TEMPO and its Derivatives: Synthesis and Applications

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Abstract: The stable, non-conjugated nitroxyl radical TEMPO was first reported by Lebedev and Kazarnovskii in 1960 [1d]. The unpaired electron in this radical is delocalized over the nitrogen-oxygen bond, and this accounts for their high stability. TEMPO has emerged as a mild and highly selective catalyst for the oxidation of alcohols to carboxyl compounds and for other synthetically useful oxidative transformations during the last decade. In particular, TEMPO has attracted much attention as a catalyst in combination with molecular oxygen as the stoichiometric oxidant. The use of TEMPO and its derivatives in the field of oxidation and coupling chemistry has encouraged the development of mild, safe, and highly chemoselective catalysts. The radical TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl radical) and its derivatives are well-established catalysts for oxidation processes, and now used extensively in organic synthesis and industrial applications as a mild, safe, and economical alternative to heavy metal reagents as highly selective oxidation catalysts. In this review, we attempt to fully review the recent advances in the syntheses of TEMPO and its derivatives as well as their applications in recent years. The synthesis of TEMPO and its derivatives are discussed first. The largest section focuses on their application as stoichiometric and catalytic oxidants in organic synthesis, particularly focusing on the formation of C-C, C=O, C=N, and C=N bond. Simultaneously, the oxidation of alcohols to their corresponding carbonyl compounds also is commented briefly. The last section discusses the application of the TEMPO-catalyzed reactions in the total syntheses of natural products.

Keywords: TEMPO, oxidation, radical, synthesis.

1. INTRODUCTION

The recent demand for highly efficient and environmentally benign syntheses of fine chemicals and pharmaceuticals has encouraged the development of mild, safe, and highly chemoselective catalysts. The radical TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl radical) and its derivatives are well-established catalysts for oxidation processes, and now used extensively in organic synthesis and industrial applications as a mild, safe, and economical alternative to heavy metal reagents as highly selective oxidation catalysts. In this review, we attempt to fully review the recent advances in the syntheses of TEMPO and its derivatives as well as their applications in recent years, particularly focusing on the context of TEMPO and its derivatives-catalysed C-C, C-O, C=O, C-N, and C=N bond formation. Simultaneously, the oxidation of alcohols to their corresponding carbonyls also is commented briefly. In addition, the application of the TEMPO-catalyzed reactions in the total syntheses of natural products is discussed.

2. SYNTHESIS OF TEMPO AND ITS DERIVATIVES

2.1. Modification at the 2 and 6-Position of TEMPO

TEMPO is a stable but sterically hindered radical because of the formation of C-C, C-O, C=O, C-N, and C=N bond. Simultaneously, the oxidation of alcohols to their corresponding carbonyls also is commented briefly. The largest section focuses on their application as stoichiometric and catalytic oxidants in organic synthesis, particularly focusing on the formation of C-C, C=O, C-N, and C=N bond. Simultaneously, the oxidation of alcohols to their corresponding carbonyls also is commented briefly. In addition, the application of the TEMPO-catalyzed reactions in the total syntheses of natural products is discussed.
The “fluorous concept” has rapidly expanded in recent years with many novel fluorous-tagged reagents reported and many reactions being adapted for use in conjunction with the fluorous biphasic concept. Holczknecht and co-workers developed some TEMPO derivatives bearing perfluoroalkyl substituents. These “fluorous-tagged” TEMPOs were readily isolated from the reaction products by liquid-liquid or solid-phase extraction, considerably simplifying the purification step [5] (Scheme 2). Dobbs and co-workers also prepared two light fluorous-TEMPO reagents 22 and 23 and employed them as effective catalysts for oxidation reactions [6].

Dane and co-workers developed a general method for synthesis of a biradical containing a 1,3-bisdiphenylene-2-phenylallyl (BDPA) free radical covalently attached to a TEMPO free radical [7] (Scheme 3). In addition, six new TEMPO-linked porphyrins and metalloporphyrins were synthesized [8a]. More recently, two novel bifunctional hybrid-type catalysts bearing TEMPO and iodobenzene moieties were developed and used for the environmentally benign oxidation of primary alcohols to carboxylic acids [8b].

2.3. Synthesis of Ionic Liquid-Supported TEMPO

Ionic liquids (ILs) have received much attention in recent years from the scientific community, mainly as environmentally benign reaction media. Their unique properties such as high thermal and chemical stability, negligible vapor pressure, non-flammability, high loading capacity, and easy recyclability make them appealing for an organic chemist. Many ionic liquid-supported TEMPOs 25-28 were prepared [9-14] (Fig. 2).

Fall and co-workers described an efficient synthesis of anionic liquid-supported TEMPO 33 via click chemistry [9] (Scheme 4). The predictable solubility of ionic liquids allows an easy separation of the oxidation products from reagents. Additional advantages of 33 over free TEMPO are: simplified workup procedure and easy recovery and recycling.

More recently, a novel magnetic silica supported bifunctional hybrid material (IL/SMNP) 25 combining TEMPO based ionic liquid and polyanion metallocenes was developed [10] (Fig. 2). In particular, attributed to the magnetic Fe₃O₄/SiO₂ system, it was a pseudohomogeneous process and after reaction, IL/SMNP could be easily recovered with the help of an external magnet to be reused.

2.4. Synthesis of Solid-Supported TEMPO

With the demand for “green chemistry”, solid supported reagents have gained much prominence due to environmental benefits and easy separation of the products [15]. From the view points of product separation and catalyst recycle, many supported TEMPO catalysts have been synthesized based on organic as well as inorganic supports.
Scheme 2. Synthesis of “fluorous-tagged” TEMPOs.


Fig. (2). Structures of ionic liquid-supported TEMPOs.
2.4.1. Organic Polymer Supported TEMPO

In the last decade, there has been an increasing interest for the development of polymer-supported TEMPOs. Many approaches have been successfully employed to attach TEMPO on different polymer supports, affording a number of soluble and insoluble polymer-supported catalysts, which provide a solution for the problem of the separation of TEMPO from the product and the potential for recyclable catalysts.

Several polystyrene-supported TEMPOs have been reported [16] (Fig. 3). These catalysts were also shown to be easy to recycle by filtration without significant loss of activity [16c]. Unlike heterogeneous supports, poly(ethylene glycol) (PEGs) exhibit excellent solubility in a wide range of polar and non-polar solvents. Furthermore, the commercial availability of PEGs possessing very narrow but defined polydispersity indices render these polymers interesting candidates as new supports for TEMPO catalysis in biphasic media. Thus, several poly(ethylene glycol)-supported TEMPO (PEG-TEMPO) [17] have been prepared. In addition, oxammonium resins [18a], JandaJel-TEMPO [18b], poly(7-oxanorbornenes)-TEMPO [18c] and Chimassorb 944-TEMPO [18d] are some successful examples.

2.4.2. Inorganic Supported TEMPO

The sol-gel technology offers several advantages over the classical immobilization procedures employed in the preparation of heterogeneous catalysts. Inorganic sol-gel supports are indeed superior in their thermal stability, inertness towards and protectability of the entrapped molecules, and in their porosity and high surface areas. Early examples of the sol-gel entrapped TEMPOs were reported by the research group of Pagliaro [19a-c]. Subsequently, Karimi and co-workers disclosed that SBA-15 can be used to support the TEMPO to give an extremely stable and reusable catalyst [20] (Fig. 3). More recently, Wang and co-workers reported a novel strategy for the synthesis of immobilized TEMPO on multiwalled carbon nanotubes (MWNTs). The supported catalysts (MWNTs-TEMPO) [20] can be homogeneously dispersed in the reaction medium to conquer the mass transfer limitation, which leads to their catalytic activity being
far superior to their heterogeneous counterpart and similar to their parent catalysts [21] (Fig. 3).

3. APPLICATION OF TEMPO AND ITS DERIVATIVES IN ORGANIC SYNTHESIS

3.1. Oxidation of Alcohols

The oxidation of alcohols to their corresponding carbonyl compounds is one of the most fundamental and important processes in synthetic organic chemistry. Although a variety of methods and reagents have been developed, they all suffer from the general difficulty to transport redox equivalents. TEMPO-catalyzed oxidation method has attracted attention in many areas of synthetic organic chemistry because it enables the use of various safe bulk oxidants, thereby enabling a safe and extremely efficient oxidation of alcohols with considerable operational simplicity [2a].

3.1.1. TEMPO/Oxidant as Cocatalysts

The oxidation of alcohols to carbonyl compounds using TEMPO, stoichiometrically or catalytically with a stoichiometric reoxidant, has been extensively reported. In most of these transformations the active oxidant is not TEMPO but its oxidized form, the corresponding oxoammonium salt. The reactive oxoammonium salt of TEMPO can be readily generated by treatment of TEMPO with considerable operational simplicity [2a].

3.1.2. TEMPO/Metal Systems

In the last decade many TEMPO/metal systems have been discovered for using molecular oxygen as environmentally friendly oxidant for the selective oxidation of alcohols. Among the existing TEMPO/metal systems, the TEMPO/copper systems have been well investigated [28]. As copper salt alone is an inefficient catalyst, a variety of ligands is used with copper salts to increase the catalytic activity. Generally, in situ-generated copper complexes with nitrogen-containing ligands such as Cu(I)/Bipy [28], Cu(II)/Bipy [29], Cu(II)/diimine [30a], Cu(II)/2-N-arylpyrrolecarbaldimino [30b], Cu(II)/TMDP/DABCO [31], are used for alcohol oxidation to the corresponding carbonyl compounds. However, the alcohol oxidation reactions using well-defined copper complexes are less reported [32]. For example, Hossain and Shyu reported the selective aerobic alcohol oxidation using the isolated copper complex [Cu(μ-Cl)(Cl)-phen)], with TEMPO as the catalytic system at room temperature [32a].

The use of iron catalysts for the oxidation of alcohols is highly desirable because it is inexpensive and environmentally friendly. Recently, Ma and co-workers developed a mild and practical Fe(NO3)3/TEMPO-catalyzed aerobic oxidation of the most commonly used alcohols in academic and industrial laboratories such as primary as well as secondary normal alkanols, benzylic, allylic, propargylic alcohols, and allenols expedited by a catalytic amount of sodium chloride efficiently [33a]. Liang and co-workers also showed that FeCl3 in combination with TEMPO and NaNO2 [33b] as well as 4-acetamido-TEMPO and NaNO2 [33c] were able to oxidize a wide range of alcohols under mild conditions with dioxygen. In addition, Ruthenium/TEMPO [34a,b] and Co(NO3)2/DH2/TEMPO [34c] catalytic systems, for the aerobic oxidation of alcohols under mild conditions to their corresponding carbonyl compounds, have been developed. More recently, an efficient organocatalytic method for chemoselective aerobic oxidation of secondary benzylic alcohols within lignin model compounds was developed [35].

3.1.3. TEMPO/Ionic Liquid Systems

Ionic liquids as an environmentally friendly solvent represent interesting properties. Various chemical reactions have been well performed in ionic liquids. Thus, TEMPO-catalyzed aerobic oxidation of alcohols in ionic liquids has been developed [36]. Recently, increasing attention has been focused on the use of ionic liquids as a means of immobilizing catalysts, facilitating products separation and providing an alternative to recycle the catalysts. Meanwhile, ionic liquid-supported TEMPO catalysts such as IL-CLICK-TEMPO [9], IL-SMNP-TEMPO [10], imidazolium salt-TEMPO [11, 12] have been developed for transformation of a series of alcohols to the respective carbonyl compounds. More recently, Zhu and co-workers designed and synthesized novel bifunctional ionic liquid supported iodoarene-TEMPO catalysts bearing two catalytic sites, the iodoarene and TEMPO moiety [13]. These catalysts were demonstrated to be useful for the efficient and environmentally benign oxidation of alcohols to corresponding carbonyl compounds using PAA as co-oxidant.

3.1.4. Organic Polymer Supported TEMPO Systems

Based on the solution for the problem of the separation of TEMPO from the product and the potential for recyclable catalysts, organic polymer supported TEMPO systems such as PS-supported TEMPO [16], PEG-supported TEMPO [17], MPEG-supported TEMPO [37a], oxoammonium resins-supported TEMPO [18a], Jan-daFel-supported TEMPO [18b], poly(7-oxanorbornenes)-supported TEMPO [18c] and Chimassorb 944-supported TEMPO [18d]. More recently, the sequential reaction including alcohol oxidation by TEMPO/Cu system and the asymmetric aldol reaction by peptide catalysis was realized using resin-supported catalysts [37b].

3.1.5. Inorganic Polymer Supported TEMPO Systems

In order to obtain recyclable catalysts for alcohol oxidations, inorganic polymer-supported TEMPO catalysts such as sol-gel supported TEMPO [19,38], SBA-15 supported TEMPO [20] and MWNTs-TEMPO [21] have been developed.

3.2. TEMPO-Catalyzed C-C Bond Formations

The construction of C-C bonds is one of the most useful and fundamental processes in organic synthesis. Recently, Jiao and co-workers described an unprecedented TEMPO-catalyzed cross-coupling reaction for C-C bond formation from two different C(sp3)-H bonds using molecular oxygen as the oxidant under mild and neutral conditions [39] (Table 1). The dehydrogenative couplings of benzylic C(sp3)-H bonds adjacent to a heteroatom by using TEMPO oxoammonium were developed by Mancheño and co-workers [40].

The direct use of a C(sp3)-H bond of alkanes for the alkylation of arenes is apparently useful because intricate introduction of reac-
tive functional groups can be omitted and no accompanying harmful waste is produced. Pioneering examples of the formation of C(sp²)-C(sp³) bonds by oxidative coupling reaction of lactams with heterocyclic arenes was described by Tsuchimoto and co-workers [41a] (Scheme 5). More recently, a novel and general tandem α-alkylation/cyclization of N-benzyl carbamates with nonactivated olefins in the absence of metal catalysts was developed [41b].

Because trifluoromethylated compounds play an unique and important role in agricultural and medicinal chemistry, Liu and co-workers developed a novel Pd-catalyzed oxidative trifluoromethylation of indoles at room temperature, in which PhI(OAc)₂ was used as an oxidant and Ruppert-Prakash reagent, TMSCF₃ as a trifluoromethylation reagent [42] (Scheme 6).

A novel chain-growth polymerization technique that occurs by an unprecedented strongly alternating radical/anionic cross-over process was developed by Murarka and Studer [43] (Scheme 7). The new method does not use any transition metal and allows preparation of oligoarenes, which have found applications in materials science.

In addition, the trimerisation of indoles can be performed with TEMPO in air as environmentally benign oxidant [44]. In more recent studies, we reported a novel, operationally simple, and practical biomimetic synthetic method for the trimerization of indoles by using TEMPO in air as oxidant with excellent regioselectivity under mild conditions. This reaction provides a novel method for

Table 1. TEMPO-catalyzed Aerobic Oxidative C-C coupling of 9,10-dihydroacridines 40 with Various Carbon Nucleophiles

<table>
<thead>
<tr>
<th>Nu</th>
<th>Reaction Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂CO₂H</td>
<td>60 °C, O₂ (1 atm)</td>
<td>97%</td>
</tr>
<tr>
<td>40</td>
<td>TEMPO (10 mol%)</td>
<td></td>
</tr>
<tr>
<td>41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O₂</td>
<td></td>
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</tbody>
</table>

Scheme 5. Zr(OTf)₄-catalyzed oxidative coupling reaction of indole with pyrrolidinone 43.

Scheme 6. Pd-catalyzed trifluoromethylation of aromatic compounds.

Scheme 7. Poly(arenes) 51 prepared by SRN₁-type polymerization.
the generation of all-carbon quaternary centers at the C2 or C3 position of indoles (Scheme 8).

3.3. TEMPO-Catalyzed C-O and C=O Bond Formations

3.3.1. Formation of N-alkoxyamines

In the past few years, N-alkoxyamines have attracted interest as low-basicity analogues of N55 and as polymerization regulators [45]. Consequently, the synthesis of N-alkoxyamines has attracted great attention, and a number of methods have been reported [46-53]. Frey and co-workers demonstrated that sterically hindered N-alkoxyamine 57 can be synthesized in good yield by coupling nitroxide 55 with hydrocarbyl radical generated in situ by t-BuOOH hydrogen abstraction from hydrocarbon 56 [46] (Scheme 9). The reaction is catalyzed by copper halides as well as by onium iodides.

The first photocatalytic generation of alkyl, allyl, benzyl, and aryl radicals from the corresponding organoborates was developed by Koike and co-workers [47]. The protocol has been applied to catalytic C-O and C-C bond formation, i.e., oxidative coupling of organoborates with TEMPO and alkyl radicals bearing electron-withdrawing groups, mediated by photoredox catalysts under visible light irradiation. The oxidation of allyl and alkyl trifluoroborates with copper(I) salts and DMP was previously exploited by Fensterbank and co-workers [48]. This new method of radical generation is compatible with functionalization and C-C bond formation. In a representative example, a good yield of 59 was observed when trifluoroborate 58 was oxidized with Cu(OAc)2 in DMSO (Scheme 10). In addition, a novel method for the generation of α-carbonyl radicals from catecholboron ketone enolates by reaction with TEMPO [49]. In situ trapping of the α-carbonyl radicals with TEMPO provided the corresponding alkoxyamines in high yields (Scheme 11). Maruoka and co-workers developed the first metal-free direct aminooxylation reaction of aldehydes with an oxoammonium salt,

Scheme 8. Trimerisation of indoles using TEMPO in air as an oxidant.

Scheme 9. Synthesis of N-alkoxy amine 57 from nitroxide 55.

Scheme 10. Photocatalytic C-O bond formation.

Scheme 11. Aminooxylation of silyl enol ether.

Scheme 12. Aminooxylation of 3-phenylpropanal.
catalyzed by the novel binaphthyl-based amine (S)-62 [50]. This method represents a rare example of the catalytic and highly enantioselective synthesis of bench-stable α-aminoxy aldehydes (Scheme 12).

The NHC-catalyzed oxidations of aldehydes by using TEMPO as an oxidant were disclosed by Studer and co-workers [51a]. Benzenaldehyde and electron-rich and electron-poor para-substituted benzaldehyde derivatives were oxidized to the corresponding TEMPO esters in excellent yields (Scheme 1). However, by means of a copper-catalyzed fragmentation reaction of aldehyde peroxides in the presence 4-hydroxy TEMPO, N-alkoxyamines 66 were obtained in moderate to good yields [51b] (Scheme 1).

More recently, isoxazoline derivatives can be conveniently prepared from ketoximes by using TEMPO or DEAD as the radical initiator [52]. Furthermore, Crich et al. showed that S-sialosyl xanthate was photolyzed in dichloroethane at room temperature in the presence of TEMPO to TEMPO glycoside as a separable 1:2 mixture of α- and β-anomers [53a]. Interesting observations on direct C–H arylation of indoles with arylboronic acids and the direct C–H arylations of indoles with arylboronic acids were made by Studer and co-workers [53b].

**3.3.2. Formation of Ketones**

Mitsudo and co-workers developed an electrochemical method for generating cationic palladium complexes [Pd(CH$_3$CN)$_4$][X$_2$], and then used them for the in situ generation of the reagent for accomplishing the electrooxidative Wacker-type reaction [54a] (Scheme 14). Interestingly, activated alkenes and dienes are converted into the corresponding alkenones in excellent yields using TEMPO$^+$ in the presence of water and 2,6-lutidine [54b]. TEMPO$^+$ cations were regenerated electrochemically from the radical parent TEMPO at a vitreous carbon anode. Furthermore, Vatèle successfully developed two mild and environmentally friendly methods for Lewis acid catalyzed-oxidative rearrangement of tertiary allylic alcohols to β-disubstituted enones [55a].

More recently, an efficient direct TEMPO-catalyzed oxidative dimerization of alcohols to esters in high, clean yields [57]. In a representative example, primary alcohol 71 was converted to corresponding ester 73 in 85% yield under reaction conditions (Scheme 16). More recently, an efficient direct TEMPO-catalyzed oxidative dimerization of alcohols to esters was reported [58a]. The reaction uses only 1-2 mol% TEMPO, is complete within 0.5-2 hours, takes place at room temperature, and uses trichloroisocyanuric acid (TCCA), which is an inexpensive and environmentally benign stoichiometric oxidant. In addition, a methodology for the oxoammonium salt-mediated oxidative esterification of aldehydes in the presence of HFIP was developed [58b].

**3.3.4. Formation of Esters**

Bobbitt and co-workers described a new reaction in which highly functionalized primary alcohols containing a β oxygen are dimerized to esters in high, clean yields [57]. In a representative example, primary alcohol 71 was converted to corresponding ester 73 in 85% yield under reaction conditions (Scheme 16). More recently, an efficient direct TEMPO-catalyzed oxidative dimerization of alcohols to esters was reported [58a]. The reaction uses only 1-2 mol% TEMPO, is complete within 0.5-2 hours, takes place at room temperature, and uses trichloroisocyanuric acid (TCCA), which is an inexpensive and environmentally benign stoichiometric oxidant. In addition, a methodology for the oxoammonium salt-mediated oxidative esterification of aldehydes in the presence of HFIP was developed [58b].

Fernández and co-workers described the use of laccase/TEMPO catalytic system to efficiently oxidize interesting aliphatic diols in a regio- and/or monoselective manner, obtaining highly valuable lactones with excellent purity after a simple extraction [59]. This is the first report of an aerobic oxidation of 1,4- and 1,5-diols in aqueous medium using laccases and in the absence of a base. This catalytic system is compatible with the presence of unprotected secondary alcohols, activated benzyl hydroxy groups and other functionalities such as methoxy, fluorine or bromine substituents (Scheme 17).
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Scheme 17. Oxidation of 1,5-diols by the Trametes versicolor laccase/TEMPO catalytic system in aqueous medium.

More recently, Szpilman and co-workers discovered that aldehydes may be activated for oxidation by carboxylic acids [60]. This novel concept was developed into an efficient process for the TEMPO catalyzed oxidation of aldehydes to mixed anhydrides with pivalic acid. The mixed anhydrides may be converted in situ into a wealth of esters and amides in yields that certainly rival those of the multistep protocols, without their operational disadvantages and chemical waste production (Scheme 18).

3.4. TEMPO-Catalyzed C-N, C=N and C=N Bond Formations

3.4.1. TEMPO-Catalyzed C-N Bond Formation

The catalytic asymmetric aminooxygenation of olefins is a very important process due to the significance of the products as building blocks in the synthesis of drugs and natural products [61]. In 2008, Chemler and co-workers reported the first catalytic enantioselective intramolecular alkene aminooxygenation [62] (Scheme 19). The method makes use of TEMPO as both the oxidant and oxygen source. Subsequently, they developed a copper-catalyzed addition of a nitrogen and oxygen across the alkene, resulting in methyleneoxygen-functionalized isoxazolidines [63a]. A mechanistic study of the Cu(I)-catalyzed enantioselective intramolecular aminooxygenation of alkenes which involved reaction kinetics, kinetic isotope effects and deuterium-labeling studies was reported [63b]. In addition, an expedient method for the synthesis of oxymethyl dihydro-pyrroles and oxymethyl dihydroimidazoles was developed by the Cu(II)-mediated reactions of alkenylimines derivatives with TEMPO [64].

Nitroolefin is a common and versatile reagent. Its synthesis from olefin is generally limited by the formation of mixture of cis and trans compounds. Maiti and co-workers developed a highly selective and efficient protocol for nitration of olefins employing AgNO2/TEMPO under ambient conditions [65a]. The process is practical and a wide array of substrates, including aromatic, aliphatic, and heteroaromatic olefins, can be nitrated regio- and stereoselectively (Scheme 20).

N-Heterocycles can be prepared using alcohol oxidation as a key synthetic step. Cook and co-workers explored the potential of Cu/TEMPO as an aerobic oxidation catalyst for the synthesis of...
substituted indoles and quinolines [66a] (Scheme 21). More recently, a novel method of constructing the indoline core by metal-free intramolecular nucleophilic ring closing of diaryliodonium salts was elaborated [66b].

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\begin{align*}
\text{Scheme 21. Synthesis of substituted indoles.}
\end{align*}
\]

The intermolecular amination of C-H bonds with amines remains a challenging goal. A Cu-catalyzed method for intermolecular C-H bond amination of electron-deficient polyfluoro-arenes with an array of primary aromatic amines, which occurred under mild conditions using TEMPO in combination with O$_2$ as the secondary oxidizing agent, was recently disclosed by Su and co-workers [67a] (Scheme 22). Subsequently, a metal-free protocol for the highly efficient direct amination of nonactivated benzoazoles and 1,3,4-oxadiazoles with secondary amines using catalytic amounts of triflic acid and a readily recyclable TEMPO$^\cdot$BF$_4^-$ as an organic oxidant was developed [67b].

3.4.2. TEMPO-Catalyzed C=\(N\) Bond Formation

Imines are important intermediates, which can be used as electrophilic reagents in many transformations, and also serve as versatile starting materials for biological, pharmaceutical, industrial, and natural chemical synthesis. Xu and co-workers developed a general and green, mild and efficient powerful low-loading Cu-catalyzed practical and scalable synthesis of imines and \(\alpha,\beta\)-unsaturated imines directly from alcohols and amines [68a] (Scheme 23).

Cross-dehydrogenative coupling is an important method for C=\(N\) bond formations. A simple catalyst system for CuBr$_2$-TEMPO catalyzed aerobic oxidation of amines has been developed [68b]. Primary and secondary benzylic amines can be oxidized to the corresponding imines in excellent yields.

Recently, the Cu/N-ligand/TEMPO catalytic system was first applied to the aerobic oxidative synthesis of 2-substituted quinazolines and 4H-3,1-benzoxazines from the one-pot reaction of aldehydes with 2-aminobenzylamines and 2-aminobenzylalcohols, respectively [69a,b] (Scheme 24). Furthermore, a novel and efficient aerobic oxidative synthesis of various heterocycles was developed by Han and co-workers [69c].

Multimetallic catalytic systems including their synergystic co-operation can potentially achieve chemical transformations that are unprecedented with monometallic catalysts. Recently, Chiba and co-workers developed a synthetic method to deliver highly substituted isoquinolines from readily available \(\alpha\)-aryl vinyl azides and internal alkynes in the presence of a [[Cp*RhCl$_2$]$_2$]/Cu(OAc)$_2$ bimetallic catalyst system [70] (Scheme 25).

3.4.3. TEMPO-Catalyzed C=\(N\) Bond Formation

A very recent application of copper/TEMPO catalysts to prepare nitriles from aldehydes or alcohols using aqueous ammonia was disclosed by Cook and co-workers [71] (Scheme 26).
Scheme 26. Synthesis of nitriles using Cu/TEMPO.

3.5. TEMPO-Catalyzed Coupling Reactions

Transition-metal-catalyzed coupling reactions are widely recognized as selective, high-yielding methods for the synthesis of organic compounds and have proven to be one of the most powerful arsenals for the formation of carbon-carbon bonds [72].

3.5.1. TEMPO-Catalyzed Homocoupling Reactions

Homocoupling reactions of aryl, alkenyl, and alkynyl Grignard reagents are an easy and efficient access to symmetrical di- or polyanomatic, olefinic, or acetylenic conjugated compounds. Studer and co-workers reported a highly efficient homocoupling of organomagnesium compounds with TEMPO [73] (Scheme 27). Furthermore, the Pd/TEMPO-catalyzed electrooxidative homocoupling of aryl boronic acids has been developed [74].

Scheme 27. Homocoupling of RMgBr with catalytic amounts of TEMPO.

3.5.2. TEMPO-Catalyzed Cross-Coupling Reactions

Sonogashira cross coupling of terminal alkynes with aryl or alkynyl halides is one of the most widely used methods to build up internal alkyne moieties. Studer and co-workers described a highly efficient transition metal-free cross-coupling reaction between nitrones and alkynyl-Grignard reagents by using TEMPO as a mild organic oxidant [75a] (Scheme 28). It is meanwhile well established that Sonogashira couplings can also be accomplished by using TEMPO [75b]. This coupling reaction can be performed without adding any transition metal on various ortho-substituted aryl and alkynyl Grignard reagents.

Scheme 28. TEMPO-catalyzed oxidative cross-coupling of nitrones with phenyl-Grignard reagent.

Heteroarenes equipped with aryl groups (heterobiaryls) are often found in biologically active compounds, organic materials, and pharmaceuticals. Studer and Vogler developed an oxidative Rh-catalyzed coupling reaction of arynes and heteroarenes with aryloboronic acids via direct C-H arylation [76]. A 2-pyridyl group and amine functional group served as ortho-directing groups to mediate the direct C-H arylation by a Rh complex (Scheme 29). In related studies, Studer and co-workers showed that the Pd/TEMPO-catalyzed oxidative C-H arylation of thiophenes and thiazoles with aryloboronic acids manifests the otherwise difficult C4 regioselectivity [77].

Scheme 29. Rh-catalyzed coupling of aniline with aryloboronic acids.

3.5.3. TEMPO-Catalyzed Three-Component Reactions

Tandem oxidative processes (TOP) in which oxidation of alcohols are combined with the subsequent laboration of the carbonyl intermediates have been developed into powerful synthetic tools. Zhu and co-workers documented the first examples of an efficient Passerini reaction of alcohols under aerobic conditions in the presence of acatalytic amount of a ternary system, CuCl2-NaNO2-TEMPO, using molecular oxygen as a terminal oxidant [78] (Scheme 30). Homogeneous gold-catalyzed reactions are typically run at loadings of one to five mole percent catalyst because it is readily reduced to colloidal Au(0) which decreases its turnovers. Bowden and co-workers developed a new way to greatly increase the turnovers of AuCl3 with the addition of TEMPO and CuCl2 [79].

Scheme 30. Passerini reaction of alcohol under catalytic oxidative conditions.

3.6. Application of the TEMPO-Catalyzed Reactions in the Total Syntheses of Natural Products

One of the greatest tests of any synthetic methodology is the application into complex molecules, in particular natural products. The TEMPO-catalyzed oxidative reaction has proven to be of considerable value in natural product syntheses, especially in the selective oxidation of diol with complex fragments [80]. For example, selective oxidation of the primary hydroxy group of diol 112 led to aldehyde 113 using TEMPO as oxidant [80a] (Scheme 31).

Carreira and co-workers have demonstrated the chemoselective two-step oxidation for the synthesis of erythronolide A seco acid 115 [81] (Scheme 32).
Grainger and Welsh found that irradiation of a solution of dithiocarbamate with a medium-pressure mercury arc lamp in a quartz reaction vessel in the presence of TEMPO resulted in the formal replacement of a carbon-sulfur bond with a carbon-oxygen bond and the clean formation of a single adduct [82]. The TEMPO adduct was directly oxidized to ketone using mCPBA (Scheme 33).

Studer and co-workers developed a mild and highly stereoselective sequential oxidative Pd-catalyzed C-H arylation of alkenes for the synthesis of alkyl triaryl ethenes [83]. For example, the oxidative Heck sequence was applied to the synthesis of

\[ \text{Z-Tamoxifen} \]

More recently, a novel TEMPO-catalyzed aerobic oxygenation and nitrogenation of hydrocarbons via C=C double bond cleavage has been disclosed [84]. This method provides many opportunities to synthesize useful intermediates. For instance, the widely used anesthetic and analgesic medicine, the (S)-ketamine, was enantiomerically prepared from oxo nitrile in many steps (Scheme 35).

4. CONCLUSIONS AND OUTLOOK

Oxidation reactions are among the most commonly used reactions in industry. However, many of the industrial processes still use stoichiometric amounts of high oxidation state metal reagents [85]. Moreover, there is currently an active search for environmentally friendly procedures, which are based on the use of catalytic amounts of the metal. Thus, the development of new methodologies...
that employ environmentally friendly catalysts such as TEMPO or TEMPO combined with molecular oxygen is one of the most important goals in oxidation chemistry today. Many exciting results are expected in the field of transition-metal-free oxidation reactions by using TEMPO- or its derivatives as catalysts.

This review highlights the broad array of TEMPO- or its derivatives-catalyzed reactions that have been developed in recent years, and it also clarifies key challenges that lie ahead. For example, the efficient regeneration of the oxoammonium salt from the hydroxylamine is still a challenge. Specifically, metal-free benign oxidations, which are important for industry, are highly desirable. Moreover, we believe that many transition-metal-mediated processes requiring an external oxidant can be conducted with the use of TEMPO or its derivatives. In view of the ever-increasing level of activity in this rapidly developing area, one can reasonably expect that solutions to these challenges will quickly emerge in the near future. Most recently, Studer and co-workers have documented the potential of the nitroxide-mediated Pd-catalyzed oxidative Heck arylation for the stereoselective synthesis of tetrasubstituted triarylated olefins [83]. Importantly, other oxidants such as Cu(OAc)$_2$, AgOAc, benzoquinone, and PhI(OAc)$_2$ did not work well.

If the rapid pace of advances in this field over the past ten years is a representative guide, it seems reasonable to expect that these challenges will be addressed and many new opportunities in TEMPO- or its derivatives-catalyzed reactions will be realized. Although not discussed in this review, it is important to mention that TEMPO- or its derivatives have been used successfully as spin probes in biochemistry [1c]. Many new developments are also expected in that field. Moreover, TEMPO- or its derivatives have been used successfully as building blocks for the preparation of organic magnets. In addition, the organic radical 2-azaadamantane-N-oxyl (TEMPO derivative) as table and highly reactive redox mediator in a dye-sensitized solar cell (DSSC) is reported [86].

Two other future trends are easy to predict: the development of enantioselective TEMPO-catalyzed reactions and functionalization of C-H bonds. Thus, we hope with this review to have provided appropriate background for such developments and the encouragement to synthetic organic chemists to employ these valuable methodologies in organic synthesis and medicinal chemistry.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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ABBREVIATIONS

acac = Acetylacetone
ABNO = 9-azabicyclo[3.3.1]nonane N-oxyl
AZADO = 2-azaadamantane N-oxyl
Bu = Butyl
Bn = Benzyl
Bipy = 2,2'-bipyridine
Boc = tert-butoxycarbonyl
BPO = Benzoyl peroxide
BzI = Benzyl
Cbz = Benzoxycarbonyl
DABCO = 1,4-diazabicyclo[2.2.2]octane
DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene
DCE = Dichloroethane
DEAD = Diethyl azodicarboxylate
DH$_2$ = Dimethylglyoxime
DME = Ethylene glycol dimethyl ether
DMP = Dess-Martin periodinane
HFIP = Hexafluoroisopropyl
LAH = Lithium aluminium hydride
MPEG = Poly(ethylene glycol) monomethyl ether
MS = Molecular sieve
NHC = N-heterocyclic carbene
NMI = N-methylimidazole
PAA = Peracetic acid
phen = 1,10-phenanthroline
PS = Polymer Supported
TMODP = 4,4'-trimethylenebipyridine
TMS = Trimethylsilyl
$p$-TsCl = 4-methylbenzene-1-sulfonyl chloride
$p$-TsOH = 4-methylbenzenesulfonic acid
SBA-15 = Amorphous SiO$_2$ (Santa Barbara Amorphous)
SNMP = Silica coated magnetic nanoparticles
UHP = Urea hydrogen peroxide

REFERENCES


