Synthetic Methods

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Nitroxides: Applications in Synthesis and in Polymer Chemistry

*Ludger Tebben and Armido Studer**

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Dedicated to Professor Gerhard Erker on the occasion of his 65th birthday

This Review describes the application of nitroxides to synthesis and polymer chemistry. The synthesis and physical properties of nitroxides are discussed first. The largest section focuses on their application as stoichiometric and catalytic oxidants in organic synthesis. The oxidation of alcohols and carbanions, as well as oxidative C–C bond-forming reactions are presented along with other typical oxidative transformations. A section is also dedicated to the extensive use of nitroxides as trapping reagents for C-centered radicals in radical chemistry. Alkoxyamines derived from nitroxides are shown to be highly useful precursors of C-centered radicals in synthesis and also in polymer chemistry. The last section discusses the basics of nitroxide-mediated radical polymerization (NMP) and also highlights new developments in the synthesis of complex polymer architectures.

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1. Introduction and Brief History

Nitroxyl radicals, which are also called nitroxides, are N,N-disubstituted NO radicals with a delocalized unpaired electron shared between the nitrogen and oxygen atoms. The delocalization of the unpaired electron is indicated by the three resonance structures **A**, **B**, and **C** (Figure 1). The spin density can, depending on the N substituents R^1 and R^2, be further delocalized over the substituents. The first nitroxide reported in the literature (1845) was an inorganic nitroxide called Fremy's salt (**1**, $^{\bullet}ON(SO_3K)_2$), which has been used extensively as an oxidant in organic synthesis.[1,2] Porphyrexide (**2**), although not recognized as a radical species at that time, was introduced in 1901 by Piloty and Schwerin as the first organic nitroxide.[3] Diaryl nitroxides **3** were initially studied by Wieland and Offenbächer[4] in 1911, and a very important contribution to the field of nitroxide chemistry was made by Lebedev and Kazarnovsky, who introduced 4-oxo-2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (4-oxo-TEMPO, **4**) as a readily prepared persistent nitroxide in 1959.[5] 4-Oxo-TEMPO is used as a starting material for other highly synthetically useful nitroxides such as TEMPO (**5**) and 4-*N*-acetylamino-TEMPO (**6**), which are both commercially available. Nitroxide chemistry has greatly evolved and many nitroxides have been successfully synthesized and studied since their discovery. The substituents R^1 and R^2 can be primary, secondary, or tertiary alkyl groups. However, nitroxides bearing secondary and primary alkyl groups are generally less stable due to a possible disproportionation reaction of two nitroxides to the corresponding nitrone and hydroxylamine.[6] Heteroatom-substituted nitroxides (R^1 or $R^2 = OR$, SR, NR_2, PR_2, and SiR_3) have also been prepared, and book chapters, reviews, and books describing the synthesis and applications of nitroxides in various fields have appeared.[7] The present Review will mainly cover recent developments in the application of nitroxides in synthesis and in polymer chemistry; however, important earlier achievements will also be discussed. The application of nitroxides as spin probes in biochemistry and newer developments in the application of nitroxides as building blocks for the preparation of organic magnets will not be discussed. For detailed information on these two application-oriented areas, we refer the reader to a recently published book on nitroxides.[7e]

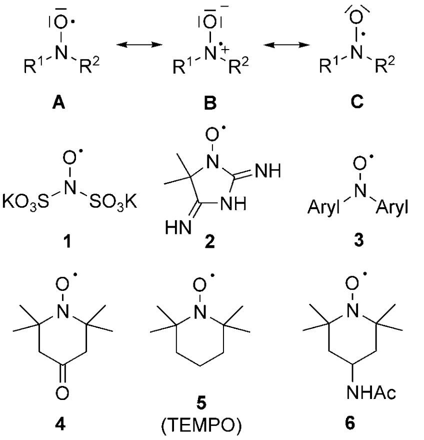

Figure 1. Nitroxides: Resonance structures and various important examples.

2. Physical Properties

Nitroxides are paramagnetic compounds that can be readily analyzed by ESR spectroscopy.[8] The spectra give the nitrogen coupling constant α^N, which provides information on the spin density at the nitrogen atom (extent of the population in resonance structure **B**). Values of α^N ranging from 0.2 to 0.5 have been reported for nitroxides, and they depend on the substituents on the nitrogen atom.[7b] The spin density at the oxygen atom lies between 0.35 and 0.55. The remaining electron density is found on the nitrogen substitu-

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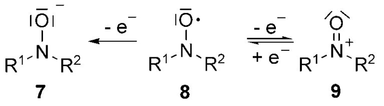
[*] Dr. L. Tebben, Prof. Dr. A. Studer
Organisch-Chemisches Institut, Westfälische Wilhelms-Universität
Corrensstrasse 40, 48149 Münster (Germany)
Fax: (+49) 251-833-6523
E-mail: studer@uni-muenster.de

ents. The delocalization energy of the unpaired electron was reported to be around 120 kJ mol^{-1}.[9] Hence, the N−O bond can be described as a three-electron N−O bond with a bond order of 1.5. If the nitroxides bear protons at the α position to the N atom, ESR delivers information on the conformation of the nitroxide.[7b,10]

Most nitroxides can be stored in the solid state for several years. X-ray scattering and electron diffraction have revealed N−O bond lengths of about 1.23 to 1.29 Å.[7b] Since an N−O single bond has a length of about 1.44 Å and a double bond is 1.20 Å, it clearly indicates that the N−O bond in nitroxides bears double-bond character (bond order 1.5). As the zwitterionic resonance structure **B** is populated, nitroxides have a rather large dipole moment which depends on the solvent polarity (TEMPO in THF: 3.88 D; TEMPO in cyclohexane: 3.30 D).[11] The n–π visible band of nitroxides at 410–460 nm in the UV/Vis spectrum shows solvatochromism. Increasing the solvent polarity leads to a blue shift of the n–π band.[7b,11] An additional stronger absorption band is observed at around 240 nm for dialkyl nitroxides.

Nitroxides show very weak Brønsted basicity and the oxygen atom is only partially protonated under strong acidic conditions (the pK_a value of protonated TEMPO is −5.8).[12] As will be discussed in Section 4, TEMPO exerts Lewis basic character by acting as a ligand for metal ions.

The electrochemical properties of various nitroxides have been studied intensively: Many nitroxides **8** undergo reversible oxidation to the corresponding oxoammonium salts **9** (Scheme 1).[13] The oxidation potential for TEMPO was reported to lie at 0.64 V (vs. SCE).[14] Modification of the structure of the nitroxide resulted in slightly higher or lower values compared to that of TEMPO: Whereas the 4-oxo-TEMPO derivative **4** has a higher oxidation potential (0.67 V vs. SCE) than TEMPO, the oxidation potential of 4-hydroxy-TEMPO lies below that of TEMPO (0.48 V vs. SCE).[15] Compared to the six-membered TEMPO derivatives, the corresponding five-membered cyclic nitroxides show slightly higher oxidation potentials. Aryl alkyl nitroxides are oxidized at higher potential than TEMPO.[13a]

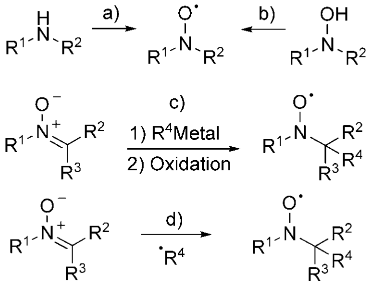


Scheme 1. Electrochemical oxidation (reversible) and reduction (irreversible) of nitroxides.

The reduction of a nitroxide to the corresponding aminoalkoxide anion **7** is a known process. As will be discussed in Section 4.1.4, TEMPO itself shows only weak reactivity as an oxidant in organic synthesis. In contrast to oxidation, the electrochemical reduction of a nitroxide is not a reversible process. The reduction potential is heavily influenced by the pH value of the reaction mixture; at pH 4.3, TEMPO is reduced at −0.4 V (vs. SCE).[13b,16]

3. Preparation of Nitroxides

Nitroxides are prepared generally by four different methods. Method a (Scheme 2), which is the most important one, uses secondary amines as substrates that are oxidized directly to the corresponding nitroxides. Tungstate-, molybdate-, and vanadate-based catalysts in combination with hydrogen peroxide as a stoichiometric oxidant have been used for these oxidations.[17,18] In addition, organic peroxides such as *meta*-chloroperbenzoic acid efficiently oxidize secondary amines to the corresponding nitroxides.[19] Method b starts with hydroxylamines, which can be readily oxidized to the corresponding nitroxides by using milder oxidants.[19] Nickel peroxide,[20] potassium ferricyanide,[20] lead dioxide,[21]



Scheme 2. The most important methods for the preparation of nitroxides.

Armido Studer received his PhD in 1995 from ETH Zurich under the direction of Prof. Dieter Seebach. He then worked 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 at the Philipps University in Marburg, Germany, and in 2004 as Full Professor of Organic Chemistry at the Westfälische Wilhelms-University in Münster, Germany. In 2006 he received the Novartis Young Investigator Award in Chemistry and in 2007 the Solvias Ligand Contest Award.

Ludger Tebben studied chemistry and biology at the Westfälische Wilhelms-Universität Münster. He received his PhD there within the Graduate program IRTG 1143 (Münster/Nagoya) under the guidance of Prof. Gerhard Erker in 2007 on ferrocenes as ligands in asymmetric transition-metal catalysis and as peptide conjugates. In 2007 he was appointed as senior researcher and lecturer within the research group of Prof. Armido Studer. Since 2010 he has also worked as managing director within the Collaborative Research Center (Sonderforschungsbereich) 858 "Synergetic Effects in Chemistry".

silver oxide,[22] manganese dioxide,[23] and often sodium periodate[24] have been used successfully for this transformation. Furthermore, in some cases oxygen can be applied as an oxidant under basic conditions in the absence of any additives. This pH-dependent reaction is retarded under acidic conditions. Furthermore, hydroxylamines have been oxidized to the corresponding nitroxides with oxygen in combination with copper(II) salts as catalysts.[25]

Nitroxides have also been prepared by the reaction of nitrones with organometallic compounds (mostly Grignard or organolithium compounds) to provide the corresponding metalated (deprotonated) hydroxylamines, which can be directly oxidized to nitroxides (method c).[25] Alternatively, the adducts obtained on nucleophilic addition to nitrones can by hydrolyzed to give the corresponding hydroxylamines, which are subsequently oxidized to nitroxides by using method b.[18] Nitrones are known to be good traps for radicals to give the corresponding nitroxides (method d). However, since nitroxides are generated in the presence of radicals by this method, the nitroxides generated as intermediates further react to give the corresponding alkoxyamines.[25]

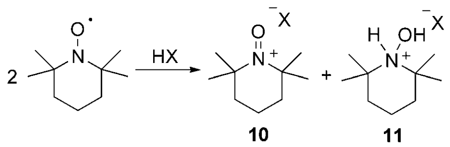
Other methods, besides these most often used approaches, have been reported for the synthesis of nitroxides. Tertiary nitroalkanes react directly on treatment with sodium metal to give the corresponding di-*tert*-alkyl nitroxides. This method is not generally applicable, but for example was used successfully for the synthesis of di-*tert*-butylnitroxide.[26] Moreover, the reaction of nitroalkanes with Grignard reagents and organolithium compounds can also lead to nitroxides,[27] for example by treating C-centered radicals with nitroso derivatives. This reaction occurs by thermal or photochemical decomposition of the nitroso derivative to NO and the corresponding alkyl radical, which is subsequently trapped by the excess of nitroso compound present in the reaction mixture to afford the corresponding nitroxide.[28] Finally, nitroxides can be prepared directly by the reaction of C-centered radicals with nitroso and nitrone derivatives.[29]

4. Applications of Nitroxides in Synthesis

4.1. Oxidation Reactions

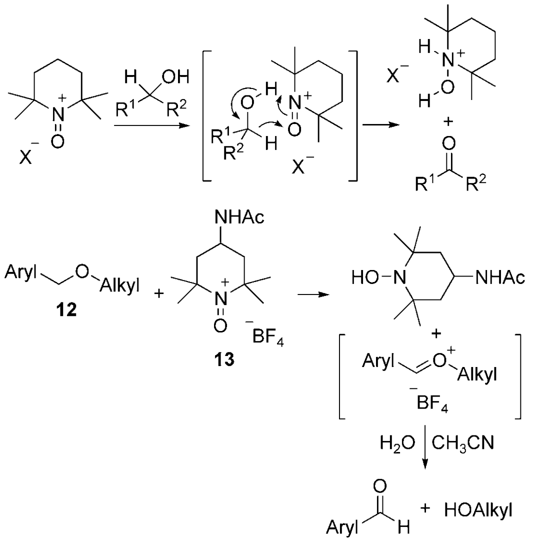
4.1.1. Oxidation of Alcohols

Nitroxides have found widespread application as catalysts for the oxidation of primary and secondary alcohols to the corresponding aldehydes, ketones, and acids.[7d,30] However, in most of these transformations the active oxidant is not a nitroxide but its oxidized form, the corresponding oxoammonium salt. The reactive oxoammonium salt of TEMPO can be readily generated by treatment of TEMPO with an acid HX to give the oxoammonium salt **10** along with protonated hydroxylamine **11** in a disproportionation reaction (Scheme 3). Depending on the counteranion, these salts can be stable and can be isolated and used as stoichiometric oxidants in synthesis. HBF_4 has often been used as the acid, and leads to the stable oxoammonium salt **10** ($X = BF_4$).[31] This salt is commercially available. Chloride (less stable), bromide, tribromide, and perchlorate have also been used as the counterion. Importantly, under basic conditions **11** is readily oxidized to TEMPO upon treatment with air.[32]



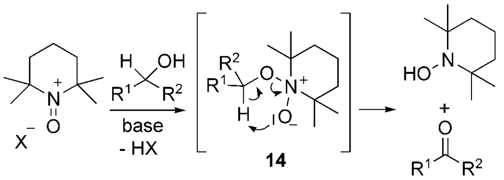
Scheme 3. Disproportionation of TEMPO by treatment with an excess of acid HX.

The mechanism for the oxidation of alcohols with oxoammonium salts has been intensively studied. Interestingly, the chemoselectivity in the oxidation of primary versus secondary alcohols changes as a function of the pH value of the reaction medium: oxidation is slow and favors the secondary alcohols at low pH values, whereas fast oxidation with high selectivity for primary alcohols is observed at higher pH values. Most of the TEMPO-mediated oxidations have been conducted under basic conditions. Nevertheless, we will briefly focus on the mechanism suggested for oxidations at a low pH value. These reactions are proposed to occur by hydride transfer according to Scheme 4.[33,34] Selectivity arises from the fact that secondary alcohols are better hydride donors than primary alcohols. The feasibility of oxoammonium salts to act as hydride acceptors was recently further documented by the selective oxidative cleavage of benzyl alkyl ethers **12**. This reaction proceeds by a selective hydride transfer from the benzylic position to the oxoammonium salt **13** to give an aromatic aldehyde and the corresponding aliphatic alcohol after hydrolysis. The alcohol is further oxidized under the reaction conditions to its acid.[35] A mechanism involving single-electron transfer followed by deprotonation instead of direct hydride abstraction might also be feasible for this oxidation.



Scheme 4. Oxidation of alcohols with oxoammonium salt **13** in acidic media and oxidative ether cleavage by hydride abstraction.

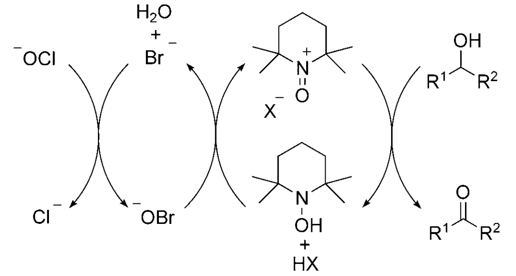
Under basic conditions the alcohol reacts at the nitrogen atom of the oxoammonium salt to deliver adduct **14**, which subsequently decomposes to TEMPOH and the corresponding aldehyde or ketone (Scheme 5).[34,36] The formation of adduct **14** is faster for primary alcohols than secondary alcohols because of the shielding of the electrophilic nitrogen atom by the four methyl groups of the oxoammonium salt. The formation of this adduct is probably rate-determining, and this explains the preferential oxidation of primary alcohols in the presence of secondary alcohols under basic conditions in TEMPO-mediated transformations.



Scheme 5. Oxidation of alcohols with oxoammonium salts under basic conditions.

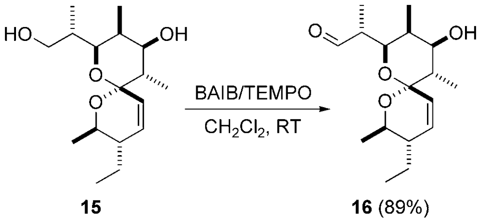
Oxoammonium salts of type **10** have been used successfully as stoichiometric mild oxidants for the oxidation of alcohols under acidic conditions (in the presence of SiO_2)[37] and also under basic conditions.[37,38] However, more interestingly, and more importantly in terms of atom economy, are nitroxide-mediated oxidations in which the nitroxide compound is used in catalytic amounts. In these cases, a secondary cooxidant is used for reoxidation of the hydroxylamine (TEMPOH) to the oxoammonium salt, and different organic and inorganic terminal oxidants have been used for this two-electron oxidation process. The most often used cooxidant in nitroxide-catalyzed alcohol oxidations is sodium hypochlorite in CH_2Cl_2 (Anelli conditions).[39] HOCl-mediated oxidations occur under mild conditions, and bromide anions have been shown to act as co-catalysts in these reactions.[30c,40] It is presumed that the bromide is oxidized with NaOCl to hypobromite, which is the active oxidant for regeneration of the oxoammonium salt (Scheme 6). Acceleration of the regeneration of the oxoammonium salt has also been achieved by sonication.[41]

Carboxylic acids are obtained in excellent yields if the oxidation of alcohols is conducted with stoichiometric amounts of $NaClO_2$ as a terminal oxidant in the presence of TEMPO (cat.) and NaOCl (cat.) in aqueous acetonitrile.[42] TEMPO in combination with NaOCl generates the oxoammonium salt, which oxidizes the alcohol to the corresponding aldehyde as described above. In a subsequent process the aldehyde further reacts with $NaOCl_2$ to give the acid and NaOCl, which eventually acts as the oxidant in the reaction with TEMPOH to regenerate $TEMPO^+$ (**10**). Amberlite·-NEt_3^+/ClO_2^- was successfully used as a polymeric secondary oxidant[43] for similar transformations, and good results were also achieved when $NaBrO_2$ was used as a secondary oxidant.[44]



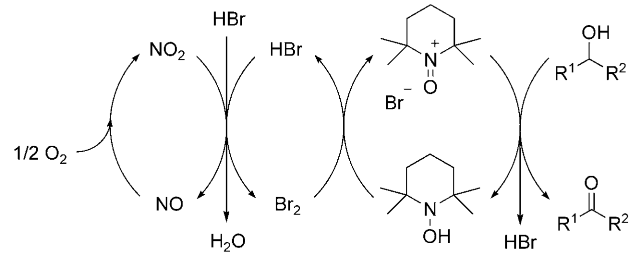
Scheme 6. Oxidation of alcohols with TEMPO in the presence of NaOCl and KBr.

Another useful cooxidant that is frequently applied in TEMPO-mediated oxidations is bis(acetoxyiodo)benzene (BAIB, $PhI(OAc)_2$).[45] The mechanism for the regeneration of the oxammonium salt by $PhI(OAc)_2$ is not fully understood. A typical example from the recent literature is depicted in Scheme 7. The primary alcohol of complex diol **15** was selectively oxidized with TEMPO and $PhI(OAc)_2$ in CH_2Cl_2 to give aldehyde **16** in a good yield.[46] The reaction was performed at room temperature and no epimerization was observed.[47,48] These transformations have generally been conducted under anhydrous conditions; however, if water is present, over-oxidation to the acid via the hydrate can occur.[49] Other iodine-based oxidants such as periodic acid,[50] 1-chloro-1,2-benziodoxol-3(1*H*)-one,[51] iodine pentoxide (I_2O_5),[52] and sodium periodate[53] have been applied as stochiometric cooxidants in TEMPO-mediated oxidations of alcohols. The reaction was found to occur under acidic conditions when periodic acid is used, and the following reactivity order was found: allylic ≈ benzylic > secondary > primary alcohols, which is in agreement with the mechanistic discussion above (the reaction probably proceeds by hydride abstraction; see Scheme 4). Other cooxidants which have been used successfully for the oxidation of alcohols in combination with catalytic amounts of TEMPO are *m*-chloroperbenzoic acid,[54] oxone,[55] trichloroisocyanuric acid,[56] *N*-chlorosuccinimide,[57] iodine,[58] chlorine or bromine,[59] pyridine/HBr_3,[60] and hydrogen peroxide.[61]



Scheme 7. TEMPO/BAIB-mediated oxidation of diol **15**.

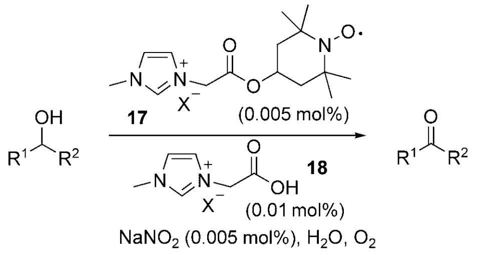
Liang, Hu, and co-workers first reported that transition-metal-free aerobic alcohol oxidations with TEMPO as a catalyst are feasible.[62] Reactions were performed with substochiometric amounts of bromine and $NaNO_2$ (0.4 equiv each) in the presence of TEMPO (10 mol%) in CH_2Cl_2 under air, and aromatic aldehydes were oxidized in excellent yields. A possible oxidative cycle for this interesting reaction is depicted in Scheme 8. Alcohol oxidation occurs via the oxoammonium salt, as discussed above. The TEMPOH



Scheme 8. Oxidative cycle of aerobic transition-metal-free oxidations with Br_2 and $NaNO_2$.

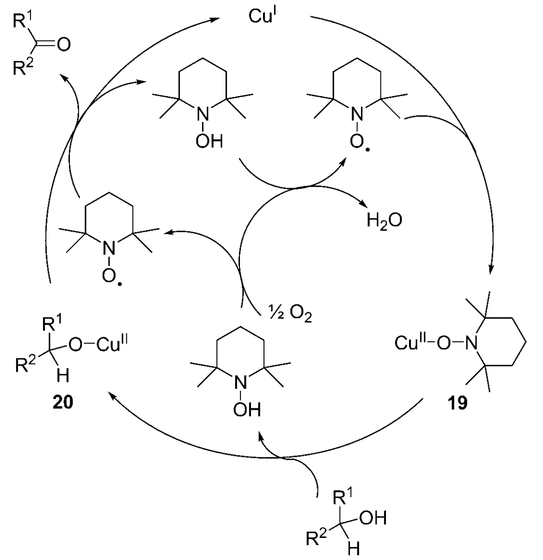
formed is then reoxidized to $TEMPO^+Br^-$ and HBr with bromine, which itself is generated in a second catalysis cycle from HBr and NO_2. The NO_2 is formed by the oxidation of NO in air. Environmentally friendly water is generated as a coproduct in this oxidation reaction.

This process has found high visibility, and recently an immobilized TEMPO derivative was used as a readily recoverable catalyst under similar conditions.[63] $NaNO_2$ acts as an NO precursor in these reactions. $NaNO_2$ in combination with 1,3-dibromo-5,5-dimethylhydantoin was also a suitable system for TEMPO-catalyzed aerobic alcohol oxidations.[64] It was found that HCl in combination with $NaNO_2$ also works.[65] Moreover, *tert*-butylnitrite has been shown to be a valuable NO precursor for TEMPO-catalyzed aerobic oxidations of alcohols.[66] Additionally, HNO_3 and hydroxylamine have been shown to function as suitable precursors for NO in such transformations.[66b,c] Recently, a TEMPO-functionalized imidazolium salt **17** was successfully used in very low loading together with a carboxylic acid substituted imidazolium salt **18** and catalytic amounts of $NaNO_2$ for the oxidation of alcohols (Scheme 9).[67]



Scheme 9. Mild aerobic transition-metal-free oxidation of alcohols with a nitroxide-conjugated imidazolium salt.

There are many reports on the aerobic oxidation[68] of alcohols by using both TEMPO and transition metals as co-catalysts.[69] Ceric ammonium nitrate (CAN),[70] $H_5PV_2Mo_{10}O_{40}{\cdot}34\,H_2O$,[71] $FeCl_3/NaNO_2$,[72] $[RuCl_2(PPh_3)_3]$,[73] and the couple $Mn(NO_3)_2/Co(NO_3)_2$[74] have been used successfully as co-catalysts in aerobic TEMPO-mediated oxidations. Without doubt, copper-based co-catalysts have been most intensively studied in this regard. Alcohol oxidations can occur via the oxoammonium salt, as discussed in Scheme 5. The copper co-catalyst in these processes is then used for the oxidation of TEMPOH to regenerate the oxoammonium ion and a reduced copper species. Air is eventually necessary for the regeneration of the Cu^{II} salt. Aerobic oxidations with the copper-dependent enzyme laccase and TEMPO were suggested to follow this mechanism.[75] Alternative mechanisms where the metal complex mediates the oxidation of the alcohol have been suggested. The nitroxide reacts with the metal complex as a one-electron oxidant in these cases and is itself directly regenerated by oxygen (Scheme 10).[30a,32,69,73] A Cu^I complex is oxidized by TEMPO to the corresponding Cu^{II}–TEMPO adduct **19**.

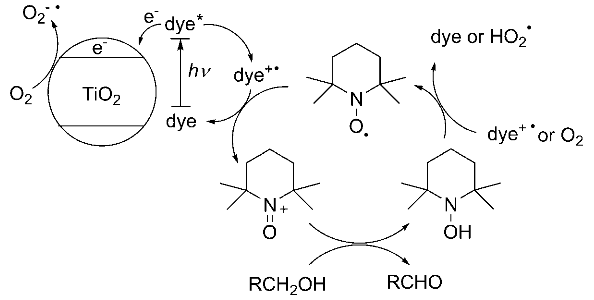


Scheme 10. Proposed mechanism for copper co-catalyzed aerobic alcohol oxidations with catalytic amounts of TEMPO.[32]

Subsequent ligand exchange with the alcohol gives complex **20** and TEMPOH. The copper alcoholate **20** reacts with TEMPO through intermolecular hydrogen transfer to the corresponding aldehyde or ketone and the starting Cu^I complex. TEMPO is regenerated from TEMPOH by air oxidation, a process which is heavily influenced by the pH value of the reaction medium.[30a,32] Different ligands and conditions have been applied for such aerobic alcohol oxidations co-catalyzed by copper.[76–79]

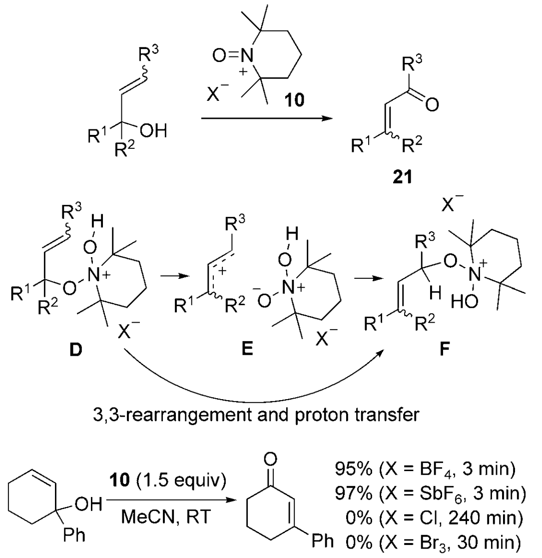
As an alternative to the reagents discussed above, electrochemistry has been successfully used for the regeneration of the oxoammonium ion from the hydroxylamine. These electrooxidations with catalytic amounts of a nitroxide are generally conducted in a polar organic solvent, such as acetonitrile or CH_2Cl_2, by using a high concentration of supporting electrolytes under regulated potential conditions in a divided cell.[80] The electrochemical oxidation of alcohols can also be performed in undivided cells in acetonitrile/water.[81] Moreover, TEMPO-catalyzed oxidations of carbohydrates were successfully conducted electrochemically in water.[82] The reaction workup is simplified if the nitroxide is immobilized on the electrode.[83]

An interesting photochemical method for the regeneration of $TEMPO^+$ from TEMPO was recently published,[84] whereby efficient alcohol oxidations were induced with visible light by using dye-sensitized TiO_2. The reactions were conducted with commercially available Alizarin Red as the sensitizer and TEMPO as a co-catalyst in a suspension of TiO_2 in trifluorotoluene under irradiation with visible light ($\lambda > 450$ nm). The oxidation was suggested to occur through two catalytic cycles (Scheme 11). The first one comprises an injection of an electron from the excited dye into the conduction band of TiO_2 to generate the dye radical cation, which oxidizes TEMPO to the oxoammonium salt. The reaction of $TEMPO^+$ with an alcohol provides the aldehyde or ketone along with TEMPOH (second catalytic cycle) as discussed above. The TEMPOH can eventually be reoxidized to TEMPO either by reaction with the dye radical cation or dioxygen.



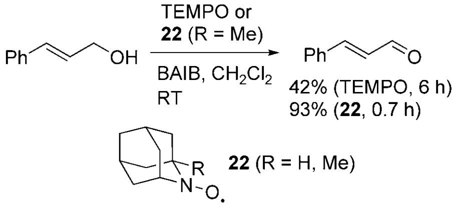
Scheme 11. Proposed catalytic cycle for the aerobic oxidation of alcohols induced by visible light.[84]

The oxidation of tertiary allylic alcohols with oxoammonium salts **10** provides the corresponding α,β-unsaturated ketones **21** through an oxidative rearrangement (Scheme 12).[85] Reactions occur via the adduct **D**, which is obtained by reaction of the tertiary alcohol with salt **10**. Heterolysis of the C–O bond will lead to ion pair **E**, which then collapses to **F**. Intermediate **F** can eventually fragment to product **21** and the protonated hydroxylamine **11**. Alternatively, intermediate **D** may undergo a concerted 3,3-rearrangement followed by proton transfer to directly give **F**. It was found that reaction works only with BF_4^- and SbF_6^- as counterions; later it was found that IO_4^- is also a suitable counterion for that reaction.[53b] This is in line with the stability of the corresponding oxoammonium salts (see Section 4.1.1). It was shown that this useful oxidative rearrangement reaction can also be carried out in the presence of catalytic amounts of TEMPO,[53b] with $NaIO_4$ on SiO_2 used as a terminal oxidant in CH_2Cl_2. Moreover, the reaction is also effected by using PhIO, the Lewis acidic $Bi(OTf)_3$ (cat.), and catalytic amounts of TEMPO.[86]



Scheme 12. Oxidation of tertiary allylic alcohols.

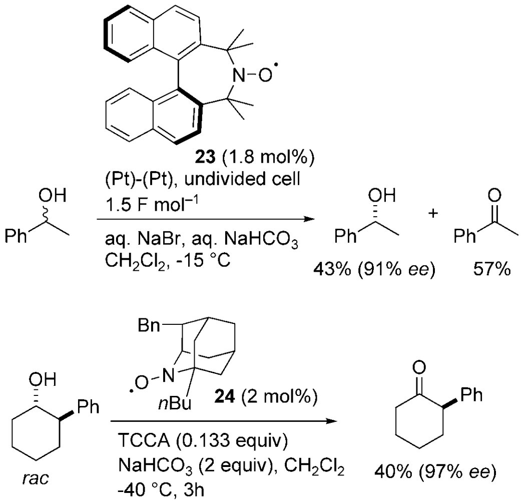
The discussions have so far mainly focused on the use of TEMPO or TEMPO derivatives as catalysts. In fact, almost all the studies were performed with the ubiquitous TEMPO. However, other nitroxides have also been tested as catalysts for alcohol oxidations, but unfortunately most compounds showed decreased activities.[87] Recently, the use of rigid tricyclic nitroxides in catalytic alcohol oxidations was investigated. It was found that the 2-azaadamantane *N*-oxyls **22** (R = H, Me) exhibited superior activity compared to TEMPO in typical alcohol oxidation reactions under Anelli conditions as well as when using BAIB as the cooxidant[88] or under electrochemical conditions.[89] For example, cinnamaldehyde was obtained in 93 % yield within 0.7 h at 1 mol % loading of **22** (R = Me), whereas with TEMPO only a 42 % yield was achieved in 6 h under identical conditions (Scheme 13).[88a] The use of $NaClO_2$ as a cooxidant led to the reaction of alcohols with **22** (R = Me) providing the corresponding acids in high yields. Again, the azaadamantane derivative showed higher reactivity than TEMPO.[90]



Scheme 13. Oxidation with 2-azaadamantane *N*-oxyl **22** as catalyst.

4.1.2. Kinetic Resolution of Alcohols

Various chiral nitroxides have been prepared successfully.[91] Some of these asymmetric nitroxides have been tested as chiral catalysts for the kinetic resolution of alcohols. The axially chiral C_2-symmetric nitroxide **23** was prepared by a multistep synthesis and was used as a catalyst in the kinetic resolution of chiral secondary alcohols. Selectivity (S) values of up to 7 were achieved for reactions of 1-aryl ethanol derivatives under Anelli conditions.[92] Electrooxidative kinetic resolution of secondary alcohols with **23** afforded S values of up to 20 under optimized conditions (Scheme 14).[93] Enantioselective electrocatalytic oxidation was also reported for a TEMPO-modified graphite felt electrode in the presence of (−)-sparteine.[94] Highly enantioselective organocatalytic oxidative kinetic resolutions of



Scheme 14. Oxidative kinetic resolution of secondary alcohols.

secondary alcohols by using the chiral rigid azaadamantol-*N*-oxyl radical **24** were recently reported.[95] Excellent *S* values of up to 82 were reported in these reactions. Aerobic TEMPO-catalyzed stereoselective oxidations were achieved by using (−)-sparteine or other chiral C_2-symmetric diamines as ligands for the copper co-catalyst. Acceptable selectivities were reported for the kinetic resolution of nonsymmetrical diaryl methanols[96] and for various benzoin derivatives.[97]

4.1.3. Immobilized Nitroxides as Reusable Catalysts in Oxidations

The immobilization of catalysts is a heavily investigated field of research because the immobilized catalysts are readily separable and reusable.[98,99] Although homogeneous catalysis has been extremely successful in the past, several problems can occur by using homogeneous systems. It is sometimes difficult to separate the catalyst from the product, and this is a particularly significant problem in the synthesis of pharmaceutical compounds, which should ideally be completely free of catalyst. In addition, catalyst recovery is an important issue for economic reasons, especially if expensive systems are used in the reactions. Along this line, many studies on the immobilization of nitroxides, in particular TEMPO and of TEMPO-derivatives, have been reported, and this of course is important for possible industrial applications, as highlighted in a recent review.[100]

Silica-supported TEMPO catalysts of type **25** have been intensively investigated as recyclable mediators for the oxidation of various alcohols (Figure 2). The catalyst can be readily separated by simple filtration. The generally high surface area of mesoporous silica means that high catalyst activity can be achieved. Regeneration of the oxoammonium salt of TEMPO was achieved under typical Anelli conditions.[101] In most of the cases the immobilized catalyst system showed high activity over several runs. Moreover, immobilization can lead to altered reactivity. For example, sol–gel organic–inorganic hybrid catalysts doped with TEMPO showed improved selectivity in the oxidation of 3-phenyl-substituted 2-amino-1,3-diols to the corresponding α-amino-β-hydroxy acids by using NaOCl in aqueous acetone compared to the use of a homogeneous TEMPO catalyst. The use of the homogeneous catalyst resulted in the unselective degradation of the targeted acids, thereby showing an additional benefit of the immobilization strategy.[102] Silica-supported TEMPO was used in transition-metal-free aerobic oxidation reactions of alcohols,[53] and the electrochemical regeneration of silica-immobilized TEMPO was also reported to be feasible.[83c] Two different silica-supported TEMPO systems have been used industrially and were introduced under the trade names SilicaCat TEMPO[103] and FibreCat TEMPO.[104]

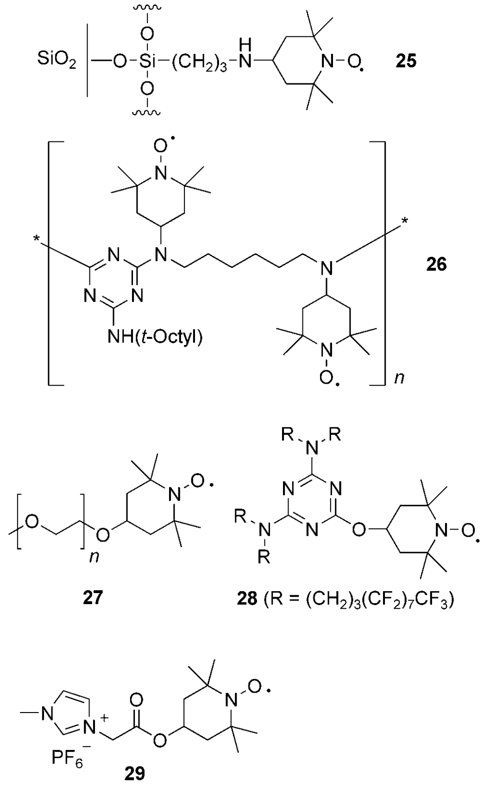


Figure 2. Various immobilized TEMPO derivatives.

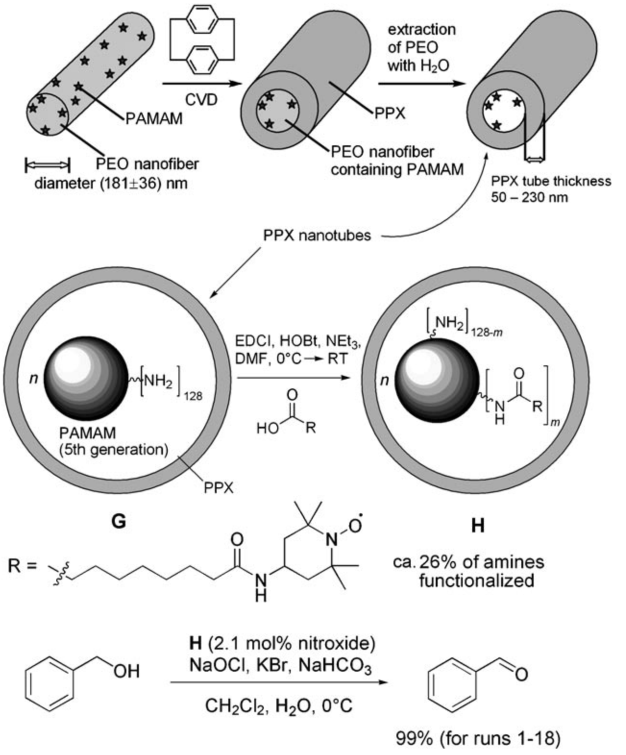
As an alternative solid matrix material, graphene-coated nanobeads containing magnetic cobalt were prepared by using azide/alkyne click chemistry.[105] The heterogeneous cobalt nanoparticle/TEMPO system turned out to be highly active for the selective oxidation of primary alcohols. Importantly, the heterogeneous catalyst could be readily separated from the product aldehyde by simple magnetic decantation. Very recently, TEMPO ammonium salts were immobilized in commercially available saponite by a simple cation-exchange reaction.[106] The organic–inorganic hybrid material was characterized by solid-state ^{1}H NMR spectroscopy, and was successfully used as a recyclable catalyst for the oxidation of various alcohols under Anelli conditions. The catalyst was recovered by simple filtration. High catalytic activity for up to ten runs was obtained and the nitroxide salt leached out of the saponite to only a small extent. The original high activity of the hybrid material was restored by simply reloading the hybrid material with the nitroxide salt by a cation-exchange process.

Different polymers have been used as matrix materials to covalently bind TEMPO derivatives. In contrast to immobilization on mesoporous silica, the TEMPO–polymer conjugates can, depending on the structure of the polymer used, be soluble in the reaction medium. Thus the disadvantage of operating with a heterogeneous catalyst system, which often shows lowered activity compared to the parent homogeneous system, does not hold. Separation is achieved by changing the solvent system to induce a change in the morphology of the polymer–TEMPO conjugate so that it becomes an insoluble, readily separable material. Hence, this approach combines the benefits of both homogeneous as well as heterogeneous catalysis. In fact, higher catalytic efficiency was reported for the polymeric TEMPO derivative **26** compared to a silica-supported catalyst.[107] Electrochemistry can be used to regenerate the polymeric oxoammonium salts.[108] Poly(ethylene glycol)-supported (PEG-supported) TEMPO radical **27** has been used as a readily recoverable catalyst for the oxidation of alcohols. Depending on the solvent used, the solubility of the polymer-bound nitroxides containing PEG with a mean molecular weight of about 4000 to 6000 $\mathrm{g\,mol^{-1}}$ can be changed from very soluble (dichloromethane) to completely insoluble (diethyl ether), which makes this particular polymeric tag highly useful as a phase marker for recoverable catalysts. NaOCl has been widely used as a stoichiometric terminal oxidant in combination with the PEG-TEMPO system.[109] In addition, the use of CuCl as a co-catalyst in compressed CO_2 as the reaction medium allowed the aerobic oxidations of alcohols.[110] The $Co(NO_3)_2/Mn(NO_3)_2$ system also showed high activity in combination with poly(ethylene glycol)-supported TEMPO.[74c] Other polymers which do not have phase-change properties and, therefore, act exclusively as insoluble catalysts have been used to conjugate TEMPO. Along this line, polystyrene–TEMPO conjugates,[74b,111] polyurethane-based TEMPO derivatives,[112] and other polymers[113] have been applied as recyclable catalysts for the oxidation of alcohols. In addition, TEMPO has been covalently bound to a graphite felt electrode and was successfully used for electrocatalysis.[83a]

Fluorous phase tags[114] have been conjugated with TEMPO derivatives and have been used as reusable readily recoverable catalysts in various nitroxide-mediated alcohol oxidations. Perfluoroalkyl chains covalently bound to organic compounds render these molecules highly soluble in fluorous solvents. In contrast, "normal" organic compounds that are not fluorinated show little or no solubility in fluorous solvents. This in turn can be applied to biphasic (organic phase/fluorous phase) extraction, where the fluorinated compound is extracted into the fluorous phase and all the nonfluorinated compounds are left in the organic phase. This approach requires the phase marker to have a high fluorine content. However, as nicely documented by Curran, fluorous reversed-phase silica gel has recently been used to separate "light" fluorous compounds containing a small number of fluorine atoms from nonfluorinated compounds.[115] For example, TEMPO derivative **28** with four fluorinated tails was prepared and used as a recyclable oxidant in combination with the terminal oxidants NaOCl and trichlorocyanuric acid.[116] Excellent yields were achieved and fluorous biphasic extraction allowed the ready separation of the catalyst from the product aldehyde. Other highly or moderately fluorinated TEMPO derivatives were prepared and used as readily separable catalysts for the oxidation of various alcohols.[117]

The imidazolium salt conjugated TEMPO compound **29** (Figure 2) was applied as a catalyst for nitroxide-mediated oxidations.[118] The modified TEMPO derivative showed similar catalyst activity as unmodified TEMPO. Separation of **29** from the product was readily achieved by biphasic extraction with an ionic liquid (IL) and diethyl ether. In this simple workup process, **29**, thanks to its ionic liquid tag, was extracted into the ionic liquid phase, whereas the aldehyde products remained in the organic phase.[67]

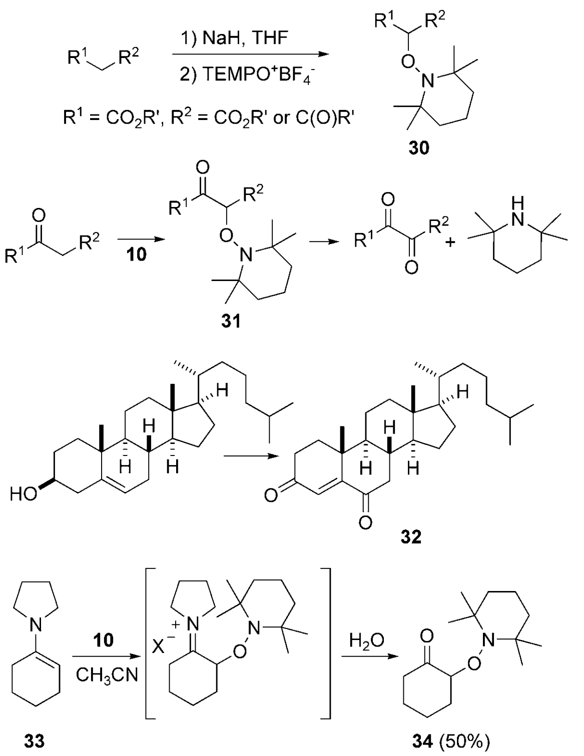
Recently we have shown that polyamidoamine (PAMAM) dendrimers of the fifth generation can be co-electrospun with polyethylene oxide (PEO) to give dendrimer-containing PEO nanofibers.[119] These nanofibers were then coated with a poly(paraxylylene) (PPX) shell by chemical vapor deposition (CVD) of [2.2]-parayclophane. Removal of the PEO core by extraction resulted in PPX nanotubes **G** with the PAMAM dendrimers entrapped inside (Scheme 15). PAMAM was then successfully chemically modified inside the tube by amide bond formation (see **H**). This reaction allowed the synthesis of TEMPO-conjugated PAMAM derivatives, which turned out to be highly active as reusable catalysts in the TEMPO/NaOCl oxidation of benzyl alcohol.



Scheme 15. PAMAM–TEMPO conjugates "bottled" into PPX nanotubes: PAMAM G5 immobilized in a PPX nanotube before (**G**) and after acylation (**H**). EDCI = *N'*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide, HOBt = 1-hydroxy-1*H*-benzotriazole.

4.1.4. Oxidation of Enolates and of Electron-Rich Olefins with TEMPO and TEMPO$^+$X$^-$

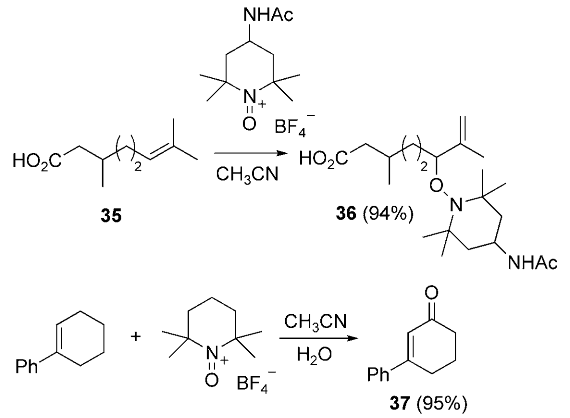
Ester and amide enolates do not generally react with TEMPO to give the corresponding radical and TEMPO$^-$. An external oxidant is required to generate the enoyl radical from the metal enolate.[120] However, the oxoammonium salt of TEMPO, which is a far stronger oxidant (see Section 2), spontaneously reacts with metal enolates to give alkoxyamines. Sodium and lithium enolates derived from β-ketoesters and malonates were shown to react with the TEMPO$^+$BF$_4^-$ salt at 0 °C to give alkoxyamines of type **30** in 47–89 % yield (Scheme 16).[121]



Scheme 16. Reaction of enolates and enols with TEMPO$^+$X$^-$ salts.

These reactions probably proceed by an ionic C-alkylation. Moreover, it was shown that enolizable ketones react with TEMPO oxoammonium salts to give the corresponding α-diketones.[111c,122] In this sequence, the alkoxyamine **31** formed as an intermediate reacts further through an ionic β elimination to give the corresponding diketone and 2,2,6,6-tetramethylpiperidine. For example, the oxidation of cholesterol with a polymer-bound oxoammonium salt afforded diketone **32**. This interesting reaction comprises a sequence of alcohol oxidation followed by alkoxyamine formation via the corresponding dienol intermediate, and finally piperidine elimination to give diketone **32**.[111c] Two equivalents of the oxoammonium salt were necessary for that transformation. The reaction of enamine **33** with TEMPO$^+$X$^-$ in acetonitrile provided, after hydrolysis, α-oxygenated ketone **34** in 50 % yield.[123] Recently, an enantioselective catalytic version of this reaction was described.[123b] Electron-rich enol ethers and enamides were also reported to undergo oxidative coupling with TEMPO-derived oxoammonium salts.[124]

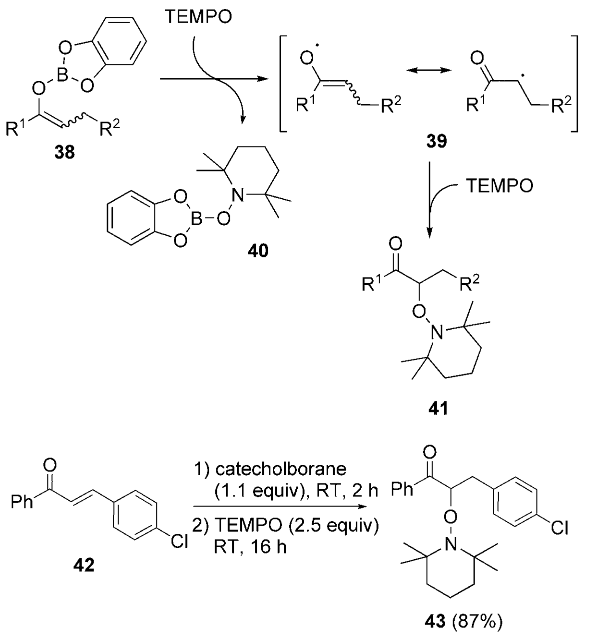
It is even possible to convert trisubstituted olefins into alkoxyamines by using oxoammonium salts.[125] Reactions occurred at room temperature and an ene-type mechanism was suggested for these transformations. As an example, the transformation of acid **35** to alkoxyamine **36** is presented in Scheme 17. Interestingly, 1-phenylcyclohexene reacted with TEMPO$^+$BF$^-$ in aqueous acetonitrile to give ketone **37**.[126] That reaction was suggested to occur by hydride abstraction from the allylic position with subsequent trapping of the thus-generated allylic cation with water to form an intermediate allylic alcohol, which in turn is further oxidized to the α,β-unsaturated ketone **37**. Moreover, 1,2,3,4-tetrahydrocarbazole was successfully oxidized under similar conditions to afford 4-keto-1,2,3,4-tetrahydrocarbazole in good yield.[127]



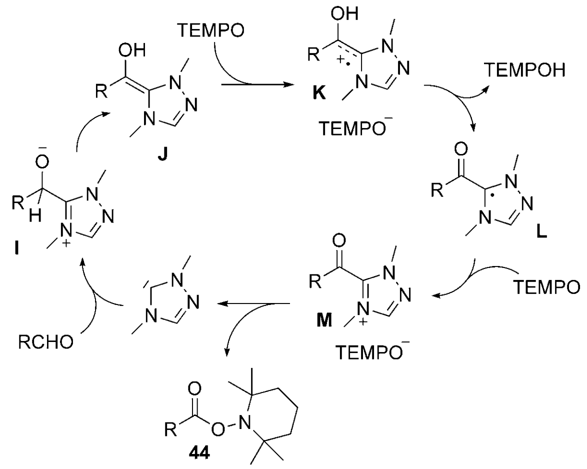
Scheme 17. Reaction of olefins with TEMPO$^+$X$^-$ salts.

Compared to the oxidations of olefins induced by oxoammonium salts discussed above, direct reactions of activated olefins with TEMPO are rare.[128] Recently, in collaboration with Renaud and co-workers we showed that catecholboron ketone enolates react efficiently with TEMPO at low temperature.[129] Since TEMPO is too weak an oxidant, enolate oxidation can not occur by single-electron transfer (SET). It was, therefore, suggested that TEMPO reacts with the boron enolate **38** in a formal homolytic substitution at boron[130] by an addition/fragmentation process to afford enoyl radical **39**, which is then trapped by a second equivalent of TEMPO to give oxidized ketone **41** (Scheme 18). Boronate **40** is formed as a side product. The boron enolates were generated either by 1,4-reduction of α,β-unsaturated ketones with catecholborane or by transmetalation of silyl enol ethers with chlorocatecholborane. An example of the former process is the transformation of ketone **42** to **43** depicted in Scheme 18.

TEMPO has also been applied as a stoichiometric oxidant in biomimetic carbene-catalyzed oxidations of various aromatic and α,β-unsaturated aldehydes to give the corresponding TEMPO esters **44**.[131] As shown in Scheme 19, the TEMPO radical acts as an organic oxidant in these processes and the TEMPO esters **44** were formed in moderate to



Scheme 18. Oxidation of catecholboron ketone enolates with TEMPO.

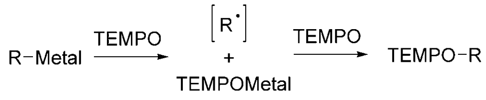


Scheme 19. Biomimetic carbene-catalyzed aldehyde oxidations with TEMPO as an oxidant.

excellent yields. The following mechanism was suggested for this interesting oxidation. Reaction of the carbene with RCHO provides enamine **J** via **I**. Single-electron transfer (SET) from the electron-rich olefin to TEMPO should lead to radical cation **K** and TEMPO$^-$.[132] Deprotonation of **K** by TEMPO$^-$ generates radical **L** and TEMPOH. Renewed SET from **L** to TEMPO provides activated ester **M**, which eventually further reacts with TEMPO$^-$ to give **44** and the catalytically active carbene.

4.1.5. *Oxidation of Carbanions with Nitroxides*

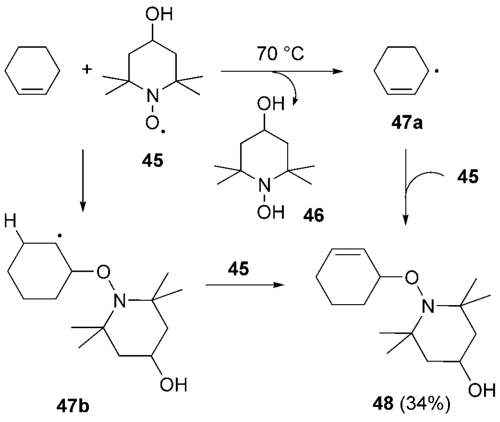
In contrast to enolates, various alkyl metal compounds can be oxidized with TEMPO. The first report on this chemistry described the reaction of butyllithium with TEMPO in THF at low temperature to provide TEMPO-Bu in 65% yield.[133] It was suggested that the butyl anion is oxidized with TEMPO to give TEMPOLi and the butyl radical, which is subsequently trapped by a second equivalent of TEMPO. The same method was later used for the oxidation of chiral benzyllithium compounds.[134] It was also shown that other alkyl metal compounds such as RMgBr (70%), RTi(O*i*Pr)$_3$ (63%), [RZr(Cl)Cp$_2$] (58%), RCuCN·Li (68%), and RSmI$_2$ (70%) undergo efficient oxidation with two equivalents of TEMPO in a two-step process to the corresponding alkoxyamines (Scheme 20, yields given for R = n-C$_6$H$_{13}$).[135] The trapping of C-centered radicals with TEMPO will be discussed in detail in Section 4.2.1.



Scheme 20. Oxidation of organometallic compounds with TEMPO.

4.1.6. *H Abstraction by Nitroxides*

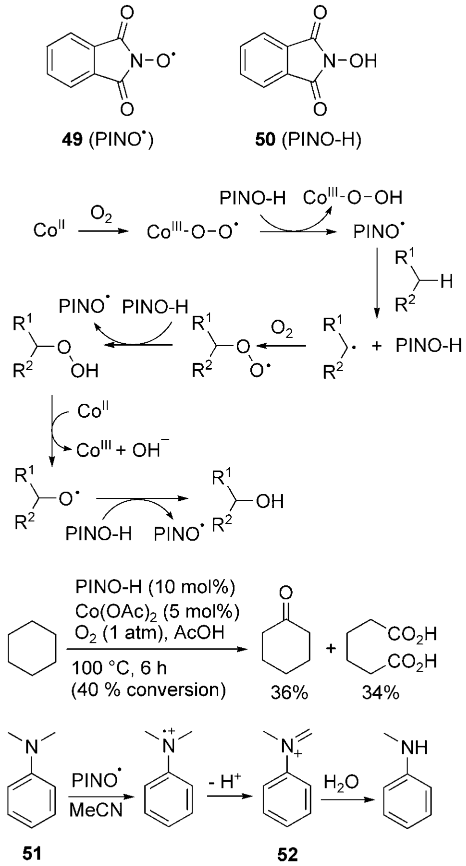
The persistent TEMPO radical was proposed to react with activated compounds by direct C−H abstraction if the substrate is present in large excess as a solvent. For example, this was claimed for the reaction of hydroxy-TEMPO (**45**) with cyclohexene to generate the hydroxylamine **46** along with the stabilized radical **47a**, which is eventually trapped with hydroxy-TEMPO to give alkoxyamine **48** in a moderate yield (Scheme 21). However, it was also suggested that the hydroxy-TEMPO (**45**) might undergo addition to cyclohexene to give adduct radical **47b**, which reacts with **45** by H transfer to afford **48**.[136]



Scheme 21. C−H abstraction by using TEMPO.

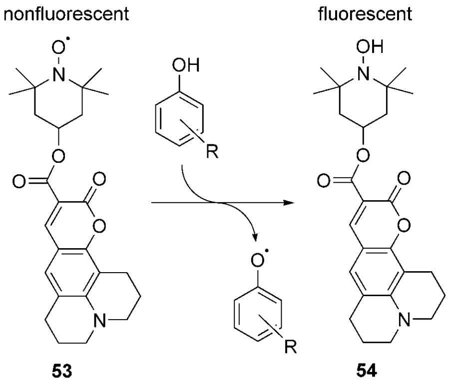
The rather weak O−H bond in TEMPOH (69 kcal mol^{-1})[137] meant that the H abstractions by TEMPO were not efficient, and the reaction had to be conducted by using a large excess of heated cyclohexene, which was used as the solvent in that particular case. Upon photochemical excitation, TEMPO can be turned into a far more reactive O-centered radical, which is then able to abstract H atoms from acetonitrile and toluene.[138] As already discussed above, α-H atoms in Cu^{II} alcoholates can be abstracted by TEMPO to give the corresponding aldehydes or ketones (see Scheme 10).

The phthalimide *N*-oxyl radical (**49**, PINO), which can be readily generated by oxidation of *N*-hydroxyphthalimide (**50**, PINO-H) with various oxidants, is a far more reactive nitroxyl radical than TEMPO.[139] The bond dissociation energy of the O–H bond in PINO-H is 88 kcal mol^{-1}.[140] Therefore, PINO should be able to abstract H atoms from activated alkenes. Indeed, initial studies showed that with PINO as a catalyst, alcohols can readily be oxidized to the corresponding aldehydes or ketones by α-H abstraction reactions. Oxidations were performed with $Co(OAc)_2$ as a co-catalyst and with dioxygen as a terminal stoichiometric oxidant.[141] The proposed mechanism is depicted in Scheme 22. Besides $Co(OAc)_2$, $Mn(OAc)_3$ has also been used successfully as a co-catalyst for these transformations.[141] More importantly, this method also allowed the oxidation of unactivated alkanes such as cyclohexane or octane (the oxidation of cyclohexane to provide cyclohexanone and adipic acid is presented as an example).[142] It was later found that the addition of *meta*-chloroperbenzoic acid allows the alcohol oxidations to be accomplished at ambient temperature.[143] Various PINO derivatives have been synthesized and tested as catalysts in these oxidation reactions. The reactivity of the *N*-oxyl radical can be tuned through the substituents of the PINO arene moiety.[139] It was also shown that PINO and derivatives thereof can react through electron-transfer reactions when the substrates have appropriate electron-donating properties. For example, N-demethylation of *N*,*N*-dimethylaniline (**51**) probably occurs by an initial electron-transfer process followed by deprotonation to give the imminium ion **52**, which is eventually hydrolyzed to *N*-methylaniline.[144]



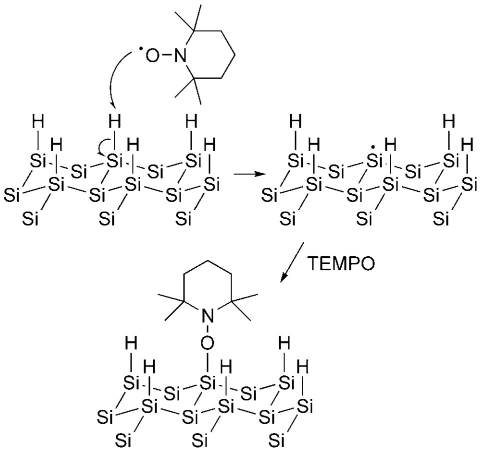
Scheme 22. Mechanisms for oxidations with PINO as the oxidant.

Phenols were also reported to transfer H atoms to TEMPO. The use of TEMPO derivatives carrying a fluorescent probe enables the H transfer to be readily followed. It is well known that the nitroxide moiety is able to quench the fluorescence of various fluorophores, however, TEMPO-H does not.[145] Therefore, chromophore-conjugated TEMPO derivatives can be used as fluorescence probes to analyze the antioxidant properties of phenols. In this regard, compound **53**, which is nonfluorescent, was used to study the H-transfer reactions of various phenols with **53**.[146] The reduced TEMPO-H derivative **54** shows strong fluorescence (Scheme 23). The change in the fluorescence intensity allowed the kinetics of the H-transfer process to be determined. Hydrogen transfer to TEMPO can be extremely fast, as tunneling was noted for H transfer from TEMPO-H to 4-oxo-TEMPO.[147] The O–H bond in monomeric Mn and Fe complexes bearing terminal hydroxo ligands is activated, and efficient H transfer from the OH group to the TEMPO was observed in these complexes.[148]



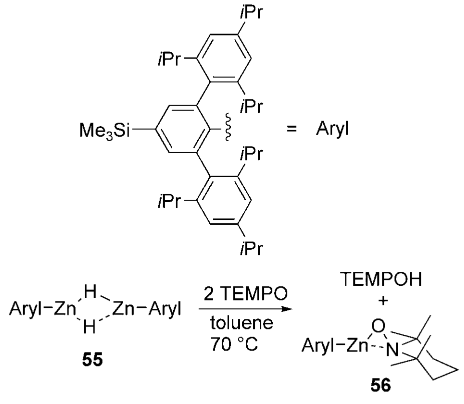
Scheme 23. A TEMPO derivative used as a fluorescence probe.

Group 14 hydrides such as Bu_3SnH and Ph_3GeH were shown to react with TEMPO by hydrogen atom transfer to give TEMPOH and the corresponding stannyl or germyl radicals, respectively. The stannyl or germyl radicals eventually dimerize to afford $Bu_3SnSnBu_3$ or $Ph_3GeGePh_3$.[149] TEMPO does not react with Et_3SiH even at elevated temperature because of the rather strong Si–H bond in this silane. However, $(Me_3Si)_3SiH$, which contains a weaker Si–H bond, reduces TEMPO efficiently by H transfer. The Si–H bond of the H-terminated Si(111) surface shows similar activity as $(Me_3Si)_3SiH$; therefore, not surprisingly, it was found that TEMPO radicals are able to abstract H atoms from that surface, thus generating surface Si radicals which are subsequently trapped by additional TEMPO (Scheme 24).[150] This led to partial passivation of the hydrogen-terminated Si(111) surface. The same behavior was also observed in the reaction of the H-terminated Si(100) surface with TEMPO.



Scheme 24. Reaction of TEMPO with the H-terminated Si(111) surface.

The reaction of Group 13 metal hydrides with TEMPO has also been investigated. It was found that $[MH_3(quin)]$ (quin = quinuclidine, M = Al or Ga) reacts with TEMPO (1 equiv), probably via the corresponding metal trihydride/TEMPO adduct, by a formal homolytic substitution at the Group 13 metal to generate quinuclidine-complexed TEMPOMH$_2$ along with dihydrogen.[151] Moreover, the reaction of $[AlH_3(quin)]$ with two equivalents of TEMPO provided $[(TEMPO)_2AlH(quin)]$. In analogy to some Group 13 metal hydrides, aryl zinc hydride dimer **55** reacted with TEMPO at elevated temperature to generate aryl zinc alkoxide **56**, probably through an associative mechanism, as also suggested above for the Group 13 metal hydrides (Scheme 25).[152]

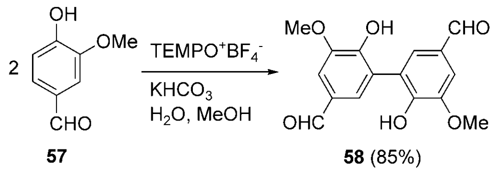


Scheme 25. Hydrogen abstraction from aryl zinc hydride **55** by TEMPO.

Other transition-metal hydride complexes (rhodium and iridium hydrides) were also shown to react with TEMPO through H transfer to give TEMPOH and the corresponding metalloid radicals, which then undergo further reactions such as dimerization, addition to olefins, or homolytic substitution at the carbon atom.[153] Besides zinc–TEMPO complexes, other metal–TEMPO complexes of unsaturated transition metals (Mn,[154] Co,[155] Ni,[156] Cu,[157] Mo,[158] Ti,[159] and Pd[160]) have been synthesized and fully characterized. Mg–TEMPO complexes were also prepared and studied by X-ray analysis.[161] In addition, the interaction of gold nanoparticles with nitroxides was reported to lead to a loss of the EPR signal.[162] This is probably due to interaction of the unpaired electron of the adsorbed radicals with the conduction-band electrons of the metallic particles or extreme broadening of the nitroxide signal due to restricted mobility upon bonding to the nanoparticle. Dicobalt octacarbonyl can be oxidized with TEMPO, and this method was used for the synthesis of cobalt oxide nanoparticles.[163]

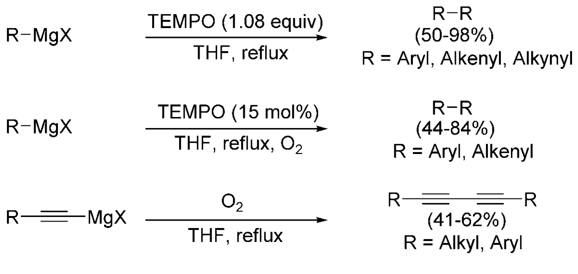
4.1.7. *Oxidative C–C Bond-Forming Reactions*

TEMPO$^+$ salts can be used for the oxidative coupling of phenols. For example, 2-naphthol was transformed nearly quantitatively to binaphthol. In this case, a TEMPO$^+$ salt was generated electrochemically by using a TEMPO-modified graphite electrode.[164] Oxidative phenol coupling can also be achieved by using stochiometric amounts of a TEMPO$^+$ salt without electrochemical equipment.[165] For example, phenol **57** underwent a high-yielding homocoupling to biaryl **58** upon oxidation with a TEMPO$^+$ salt (Scheme 26). The reaction likely occurs by electron transfer from the phenol to the TEMPO$^+$ salt, with subsequent deprotonation leading to the corresponding phenoxyl radical, which provides **58** upon dimerization.



Scheme 26. Oxidative coupling of phenols.

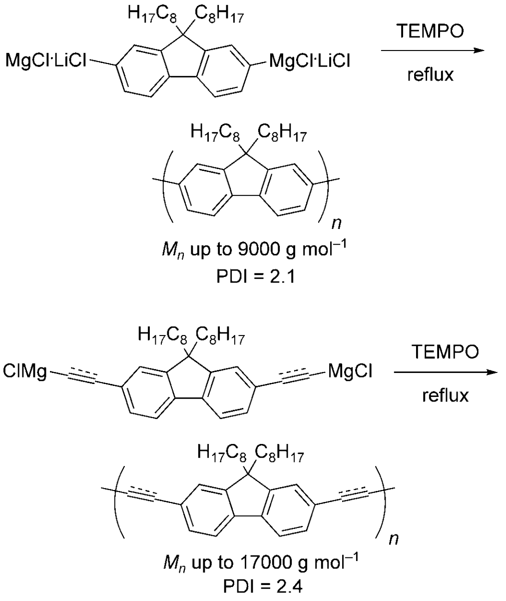
We recently reported on the transition-metal-free homocoupling of various aryl Grignard reagents by using TEMPO as an oxidant to give the corresponding biaryls in near quantitative yields (Scheme 27).[166] The homocoupling reactions were highly efficient, and the TEMPOMgX formed as a side product could be readily reoxidized to TEMPO upon treatment with dioxygen. The use of an in situ TEMPO regeneration protocol enabled aryl Grignard homocoupling reactions to be conducted with 15 mol% TEMPO by using dioxygen as a terminal oxidant. It was also shown that alkenyl



Scheme 27. Oxidative homocoupling of various Grignard reagents with TEMPO as an oxidant.

as well as alkynyl Grignard reagents were oxidatively homocoupled to dienes and diynes upon treatment with TEMPO. The mechanism of these oxidative C–C coupling reactions is currently not understood.

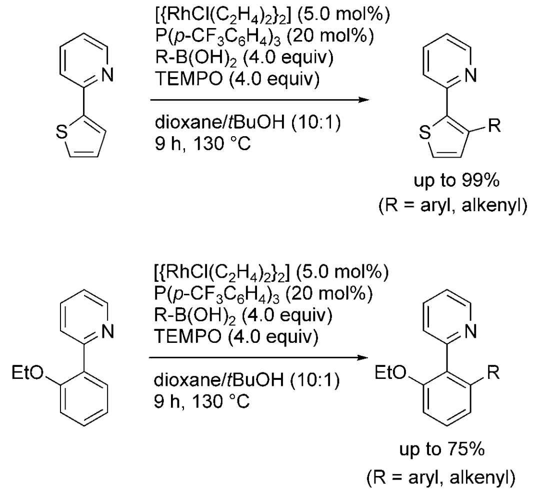
Since excellent yields were obtained for these TEMPO-mediated homocoupling reactions of Grignard compounds, it was assumed that these processes might be applicable for polymer synthesis, where excellent yields for the individual coupling steps are mandatory. Indeed, transition-metal-free multiple homocoupling reactions of 2,7-dimagnesiated fluorenes with TEMPO provided polyfluorenes with a mean molecular weight M_n of up to 9000 g mol^{-1} (Scheme 28).[167]



Scheme 28. TEMPO-mediated oxidative homocoupling of a bis-Grignard reagent for the preparation of conjugated polymers.

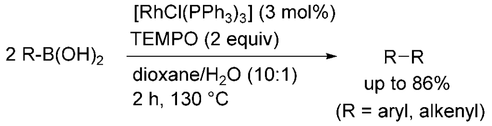
The method also allowed formation of copolymers containing the butadiynylene or butadienylene moiety as alternating building blocks with the fluorene unit in the polymer backbone. Polymers with M_n values of up to 17000 g mol^{-1} were formed by this novel polymerization method. The absorption and emission spectra showed that the polymers formed were regular without any defect sites.

Furthermore, we realized that TEMPO can act as a mild oxidant in palladium- and rhodium-catalyzed direct C–H arylation reactions. This led to the development of a rhodium-catalyzed oxidative coupling of aryl and alkenylboronic acids with arenes and hereroarenes.[168] This reaction allowed the preparation of bi- and triaryls in good to excellent yields by using commercially available aryl and alkenylboronic acids (Scheme 29). TEMPO acts as the oxidant to convert the aryl–rhodium(I) complex, formed by transmetalation of $ArB(OH)_2$ to Rh^IX, into the corresponding $[(TEMPO)_2Rh(Ar)]$ complex (two equivalents of TEMPO are necessary). This rhodium(III) complex then coordinates to the pyridyl N atom of the substrate, followed by an electrophilic rhodation (C–H activation). Reductive elimination finally delivers the isolated biaryl. It is important to note that these reactions could also be conducted with catalytic amounts of TEMPO in the presence of dioxygen or air as the terminal oxidants. However, slightly lower yields were achieved under these catalytic conditions.



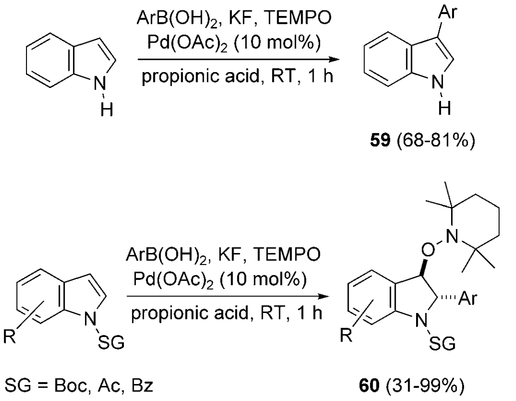
Scheme 29. Rhodium-catalyzed direct C–H arylations with TEMPO as an oxidant.

Homocoupling of the aryl boronic acid was observed as a side reaction in the rhodium-mediated C–H arylation. This useful homocoupling reaction was optimized and a catalyst screening revealed that the Wilkinson catalyst was the most efficient for the oxidative homocoupling of various aryl and alkenyl boronic acids when TEMPO was used as a stoichiometric terminal oxidant (Scheme 30).[169]



Scheme 30. Rhodium-catalyzed oxidative homocoupling of aryl boronic acids with TEMPO as an oxidant.

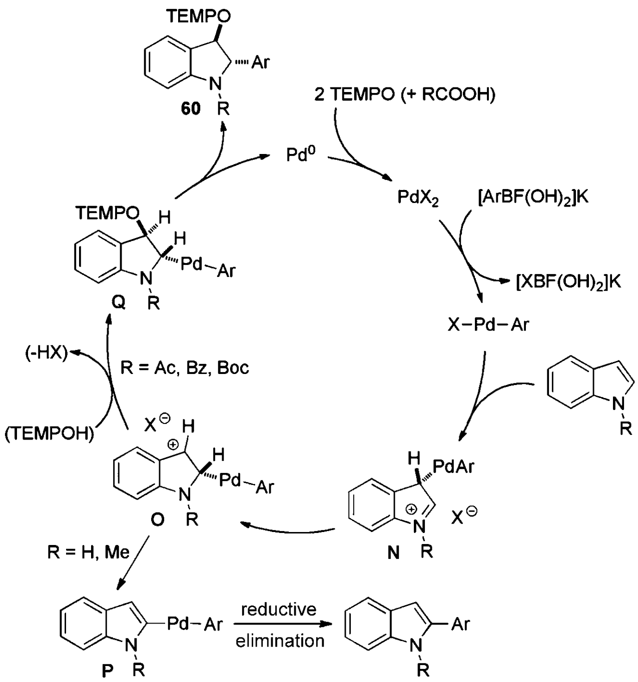
More recently it was found that oxidative direct C–H arylations of 2-phenylpyridine with various aryl boronic acids can also be conducted with palladium catalysts ($Pd(OAc)_2$). As in the rhodium case, TEMPO was found to be a highly efficient oxidant for these oxidative C–C bond-forming processes.[170] Reactions were conducted at 50 °C for a prolonged time (up to 72 h). Interestingly, the direct palladium-catalyzed C–H arylation of indole with aryl boronic acids occurred under very mild conditions at room temperature within 1 h.[171a] The 3-arylated indole **59** was obtained as the major product in good to excellent yields (Scheme 31). The regioisomeric 2-arylated indole was isolated as a side product in up to 10% yield. However, installation of a nitrogen protecting group (Boc, benzoyl, and acetyl; PG) resulted in a different reaction outcome under identical conditions, and the product of an aryl carboaminoxylation (dihydroindol derivative **60**) was obtained in moderate to excellent yield. The C–C bond-forming reaction with con-



Scheme 31. Palladium-catalyzed oxidative transformations of indoles.

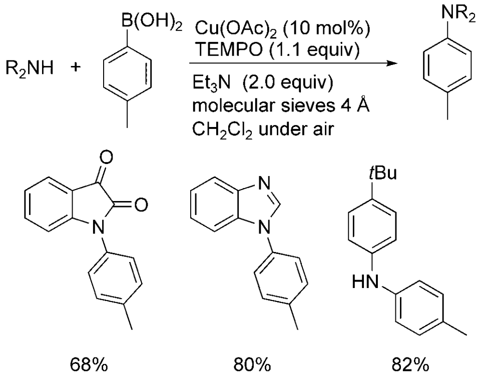
comitant C–O bond formation occurred with perfect *trans* diastereoselectivity. The N–O bond in the product indoles was cleaved quantitatively under reducing conditions of zinc in acetic acid at room temperature to give, stereospecifically, the corresponding 2-arylated 3-hydroxyindole derivatives.

The following mechanism was suggested for the aryl carboaminoxylation (Scheme 32). Transmetalation from boron to palladium by reaction of PdX$_2$ with [ArBF(OH)$_2$]K should provide X-Pd-Ar, which can add at the 3-position of the indole to give intermediate **N**. A 1,2-metal migration would then lead to intermediate **O**. For intermediate **O** derived from free indole (R = H), deprotonation leads to **P**, which upon reductive elimination eventually affords the arylated indole and Pd^0. The counterion X$^-$, which acts as a base, can be either EtCO$_2^-$ or TEMPO$^-$. For protected indoles (R = Ac, Bz, or Boc), intermediate **O** might be stabilized through C=O–Pd interaction. Deprotonation is slowed down, and a highly diastereoselective *trans* trapping of **O** with TEMPOH affords **Q**, which upon reductive elimination finally provides **60** and Pd^0. Oxidation of Pd^0 with two equivalents of TEMPO eventually regenerates the Pd^{II} salt. Indene derivatives have also been shown to act as suitable substrates for this type of transformation.[171b]



Scheme 32. Proposed mechanism for palladium-catalyzed oxidative transformations of indoles. Bz = benzyl, Boc = *tert*-butyloxycarbonyl.

TEMPO was also used as an oxidant in copper-catalyzed C–N bond cross-coupling reactions of amines with aryl boronic acids.[172] A stoichiometric amount of cupric acetate was used in these coupling reactions; however, it was found that the coupling reactions also proceeded in the presence of catalytic amounts of Cu(OAc)$_2$ and a terminal oxidant such as TEMPO (Scheme 33). It was suggested that the C–N bond formation likely occurred through reductive elimination from an arylCu^{III}NR$_2$ complex.

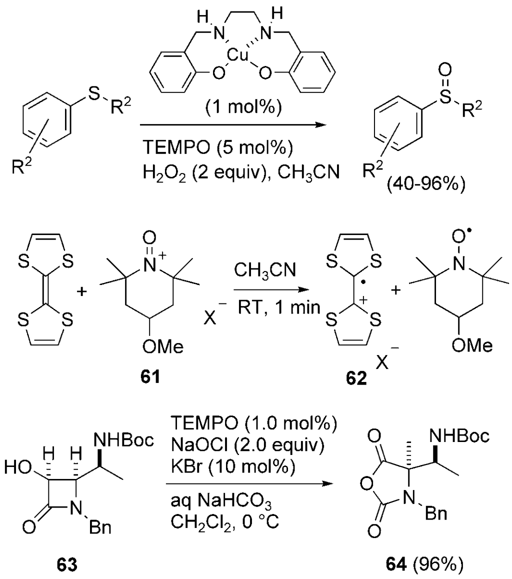


Scheme 33. Copper-catalyzed C–N bond formation with aryl boronic acids and TEMPO as a terminal oxidant.

4.1.8. Miscellaneous Oxidations

Selective conversions of sulfides into the corresponding sulfoxides can be carried out by TEMPO-mediated processes. In these reactions, TEMPO is added as a catalyst and stoichiometric amounts of a cooxidant are added. For example, various aryl alkyl and aryl allyl sulfides were oxidized to the corresponding sulfoxides in the presence of a copper catalyst and 5 mol% TEMPO by using hydrogen peroxide as a terminal oxidant (Scheme 34).[173] The addition of TEMPO enhanced the conversion and suppressed the overoxidation to the corresponding sulfones. The role of TEMPO in these reactions is not yet understood. TEMPO-conjugated iron and manganese metalloporphyrins showed high activity as catalysts for sulfide oxidation.[174] Chiral N-protected β-amino sulfides could be readily transformed into the corresponding diastereoisomeric sulfoxides with acceptable selectivities and good yields by using TEMPO and NaOCl.[175] It was also shown that the electron-rich tetrathiafulvalene (TTF) was readily transformed to 1,3-dithiolium salts **62** by one-electron oxidation with oxoammonium salts **61** (X = ClO$_4$, BF$_4$, NO$_3$ or Cl).[176]

Baeyer–Villiger-type reactions on α-diketones were also achieved with TEMPO. The α-hydroxy β-lactam **63** was converted into the mixed anhydride **64** in excellent yield and selectivity.[177] The reaction probably occurred by oxidation of



Scheme 34. Sulfide oxidations and a Baeyer–Villiger oxidation.

63 to the corresponding α-ketolactam, which then further reacted by oxidative ring enlargement to give **64**. Importantly, no epimerization was observed for this TEMPO-mediated Baeyer–Villiger oxidation. The mechanism for the key ring enlargement is not known.

4.2. Nitroxides in Free-Radical Chemistry

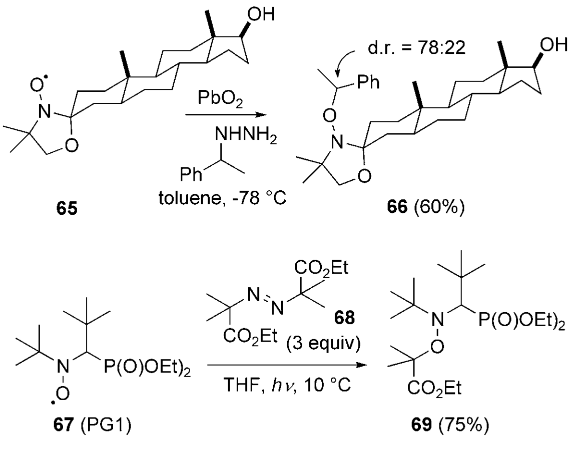
4.2.1. Trapping of C-Centered Radicals

Nitroxides have often been used as C-centered radical scavengers to form the corresponding alkoxyamines. These C–O bond-forming processes are very fast and it was found that the rate constants are strongly influenced by the structure of the C-centered radical as well as the structure of the nitroxide. The rate constants for the trapping of various C-centered radicals with TEMPO were determined to be 5×10^7 to $2\times10^9\,\text{M}^{-1}\text{s}^{-1}$ at room temperature, depending on the nature of the C-centered radical and the solvent.[178] Smaller rate constants were obtained for C-centered radical trapping with nitroxides more sterically hindered than TEMPO.[179]

Polymers are known to degrade in the presence of dioxygen upon exposure to light and heat. Nitroxides have been used successfully as polymer stabilizers as a consequence of their efficient radical-trapping properties to protect polymers against damage. To this end, sterically highly hindered secondary amines (hindered amine light stabilizer, HALS) such as 2,2,6,6-tetramethylpiperidine have been used, which are oxidized in situ to the corresponding nitroxides within the polymeric matrix. The polymeric radicals formed during damage are then trapped by the nitroxide to form polymeric alkoxyamines. Only a small amount (ca. 0.1 %) of the HALS is necessary, and it is believed that the stabilizing nitroxides are regenerated from the polymeric alkoxyamines.[180]

Besides the stabilization of polymers, nitroxides can also act as antioxidants in biological systems, since they are able to degrade superoxide and peroxides, are known to inhibit the Fenton reaction, and undergo efficient coupling with damaging C centered radicals.[181] For example, nitroxide–peptide conjugates with a high affinity for mitochondrial membranes have been shown to react with reactive oxygen species and prevent mitochondria from oxidative damage and apoptosis.[182] Moreover, nitroxide derivatives have been used as biological tools.[7e,181] For example, the trapping of radicals with nitroxide conjugates has allowed the indirect identification/analysis of reactive radicals in biological systems: the trapping reaction with TEMPO was used successfully to study metabolism by treating biologically interesting C centered radicals with TEMPO followed by mass spectrometric analysis of the TEMPO-tagged products.[183]

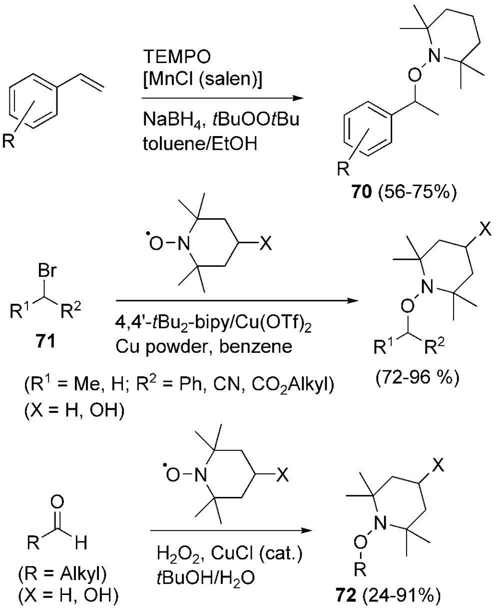
The trapping of nitroxide radicals has been applied in synthetic organic chemistry for the preparation of alkoxyamines. Various methods have been used for the generation of C centered radicals, and radical trapping can be combined with typical radical C–C bond-forming reactions. Bu_3SnH in combination with a radical initiator is generally used for the generation of C centered radicals from the corresponding bromides or iodides. Since nitroxides are reduced by tin hydrides (see Section 4.1.6), no additional radical initiator is necessary. These reactions are not chain processes, and an excess of tin hydride and nitroxide was used. This approach was applied to the synthesis of tertiary TEMPO-derived alkoxyamines from the corresponding tertiary alkyl iodides and TEMPO.[184] Since Bu_3SnH is toxic,[185] a tin-free protocol for the transformation of alkyl halides to the corresponding alkoxyamine was developed, in which $(Me_3Si)_3SiH$ is used as a tin hydride substitute.[186] The oxidation of alkyl hydrazines with PbO_2 allows for the generation of alkyl radicals, which in the presence of nitroxides react to form alkoxyamines. This method was used for the stereoselective formation of a C–O bond between prochiral C centered radicals and chiral nitroxides. The reaction of nitroxide **65** with 1-phenylethylhydrazine in the presence of PbO_2 at low temperature provided alkoxyamine **66** with moderate diastereoselectivity (Scheme 35).[187]



Scheme 35. Trapping of C-centered radicals with nitroxides for the preparation of alkoxyamines.

C_2-Symmetric nitroxides were also studied in the diastereoselective trapping of prochiral C centered radicals.[188] Photochemical or thermal decomposition of dialkyl azo compounds generates C-centered radicals which can be efficiently trapped by nitroxides. This has been applied for the synthesis of various alkoxyamines which can be used as initiators/regulators for controlled nitroxide-mediated radical polymerization (see Section 5). The photochemical decomposition of azo compound **68** in the presence of nitroxide **67** gave alkoxyamine **69** in good yield.[189] Other alkoxyamines were prepared successfully by this method.

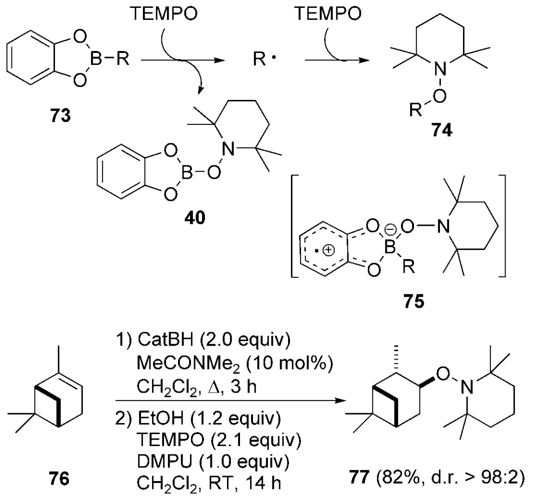
Various styrene derivatives were readily transformed to styryl-TEMPO-alkoxyamines **70** by reaction with [MnCl(salen)] and $NaBH_4$ in the presence of TEMPO (Scheme 36).[190] Moderate to good yields were obtained for these interesting transformations. The mechanism is believed to occur via a Mn=O species with styrene to give a benzylic radical, which is then trapped by TEMPO. Reductive deoxygenation of the MnO−C bond eventually affords the corresponding alkoxyamines.



Scheme 36. Different methods for the preparation of alkoxyamines. Salen = *N*,*N*-bis(salicylidene)ethylenediamine.

The synthesis of alkoxyamines from activated bromides was also achieved upon treating halides **71** with Cu powder and catalytic amounts of $Cu(OTf)_2$/4,4′-di-*tert*-butyl-2,2′-bipyridine in the presence of a nitroxide.[191] Moreover, the copper-catalyzed decomposition of various aldehydes (RCHO) under oxidative conditions (H_2O_2) afforded alkoxyamines **72** by a formal acyl radical decarbonylation and subsequent nitroxide trapping.[192] However, the mechanism of that reaction is currently not understood.

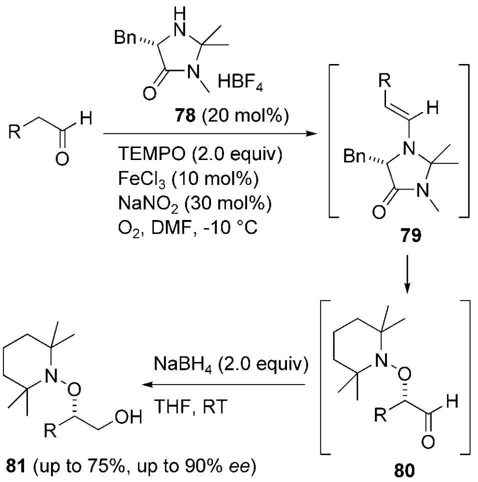
Alkyl catecholboranes **73**, which are readily obtained by hydroboration of commercially available catecholborane, were shown to be valuable precursors for the preparation of alkoxyamines.[193] The interaction of the Lewis acidic alkyl catecholborane with TEMPO provides adduct **75**, which can fragment to radical R$^\bullet$ and boric acid ester **40**. The radical R$^\bullet$ is then trapped by a second equivalent of TEMPO to give the corresponding alkoxyamine **74**. As an example, the transformation of α-pinene (**76**) to alkoxyamine **77** by a highly diastereo- and regioselective hydroboration and subsequent TEMPO oxidation is presented in Scheme 37.[194]



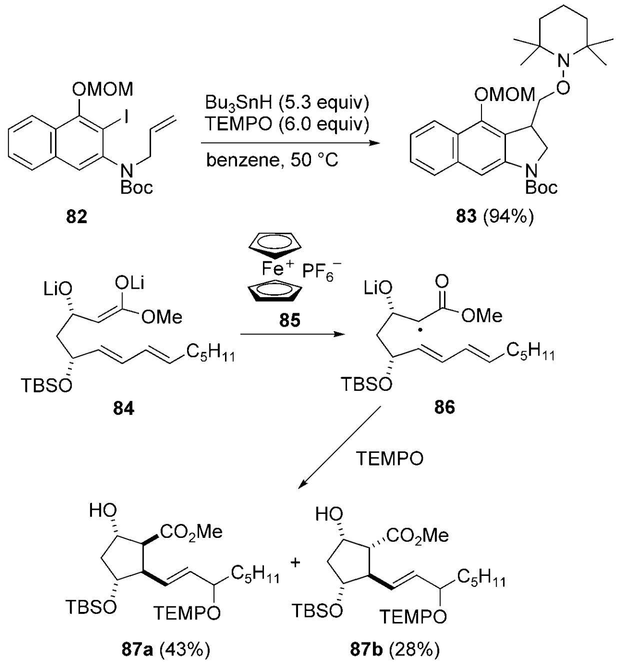
Scheme 37. Alkyl catecholboranes as precursors for alkoxyamines. Cat = catecholato, DMPU = 1,3-dimethylhexahydro-2-pyrimidinone.

The trapping of α-carbonyl-type radicals with TEMPO is a valuable route to the corresponding alkoxyamines. However, as reported above, since TEMPO is too weak an oxidant, enamines or enolates do not spontaneously react with TEMPO. Thus, other methods had to be developed for the in situ generation of these α-carbonyl radicals in the presence of TEMPO. It was found that TEMPO undergoes efficient addition to the ketene carbonyl carbon atom in aryl ketenes to generate an α-enoyl radical, which is subsequently trapped by a second equivalent of TEMPO to give the corresponding α-aminoxylated TEMPO ester.[195] Lithium and magnesium enolates can be oxidized with ferrocenium ions in the presence of TEMPO to give α-ester type radicals, which then further react with TEMPO to afford the α-oxygenated esters (see also Scheme 39).[120] Lithium carbanions, which were readily obtained by lithiation of α,α-disulfonylalkanes were oxidized with ferrocenium ions to the corresponding C-centered radicals. These α-disulfonyl radicals could be trapped with TEMPO to give the corresponding alkoxyamines in good yields.[196]

Organocatalyzed stereoselective α-oxyaminations of aldehydes with TEMPO under oxidative conditions was also achieved.[197a] This interesting cascade reaction occurs via enamine **79**, which is readily formed by condensation of the aldehyde with the chiral imidazolidinone **78**. A single-electron transfer (SET) will probably generate the corresponding radical,[197b] which then undergoes stereoselective coupling with TEMPO to give the corresponding iminium ion, which upon hydrolysis provides aldehyde **80** (Scheme 38).



Scheme 38. Stereoselective trapping of C-centered radicals with TEMPO.



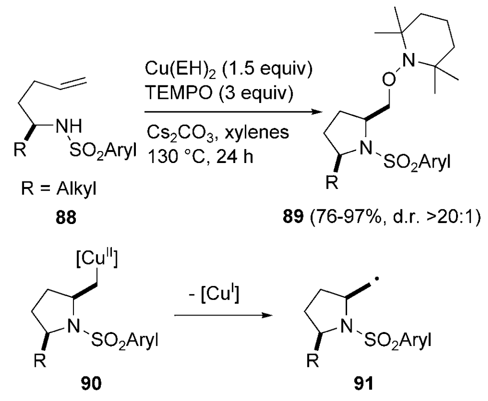
Scheme 39. Radical 5-*exo*-cyclization with subsequent trapping with TEMPO. Boc = *tert*-butoxycarbonyl, MOM = methoxymethyl, TBS = *tert*-butyldimethylsilyl.

Since these aldehydes racemize readily, the crude aldehyde was reduced to the primary alcohol **81**, which was obtained with high selectivity. Photoinduced oxyamination of enamines with TEMPO by using tris(bipyridyl)ruthenium salts was recently published.[198] It was suggested that the photoexcited ruthenium complex oxidizes the enamine by SET, thus generating a C-centered radical, which is subsequently trapped by TEMPO. Mechanistically, this process resembles the reaction shown in Scheme 38. Aerobic one-pot conversion of primary alcohols into racemic α-oxyaminated alkanals with TEMPO and a ruthenium complex was shown to be feasible;[199] the mechanism of the key C−O bond formation was not discussed. It might involve an ionic reaction of the enol form of the aldehyde formed as an intermediate with a TEMPO-derived oxoammonium salt instead of the TEMPO trapping an enoyl radical derived by SET of the intermediate aldehyde (see also Ref. [123b]).

Importantly, trapping reactions with TEMPO can be combined with radical C−C bond formations, which render these processes even more valuable. Several reports on radical cascades involving radical cyclization reactions followed by nitroxide trapping have so far been published. Mostly, TEMPO has been used as the trap for the cyclized radicals. The C−C bond formation has to be faster than the trapping of the noncyclized radical by TEMPO to allow the radical cyclization to proceed efficiently. This is the reason why these cascade reactions only work efficiently with fast 5-*exo*-type cyclizations. Aryl radical C−C bond formations with subsequent TEMPO trapping have been used successfully in natural product synthesis.[200] As an example, treatment of iodide **82** with Bu_3SnH and TEMPO gave alkoxyamine **83** in good yield (Scheme 39).

Enoyl radical cyclization with subsequent trapping by TEMPO has also been reported. The anionic enoyl radical **86** was readily generated by oxidation of lithium enolate **84** with ferrocenium ion **85**.[201] A subsequent 5-*exo* cyclization and trapping of the allyl radical formed as an intermediate with TEMPO afforded alkoxyamines **87a** and **87b** as major isomers in a good combined yield (71 %). The stereocenter next to the alkoxyamine O atom was not controlled in the trapping reaction. Product **87a** was then successfully further transformed to 15-F_{2t}-isoprostane.

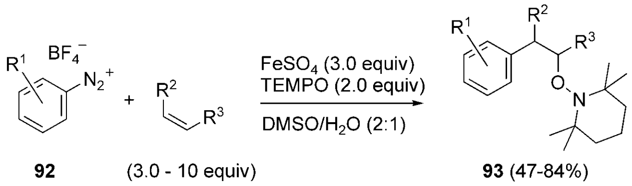
Copper(II)-promoted aminooxygenation of sulfonamides proceed stereoselectively with good to excellent yields. Treatment of α-substituted 4-pentenyl sulfonamides **88** with excess amounts of $Cu(EH)_2$ (EH = 2-ethylhexanoate) in xylenes in the presence of base and TEMPO afforded the cyclized aminoxylated sulfonamide **89** with high *cis* diastereoselectivity (Scheme 40).[202] The reactions are presumed to occur by a highly diastereoselective amidocupration of the olefin with a Cu^{II} sulfonamide to give copper(II)–alkyl intermediate **90**, which affords the primary C radical **91** after homolysis of the Cu−C bond. Trapping with TEMPO finally leads to the product alkoxyamine **89**. More recently, it was reported that similar reactions can be conducted by using



Scheme 40. Intramolecular aminoxygenation of alkenes.

catalytic amounts of $Cu(OTf)_2$ with dioxygen as a terminal oxidant.[203]

Since the trapping of C-centered radicals with nitroxides is a very fast process, there are only a few examples of the successful intermolecular addition of C-centered radicals to olefins and subsequent trapping of the nitroxide. Surprisingly, very reactive aryl radicals were shown to react with various olefins in the presence of TEMPO to afford the corresponding carboaminoxylation products.[204] In these cases, the aryl radicals were generated by reductive decomposition of the corresponding aryl diazonium salts **92** with iron sulfate. The aryl radicals formed were then allowed to add to the alkenes, and subsequent trapping of the adduct radicals finally gave alkoxyamines of type **93** in moderate to good yields (Scheme 41).

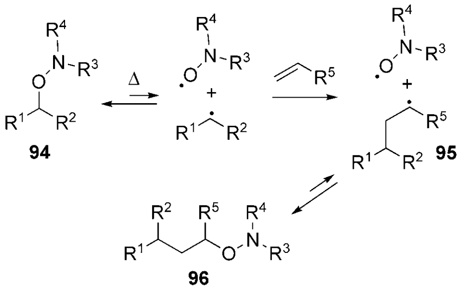


Scheme 41. Radical carboaminoxylation of olefins.

4.2.2. Alkoxyamine Additions to Various Radical Acceptors

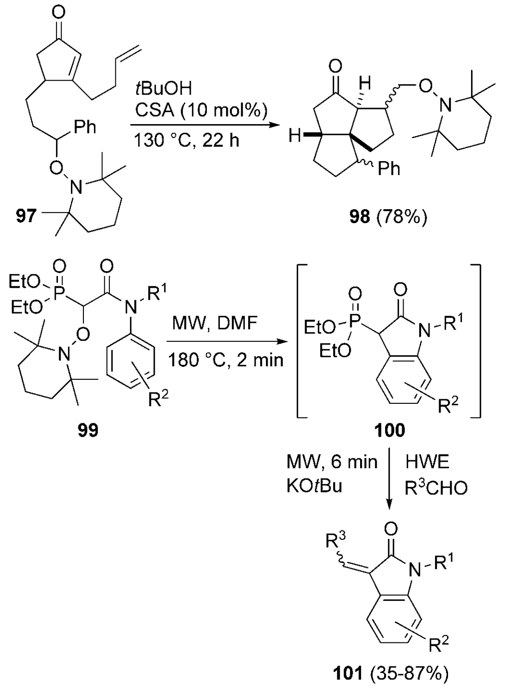
The C–O bond in alkoxyamines derived from persistent nitroxides is generally weak. In particular, if a stabilized C-centered radical is generated, efficient homolysis can be achieved at temperatures as low as 90 °C.[184,205] Importantly, C–O bond homolysis is a reversible process. Nevertheless, these reversible reactions occur with high fidelity and little decomposition, although reactive radicals are generated continuously. This is due to the persistent radical effect (PRE).[206] The PRE is a general principle that explains the highly specific formation of the cross-coupling product (R^1-R^2) between two radicals R^1 and R^2 when one radical is persistent (in these reactions the nitroxide) and the other transient (which is the C-centered radical generated upon C–O bond homolysis), and the two radicals are formed at equal rates. The latter prerequisite is fully ensured by the process of thermal homolysis. An initial build-up of the concentration of the persistent nitroxide, caused by disproportionation or dimerization of the transient C-centered radicals, forces the process to follow a single reaction pathway, which is the coupling of the C-centered radical with the nitroxide.

If thermal C–O bond homolysis is conducted in the presence of an olefin as a radical acceptor, addition of the C-centered radical to the olefin can occur and the resulting adduct radical **95** will then be trapped by the nitroxide (Scheme 42). The overall process is a thermal radical carboaminoxylation of an alkene by using an alkoxyamine **94** to give product **96**. If the adduct radical **95** obtained is not stabilized, trapping with the nitroxide to give **96** is an irreversible process. However, if radical **95** is stabilized, trapping of the nitroxide becomes a reversible process and additional alkene moieties can add. This will eventually lead to telomers or polymers, and one enters the field of nitroxide-mediated radical polymerization (see Section 5).



Scheme 42. Thermal radical addition of alkoxyamine to olefins.

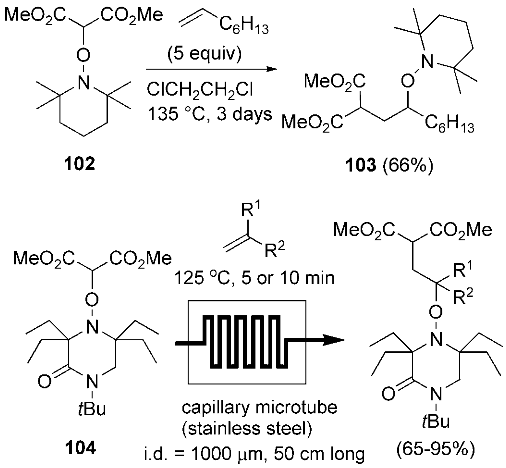
An interesting example of an intramolecular thermal radical carboaminoxylation, which can also be called an alkoxyamine isomerization reaction, is depicted in Scheme 43. Heating alkoxyamine **97** in *t*BuOH in the presence of camphor sulfonic acid (CSA; 10 mol %) at 130 °C for 22 h provided alkoxyamine **98** as a mixture of four isomers.[207] The product was formed by an initial thermal generation of a C-centered radical by C–O bond homolysis, two consecutive radical 5-*exo*-type cyclizations, and finally an irreversible trapping with TEMPO. It was later found that such thermal alkoxyamine isomerizations can be accelerated by the addition of catecholborane.[208] Moreover, alkoxyamines were successfully used as precursors for C-centered radicals for intramolecular homolytic aromatic substitutions.[209] These reactions were best conducted under microwave (MW) heating. For example, irradiation of alkoxy-



Scheme 43. Isomerization of alkoxyamines and radical homolytic aromatic substitution.

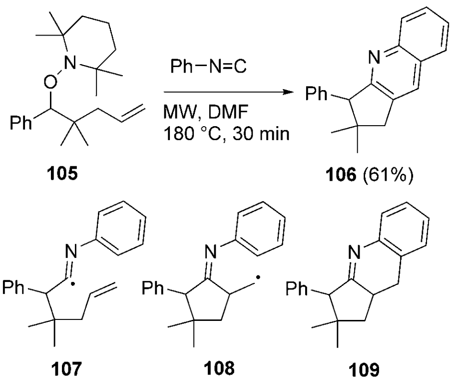
amines of type **99** with microwaves for two minutes in DMF provided the products of a homolytic aromatic substitution (**100**), which were then subjected in a one-pot process to a Horner–Wadsworth–Emmons (HWE) olefination to finally give biologically interesting oxindoles of type **101** in moderate to good overall yield.[210] The final process was also conducted efficiently under irradiation with microwaves.

More challenging intermolecular carboaminoxylations were also achieved by using PRE-controlled alkoxyamine additions, with alkoxyamines derived from malonates giving the best results. Heating alkoxyamine **102** in dichloroethane for three days with 1-octene (5 equiv) afforded adduct **103** in 66% yield (Scheme 44).[211] It was found that replacing the TEMPO moiety in the starting alkoxyamine with sterically more hindered nitroxides provides compounds which undergo thermal radical carboaminoxylation with 1-octene in higher yields (up to 86% yield) in a much shorter reaction time (1.5 h).[212] The reaction time for the radical carboaminoxylation of 1-octene with alkoxyamine **102** to give **103** was reduced to ten minutes by switching to microwave heating.[213,214] More recently, microflow radical carboaminoxylations of 1-octene and other olefins by using the sterically highly hindered alkoxyamine **104** were reported.[215] Residence times of five to ten minutes in the reactor at 125 °C were sufficient to obtain efficient carboaminoxylation reactions and good to excellent yields.



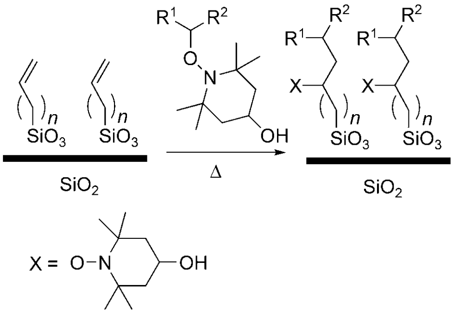
Scheme 44. Intermolecular alkoxyamine additions.

In addition to olefins, carbon monoxide[216] and isonitriles[217] were shown to be suitable radical acceptors for thermal carboaminoxylation reactions. For example, microwave heating of alkoxyamine **105** in the presence of phenyl isonitrile provided quinoline **106** in an acceptable yield (Scheme 45). This cascade reaction comprises an initial C–O bond homolysis to generate the corresponding secondary benzylic radical, which upon reaction with phenyl isonitrile provides iminoyl radical **107**. A radical 5-*exo* cyclization then leads to **108**, which subsequently undergoes a homolytic aromatic substitution to give **109**. Oxidative aromatization finally affords the quinoline **106**.



Scheme 45. Synthesis of quinolines by the thermolysis of alkoxyamines and trapping with isonitrile.

Intermolecular radical carboaminoxylation was also conducted on olefin-terminated self-assembled monolayers (SAMs). This method was introduced as a novel process for the chemical modification of Si wafers (Scheme 46).[218] Various functional groups were successfully attached to the Si wafer by using this approach. X-ray photoelectron studies revealed that 30 to 90% of the olefins at the Si surface were functionalized.

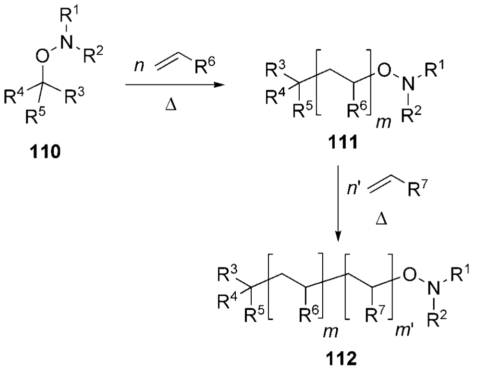


Scheme 46. Carboaminoxylation on the surface of a silicon wafer.

5. Nitroxides in Polymer Chemistry

5.1. Nitroxide-Mediated Polymerization

Various methods which allow the controlled polymerization of various monomers by radical chemistry have been developed. The most prominent candidates in this field are atom-transfer radical polymerization (ATRP),[219] reversible addition-fragmentation chain-transfer polymerization (RAFT),[220] I-group-transfer polymerization,[221] Te-, Sb- and Bi-group transfer polymerization,[222] cobalt-mediated polymerization[223] and nitroxide mediated polymerization (NMP).[224] These processes allow the preparation of various polymers with adjustable molecular weights and polydispersities below the theoretical limit (PDI < 1.5). Similar to the thermal radical carboaminoxylations discussed in Section 4.2, NMP processes are also controlled by the persistent radical effect.[206] Control over the polymerization in NMP is based on the reversible formation of a dormant alkoxyamine from the corresponding nitroxide and the chain-growing polymer radical. Thanks to the PRE, the concentration of the polymeric radicals remains low during polymerization. Therefore, termination of the polymerization by dimerization or disproportionation of the polymeric radicals is suppressed to a large extent, and a controlled polymerization results. These polymerizations are mostly conducted by using an alkoxyamine of type **110** as an initiator/regulator and the monomer is used as a solvent at temperatures between 90 and 130 °C to give polymers **111** (Scheme 47). Polymers are isolated by precipitation or by simple removal of any remaining monomer. For solid or more sophisticated monomers, polymerization can also be conducted with the help of a solvent. Importantly, since NMP is a living polymerization process, most of the polymers **111** bear an alkoxyamine moiety at the terminus. These macroalkoxyamines can then be used as macroinitiators for subsequent block copolymerization. Thus, renewed heating of **111** in the presence of a second monomer provides diblock copolymers of type **112**. Even triblock copolymers can be prepared by this method. To this end, polymers of type **112** have to be used as macroinitiators.



Scheme 47. Nitroxide-mediated polymerization (NMP).

As already discussed in Section 4, the rate constant for the trapping (k_c) of a C-centered radical with a nitroxide strongly depends on the structure of the nitroxide and the structure of the C-centered radical. As a direct consequence, the rate constant for the the reverse reaction, the thermal C–O bond homolysis (dissociation, k_d), also varies greatly as a function of the structure of the alkoxyamine.[179,205,206a] The equilibrium constant K ($k_c/k_d = K$) for the reversible C–O bond homolysis of an initiator alkoxyamine or a polymeric alkoxyamine is of key importance for the success of NMP. The equilibrium constant K has to lie in between 10^7 to 10^{11} L mol^{-1} for a successful NMP.[225] Intensive research has been conducted towards the development of nitroxides for NMP with appropriate K values (ideally small) for the corresponding alkoxyamines.

The most natural choice of a nitroxide component is TEMPO, which indeed has been used frequently to control the radical polymerization of styrene.[226] TEMPO-controlled polymerization of styrene and styrene derivatives has mostly utilized styryl-TEMPO **113** as an initiator/regulator (Figure 3).[224] Alternatively, one can use a typical radical initiator such as benzoylperoxide in the presence of free TEMPO to perform the controlled radical polymerization of styrene.[226]

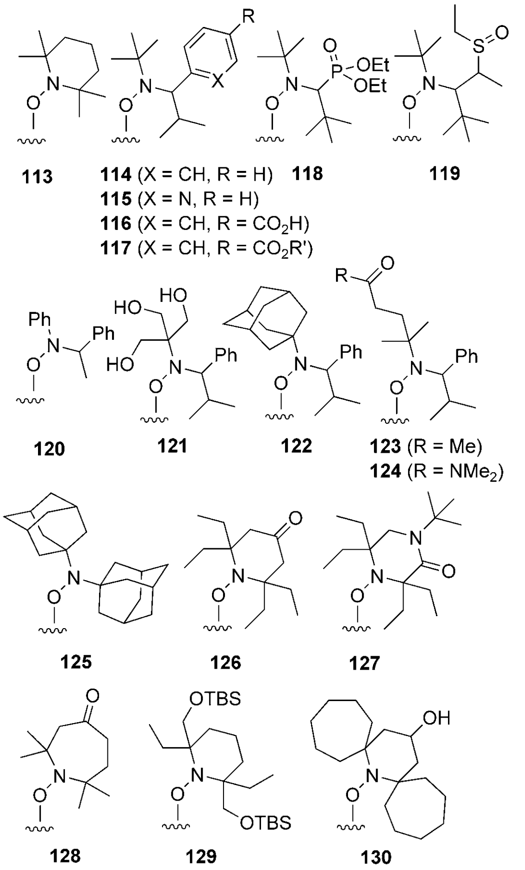


Figure 3. Various alkoxyamines used as initiators/regulators in NMP.

Unfortunately, TEMPO-derived regulators are only suitable for the polymerization of styrene derivatives, and the polymerization of acrylates cannot be controlled by the use of **113**. Therefore, many new nitroxides and their respective alkoxyamines, including **114**,[227] **115**,[228] **116**,[229] **117**,[230] **118**,[231] **119**,[232] **120**,[233] **121**,[234] **122**,[235] **123**,[236] **124**,[237] **125**,[238] **126**,[239] **127**,[240] **128**,[241] **129**[242] and **130**,[243] have been prepared and tested as initiators/regulators in NMP (Figure 3). Some of these more sophisticated alkoxyamines (**114**, **118**, **126**, **127**) also allow the controlled NMP of acrylates, acrylic acid, dienes, and acrylamides.[244] Despite intensive studies into the design of the nitroxide, the controlled nitroxide-mediated homopolymerization of alkyl methacrylates such as methyl methacrylate (MMA) is still in its infancy.[245] However, it was found that good control over the polymerization of MMA can be achieved with alkoxyamines of type **118** upon addition of small amounts of styrene as a co-monomer (around 3 to 9 mol % styrene with respect to MMA are necessary).[246]

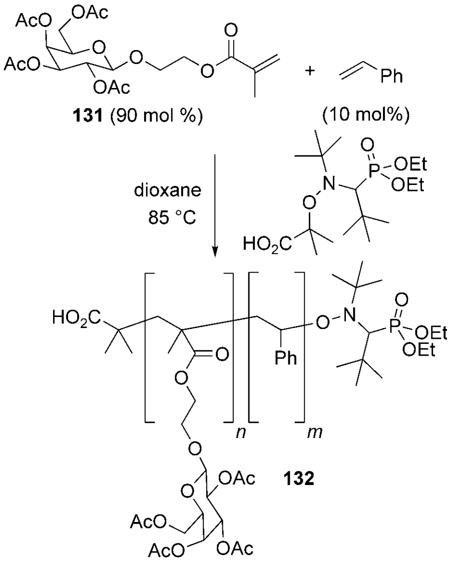
In addition to classical thermal heating, NMP under microwave irradiation was tested. However, control over the polymerization under these conditions was not perfect.[247] Interestingly, it was found that precipitation polymerizations of styrene performed with **118** in supercritical CO$_2$ as a solvent proceeded about 1.58 times faster than the corresponding polymerizations in the bulk phase.[248] The polymers become insoluble at a certain degree of polymerization, and precipitation occurs. This can be steered towards the targeted molecular weight by the initial loading of the monomer and the pressure.[249] More importantly, NMP can also be conducted in aqueous dispersed media.[250] Polymerization conducted in dispersed aqueous media is probably the most important approach for the preparation of polymers on an industrial scale. In these processes, polymer particle suspensions are obtained. Aqueous dispersed polymerizations can either be conducted as either emulsion or miniemulsion polymerizations.[250] Both of these processes have been realized in a controlled manner by using nitroxides as regulators.[251] The development of efficient alkoxyamines such as **118** was highly important, in particular for aqueous dispersion polymerizations, because the more sophisticated regulators allow the polymerization to be conducted at temperatures below the boiling point of water, in contrast to TEMPO.

Recently, Barner-Kowollik and co-workers introduced enhanced spin-capturing polymerization (ESCP) as an efficient and versatile protocol for controlling the molecular weight distributions in radical polymerizations.[252] In ESCP, radical polymerization is conducted in the presence of a nitrone. It is well known that nitrones react with C-centered radicals to generate the corresponding nitroxides (see Scheme 2). A macronitroxide is formed if the trapping by the nitrone is conducted during the polymerization process. This polymeric nitroxide is immediately trapped by a polymeric radical to finally provide a macroalkoxyamine. Hence, two polymeric radicals are installed through a nitrone moiety. The molecular weight of the resulting polymer can be adjusted by altering the concentration of the nitrone. This process neither belongs to NMP nor is a controlled radical polymerization. Nevertheless, as a result of its simplicity and the good results obtained, it is a highly valuable approach for controlling the molecular weight of a polymer by using nitroxide chemistry.

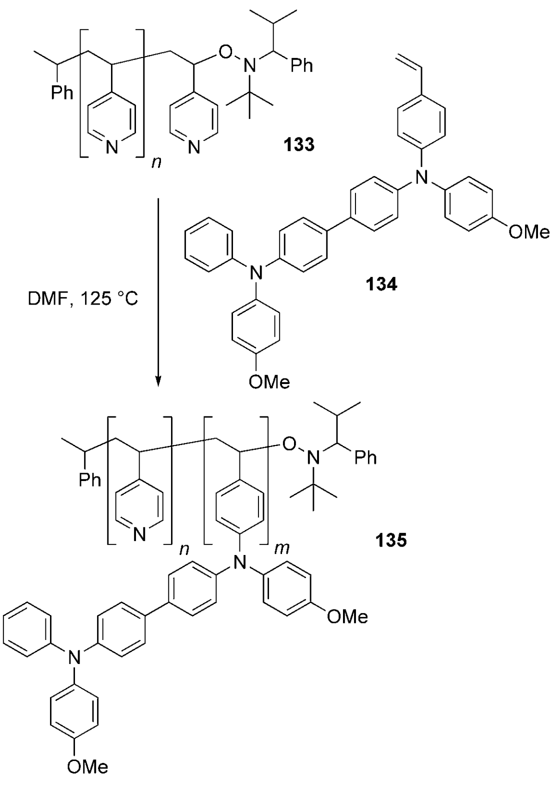
In the following discussion, we will briefly present applications of NMP in various fields of modern polymer chemistry. However, because of space limitations, it is not possible to fully cover the entire literature in this highly active and growing area. We have, therefore, focused on documenting the various aspects and the huge potential of NMP from the recent literature.

Radical processes are tolerant to many functional groups. This opens the door to the preparation of functional polymers. Thus, controlled nitroxide-mediated polymerization has been used extensively for the synthesis of functional polymers, for example, glycopolymers.[253] Scheme 48 shows the synthesis of the lectin-recognizable material **132** through the use of a methacryloyl galactose monomer **131** in the presence of styrene as a co-monomer.[254]

Moreover, NMP has often been applied to the preparation of various block copolymers, and different procedures have been followed. The most extensively applied approach (depicted in general terms in Scheme 47) makes use of a polymer prepared by NMP that bears an alkoxyamine moiety at the polymer terminus as a macroinitiator/-regulator for the synthesis of block copolymers.[255] For example, this procedure was successfully applied to the synthesis of block copolymers for semiconductor nanocomposites.[256] Towards this end, the polyvinylpyridine macroalkoxyamine **133** was used as an initiator for polymerization of monomer **134** to give diblock copolymer **135** in a controlled manner (Scheme 49). Polymer **135** contains a hole conductor block—which carries the



Scheme 48. Synthesis of a glycopolymer by NMP.

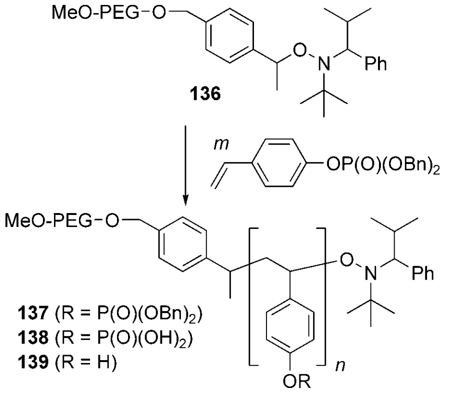


Scheme 49. Synthesis of a functional diblock copolymer.

tetraphenylbenzidine moiety—and a polyvinylpyridine block, which can be used for incorporation of n-type semiconductor crystals. Self-condensation of block copolymer **135** results in it showing a lamellar morphology.

The great functional group compatibility of NMP has enabled various interesting monomers to be prepared that bear functional groups that can readily be further modified chemically, and these monomers have been used for the synthesis of block copolymers. Useful functional groups such as epoxides,[257] silyloxysilylphenyl,[258] aryl sulfonates,[259] alkynes,[260] olefins,[261] perylene bisimide,[262] terpyridyl,[263] and dialkyl phosphonates[264] are tolerated as subunits on the monomer in NMP.

Macroalkoxyamines, which are subsequently used as initiators in the synthesis of block copolymers, can also be prepared by covalent attachment of an alkoxyamine initiator/regulator to a polymer prepared by a "non-NMP" method. This represents the second important route to block copolymers. For example, polyethylene glycol (PEG) has been selectively functionalized at one terminus with an alkoxyamine initiator/regulator by ionic reactions. The PEG macroalkoxyamine then allowed the controlled formation of diblock copolymers.[265] PEGylated alkoxyamine **136** was synthesized and used in NMP to form phosphorylated polymer **137** (Scheme 50).[266] This polymer was then transformed to polymer **138**, which bears repeating phosphoric acid units. Finally, dephosphorylation to give diblock copolymer **139** was achieved enzymatically with acid phosphatase.

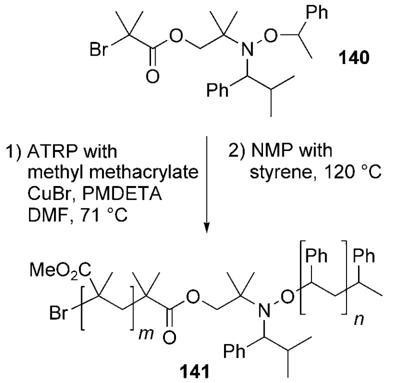


Scheme 50. Synthesis of diblock copolymers.

Oligothiophene derivatives with an alkoxyamine terminus were synthesized by attaching the regulator containing the nitroxide through formation of an ester bond,[267] Wittig olefination,[268] or by nucleophilic addition of a metalated alkoxyamine to an aldehyde-terminated oligothiophene.[269] These oligothiophene alkoxyamine conjugates were then successfully used as regulators/initiators in NMP.

A third route towards block copolymers involves a non-NMP polymerization process to install an alkoxyamine moiety during termination. For example, direct incorporation of an NMP regulator/initiator at the terminus of an oligothiophene was achieved by stopping the Grignard metathesis polymerization used for the synthesis of the oligothiophene with an alkoxyamine-containing Grignard reagent.[270]

In a fourth approach to block copolymers, an alkoxyamine moiety is used to initiate a non-NMP polymerization process that delivers a polymer containing an alkoxyamine moiety at the beginning of the polymer. This alkoxyamine functionality is then used as a regulator/initiator for a subsequent NMP to give a diblock copolymer. For example, an alkoxyamine bearing an ionic initiator was used as an initiator for a $Sn(Oct)_2$-catalyzed ring-opening polymerization of ε-caprolactone. The thus obtained poly(ε-caprolactone) containing an alkoxyamine was subjected to controlled living radical polymerization of *n*-butyl acrylate to eventually give poly(*n*-butyl acrylate)-*b*-poly(ε-caprolactone).[271] The same concept for the synthesis of the block copolymer was applied by using an ATRP initiator which also carries an alkoxyamine. Under ATRP conditions, the alkoxyamine stays dormant and subsequent NMP allows the synthesis of diblock copolymers.[272] The bidirectional ATRP-NMP initiator **140** was synthesized and used for MMA polymerization by ATRP to give a macroalkoxyamine, which was subsequently applied as an initiator/regulator for the NMP of styrene to eventually afford diblock copolymer **141** (Scheme 51).[273] Bisalkoxyamines and bisnitroxides have been successfully used in bidirectional polymerizations for the synthesis of ABA triblock copolymers.[274] Alternating,[275] random,[276] and gradient copolymers[277] have also been synthesized by NMP. Monomers containing polymeric side chains lead to comblike polymeric structures. Polymethacrylates containing poly(ethylene glycol) side chains were synthesized by this approach.[278] Norbornenes that were conjugated with an alkoxyamine initiator/regulator were polymerized by ring-opening metathesis polymerization with the Grubbs catalyst to provide polyolefins bearing multiple alkoxyamines on the backbone. NMP eventually provided comblike polymeric architectures, which showed interesting aggregation behavior in solution.[279]



Scheme 51. Synthesis of a diblock copolymer by bidirectional ATRP and NMP. PMDETA = *N,N,N′,N′,N″*-pentamethyldiethylenetriamine.

Block copolymers can be obtained by noncovalent interactions between the two blocks. Metal complexes were used successfully to install the two blocks to form the corresponding diblocks. For example, terpyridine-terminated homopolymers were synthesized by NMP. These homopolymers were then transformed into metallo-supramolecular block copolymers upon addition of a transition metal able to undergo complexation with terpyridine ligands.[280] Star polymers, which represent interesting polymer architectures, have also been prepared successfully by NMP. These materials can be prepared by the core-first approach, where a core entity bearing multiple alkoxyamine moieties is used as a radical initiator/regulator. Figure 4 shows the core alkoxyamine **142**, which bears three active alkoxyamine moieties. This initiator was successfully used for the synthesis of a three-arm star polymer.[281] The number of arms in these systems is defined by the number of alkoxyamines present in the core. Besides TEMPO, other nitroxides have been applied for the preparation of star polymers by using multialkoxyamine core molecules.[282] Star polymers containing up to 16 arms were synthesized successfully by NMP.[283] The preparation of star polymers by applying the arm-first approach has also been described.[284] Moreover, supramolecular chemistry has been used to form star polymers: in this case the strong interaction between crown ethers and paraquat-terminated polystyrene was used to connect the polystyrene arms prepared by NMP to the core tris(crown ether) entity.[285]

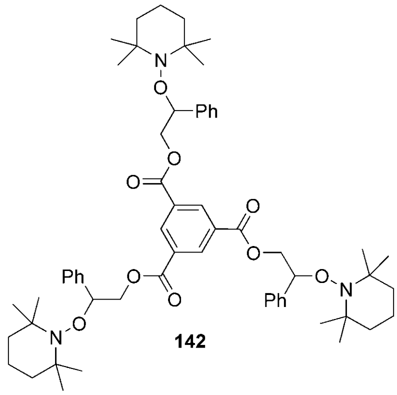
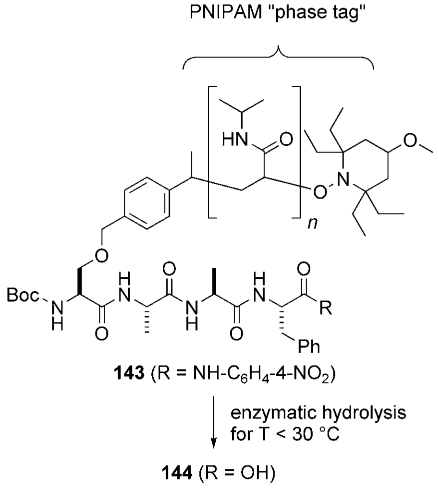


Figure 4. The alkoxyamine used for the synthesis of a three-arm star polymer.

Biohybrid materials such as peptide–polymer and protein–polymer conjugates have also been prepared by NMP.[286] Peptides bearing covalently bound alkoxyamines were used as initiators for the controlled radical polymerization of acrylates and styrene.[287] The thermoresponsive poly-*N*-isopropylacrylamide (PNIPAM) has often been used as a phase tag for the synthesis of smart materials.[288] Temperatures above 32 °C lead to a change of the morphology and hydrophilicity of PNIPAM in water. Below 32 °C, the polymer is soluble in water in the chain-extended, highly hydrated state. Above this so-called lower critical solution temperature (LCST), water is expelled due to entropy and the polymer chains collapse into their hydrophobic state. This highly aggregated polymer is then insoluble in water. This phase switch can be used to induce biological responses of PNIPAM–biomolecule conjugates.[289] The PNIPAM–peptide conjugate **143** was synthesized by NMP with a peptidic alkoxyamine as a regulator/initiator for the controlled polymerization of *N*-isopropylacrylamide (Scheme 52).[290] This conjugate showed thermoresponsive behavior in the chymotrypsin-mediated hydrolysis of the terminal amide bond to give peptide **144**. At 37 °C, the enzymatic hydrolysis was completely suppressed, whereas at 22 °C, **143** is soluble in H_2O and the enzymatic reaction gives **144**. More recently, smart azurin–PNIPAM conjugates were successfully prepared by site-directed mutagenesis followed by protein reconstitution by using imidazole-conjugated poly(*N*-isopropylacrylamides).[291] The imidazole-terminated PNIPAM was obtained by NMP. The polymeric imidazole acts as a ligand in the active site of the blue copper protein azurin. The bioconjugates showed thermosensitive behavior in electron-transfer processes from ferrous cytochrome c.



Scheme 52. Enzymatic hydrolysis of a smart peptide–polymer conjugate.

5.2. Preparation of Polymer Brushes by NMP

Surface properties such as wettability, corrosion protection, and biocompatibility can be altered by covering the surface with a thin polymer film. Such polymer layers or films can be placed on surfaces by deposition or spray coating the polymers from solutions. In these cases, the polymer film is physically adsorbed on the surface, which might lead to unstable surfaces. Improved film stability can be achieved by covalent attachment of one end of the polymer chain to the surface. This leads to polymer films called polymer brushes.[292] In these brushes, the polymer chains are stretched away from the surface if a high grafting density of the polymer is achieved. A significant advantage of polymer brushes compared to other methods for surface modification is their mechanical and chemical stability as well as their high level of synthetic flexibility towards the introduction of functional groups.

Two methods for the preparation of polymer brushes have been introduced. In the “grafting to” route, polymerization is conducted prior to attachment on the surface. However, polymers already covalently bound to the surface hinder diffusion of additional polymer chains to the substrate surface, thereby leading to brushes that generally show low grafting densities and low film thicknesses (Figure 5).[293]

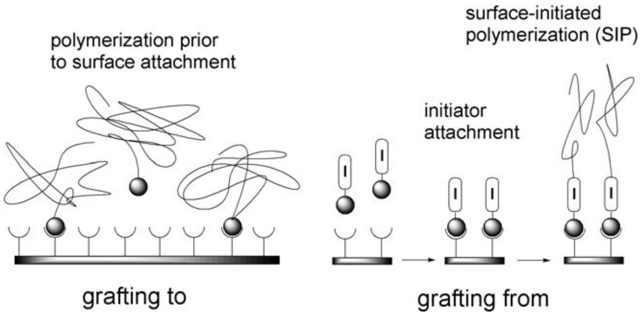


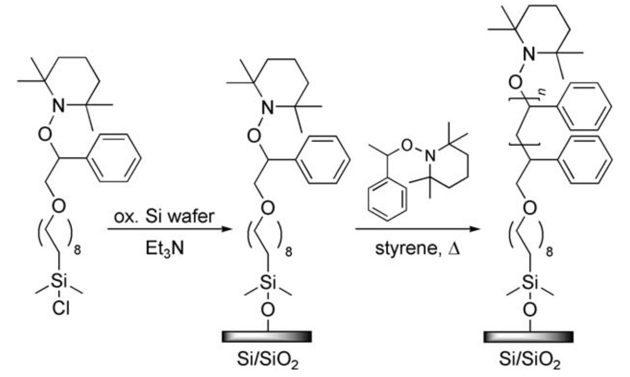
Figure 5. Synthesis of polymer brushes by two different approaches.

Higher grafting densities are generally achieved by using surface-initiated polymerization (SIP), where the polymer chains are grown from the surface of the substrate by first installing a sterically small polymerization initiator onto the surface, followed by polymerization. This latter approach is known in the literature as the "grafting from" approach.

The first report on polymer brushes prepared by NMP[294] by applying the "grafting to" approach dates back to 1997.[295] Random copolymers which bear free OH groups at the terminus of the polymers were prepared by NMP. Spin coating these random copolymers on a silicon wafer and subsequent heating allowed some of the the polymers to be covalently bound through their hydroxy groups to the oxidized Si surface. However, as expected for a "grafting to" process, a brush thickness of only around 5 nm was reported in these experiments.[296] Polystyrene chains bearing an azide functionality at the terminus were successfully synthesized by NMP by using an alkoxyamine initiator/regulator that contains a benzylic chloride. The polymeric chloride obtained after NMP was transformed to the corresponding azide, which was then grafted to an alkyne-terminated Si surface by using click chemistry.[297]

Thicker brushes were achieved by using the grafting-from route. Towards this end, an alkoxyamine regulator was first attached to the oxidized Si wafer by self-assembly (Scheme 53). The corresponding brushes were obtained by a surface-initiated nitroxide-mediated radical polymerization.[298] The brush thickness could be readily adjusted by varying the reaction time, and surfaces with a polymer thickness of up to 80 nm were obtained. Moreover, since NMP is a living radical process, block copolymer brushes were also accessible by this method.

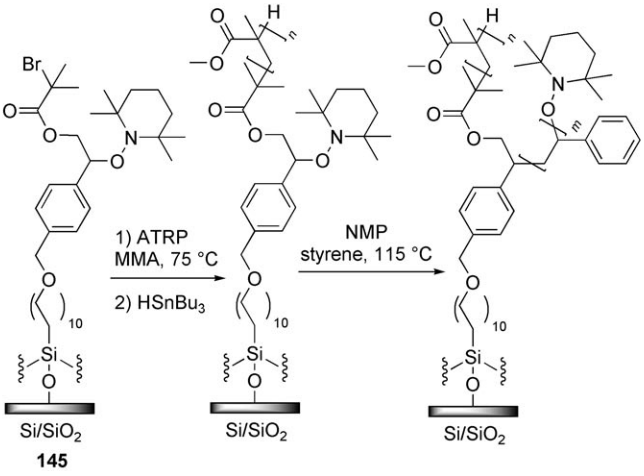
As discussed in Section 5.1, TEMPO only allows the controlled radical polymerization of styrene and styrene derivatives. More sophisticated surface-bound alkoxyamines are required for the controlled surface-initiated polymerization (SIP) of acrylates. Since the nitroxide moieties in thermally labile alkoxyamines undergo crossover during polymerization, the controlled acrylate SIP can be achieved by using surface-bound TEMPO–alkoxyamines in the presence of free sacrificial alkoxyamines bearing more sophisticated nitroxides of the second generation.[299] The nitroxide exchange process allows the generation of surface-bound macroalkoxyamines which bear the more sophisticated nitroxides. This elegant approach was used successfully for the preparation of poly(*n*-butyl acrylate) brushes. As an alternative, azo initiators can be covalently bound to oxidized Si wafers. Decomposition of these azo derivatives in the presence of a monomer such as *n*-butyl acrylate and an appropriate nitroxide leads to controlled SIP of *n*-butyl acrylate.[300]



Scheme 53. Preparation of styrene polymer brushes.

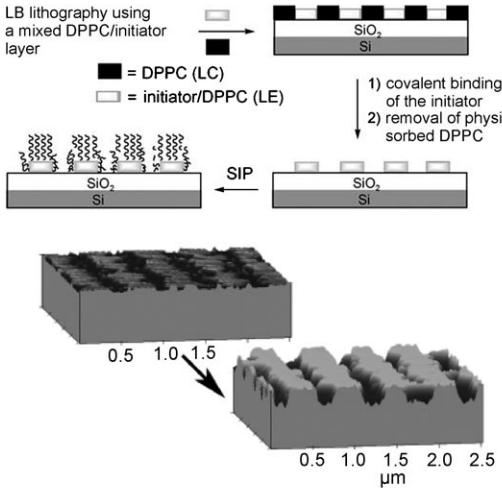
Mixed styrene/MMA polymer brushes were prepared by surface ATRP and subsequent surface NMP. Towards this end, a monolayer of type **145** was prepared by covalently binding a bifunctional ATRP/NMP initiator to a Si wafer by trans-silyletherification (Scheme 54).[301] Methyl methacrylate was first polymerized at low temperature (75 °C) by the ATRP process. This was followed by surface NMP of styrene at a higher temperature (115 °C) to afford mixed polystyrene/polyMMA brushes, which showed interesting wetability properties.[302]

Structured polymer brushes have also been generated by NMP on Si wafers. Langmuir–Blodgett lithography (LB lithography), which is based on dynamic self-assembly,[303] can be used for the site-specific covalent immobilization of



Scheme 54. Preparation of mixed polymer brushes.

radical alkoxyamine initiator/regulators onto Si wafers. Towards this end, a mixed monolayer of L-α-dipalmitoylphosphatidylcholine (DPPC) and an alkoxyamine bearing a triethoxyalkylsilyl moiety can be transferred onto a Si wafer in regular stripes consisting of alkoxyamines. The stripes have submicrometer lateral dimensions (Scheme 55).[304,305] Nitroxide-mediated SIP eventually delivers regular stripes of polystyrene and polyacrylate brushes, depending on the monomer used. The width of the polymer stripe can be adjusted from about 0.2 to 1.3 μm.



Scheme 55. Synthesis of structured polystyrene brushes by LB lithography and subsequent SIP (top: schematic representation, bottom: AFM images before and after SIP of styrene).

Moreover, it was shown that dense polystyrene brushes readily prepared by nitroxide-mediated surface-initiated polymerization can be structured by mechanical nanoscratching with an AFM tip (AFM lithography is a top-down approach).[306] Figure 6 shows an array of 200 nm diameter pillars obtained by scratching a 30 nm thick polystyrene brush layer by cross-writing of single scan lines with the AFM tip. Interestingly, the areas containing the polymeric material and the scratched regions of the wafer can be selectively addressed by different dyes.

Structured polymer brushes were also obtained by using photolithography. Towards this end, a dense poly(*tert*-butyl methacrylate) brush was first prepared by surface-initiated NMP with a surface-bound alkoxyamine.[307] The brush layer was then covered with a photoresist. Site-specific acid generation by irradiation through a photomask allowed site-selective hydrolysis of the *tert*-butyl ester by the liberated protons in the brush layer, thereby generating a mixed brush with alternating polyacid and polyester regions.

Contact molding was utilized to site-specifically transfer an alkoxyamine imbedded in a photopolymer onto a flat substrate.[308] The photopolymer was first spin coated onto a Si wafer. This wafer was then brought into contact under pressure with a patterned stamp, which induced cross-linking of the photopolymer. After removal of the stamp, cross-linked polymer on the wafer was obtained site-specifically. Importantly, the photopolymer contained alkoxyamines, so the surface-initiated polymerization of the styrene allowed the growth of polymers at defined positions.[309]

So far the chemical modification of Si wafers has been discussed. However, surface-initiated nitroxide-mediated polymerization is not restricted to Si wafers as substrates. Silica particles have been used for the covalent attachement of polymers. For example, SiO_2 particles bearing a peroxo functionality were heated in the presence of TEMPO and styrene. Homolytic cleavage of the peroxy moiety provides surface-bound radicals, which then initiate the controlled polymerization as a consequence of the presence of TEMPO.[310] Along this line, hydroperoxide-activated silica particles were heated in the presence of a nitroxide and butyl acrylate to give polymer brushes with a defined molecular weight.[311] Block copolymers consisting of polystyrene and poly(*n*-butyl acrylate) were also prepared by this method. In addition to peroxides, diazo compounds can be covalently bound to the surface and used as radical initiators for polymerization. A controlled polymerization can be achieved if the azo decomposition is conducted in the presence of a nitroxide and monomer.[312]

The alkoxyamines can also be covalently bound to silica particles with subsequent SIP. As an example, alkoxyamine **146**, bearing a triethyoxysilyl moiety was covalently bound to SiO_2 particles by trans-silyletherification (Scheme 56).[313] Subsequent NMP of styrene at the particle surface provided styrene-coated SiO_2 particles. The same approach was applied

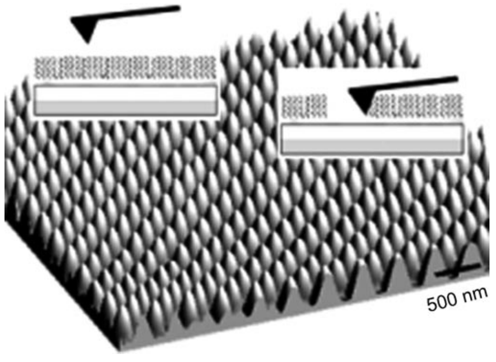
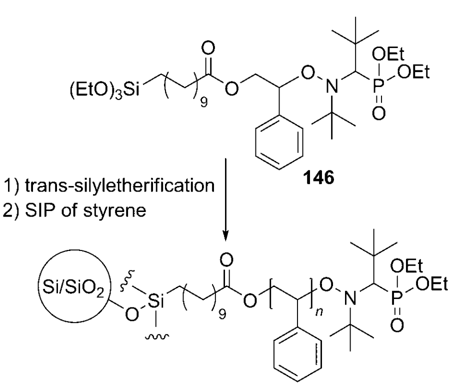


Figure 6. Synthesis of structured polystyrene brushes by AFM lithography.



Scheme 56. SIP at alkoxyamine-modified SiO_2 particles.

to the synthesis of dense poly(*n*-butyl acrylate)-*b*-polystyrene diblock copolymer brushes covalently bound to SiO_2 particles.[314]

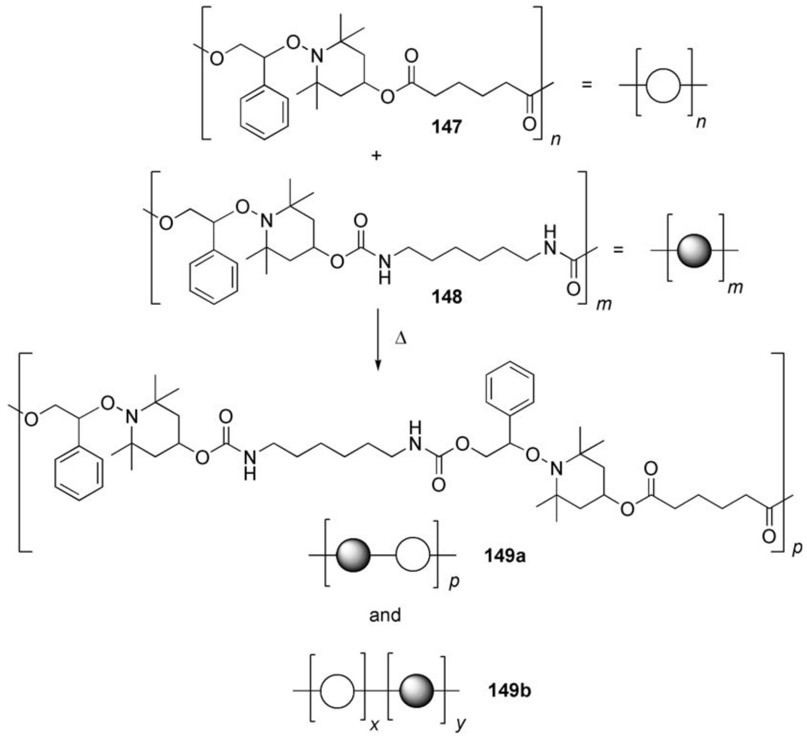
CdSe,[315] titanium oxide,[316] and magnetic γ-Fe_2O_3 nanoparticles[317] were successfully modified chemically by surface-initiated nitroxide-mediated radical polymerization. Moreover, carbon nanotubes were polymer-coated with surface-bound alkoxyamines by NMP.[318] The surface of steel[319] was chemically modified by attaching alkoxyamines. Subsequent SIP by using the "grafting from" approach resulted in polymer-coated steel, which had interesting properties.[320]

The inner surface of mesoporous silica MCM-41 was successfully functionalized with an alkoxyamine by treating MCM-41 first with 3-aminopropyltriethoxysilane, then with terephthaloyl chloride, and finally with 1-hydroxy-2-phenyl-2-TEMPO-ethane.[321] This three-step process allowed the covalent bonding of the alkoxyamine through an ester linkage. The same approach was also applied to position alkoxyamines between the layers of a laponite clay material.[322] Subsequent NMP within the platelets provided the corresponding organic–inorganic hybrid material.

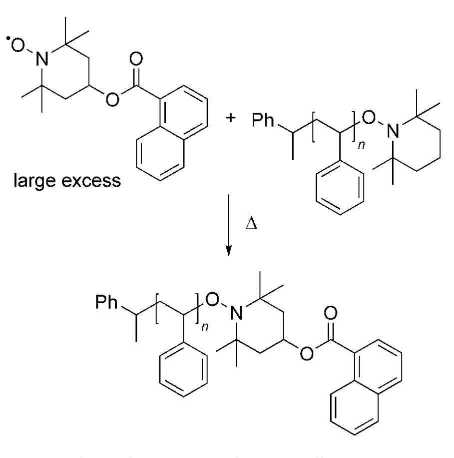
5.3. Dynamic Covalent Polymers

Nitroxide exchange during polymerization between two polymeric alkoxyamines bearing different nitroxides was proven experimentally in 1996.[323] This efficient exchange process was later used to install chromophores at the terminus of a polymeric alkoxyamine prepared by NMP.[324] Towards this end, a chromophore-conjugated nitroxide was allowed to undergo a nitroxide exchange reaction with a polymeric TEMPO-terminated alkoxyamine (Scheme 57). The nitroxide exchange reaction was also used for the chemical modification of alkoxyamine-terminated polymer brushes[325] and also in solution for the synthesis of a small alkoxyamine library.[326]

Importantly, reversible thermal nitroxide exchange of alkoxyamines can be used for the preparation of dynamic covalent polymers. Polymeric alkoxyamines were prepared by the reaction of a polymeric activated bromide with a polymeric nitroxide under copper catalysis (see Scheme 36).[327] Heating polymeric alkoxyamines **147** and **148**, which bear multiple alkoxyamine units in the polymer backbone, led to the exchange of polymeric subunits (polymer scrambling) to provide new polymeric polyalkoxamines of type **149** that show different materials properties (Scheme 58).[328] The composition of the scrambled polymeric material can be adjusted by adjusting the feed ratio of **147** to **148**. Polymer scrambling by reversible radical ring-crossover polymerization was also applied to the synthesis of macrocyclic alkoxyamines.[329]

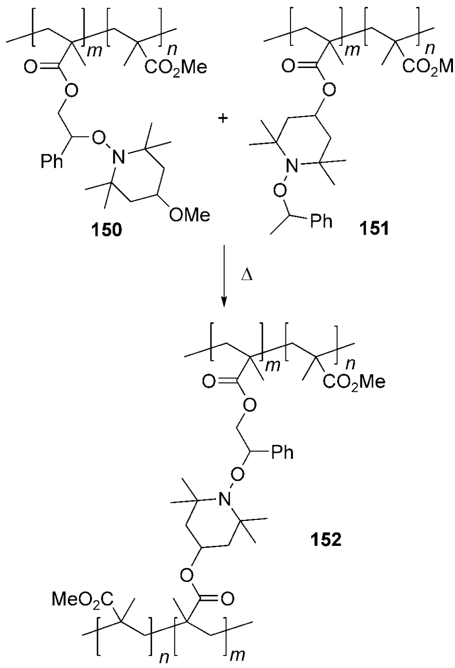


Scheme 58. Exchange of an entire polymer subunit through nitroxide exchange (polymer scrambling).



Scheme 57. Nitroxide exchange in polymeric alkoxyamines.

Moreover, poly(methyl methacrylates) bearing alkoxyamine units in the side chain can be cross-linked by covalently attaching their side chains through nitroxide exchange reactions. Heating polymer **150** in the presence of **151** afforded cross-linked polymer **152** (Scheme 59).[330] Since thermal nitroxide exchange is a reversible reaction, removal of the cross-links was achieved by heating the polymer **152** in the presence of a small molecular weight alkoxyamine such as styryl–TEMPO or TEMPO.[331] This approach allowed the synthesis of starlike nanogels through the cross-linking reaction of complementary reactive diblock copolymers.[332]



Scheme 59. Cross-linking of PMMA by thermal nitroxide exchange.

6. Summary and Outlook

This Review provides an overview of the broad applicability of nitroxides in synthesis as well as in polymer chemistry. Numerous recent reports show the high number of ongoing studies in these research fields. Nitroxides, in particular TEMPO, have been used extensively as catalysts for the oxidation of alcohols. Recent developments show that these oxidations can be conducted in the absence of any transition metal by using dioxygen as a terminal oxidant. Many exciting results are expected in the field of transition-metal-free oxidation reactions by using nitroxides as catalysts.

As documented in this Review, not only alcohol oxidations, but also other interesting reactions can be conducted by using nitroxides as oxidants. Scattered reports clearly show that nitroxides have the potential to act as non-innocent ligands in transition-metal-based oxidations. Since nitroxides are generally very mild oxidants, there is great potential for their use as stochiometric or even catalytic oxidants in metal-catalyzed processes (both oxidations as well as C–C bond-forming reactions). The use of chiral nitroxides as oxidants in metal-mediated reactions has not been extensively investigated to date. Recent results document that oxidative transition-metal-free C–C bond-forming reactions are feasible when nitroxides are used as mild oxidants. However, so far these reactions have been mainly conducted using nitroxides as stoichiometric reagents. Catalytic variants of these nitroxide-mediated C–C bond-forming reactions are almost unexplored.

Nitroxides have been widely used as trapping reagents in radical chemistry. In particular in the field of tin-free radical processes, nitroxides have found wide application as terminal oxidants in non-chain radical processes. The reversible generation of C-centered radicals starting from thermally labile alkoxyamines has been used in organic synthesis, and also for the modification of surfaces. The reversible thermal homolysis of alkoxyamines is the key to nitroxide-mediated radical polymerization (NMP), which has earned great attention during the past 15 years. Early studies were mainly devoted to the design of nitroxides. Although originally restricted to the polymerization of styrene and of styrene derivatives, many monomers can now be polymerized in a controlled manner by NMP thanks to the development of more sophisticated nitroxides. Recent research in this area has focused on the application of NMP to the preparation of complex polymer architectures. Block copolymers, comb polymers, and star polymers, among others, have been prepared by this route. The great functional-group tolerance of NMP has enabled complex monomers bearing interesting functional groups to be polymerized. Since NMP is orthogonal to many other polymerization processes, the combination of NMP with other techniques has allowed the synthesis of block copolymers that are not accessible by using NMP only. Importantly, NMP has also been used successfully for the preparation of structured polymer brushes. We believe that basic research in NMP has reached a very advanced stage; future applications of this particular polymerization technique in materials science will be a major research focus. It is clear that NMP has become an important tool in materials science.

Although not discussed in this Review, it is important to mention that nitroxides have been used successfully as spin probes in biochemistry. Many new developments are also expected in that field. Moreover, nitroxides have been used successfully as building blocks for the preparation of organic magnets. However, to develop the building blocks for the preparation of these sophisticated materials, it is the duty of chemists, with a deep knowledge of the basic chemistry of nitroxides, to design and to synthesize the requested materials components.

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