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Transition-metal-free Oxidative Coupling Reactions for the Formation of C–C and C–N Bonds Mediated by TEMPO and its Derivatives

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Abstract: The application of nitroxides for the development of new synthetic methods and their implementation in polymer chemistry, material science and beyond is one of the major research topics in our laboratory in the institute of organic chemistry at the WWU Münster. This short review focuses on our recent progress towards nitroxide-based transition-metal-free oxidative coupling reactions. The demand for organic surrogates for transition metals in such transformations is in our eyes unquestionable, since environmental and economic issues have become progressively more important in recent years. For this purpose, the 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO) is shown to be a highly efficient oxidant for the homo- and cross-coupling of *Grignard* reagents. This powerful C–C bond forming strategy allows the generation of conjugated polymers from bifunctional *Grignard* reagents. Moreover, cross-coupling of alkynyl *Grignard* compounds and nitrones can be accomplished under aerobic atmosphere with catalytic amounts of TEMPO. It is also shown that TEMPO-derived *N*-oxoammonium salts can act as suitable oxidants for formation of C–N bonds between non-preactivated benzoxazoles and secondary amines under metal-free conditions.

Keywords: CH-amination · *N*-Oxoammonium salts · Oxidative coupling · 2,2,6,6-Tetramethylpiperidine-*N*-oxyl radical (TEMPO) · Transition-metal-free

Introduction

Ever since their discovery at the very beginning of the last century, transition metal-mediated C–C and C–N bond forming processes have been evolved to be of fundamental importance as synthetic tools in modern organic chemistry. Along these lines, versatile transition metal-based catalysts have been developed over the last four decades which show outstanding performance in Heck, Kumada, Suzuki, Stille, Negishi and Sonogashira C–C coupling reactions.[1] Almost simultaneously, the pioneering work of Buchwald and Hartwig resulted in the feasibility of efficient generation of C–N bonds by using transition metal catalysis.[2] In recent years, significant efforts have been made in extending the substrate scope towards non-preactivated starting materials within the emerging field of CH-activation/functionalization.[3]

Even though the importance and indispensability of these accomplishments is unquestionable, the displacement of transition metal catalysts by organic surrogates is often desirable in industrial processes. This is readily rationalized by the relatively high costs, the contingent toxicity and the demanding removal of transition metals from final industrial products. Especially in pharmaceutical commodities rigorous restrictions for trace amounts of metals in the ppm-level range account for expensive purification methods.

Consequently, the development of efficient transition-metal-free protocols for the generation of C–C and C–N bonds displays an important field of research with remarkable growth over the last few years. A divergent array of synthetic strategies for C–C bond formation which utilize for example radical chemistry, photochemical activation, activated arylhalides or transition-metal-free versions of traditional coupling reactions has been developed in this regard.[4,5]

Likewise progress has been made in establishing transition-metal-free CH-amination reactions. In particular iodine in combination with *tert*-butylhydroperoxide, hypervalent halogens[6] in stoichiometric amount or combinations thereof have very recently been demonstrated to be excellent oxidants to perform, for instance, nitrene insertion reactions,[7] intra-[8] and intermolecular[9,10] oxidative aminations onto activated CH bonds or other transformations[11] even in the absence of any transition metal.

Despite their ample application as catalysts in alcohol oxidations and in other established nitroxide-based oxidation processes,[12] TEMPO, TEMPO-derivatives and their corresponding *N*-oxoammonium cations ($TEMPO^+$) have only very recently been exploited in transition-metal-free oxidative coupling reactions.[13]

This minireview will specifically focus on our own contributions to C–C[14–17] and C–N[18] bond forming oxidative coupling processes using these oxidants under transition-metal-free conditions.

Oxidative C–C Bond Forming Reactions

A striking breakthrough in the field of transition-metal-free oxidative C–C bond formation was achieved by Knochel and Mayr in their pioneering studies towards the use of an organic oxidant for the homo-coupling of organomagnesium species.[19] Inspired by these exciting results, we

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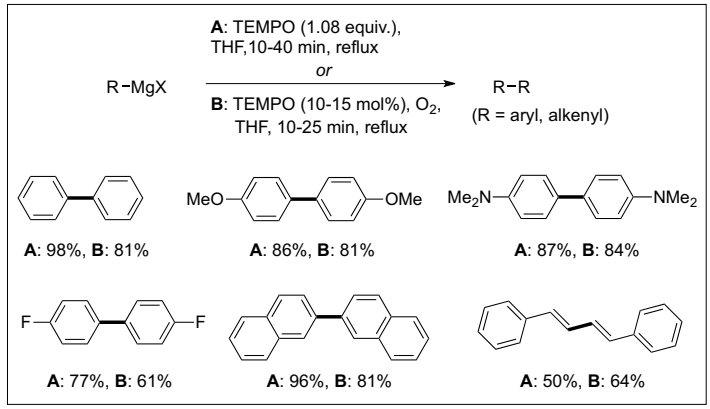
turned our attention to the development of related oxidative coupling protocols based on nitroxides as commercially available oxidants. It is important to mention that alkyl organometallic compounds R-M (M = Li, Mg, Zn, Cu, Sm, Ti) were shown to react with two equivalents of TEMPO to the corresponding alkoxyamines.[20] The organometallic species is first oxidized by TEMPO to the corresponding C-radical which in turn is trapped by TEMPO to form the alkoxyamine. However, the successful application of TEMPO or any other nitroxide for the homocoupling of aryl-, alkenyl-, and alkynylmagnesium compounds was not investigated until 2008.[14] In our initial paper in this field we showed that aryl *Grignard* reagents bearing electron-rich as well as electron-deficient substituents react highly efficiently to the corresponding biphenyls which were isolated in high yields (Scheme 1, method A).

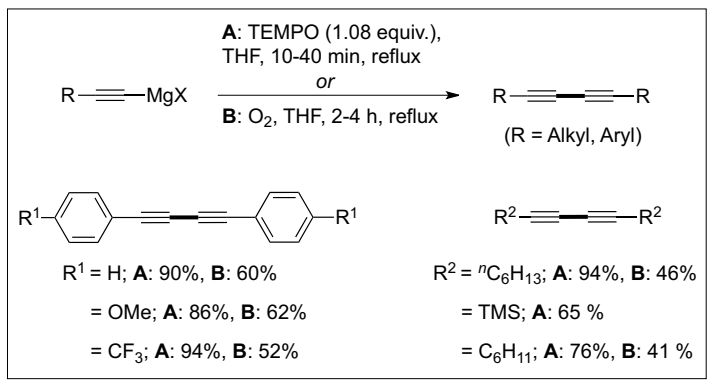
Moreover, we found that TEMPO is also an excellent oxidant for the transition-metal-free homocoupling of vinyl- and alkynyl-Mg compounds. Importantly, TEMPOMgX formed as a side product in these reactions could readily be reoxidized to TEMPO upon treatment with dioxygen. On the basis of this observations we established a TEMPO-catalyzed (10–15 mol%) aerobic homocoupling protocol for aryl- and alkenyl-*Grignard* reagents (Scheme 1, method B). Surprisingly, alkynyl-Mg compounds could be smoothly homocoupled to the corresponding bisalkynes even in the absence of any nitroxide catalyst (Scheme 2, B).

The mechanism of these TEMPO-mediated couplings is currently not fully understood. However, since reaction of *Grignard* **1** with TEMPO afforded exclusively the homocoupling product **2** in high yield (76%, not even a trace of alkoxyamine **3** derived from a *5-exo-trig* radical cyclization was detected), free aryl radicals can be excluded as intermediates (Scheme 3).

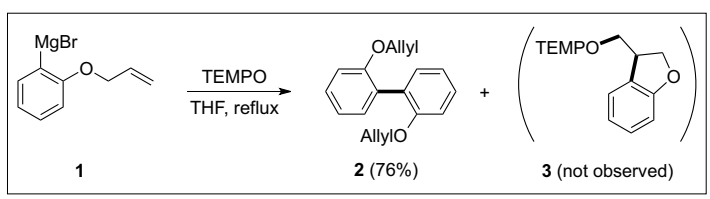
Encouraged by the excellent results on TEMPO-mediated homocoupling reactions of *Grignard* reagents, we decided to apply this new method to polymer synthesis, where a near quantitative yield for each individual coupling step is mandatory in order to achieve high molecular weights for the targeted polymer. Indeed, transition-metal-free multiple homocoupling of 2,7-di-magnesated fluorenes with TEMPO provided polyfluorenes with a mean molecular weight of up to 9000 g/mol (Scheme 4).[15] Our method also allowed formation of conjugated copolymers containing the bisalkyne or the bisethene moiety as alternating building blocks with the fluorene unit in the polymer backbone. Absorption and emission spectra showed that the polymers were formed highly regular without any defect sites.



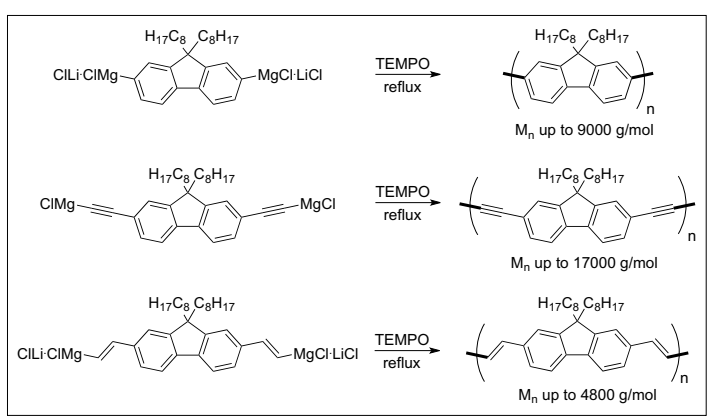
Scheme 1. Oxidative homocoupling of aryl- and alkenyl-*Grignard* reagents with TEMPO/O_2.



Scheme 2. Oxidative homocoupling of alkynyl *Grignard* reagents with TEMPO/O_2.



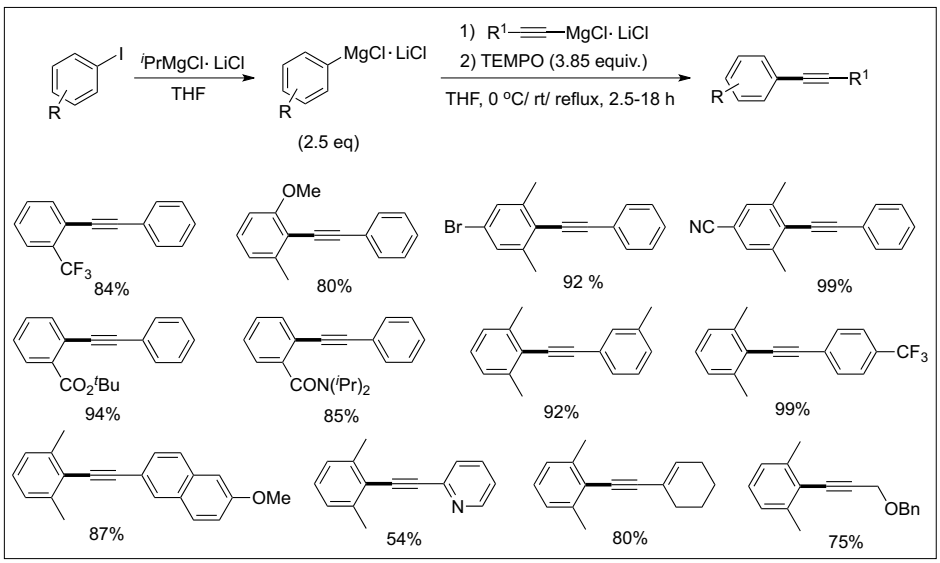
Scheme 3. Free radical probe.



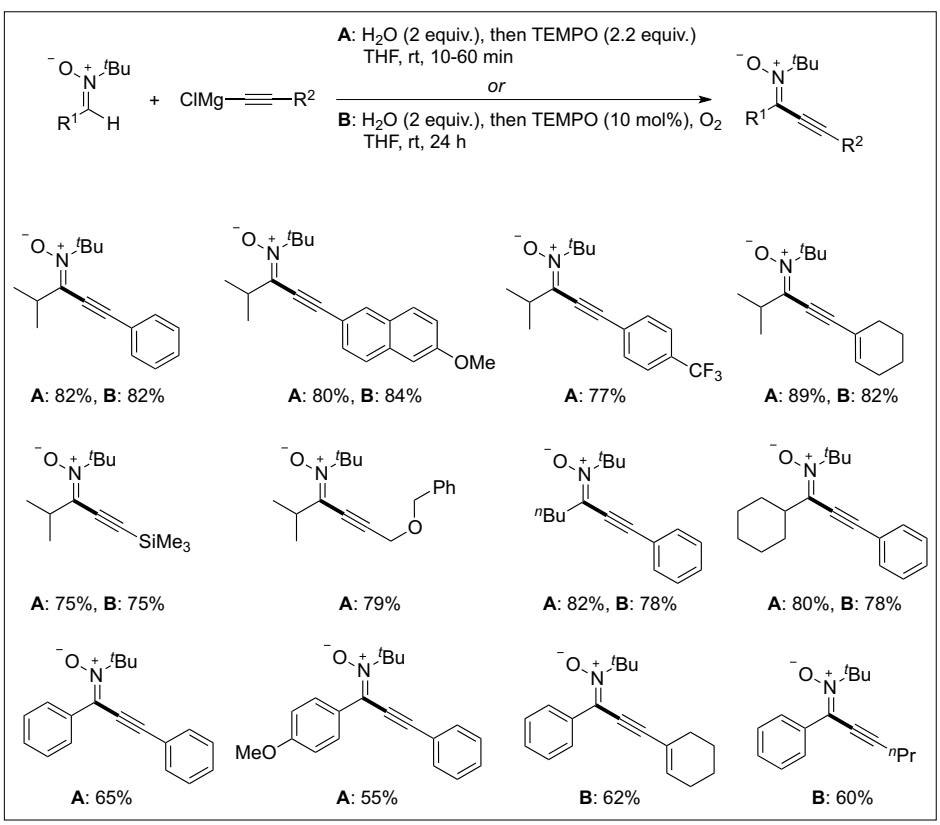
Scheme 4. TEMPO-mediated synthesis of conjugated polymers by using bis-*Grignard* reagents as monomers.

During these investigations, we observed that TEMPO-mediated homocoupling of aryl *Grignard* reagents occurs far faster compared to the analogous reaction with alkynyl *Grignard* reagents. Moreover, we also noted that sterically demanding aryl *Grignards* either react slowly or do not react at all with TEMPO. Consequently, we anticipated the possibility to realize cross-coupling reactions between aryl- and alkynyl-*Grignard* reagents to form *Sonogashira*-type products by using TEMPO as an oxidant in absence of any transition metal.[16] Indeed, these coupling reactions could be successfully conducted on various structurally and electronically diverse aryl- and alkynyl-*Grignard* reagents. Several aryl-alkynyl, pyridyl-alkynyl and less reactive alkyl-alkynyl Mg-derivatives were found to be suitable substrates for our cross-coupling process (Scheme 5). Importantly, functional groups such as esters, amides and cyanides were compatible with the conditions applied.

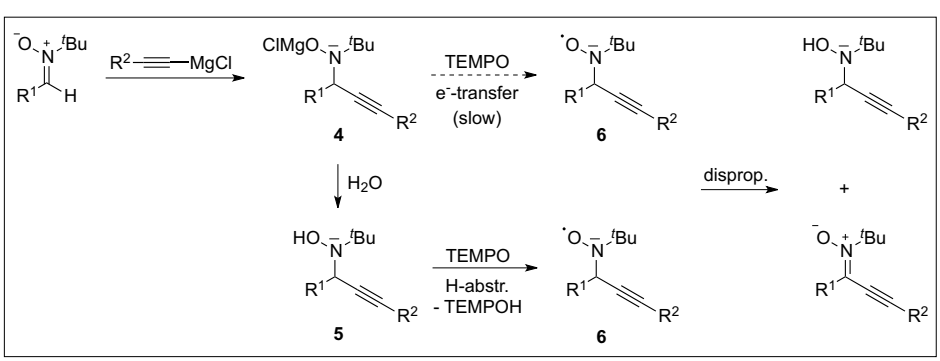
Conjugated internal alkynes occur in numerous natural products, pharmaceuticals, and organic materials.[21] C–C bond formation *via* nucleophilic addition of alkynyl metal compounds to unsaturated electrophiles is a classical approach for alkynylation. Along these lines, we have



Scheme 5. Oxidative cross-coupling of aryl- and alkynyl-*Grignard* reagents by using TEMPO as an oxidant.



Scheme 6. Oxidative cross-coupling of various Mg-acetylides with various nitrones using TEMPO/O_2.



Scheme 7. Proposed mechanism for oxidative coupling between nitrones and alkynyl *Grignard* reagents.

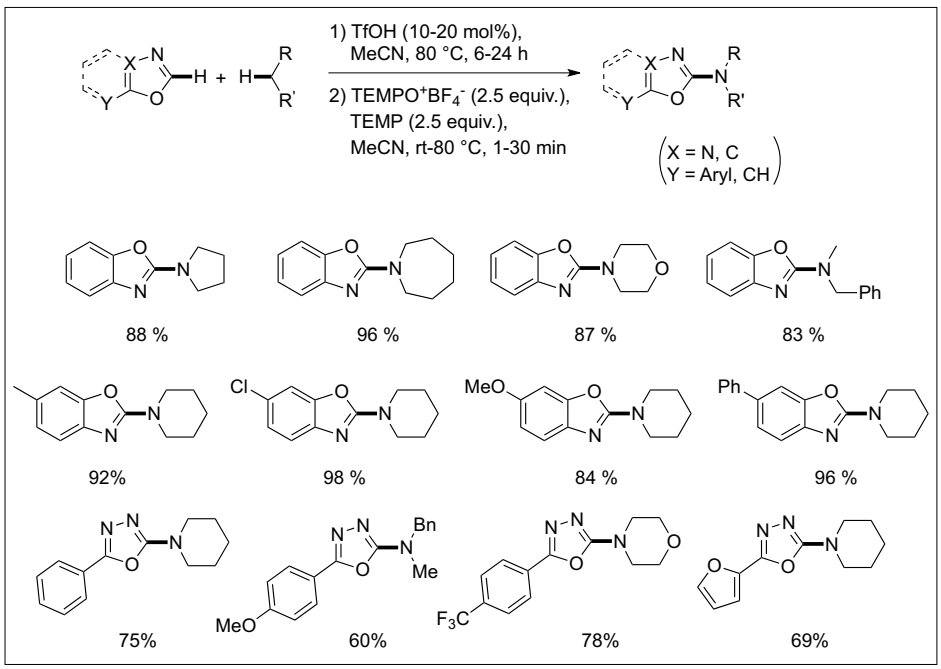
recently reported first examples of transition-metal-free oxidative cross-coupling reactions between nitrones and alkynyl *Grignard* reagents with TEMPO as an environmentally benign and commercially available organic oxidant.[17] Moreover, we showed that these cross-couplings can be conducted by using catalytic amounts of TEMPO in combination with O_2 as a terminal oxidant. These coupling reactions worked well on various aliphatic and aromatic nitrones with various electronically and structurally diverse alkynyl *Grignard* reagents (Scheme 6).

Our proposed mechanism consists of initial addition of an alkynyl *Grignard* to a nitrone to give Mg-intermediate **4** which undergoes hydrolysis (2 equiv. water were used) to give hydroxylamine **5**. Nitroxide **6** is generated by H-transfer from **5** to TEMPO. Subsequent disproportionation eventually provides the alkynylated nitrone along with hydroxylamine **5** which then undergoes H-transfer to TEMPO to give **6** (Scheme 7).

Oxidative C–N Bond Forming Reactions

The synthesis of C(2)-aminated azoles from non-preactivated precursors has recently gained considerable attention in the community. Such compounds are important as core structures in various pharmaceutically active compounds.[10,22] Many reactions for formation of C(2)-aminated azoles occur *via* formation of organometallic intermediates by CH or NH insertion. An alternative approach uses transition metal-mediated oxidative rearomatization of amine/azole adducts, which are obtained as intermediates upon *Lewis* or *Brönsted* acid activation of the heterocycle in the presence of an amine. We found that the TEMPO-derived *N*-oxoammonium tetrafluoroborate performs very well as an organic substitute for transition metals for oxidative rearomatization of amine/azole adducts.[18,23] Hence, various 2-aminobenzoxazoles were obtained using a one-pot two-step protocol starting with non-prefunctionalized substrates under metal-free conditions.[10] Best results were obtained upon first stirring the heteroarene with the amine in acetonitrile in the presence of catalytic amounts of trifluoromethanesulfonic acid (triflic acid, TfOH; Scheme 8). The thus formed adducts were then readily oxidized with TEMPO$^+BF_4^-$ in the presence of base to give the corresponding 2-aminobenzoxazoles in high yields.

Upon increasing the catalyst loading and reaction time, 2-arylated 1,3,4-oxadiazoles could also be functionalized with this approach. The corresponding aminated heterocycles were isolated in good yields.



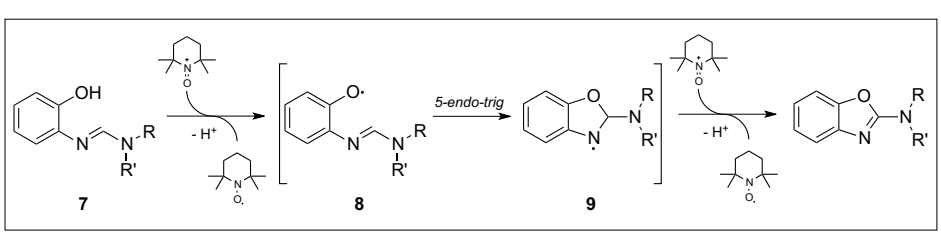
Scheme 8. Conditions and selected examples for metal-free oxidative amination with $TEMPO^+BF_4^-$ as oxidant.

Our proposed mechanism, which is supported by ^1H NMR studies, involves the formation of amidine adduct **7** upon Brönsted acid activation of the starting benzoxazole, followed by a concerted or stepwise SET/deprotonation sequence to the *N*-oxoammonium cation. The resulting phenoxyl radical **8** subsequently cyclizes in a *5-endo-trig* fashion to deliver aminyl radical **9**. Finally, **9** undergoes oxidation by another equivalent of $TEMPO^+$ to afford the desired final product (Scheme 9).

We also demonstrated the potential of our novel method for medicinal chemistry by successful synthesis of a pharmaceutical active compound *via* late-stage CH amination of a benzoxazole derivative with a complex secondary amine.[18]

Conclusion

We have presented an overview on the applicability of nitroxides for development of new synthetic methods and their implementation for the buildup of complex molecular scaffolds. Our recent results convincingly document that oxidative transition-metal-free C–C and C–N bond forming reactions are feasible with the help of nitroxide-based oxidants, thus paving a new avenue as a fascinating complementary tool to the traditional transition metal-catalyzed cross-coupling reactions. To this endeavor, we have reported on a highly efficient TEMPO-mediated homocoupling of aryl-, alkenyl- and alkynyl-*Grignard* reagents and successfully applied this methodology to the synthesis of conjugated polymers. Moreover, aryl- and alkynyl-*Grignard* reagents can be cross-coupled to give the corresponding *Sonogashira*-type products by using this strategy. It is obvious that a comprehensive understanding of detailed mechanistic aspects of these transformations is of great importance for further improvement of their efficacy and generality. Along these lines, we have successfully demonstrated that nitrones can be cross-coupled with alkynyl *Grignards* by using catalytic amount of TEMPO and dioxygen to give the corresponding alkynylated nitrones which can further be transformed into biologically important isoxazoles.[17] Moreover, a valuable metal-free route towards highly important aminated heterocycles such as 2-aminobenzoxazoles and 2-amino-5-aryl-1,3,4-oxadiazoles using $TEMPO^+BF_4^-$ as an oxidant has been introduced. Follow up studies to realize these conversions by the use of catalytic amounts of oxidant under aerobic atmosphere and to extend the substrate scope towards other heterocycles, *e.g.* thiazoles or imidazoles are currently ongoing in our laboratory.



Scheme 9. Suggested mechanism for oxidative amination of benzoxazoles.

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