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Paper

TEMPO-Mediated Homocoupling of Aryl Grignard Reagents: Mechanistic Studies

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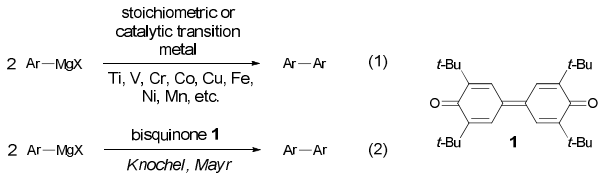
The mechanism of the TEMPO mediated oxidative homo-coupling of aryl Grignard reagents is investigated in detail by experimental and computational studies. Experimental data reveal that the nitroxide-mediated homocoupling reaction of aryl Gignard reagents does not occur via free aryl radicals. Evidence for the presence of biaryl radical anions as intermediates in the coupling reaction is provided. It is also shown that PhMgPh under bromide free conditions in the presence of TEMPO does not undergo homocoupling. However, upon addition of $MgBr_2$, C-C bond formation smoothly proceeds documenting the important role of the bromide anions in the oxidative homocoupling. DFT calculations show that an intramolecular electron transfer to a Mg-complexed TEMPO ligand with subsequent biaryl formation in a dimeric complex is viable and in agreement with experimental reaction conditions.

Introduction

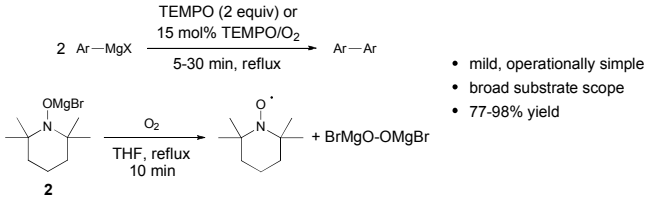
Transition metal mediated/catalyzed oxidative homo-coupling reactions of aryl-metal reagents are among the most powerful and efficient synthetic tools in modern organic synthesis for the construction of symmetrical biaryls.[1] Among other aryl metal compounds, arylmagnesium derivatives have been successfully used in such homo-coupling reactions. In these C-C bond forming processes, a formal one electron oxidation of the two reacting arylmagnesium components is necessary. Various high-valent transition metals in stoichiometric amounts have been successfully applied as oxidants to mediate these coupling reactions.[2] On the other hand, transition metals as catalysts in combination with a terminal oxidant have been successfully used for the homo-coupling of arylmagnesium compounds (Scheme 1, eq. 1): the research groups of Hayashi[3a] and Cahiez[3b] independently developed an efficient iron-catalyzed homocoupling of aryl Grignard reagents using 1,2-dihaloethanes as oxidants. Soon after, Cahiez et al. demonstrated two more general, mild and economic iron- and manganese-catalyzed homo-coupling protocols using molecular oxygen as terminal oxidant[3c] and Severin et al. disclosed homocoupling of aryl-Mg-derivatives with Fe and Co-based catalysts using nitrous oxide as a terminal oxidant.[3d] However, there are only few reports on transition-metal-free oxidative homocoupling of organomagnesium compounds using organic oxidants as mediators.[4] For example, Knochel, Mayr and co-workers showed that arylmagnesium reagents undergo efficient transition-metal-free homo-coupling in the presence of a stoichiometric amount of 3,3',5,5'-tetra-*tert*-butyldiphenoquinone (**1**) as an organic oxidant (Scheme 1, eq. 2).[4c]



Scheme 1 Oxidative homo-coupling of aryl-Mg reagents.

In 2008,[5c] we documented that a broad range of aryl-Mg compounds efficiently homocouple in the presence of a stoichiometric amount of 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO)[5a,b] as an environmentally benign and commercially available organic oxidant. Importantly, TEMPOMgBr **2**, the only byproduct in these clean coupling reactions was readily reoxidized to TEMPO with dioxygen in refluxing THF (Scheme 2). We also showed that such reactions, albeit in slightly lower yields, can be conducted with 15 mol% of TEMPO by using dioxygen as cheap terminal oxidant. Moreover, we found that the method is equally well applicable to the homo-coupling of alkenyl- and alkynyl Grignard reagents and we also successfully applied this homo-coupling process to the preparation of various conjugated polymers.[5e] More recently, an efficient transition-metal-free Sonogashira-type cross-coupling reaction between aryl and alkynyl Grignard reagents using TEMPO as an oxidant was disclosed.[5f] Despite these achievements, the mechanism of TEMPO mediated oxidative coupling reactions has not been understood and detailed mechanistic studies are lacking. It is obvious that a comprehensive understanding and systematic elucidation of mechanistic aspects are of great importance for further improvement of the efficacy of these processes which should lead to broader synthetic applicability. Herein, we wish to disclose the findings of our experimental and computational

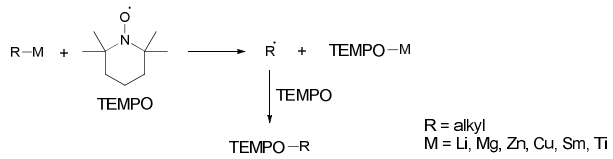
studies on the mechanism of the oxidative homo-coupling of aryl Grignard reagents in the presence of TEMPO.



Scheme 2 Homo-coupling of aryl-Mg compounds using TEMPO as an organic oxidant.

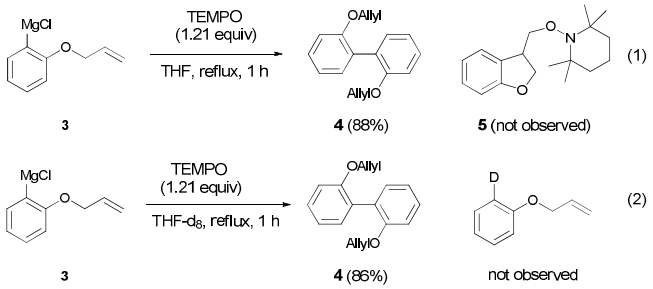
Results and Discussion

The reactivity of TEMPO towards alkyl organometallic compounds R-M (M = Li, Mg, Zn, Cu, Sm, Ti) is well documented.[6] In these reactions, one equivalent of TEMPO oxidizes the organometallic species to the corresponding carbon-centered radical, which is subsequently trapped by a second equivalent of TEMPO to eventually provide an alkoxyamine derivative (Scheme 3).



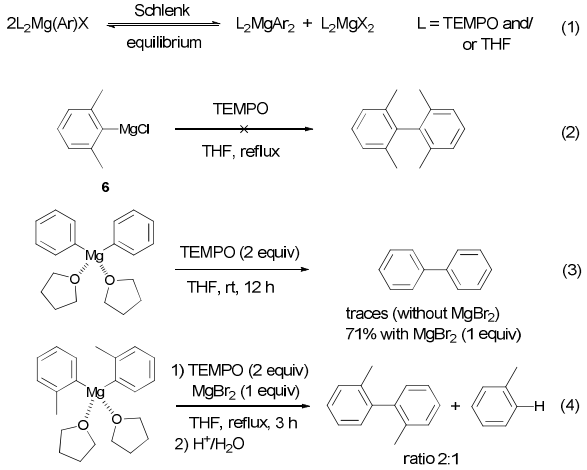
Scheme 3 Reactivity of TEMPO towards alkyl organometallic compounds.

Since aryl radicals are higher in energy than alkyl radicals, initial oxidation of the aryl-Mg compound to the corresponding free aryl radical by TEMPO is less likely. Indeed, phenyl-TEMPO derived from trapping of a phenyl radical with TEMPO in the homocoupling of PhMgBr was not identified upon treating a THF solution of PhMgBr with TEMPO. We ran other experiments to address the question of the intermediacy of a free aryl radical and reacted the Grignard reagent **3**, a radical clock substrate, with TEMPO under typical homocoupling conditions. The reaction exclusively afforded the homocoupling product **4** in a high yield (88%) and alkoxyamine **5** derived from a *5-exo-trig* radical cyclization was not identified (Scheme 4, eq. 1). Since the corresponding aryl radicals are known to undergo very fast *5-exo*-cyclization (k_c = 6.3 × 10^9 s^{-1} at 30 °C),[7] the absence of any products derived from the cyclized radical strongly indicates that free aryl radicals are not involved in the homocoupling reaction. The absence of free aryl radicals as intermediates was further supported by conducting the reaction in fully deuterated THF (THF-d_8). Mass spectrometric analysis revealed that *ortho*-deuterophenyl allyl ether was not formed when aryl Grignard reagent **3** was reacted with TEMPO using THF-d_8 as solvent. The corresponding homocoupling product **4** was isolated in 86% yield (Scheme 4, eq. 2). Based on these experiments it can be concluded that free aryl radicals are not involved in the coupling reaction.



Scheme 4 Oxidative coupling of **3** in THF and THF-d_8 using TEMPO as an oxidant.

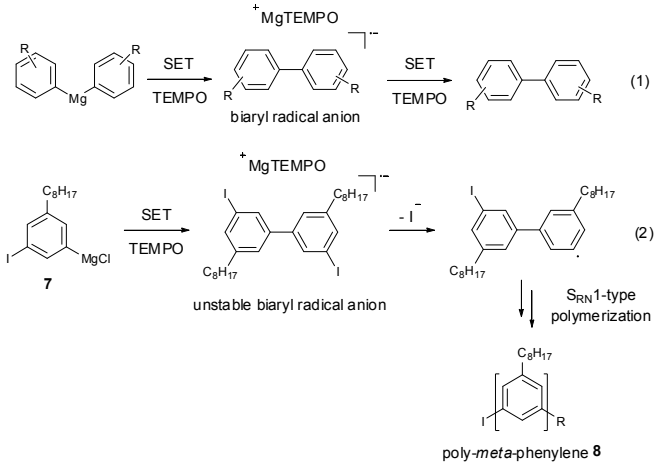
We assumed that the homo-coupling reaction is likely proceeding via diarylmagnesium species ($MgAr_2$) and not via ArMgX compounds. Therefore, the "Schlenk equilibrium"[8] between the aryl Grignard reagents (L_2ArMgX) and the corresponding diorganomagnesium species/magnesium dihalides in THF solution should preferably lie on the right hand side for these systems to undergo homocoupling (Scheme 5, eq. 1). To test this hypothesis we subjected aryl-Mg compound **6** to the homocoupling conditions either at room temperature or at reflux and did not observe the coupling product. The failure of the reaction is probably due to the steric congestion of the aryl substituent which impedes formation of the Ar_2Mg in the equilibrium (Schlenk equilibrium likely lies completely to the left side, eq. 2). Indeed, it was reported in the literature that oxidative homocoupling of aryl Grignard reagents with *p*-benzoquinone as oxidant works efficiently in an ionic liquid due to the high concentration of $MgAr_2$ in the ionic liquid whereas the analogous reaction in THF did not occur.[4d]



Scheme 5 Proposed "Schlenk equilibrium" in the TEMPO-mediated homo-coupling of aryl Grignard reagents and homocoupling starting with the $Ph_2Mg(THF)_2$-complex and with the *o*-$Tol_2Mg(THF)_2$-complex.

To further support our assumption that homocoupling proceeds via the diarylMg-species we prepared the $Ph_2Mg(THF)_2$-complex according to a literature procedure by $MgBr_2$ precipitation from the Grignard solution (see Supporting Information).[9a-d] The $Ph_2Mg(THF)_2$-complex was treated with TEMPO (2 equiv) in THF and reaction was followed by gas chromatography. To our surprise, only traces of the targeted biphenyl homocoupling product were identified (Scheme 5, eq 3). According to GC analysis various side products were formed. We repeated the experiment in the presence of $MgBr_2$

(1 equiv). GC analysis of the reaction mixture revealed, that clean homocoupling occurred showing that $MgBr_2$ is necessary for successful oxidative homocoupling to occur (Scheme 5, eq 3). In a preparative experiment biphenyl was formed in 71% yield (eq. 3). We ran the same experiment also on *o*-$Tol_2Mg(THF)_2$-complex[9e] in the presence of $MgBr_2$ (1 equiv) and found that coupling is not occurring at room temperature. However, upon increasing reaction temperature to 80 °C we noted slow TEMPO-mediated homocoupling. After 3 hours in refluxing THF we identified around 66% of product along with hydrolysed *o*-$Tol_2Mg(THF)_2$ (ratio 2:1 as determined by GC analysis, eq. 4).



Scheme 6 TEMPO-mediated oxidative homo-coupling via biaryl radical anions.

Since free aryl radicals are not involved and the coupling in the presence of $MgBr_2$ likely proceeds via diarylmagnesium compounds we assumed that oxidation must occur via single electron transfer from a Ar_2Mg species as a reductant which somehow interacts with TEMPO and $MgBr_2$ formally leading to a Mg-complexed aryl radical which can then react intramolecularily with the anionic aryl substituent of the complex leading to a Mg-complexed biaryl radical anion as an intermediate (Scheme 6, eq. 1). Note that the intermolecular addition of aryl-Grignard compounds with aryl radicals was recently suggested.[10] To experimentally prove whether biaryl radical anions might be involved in the TEMPO-mediated Mg-aryl coupling we took advantage of the knowledge that I-substituted aryl radical anions are short lived species which undergo very fast iodide fragmentation to the corresponding aryl radicals.[11] We therefore speculated that the homo-coupling of aryl Grignard reagents with I-substituted aryl-Mg-derivatives should give the corresponding biaryl radical anions which in turn will fragment I^- to generate aryl radicals. These reactive species can then further react in intermolecular fashion with another arylMgX-derivative. In fact we could show,[12] that the TEMPO-mediated oxidation of aryl-MgCl **7** initiated a polymerization process to give poly-*meta*-phenylene **8** in a process we called $S_{RN}1$-type[13] polymerization (Scheme 6, eq. 2). The successful initiation of the polymerization via homocoupling of **7**, and the fact that all polymers obtained bear at least one I-atom (see structure 8) strongly support our assumption that biaryl radical anions occur as intermediates in these TEMPO-mediated homocoupling reactions.

To further investigate the aryl Grignard coupling process we turned our attention towards computational studies to get an explicit insight into the mechanism of this homo-coupling reaction. Our study was performed with density functional theory (DFT), the hybrid functional B3LYP[14] was chosen for all calculations, using a flexible triple-zeta basis set (def2-TZVP)[15], an atom pairwise dispersion correction (D3)[16] was added. A continuum model (COSMO)[17] was used to obtain single point energies including solvation effects. All calculations were done with the Turbomole[18] program.

In dialkyl ether solutions, Grignard reagents may form dimers or equilibrate with the diaryl magnesium species (Schlenk equilibrium).[4d,8,19] In both cases, biaryl formation is an intramolecular process. We have investigated the two model reactions of free $MgPh_2$ and $(MgBrPh)_2$ with TEMPO in the presence of THF and identified intermediates and transition structures. The Mg was assumed to prefer a tetrahedral coordination in the reactant structures.

Looking into the reaction of monomeric diphenyl magnesium first (Figure 1), we find that the complex $Ph_2Mg(THF)(TEMPO)$ (**9-Cpx1**) having one ether molecule replaced by TEMPO is only slightly less stable than $Ph_2Mg(THF)_2$ and should thus be present as a minor fraction in the reaction mixture. We have also identified a transition structure (**9-TS1**) of C-C bond formation and a preceding intermediate (**9-Int1**) in which an electron was transferred from the two aryl groups to TEMPO, which then binds to Mg as an anionic ligand. This is reflected in the short Mg-O/N bonds, the elongated Mg-C1/C1' bonds, and also the N-O bond is significantly elongated from 1.277 to 1.444 Å as expected for a reduced TEMPO moiety.

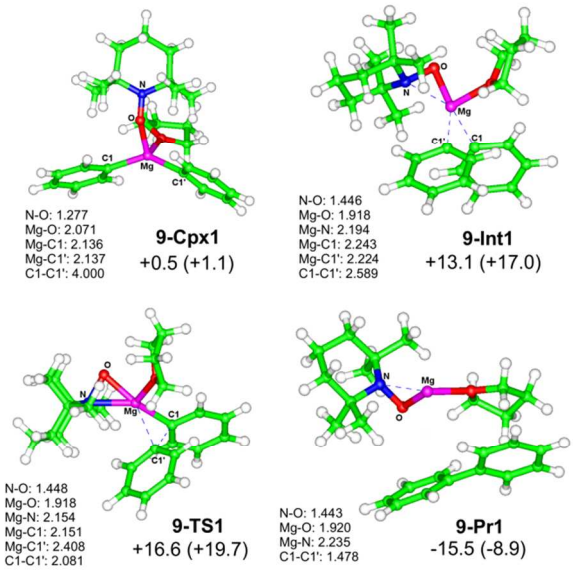


Figure 1 Intermediates and transition structure of C-C bond formation in the oxidative aryl coupling of $Ph_2Mg(THF)(TEMPO)$. Energies in kcal/mol are given relative to the $Ph_2Mg(THF)_2$ complex and free TEMPO. (B3LYP-D3/def2-TZVP, in brackets: COSMO solvation model for THF, ε=7.58). Bond lengths are given in Å.

The electronic barrier towards biaryl formation from **9-Int1** is less than 3 kcal/mol (with the solvent model), and the overall process is exothermic – even though the initial product **9-Pr1** is coordinatively unsaturated and will be further deactivated.

It is noteworthy that we were not able to identify a $Mg^{2+}/(Ph\text{-}Ph)^{\bullet-}$ (Mg-complexed biphenyl radical anion) as the first intermediate of the aryl coupling, but rather a Mg(I) species, which is not in close contact with the neutral biphenyl. Displaying the spin density of **9-Pr1** (Figure 4) clearly indicates the nature of the Mg(I) radical cation.[20] Although this is remarkable in its own right, we do not consider **9-Pr1** as an important intermediate, since it will rapidly transfer the electron to a second TEMPO to complete the reaction.

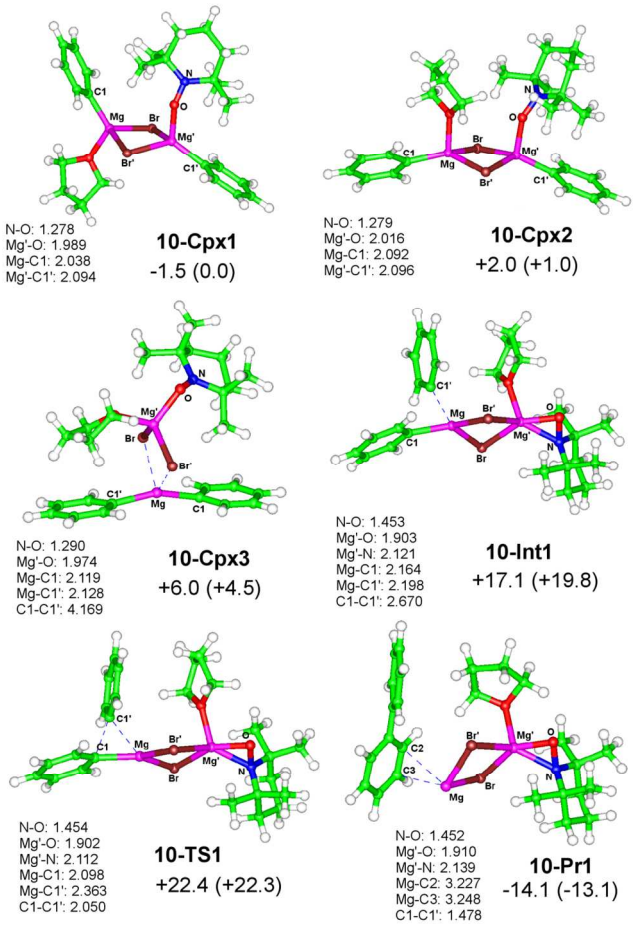


Figure 2 Intermediates and transition structure of C-C bond formation in the oxidative aryl coupling of $(PhMgBr)_2(THF)(TEMPO)$. Energies in kcal/mol are given relative to the $(PhMgBr)_2(THF)_2$ complex and free TEMPO. (B3LYP-D3/def2-TZVP, in brackets: COSMO solvation model for THF, ε=7.58). Bond lengths are given in Å.

Since we knew from the experimental studies that $MgBr_2$ is necessary for successful coupling to occur, we expected a second mechanism considering $(MgBrPh)_2(THF)_2$ as starting point to show a lower activation energy (Figure 2). TEMPO first interacts with $(MgBrPh)_2(THF)_2$ by replacing one ether molecule in a process which is exothermic (-1.5 kcal/mol) or isoenergetic, when a solvent model is employed (**10-Cpx1**). This dimeric complex may rearrange in several ways by ligand migrations (e.g. **10-Cpx2**). A complex with the substructure necessary for intramolecular biphenyl formation (Ph_2Mg) is higher in energy (+4.5 kcal/mol) than the other isomers (**10-Cpx3**). This can easily be rationalized by the unfavourable charge distribution, leaving the second Mg dication less closely bound to the counteranions. The successive biphenyl formation resembles the reaction of monomeric $MgPh_2$: the initial product of electron transfer (**10-Int1**) requires a small barrier to form the C-C bond (5.3 or 2.5 kcal/mol, in the gas phase and in the solvent, respectively). The Mg-C/C' bonds in the transition structure **10-TS1** are shorter than in **9-TS1**, presumably due to the less crowded coordination sphere around the cation in the former one. Again, the overall formation of **10-Pr1** is exothermic, and its further reduction of a second TEMPO molecule will easily occur.

However, as compared to the Br-free process presented in Figure 1, activation energy is higher by 2.5 kcal/mol for the $(MgBrPh)_2(THF)_2$-case. This does not agree with the experimental findings and therefore we considered a third mechanism starting from complex **10-Cpx4** where a TEMPO ligand bridges the two Mg-atoms (Figure 3). This complex was found to be lower in energy than **10-Cpx3**. The replacement of bromide with the TEMPO radical in the Mg_2X_2 unit is energetically favourable by almost 2 kcal/mol. The intermediate which is formed in the ET step, **10-Int2**, is stabilized by more than 14 kcal/mol by the incorporation of the nitroxide anion instead of bromide into the ring. This also lowers the activation energy of the total reaction, which is determined by the C-C bond formation step (**10-TS2**). The barrier of only 10 kcal/mol should be overcome even at low temperatures.

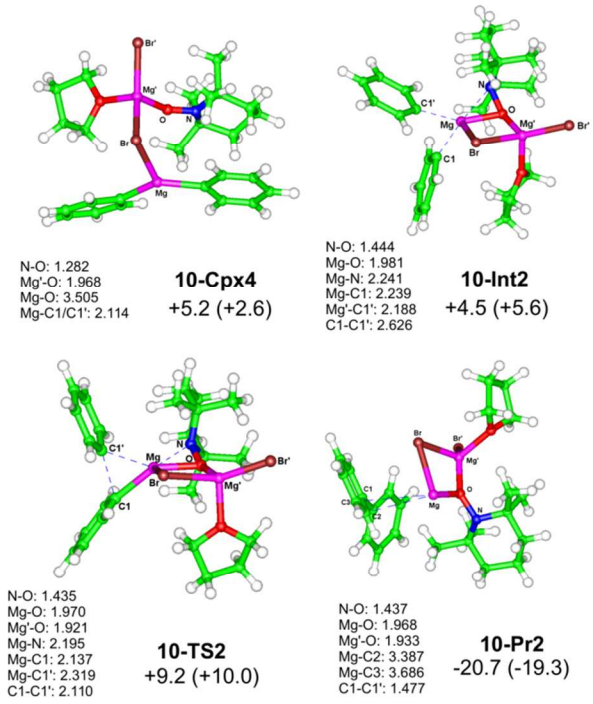


Figure 3 Intermediates and transition structure of C-C bond formation in the oxidative aryl coupling of $(PhMgBr)_2(THF)(TEMPO)$, with TEMPO acting as a bridging fragment in the Mg_2X_2 core. Energies in kcal/mol are given relative to the $(PhMgBr)_2(THF)_2$ complex and free TEMPO. (B3LYP-D3/def2-TZVP, in brackets: COSMO solvation model for THF, ε=7.58). Bond lengths are given in Å.

An inspection of the calculated spin densities of the major structures in the three investigated reactions (Figure 4) provides further insight into the mechanism: the first SET leads to the formation of a $Mg^{2+}(Ph/Ph)^{\bullet-}$ substructure (**9-Int1/10-Int2**) in which charge and spin are delocalized between the two sp^2 orbitals of the phenyl groups, constituting a partly ionic, three-

center bond with Mg. A similar structure was found in calculations for the $S_{RN}1$-type substitution of the iodide in iodobenzene with phenyl-MgBr.[10b] During the C-C bond formation, this delocalized electron is initially transferred into the π system of one of the aryl groups (**9-TS1/10-TS2**). However, during the release of Ph_2, a second SET leads to a Mg(I) cation (**9-Pr1**/**10-Pr2**), thus facilitating the replacement of the uncharged biaryl product with a polar molecule such as THF or TEMPO.

A quantitative determination of the barrier of the SET process (**9-Cpx1 → 9-Int1, 10-Cpx4 → 10-Int2**) is beyond the scope of our study. Since the geometry required to transfer the electron is probably very similar to the SET product, in which the two ipso carbon atoms C1/C1' are in closer contact and the nitrogen atom of TEMPO coordinates Mg, we expect that the SET barrier will not exceed the relative energy of **9-Int1/10-Int2** by more than a few kcal/mol. With this assumption, we arrive at an overall electronic barrier of the biaryl formation from $MgPh_2$ of ca. 10-15 kcal/mol for the dimer process (Figure 3).

Comparing all three possible reaction paths we have presented, it is most likely that the reaction occurs via a dimer of MgBrPh in which TEMPO is coordinated by two Mg cations. One of the metal ions acts as the center mediating the Ph-Ph coupling. The presumably low equilibrium concentration of $(MgBrPh)_2(THF)(TEMPO)$ is supposed to be sufficient to allow the fast coupling reaction to occur under the experimental conditions.

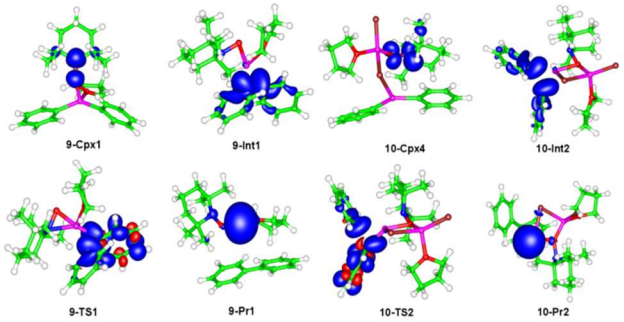


Figure 4 Spin densities (B3LYP-D3/def2-TZVP, 0.003 a.u. isosurfaces) of the intermediate structures in the formation of biphenyl from MgPh2(THF)(TEMPO) (left) and (MgBrPh)2(THF)(TEMPO) (right).

Conclusions

We have experimentally shown that the TEMPO-mediated aryl-Grignard homocoupling reaction does not proceed via free aryl radicals. Typical radical clock experiments to proof the aryl radical character of an intermediate did not show any indication for their occurrence. However, we found strong evidence that biaryl radical anions are intermediates in these homocoupling processes. A necessity for successful homocoupling is the population of the biaryl-Mg species in the Schlenk equilibrium. Moreover, we found that the $Ph_2Mg(THF)_2$-complex does not undergo oxidative homocoupling in the presence of TEMPO, which shows that additional $MgBr_2$ is necessary for successful coupling to proceed. DFT-studies revealed that homocouling can occur easily from the dimeric $Aryl_2MgBr_2Mg(THF)(TEMPO)$ species. Coupling processes are induced by initial single electron transfer from the $Aryl_2Mg$-moiety to the noninnocent TEMPO ligand rendering the ligand to become an anionic ligand. C-C coupling is then occurring leading to an intermediate which is best described as a neutral biphenyl which acts as a weak ligand for a Mg(I)-species. Since we have experimental indications of the biaryl radical anion character of such intermediates we assume that the Mg(I)-atom is close enough to the biaryl moiety to allow intramolecular back electron transfer to the weakly bound biaryl ligand. The reaction is completed by a second electron transfer to another TEMPO equivalent. This reaction will be highly exothermic and will not contribute to the barrier of the overall reaction. Therefore, we did not further analyze that second electron transfer process.

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Notes and references

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TOC text and graphic:

The mechanism of TEMPO mediated oxidative homo-coupling of aryl Grignard reagents to biphenyls is investigated in detail by experimental and computational studies.