

Scheme 12  Oxoammonium ion \(^34\) as electrophile

TEMPO-trapping reactions can be combined with radical carbon–carbon bond formations in domino processes. Various groups have used TEMPO as a trap for radicals generated by 5-exo-cyclizations.\(^9\) Obviously, 5-exo-cyclization needs to be faster than the TEMPO trapping of the non-cyclized radical. Therefore, this cascade only works well for fast 5-exo-cyclizations. Aryl radical carbon–carbon bond formations with subsequent TEMPO trapping have been used by Boger et al. in natural product synthesis.\(^{100,101}\) Hence, treatment of iodide \(^36\) with tributyltin hydride and TEMPO gave alkoxyamine \(^37\) in a good yield. Reductive nitrogen–oxygen bond cleavage with zinc in acetic acid finally afforded alcohol \(^38\) (Scheme 13). Thus, alkoxyamines can be regarded as protected alcohols.\(^101\) Moreover, oxidation of alkoxyamines with \(m\)-chloroperbenzoic acid to the corresponding aldehydes or ketones was described.\(^102\)

Scheme 13  Aryl radical cyclization and subsequent TEMPO trapping

Jahn et al. oxidized the in situ generated ester enolate \(^39\) with ferrocenium hexafluorophosphate \(^40\) to the corresponding carbon-centered radical \(^41\) which underwent 5-exo-cyclization to give the primary radical \(^42\). TEMPO trapping provided alkoxyamine \(^43\). Direct reaction of the \(\alpha\)-keto radical \(^41\) with TEMPO was observed as a side process (10% of the corresponding alkoxyamine was isolated). This oxidative anion/radical reaction sequence was introduced as a method for the synthesis of highly func-
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Enolates of bis-sulfoxides were oxidized to the corresponding radicals with ferrocenium ions. TEMPO trapping gave the desired alkoxyamines, as shown by Malacria and co-workers. Recently, Heinrich et al. published results of intermolecular radical addition/TEMPO trapping processes. The aryl radicals were generated by reductive decomposition of the corresponding aryl diazonium salts with iron sulfate. Addition of the thus-formed aryl radicals to alkenes and subsequent TEMPO trapping gave the corresponding alkoxyamines in good yields (Scheme 15). Recently, Hasegawa and Sibi reported on organocatalyzed α-oxyaminations of aldehydes with TEMPO under oxidative conditions. Reaction of an aldehyde with imidazolidinone led to the corresponding enamine. Aerobic oxidation generated radical which undergoes stereoselective coupling with TEMPO to give iminium ion. The alcohol was readily isolated after reduction in good yields and high stereoselectivities (Scheme 16). An aerobic one-pot conversion of primary alcohols into racemic α-oxyaminated alkanals with TEMPO and a ruthenium complex was also reported.

Carbon-centered radicals can be generated directly by reaction of ketenes with TEMPO. These processes require two equivalents of TEMPO. Due to the high reactivity of both ketenes and carbon-centered radicals, these processes have received only little attention to date. The sensitivity of ketenes towards oxygen was recognized very early.

Tidwell and co-workers have studied the reaction of TEMPO with various ketenes intensively. Addition of TEMPO to the carbon–carbon double bond was found to occur readily. However, for less activated substrates, this particular addition is slow and is therefore followed as minor pathway. Reaction of phenylketene with TEMPO provided the benzylic radical regioselectively. The formation of the acyl radical is energetically less favorable, as also supported by calculations. Subsequent trap-
4 Reaction of TEMPO with Organometallic Compounds

Carbon-centered radicals can be generated by reaction of an organometallic compound with TEMPO. In these processes, one equivalent of the nitroxide is used for oxidation of the organometallic species to the corresponding carbon-centered radical, which is then trapped by the second equivalent of TEMPO to eventually provide the alkoxyamine 55 (Scheme 18).

Scheme 18 Generation of radicals from organometallic compounds with TEMPO and subsequent TEMPO trapping.

The reaction of Grignard reagents and n-butyllithium with TEMPO proceeds via this mechanism. Curran and Nagashima were able to oxidize various organometallic compounds via this route. Lithium, magnesium, titanium, zirconium, copper, zinc and samarium species were transformed into the corresponding alkoxyamines by using this approach. A diastereoselective process starting from alkylolithium compounds has also been described.

Some organoboron species were shown to react with TEMPO. The reactivity of boron derivatives towards oxygen-centered radicals is strongly dependent on the Lewis acidity of the boron species. Successful reactions were reported with B-alkylcatecholboranes 56, where homolytic substitution at boron led to the formation of the boric acid ester 57. This reaction presumably proceeds via the radical intermediate 58 (Scheme 19).

Scheme 19 Reaction of B-alkylcatecholboranes with TEMPO.

Importantly, substrate 56 is readily available by hydroboration of the corresponding alkene. A further advantage is the reversible bond homolysis indicated in Scheme 20. The undesired boron–oxygen bond cleavage in intermediate 58 leads to the phenoxyl radical 59 which is in equilibrium with the boronic ester 56. Irreversible boron–carbon bond cleavage selectively liberates the desired carbon radical.

Scheme 20 Reversible boron–oxygen bond homolysis.

Renaud and co-workers obtained alkoxyamine 61 in excellent diastereoselectivity after hydroboration of α-pinene (60) with catecholborane (CatBH) and subsequent TEMPO treatment. Dimethylpropylene urea (DMPU) as an additive improved the yield for this one-pot process. However, the exact mechanistic role of this additive is still not understood (Scheme 21).

TEMPO can also react with other organometallic species. In addition to the already discussed hydrogen abstractions from metal hydrides, TEMPO has been used as a ligand for main group elements and transition metals.
TEMPO can either oxidize or reduce these species. Waymouth and co-workers reported the reversible homolysis of the weak titanium–oxygen bond in complex 62 (Scheme 22). The equilibrium constant between the homolyzed titanium(III) species 63 and TEMPO and complex 62 can be influenced by altering the ligand sphere around the titanium atom.121

Scheme 22 Reversible titanium–oxygen bond homolysis

Chromium(III)– and rhodium(III)–superoxide complexes were shown to oxidize TEMPO to the oxoammonium ion 6.122 Adsorption of nitroxyl radicals onto gold nanoparticles resulted in a loss of the EPR signal. It was suggested that this was due to exchange interactions of the unpaired electrons of the adsorbed radicals with conduction-band electrons of the metallic particles.123 Dicobalt octacarbonyl can be oxidized with TEMPO. Pericàs and co-workers developed a mild method for the synthesis of cobalt oxide nanoparticles at room temperature by using this approach.124 A Pauson–Khand reaction was accelerated by addition of TEMPO. These suggestions were supported by DFT studies.125 Release of a ligand promoted by TEMPO was also proposed for a zirconium complex.126

TEMPO was also used as an oxidant in transition-metal-catalyzed processes. Lam et al. employed TEMPO in copper-catalyzed carbon–nitrogen and carbon–oxygen bond cross-couplings of amines and phenols with arylboronic acids.127 These reactions were developed simultaneously in the groups of Chan,128,129 Evans130 and Lam.129 Stoichiometric amounts of cupric acetate were used in these coupling reactions. It was shown that they also proceed with catalytic amounts of copper salt in the presence of a terminal oxidant. Various cooxidants have been tested and TEMPO showed good activity as the terminal oxidant for the coupling reaction (Scheme 23).127

Recently, Studer and Vogler developed a rhodium-catalyzed oxidative coupling of aryl- and alkenylboronic acids with arenes and heteroarenes with TEMPO as an oxidant.131 This method allowed for the synthesis of bi- and triaryls in good to excellent yields. Aryl- and alkenylboronic acids were used for these direct C–H arylations (Scheme 24). Importantly, these reactions could also be conducted with catalytic amounts of TEMPO in the presence of oxygen or air as terminal oxidant;131 however, slightly lower yields were obtained under these conditions.
with arene 67 bearing the ortho-directing group should then lead to 68 which eventually undergoes C–H arylation to generate the rhodium(III) complex 69 and hydroxylamine 7. The TEMPO anion probably acts as a base under these conditions. Reductive elimination and ligand exchange eventually provide the coupling product 70 and the rhodium(I) complex 64 is regenerated (Scheme 25).

Scheme 25  Proposed mechanism for the C–H arylation

5  Carbon–Oxygen Bond Homolysis of Alkoxyamines

When stabilized carbon radicals are formed, TEMPO-derived alkoxyamines undergo clean thermal homolysis to the corresponding carbon-centered radicals and TEMPO. The persistent (long-lived) nitroxide and the transient (short-lived) radical are generated with the same rate and in equal concentration. As an example, thermal reversible homolysis of alkoxyamine 71 affords the benzylic radical 72 and TEMPO (Scheme 26). The rate constant for the trapping process is generally many orders of magnitude larger. Due to fast homocoupling of the carbon radicals, the concentration of radical 72 decreases. This leads to a build up of the persistent radical, because it does not undergo homocoupling. Since the cross-coupling of TEMPO with carbon-centered radicals is a fast reaction, typical side reactions such as dimerization and disproportionation of the carbon radicals are suppressed. This concept is well established and is known as the Persistent Radical Effect (PRE). This general principle explains the highly selective formation of the cross-coupling product between a persistent and a transient radical. Thus, the transient radical is reversibly protected by its reaction with the persistent radical. Therefore this concept should be highly valuable in the operation of slow radical reactions where formal long-lived radicals are necessary.

Rate constants for recombination and dissociation are strongly influenced by the structure of the nitroxide. Hence, the equilibrium between the alkoxyamine and the homolyzed species can be adjusted. Shifting the equilibrium towards the dissociated species is desired in order to achieve efficient reactions. The 5-exo- and 6-endo-cyclizations of the benzylic radical 72 lead to the radicals 73 and 74, respectively. The alkoxyamines 75 and 76 are then formed by irreversible trapping of these radicals with TEMPO (Scheme 26). Alkoxyamine isomerization is significantly slower without camphorsulfonic acid, and can also be accelerated by various other additives. The additive effect was understood through kinetic simulations. Intermolecular alkoxyamine additions, homolytic aromatic substitutions, isonitrile and carbon monoxide trapping reactions were successfully conducted through the use of these environmentally benign alkoxyamine isomerization or addition reactions. Importantly, these thermal additions could be performed highly efficiently by using microwave (MW) irradiation. In some cases, a 430-fold acceleration was achieved upon switching from classical to microwave-induced heating. As an example, addition of TEMPO–malonate 77 to oct-1-ene was complete in 10 minutes and gave the corresponding alkoxyamine 78 in a good yield (Scheme 27).

Scheme 26  PRE-mediated isomerization of alkoxyamine 71

![Scheme 26](image-url)
alkoxyamines. This scrambling process was recently used by Crich et al. in building an alkoxyamine library.

The PRE has recently gained a lot of attention because to the development of the nitroxide-mediated polymerization (NMP). NMP, controlled by the PRE, is a living radical polymerization method, which allows the controlled polymerization of various monomers. As an example, the heating of alkoxyamine initiator 79 in neat styrene led to a controlled styrene polymerization and the product polymer 81 was formed with low polydispersity. Carbon–oxygen bond homolysis in 81 generated a benzylic radical which then could add to a monomer unit and hence form the polymeric radical 80. The rate constant for propagation \( k_p \) is set by the monomer structure. The rate of the polymerization process can be strongly influenced by tuning of the nitroxide moiety. Faster dissociation \( k_d \) as well as slower recombination \( k_c \) lead to a higher concentration of the growing macroradical 80 and hence to a faster polymerization (Scheme 28).

Many research groups have studied the influence of the structure of the nitroxide on important polymerization parameters such as rate and polydispersity. It was shown that slower trapping \( k_c \) occurs by stabilization of the nitroxide by hydrogen bonding and polar effects. An increase in the steric demand of the nitroxide moiety leads to weaker carbon–oxygen bond energies in the corresponding alkoxyamine and thus to faster homolysis \( k_d \). However, if the substituents become too large, fast and uncontrolled polymerizations are observed because the trapping reaction of the nitroxide with the macroradical and the nitroxide becomes too slow.

Various nitroxides have been developed for efficient polymerizations of vinylic monomers at low temperatures. The most common among these are nitroxides from the groups of Hawker (82), Tordo (83) and Studer (84 and 85), shown in Figure 3. An advantage of the NMP over other living radical polymerization techniques is the absence of metals in the product. Furthermore, a colorless polymeric material is readily obtained by NMP.

Recently, Scaiano and co-workers described the alkoxyamine 86, which is able to undergo photochemical carbon–oxygen bond homolysis to give a benzylic radical and nitroxide 87 upon irradiation at 300–400 nm. The quinoline part acts as a chromophore and transfers energy to the nitroxide moiety of the alkoxyamine 86 which induces homolytic carbon–oxygen bond cleavage (Scheme 29). Preliminary polymerization experiments showed only little control for the polymerization process if 86 was used as a photochemical low-temperature-polymerization initiator/regulator. Based on these results, one
can assume that low-temperature NMP is conceivable through the use of photoactive alkoxamines.150

6 Conclusions

The present review clearly documents that commercially available TEMPO, which is produced in industry, has found many applications in organic synthesis. As can be readily extracted from this article, most of the recent papers deal with the use of TEMPO for the oxidation of alcohols. Despite the great achievements in this field, further developments are necessary, in particular the use of TEMPO as an organocatalyst in combination with oxygen or air as terminal oxidants. Hence, the efficient regeneration of the oxoammonium salt from the hydroxylamine is still a challenge. Specifically, metal-free benign oxidations, which are important for industry, are highly desirable. Moreover, we believe that many transition-metal-mediated processes requiring an external oxidant can be conducted with the use of TEMPO. Many results in this field are foreseen.

In radical chemistry, TEMPO has been used mainly as a radical trap. However, depending on the structure of the trapped species, this process can be reversible. In fact, recent results on successful thermal carbon–oxygen bond homolyses of TEMPO-derived alkoxamines showed that this is a highly efficient approach for the clean thermal generation of carbon-centered radicals. No other reagents are necessary to generate the radical species. The environmentally benign reversible alkoxamine homolysis is also important in the nitroxide-mediated radical polymerization. We believe that further results in this area will appear. As an example, low-temperature alkoxamine homolysis would certainly expand the applicability of these processes.

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References

(b) Wieland, H.; Offenbächer, M. Chem. Ber. 1914, 47, 2111.