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COMMUNICATION

Evidence for the Interaction Between ^tBuOK and 1,10-Phenanthroline to form the 1,10-Phenanthroline Radical Anion: A Key Step for the Activation of Aryl Bromides by Electron Transfer

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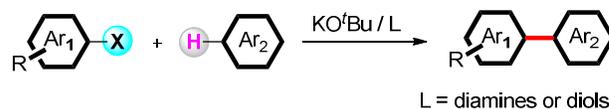
Hong Yi,^a Anny Jutand,^{b*} and Aiwen Lei^{a*}

Electron paramagnetic resonance and electrochemistry are used to evidence the interaction between 1,10-phenanthroline (Phen) and KO^tBu to form 1,10-phenanthroline radical anion Phen^{•-} and ^tBuO[•] radical via an inner-sphere electron transfer. In addition, electrochemistry is also used to explain the formation of aryl radical from aryl bromide via outer-sphere electron transfer from the key intermediate Phen^{•-}.

Transition-metal-catalyzed direct arylation of unactivated aromatic C–H bonds have been developed¹ constituting one of the predominant strategies for the synthesis of biaryls that are key components in many biologically active natural products, pharmaceuticals and polymers.² However, the inherent toxicity of most transition metals demands an alternative approach. To sustain a green environment, efforts have been made to develop transition-metal-free approaches for the formation of biaryls.³

The transition-metal-free, base-promoted homolytic aromatic substitution (BHAS) recently emerged, providing a new horizon for synthetic chemistry in the preparation of biaryls,⁴ avoiding the use of costly palladium catalysts. Pioneered by Itami and co-workers, the KO^tBu promoted coupling of electron-deficient nitrogen heterocycles with aryl iodides was reported in 2008.⁵ Later on, some of us and other groups reported transition-metal-free couplings of arenes with aryl halides, in the presence of KO^tBu and catalytic diamine or diol (Scheme 1).⁶ The mechanism of this base-promoted homolytic aromatic substitution (BHAS) is considered to be a radical process (Studer and Curran).⁷ Tentative mechanisms propose the generation of biaryls *via* diamines or diols interaction with *tert*-butoxide (^tBuO⁻) to form aryl radicals from aryl halides at the origin of the direct arylation of arenes. However, the understanding of the interaction of KO^tBu and simple diamines and the subsequent formation of the aryl radical is still unclear.⁸ Herein, it is established by means of electron paramagnetic

resonance (EPR) and cyclic voltammetry (CV) that the interaction between 1,10-phenanthroline (Phen) and KO^tBu generates the 1,10-phenanthroline radical anion Phen^{•-} and ^tBuO[•] via an inner-sphere electron transfer. In addition, electrochemistry was used to explain the formation of aryl radical from aryl halide via an outer-sphere electron transfer from Phen^{•-}.



Scheme 1. KO^tBu promoted direct Ar-H bond arylation

Evidence for the Interaction of KO^tBu and 1,10-Phenanthroline by EPR and Cyclic Voltammetry

EPR experiments. The interaction between phen and KO^tBu was investigated by EPR in order to characterize the formation of radical species. Our initial effort focused on the reaction of 1,10-phenanthroline (0.1 mmol) with KO^tBu (0.4 mmol) under N₂ atmosphere using toluene as the solvent. A strong EPR signal was observed (red line in Fig 1), while no EPR signal was detected in the absence of 1,10-phenanthroline (black line in Fig 1). The EPR signal revealed that a radical was formed with a *g* value of 2.0033. When changing toluene by benzotrifluoride, one EPR signal was observed with the same *g* value (blue line in Fig 1) but was wider than that in toluene due to optimization of the EPR parameters to get a good spectrum. Therefore, the above EPR results evidence an electron transfer process between KO^tBu and Phen.

No EPR signals were observed in the mixture of 1,10-phenanthroline and KO^tBu in CH₃CN and 1,4-dioxane but to our delight, a strong EPR signal with ten peaks was observed for the mixture of 1,10-phenanthroline and KO^tBu in DMF (Fig

1a), while no EPR signal was detected in the absence of 1,10-phenanthroline. This results indicated that 1,10-phenanthroline played an important role in this transformation.

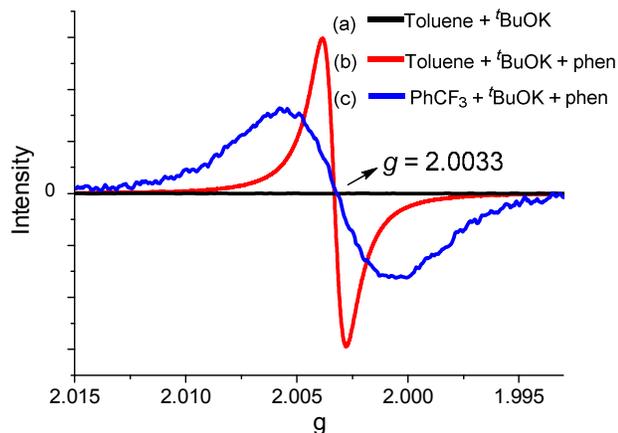


Figure 1. Electron paramagnetic resonance (EPR) spectra (X band, 9.4 GHz) of: (a) $t\text{BuOK}$ (0.4 mmol) in 2.0 mL toluene at 100 °C, the black line; (b) Phen (0.1 mmol) and $t\text{BuOK}$ (0.4 mmol) in 2.0 mL toluene at 100 °C, the red spectrum; (c) Phen (0.1 mmol) and $t\text{BuOK}$ (0.4 mmol) in 2.0 mL benzotrifluoride at 100 °C, the blue spectrum.

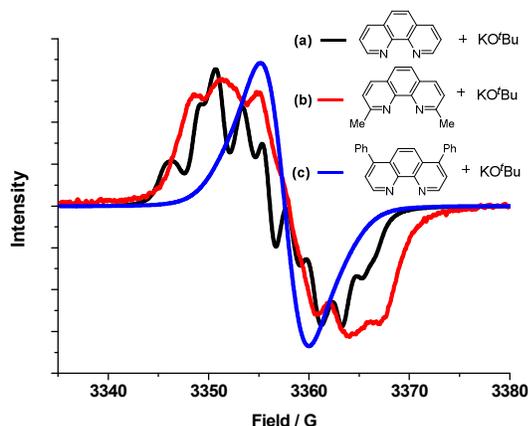
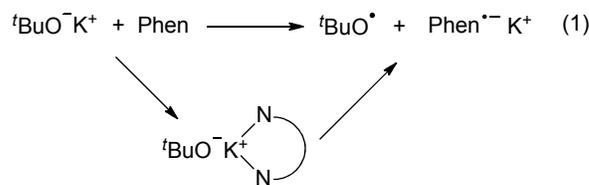


Figure 2. The electron paramagnetic resonance (EPR) spectra (X band, 9.4 GHz) of: (a) 1,10-phenanthroline (0.1 mmol) and $t\text{BuOK}$ (0.4 mmol) in DMF (2 mL) at 100 °C, the black line; (b) 2,9-dimethyl-1,10-phenanthroline (0.1 mmol) and $t\text{BuOK}$ (0.4 mmol) in DMF (2 mL) at 100 °C, the red line; (c) 4,7-diphenyl-1,10-phenanthroline (0.1 mmol) and $t\text{BuOK}$ (0.4 mmol) in DMF (2 mL) at 100 °C, the blue line.

The reaction of 2,9-dimethyl-1,10-phenanthroline and 4,7-diphenyl-1,10-phenanthroline with $t\text{BuOK}$ was also monitored by EPR. An EPR signal was detected for 2,9-dimethyl-1,10-phenanthroline (six peaks, Fig 2b) and for 4,7-diphenyl-1,10-phenanthroline (single peak, Fig 2c). These results indicated that the radical observed in Fig 2a was related to 1,10-phenanthroline. A π -type radical was formed with the electron located on the aromatic ring. Because of the stacking of π -type radical with toluene or benzotrifluoride, a single EPR peak was formed using toluene or benzotrifluoride as solvents. Therefore, the above EPR results indicates that the interaction between

1,10-phenanthroline and $t\text{BuOK}$ generates the 1,10-phenanthroline radical anion $\text{Phen}^{\cdot-}$ (Eq (1) in Scheme 2).



Scheme 2. Electron transfer between Phen and $t\text{BuOK}$ in DMF

Cyclic Voltammetry experiments. $t\text{BuO}^-$ (from $t\text{BuOK}$) exhibited in DMF, an oxidation peak at $E_{\text{ox}}^{\text{p}} = +0.10$ V vs SCE (Fig S8). The process was irreversible due to the instability of the $t\text{BuO}^{\cdot}$ radical during the time scale of the CV (Eq 2).



1,10-Phenanthroline (Phen, 4.0 mM) exhibited two successive reduction peaks: $E_{\text{R1}}^{\text{p}} = -2.06$ V and $E_{\text{R2}}^{\text{p}} = -2.23$ V (Fig 3a, Eqs 3,4 in Scheme 3).^{9a} The first reduction peak current at R_1 slowly decreased in the presence of increasing amounts of $t\text{BuOK}$, which attested a chemical reaction between Phen and $t\text{BuOK}$ (Eq 1). The high potential gap $\Delta E = 2.16$ V between the oxidation peak potential of $t\text{BuO}^-$ (+0.10 V) and the first reduction peak potential of Phen (-2.06 V) excluded a fast outer-sphere electron transfer.¹⁰ The complexation of Phen by K^+ must bring Phen closer to $t\text{BuO}^-$ and allowed a more favoured inner-sphere electron transfer within the intermediate complex $[t\text{BuO}^-\text{K}^+ \leftarrow \text{Phen}]$ (Scheme 2).¹¹

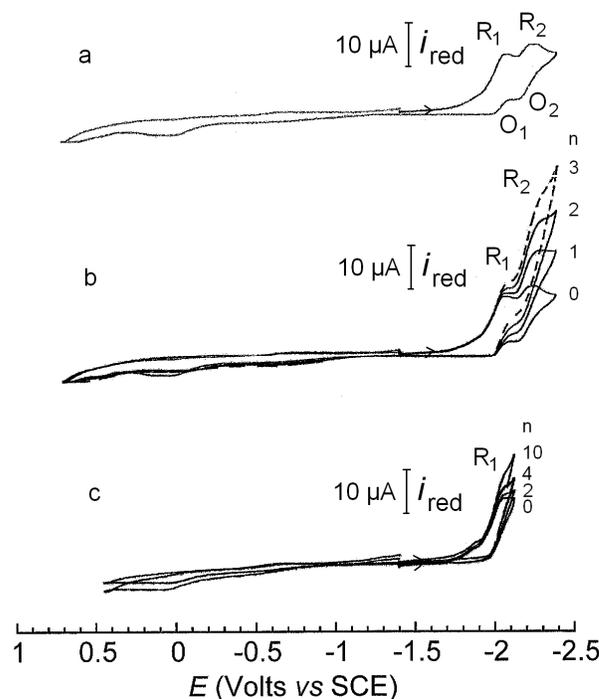
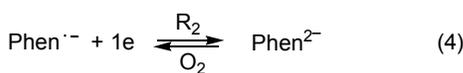
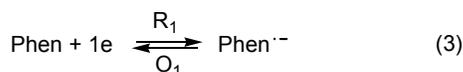


Figure 3. Cyclic voltammetry performed in DMF containing $n\text{Bu}_4\text{NBF}_4$ (0.3 M) at a gold disk electrode ($d = 1$ mm) at the scan rate of $0.5 \text{ V}\cdot\text{s}^{-1}$ at 22 °C. a) Reduction of 1,10-phenanthroline (4 mM). b) Reduction of 1,10-phenanthroline (4.0 mM) in the presence of $n = 1, 2, 3$ equivalents

of PhBr as indicated. c) Reduction of 1,10-phenanthroline (4.0 mM) in the presence of $n = 2, 4, 10$ equivalents of PhBr.

Evidence of the Reduction of PhBr Mediated by 1,10-Phenanthroline by Cyclic Voltammetry (Redox Catalysis)

As above stated, Phen exhibited two successive reduction peaks R_1 and R_2 (-2.06 V and -2.23 V respectively) whereas PhBr alone is reduced at a more negative potential ($E_{R0}^p = -2.67$ V, Fig S9a).^{9b} When the reduction of Phen (4 mM in DMF) was performed in the presence of PhBr (1 equiv), the peak current of R_1 was not significantly affected but that of R_2 increased (almost double, Fig 3b) whereas the reduction peak of PhBr was no longer observed (Fig S9c). The peak current of R_2 increased again when increasing the amounts of added PhBr ($n = 1$ to 3 equiv) (Fig 3b) and thus became catalytic. This means that the radical anion $\text{Phen}^{\bullet-}$ electrogenerated at R_1 and reduced at R_2 to Phen^{2-} was regenerated in the diffusion layer in the presence of PhBr. In other words, the dianion Phen^{2-} generated at R_2 activated PhBr by electron transfer to generate $\text{PhBr}^{\bullet-}$ and $\text{Phen}^{\bullet-}$ (Eq 5).¹² The low potential gap $\Delta E_2 = 0.50$ V between the reduction peak potential of PhBr (-2.67 V) and the oxidation peak potential of Phen^{2-} ($E_{O2}^p = -2.17$ V) allowed an outer-sphere electron transfer (SET) to PhBr.¹⁰ The reduction peak of PhBr was not observed up to $n = 3$ equiv of PhBr, due to the redox catalysis. But it started to be detected at -2.72 V at higher PhBr loading because the time scale of the CV (scan rate: 0.5 Vs^{-1}) was too short to allow a full conversion of PhBr to $\text{PhBr}^{\bullet-}$ by Phen^{2-} .



Redox catalysis

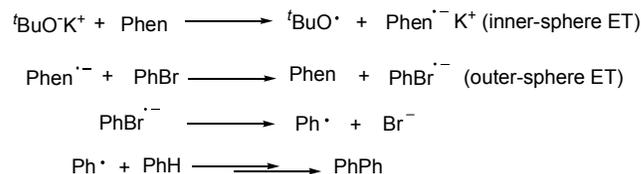


Scheme 3. Electrochemical reduction of Phen (Eqs 3,4) and redox catalysis for the reduction of PhBr (Eqs 5,6)

A catalytic peak was also observed for the first reduction process at R_1 (Fig 3c) but higher amounts of PhBr were required to observe a significant increase of the current at R_1 (compare Fig 3b and 3c). This means that $\text{Phen}^{\bullet-}$ (generated by the reduction of Phen at R_1) also activated PhBr by electron transfer to generate $\text{PhBr}^{\bullet-}$ and Phen (Eq 6), leading to the observed catalytic current at R_1 . However, the redox catalysis by $\text{Phen}^{\bullet-}$ was less efficient than that involving Phen^{2-} , in agreement with the higher potential gap $\Delta E_1 = 0.67$ V between the reduction peak potential of PhBr (-2.67 V) and the oxidation peak potential of $\text{Phen}^{\bullet-}$ ($E_{O1}^p = -2.00$ V). Indeed, lower ΔE , faster the outer-sphere electron transfer.¹⁰ The reaction of $\text{Phen}^{\bullet-}$ with PhBr was also observed by EPR. The EPR signal of $\text{Phen}^{\bullet-}$ in toluene (Fig 1) almost disappeared upon addition of PhBr (4 equiv) (Fig S7). Therefore, it is

established that 1,10-phenanthroline plays the role of redox catalyst for the reduction of PhBr to $\text{PhBr}^{\bullet-}$ via $\text{Phen}^{\bullet-}$; ${}^t\text{BuO}^-\text{K}^+$ alone being unable to activate PhBr by electron transfer.

A mechanism is proposed in Scheme 4 for the arylation of benzene. A first activation by electron transfer takes place between ${}^t\text{BuO}^-\text{K}^+$ and Phen that generates $\text{Phen}^{\bullet-}$ in a slow process. $\text{Phen}^{\bullet-}$ activates PhBr in a faster outer-sphere electron transfer to generate the radical anion $\text{PhBr}^{\bullet-}$ which is a source of a phenyl radical in the solution after cleavage of its C-Br bond.



Scheme 4. Mechanism for the direct arylation of benzene. For the mechanism of the last multistep reaction see ref 7.

In conclusion, electron paramagnetic resonance and cyclic voltammetry have been used to characterize the interaction between 1,10-phenanthroline (Phen) and KO^tBu to form 1,10-phenanthroline radical anion, $\text{Phen}^{\bullet-}$ and ${}^t\text{BuO}^{\bullet}$ radical. In addition, cyclic voltammetry was used to explain the formation of aryl radical from aryl bromide by single-electron transfer from $\text{Phen}^{\bullet-}$. Therefore, Phen serves as a relay for the reduction of phenyl bromide to the phenyl radical via its radical anion $\text{Phen}^{\bullet-}$ (outer-sphere electron transfer).

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Notes and references

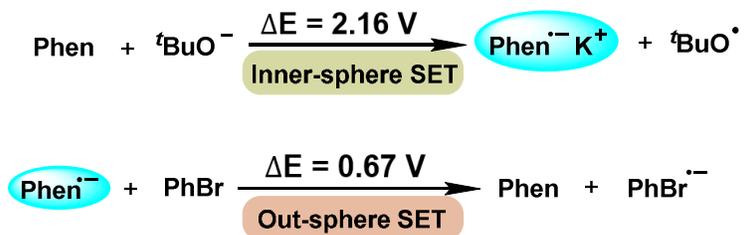
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† Electronic Supplementary Information (ESI) available: Experimental part for EPR and CV experiments. See DOI: 10.1039/c000000x/

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12. The detailed explanation is put in the Supporting information 2.6.



In this work, electron paramagnetic resonance and electrochemistry are utilized to evidence the interaction between 1,10-phenanthroline (phen) and KO^tBu to form 1,10-phenanthroline radical anion phen^{•-} and ^tBuO[•] radical via an inner-sphere electron transfer. In addition, electrochemistry is also used to explain the formation of aryl radical from aryl bromide via outer-sphere electron transfer from the key intermediate phen^{•-}.