SET-Induced Biaryl Cross-Coupling: An $S_{RN1}$ Reaction
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ABSTRACT: The SET-induced biaryl cross-coupling reaction is established as the first example of a Grignard $S_{RN1}$ reaction. The reaction is examined within the mechanistic framework of dissociative electron transfer in the presence of a Lewis acid. DFT calculations show that the reaction proceeds through a radical intermediate in the form of an Mg ion-radical cage, which eludes detection in trapping experiments by reacting quickly to form an MgPh$_2$ radical anion intermediate. A new mechanism is proposed.

The cross-coupling of aryl metal reagents with aryl halides is a widely used method for the synthesis of biaryl compounds, which are of great interest in the preparation of bioactive molecules, natural products, and polymers.$^{1-5}$ This reaction is most commonly performed by transition-metal catalysis, but there is significant interest in transition-metal-free cross-coupling reactions due to advantages in ease of purification as well as lower toxicity and cost.$^{6-9}$ While various advances in the transition-metal-free synthesis of biaryls have thus been reported,$^{10-13}$ Hayashi and co-workers have demonstrated an important example by coupling easily accessible aryl magnesium bromides with aryl iodides and bromides as illustrated in Scheme 1.$^{14}$

The mechanism of this reaction is unclear. Based on the reactivity differences between aryl bromides and iodides,$^{14}$ the reaction was originally classified as a nucleophilic radical chain ($S_{RN1}$) reaction where the aryl halide (ArX) is activated via single-electron transfer (SET). However, there is little precedent for an organometallic reagent acting as the nucleophile in an $S_{RN1}$ reaction.$^{15}$

Further questions about the mechanism of the reaction arose based on a radical clock reaction using 2-(3-butenyl)phenyl iodide ($k_{cyclization} = 5 \times 10^8$ s$^{-1}$ at 50 °C).$^{16}$ The coupling product was formed in 90% yield with essentially none of the radical-trapping products.$^{17}$ Hayashi and co-workers have also reported a coupling reaction between arylmagnesium bromides and alkenyl halides that is suggested to occur via the same mechanism. In this reaction, retention of the stereochemistry of the double bond is observed.$^{18}$ These results were interpreted as evidence that the reaction proceeds without the formation of a radical intermediate. This mechanism, shown in Scheme 2, postulates a direct coupling of ArX$^+$ and ArMgBr. Such an $S_{RN2}$ mechanism has been discussed extensively in the literature and is unlikely due to charge repulsion, orbital arguments, or expected radical anion lifetime.$^{19-21}$ In agreement with these previous findings, we were unable to locate stationary points associated with an $S_{RN2}$ mechanism during the studies described here. Instead, all optimizations led to a dissociation of the carbon–iodide bond and the structures described below.

Given these unresolved questions and the high level of interest in the reaction, we undertook a computational study and propose a new mechanism that is consistent with the

Scheme 1. Reaction Conditions for the SET-Induced Biaryl Cross-Coupling Reaction$^{14}$

Scheme 2. Proposed Mechanism for the SET-Induced Biaryl Cross-Coupling Reaction$^{17}$

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available experimental results. We started our investigation by considering the interaction of the THF-complexed Grignard reagent with the phenyl iodide radical anion. It was shown previously that aryl halides generally have sufficiently low energy π* orbitals to form a stable π-radical anion (π-RA) species upon accepting an electron. A calculation of the activated complex for the analysis of the electronic structure of the resulting phenyl iodide π-RA shows that the SOMO has nodes at the ipso- and para-carbons relative to the halide, indicating that no interactions can take place at these positions. The lowest energy structures, o-1 and m-1, with the Mg atom localized at the ortho- and meta-positions of the phenyl iodide π-RA, respectively, are shown in Figure 1 (see Figure S1 in the Supporting Information) and located a transition structure at a C1–I distance of 2.72 Å. The calculated barrier of 1.0 kcal/mol is significantly lower than the experimentally determined activation energy for the radical clock cyclization reaction of approximately 3.5 kcal/mol at 50 °C.16 The experimentally observed lack of cyclization product is therefore in agreement with the computational results.

In addition to the lower barrier, the analysis of the electronic structure of the product 7 (see the spin plots in Figure S3 of the Supporting Information) shows that the radical is delocalized across both aryl groups to form a MgBrIPh2 radical anion. This delocalization process lowers the spin density and should make trapping of the radical difficult as there are few radical clock reactions fast enough to compete with it. Conversely, the complete dissociation of the aryl radical away from the Mg ion...
There are two possible pathways for the conversion of the MgBrIPh$_2$ radical anion to the aryl coupling product. To study the pathway where ET occurs after the coupling reaction, the distance between C1 and C1’ was scanned, and a transition structure 8 was located at a C1–C1’ distance of 2.19 Å as shown in Figure 3. The product biaryl radical anion 9 is complexed with MgBrI, and the barrier is predicted to be 0.7 kcal/mol. In the alternative pathway, where the ET occurs from MgBrIPh$_2$, the barrier is predicted to be 0.7 kcal/mol. In the alternative pathway, where the ET occurs after the coupling reaction, the distance between C1 and C1’ was scanned, and a transition structure 8 was located at a C1–C1’ distance of 2.19 Å as shown in Figure 3. The product biaryl radical anion 9 is calculated to form a MgBrIPh$_2$ radical anion through the MgBrIPh$_2$ radical anion.

**Scheme 3. Proposed Mechanism of the SET-Induced Biaryl Cross-Coupling Reaction**

Phenylmagnesium bromide and phenyl iodide were used to model the reaction. The Grignard reagent was represented as a monomer with various degrees of THF coordination based on the hypothesis that the presence of THF breaks up higher order aggregates of the Grignard reagent. Because the focus of this work is on the coupling mechanism and the energy of the activated complex for the electron-transfer step cannot be calculated reliably with the methods used here, the phenyl iodide radical anion was used as the starting point. It should be noted that the initiation and propagation electron-transfer steps are likely to be the rate-determining steps, accounting for the high temperatures and long reaction times necessary for the reaction.

All calculations were carried out with the Gaussian 09 (G09) suite of programs. Full geometry optimizations of stationary points were calculated at the M06/6-31+g(d) for all other atoms. The integral equation formalism polarizable continuum (IEFPCM) solvation model with solvation correction from the IEFPCM model. Energies reported for stationary points are Gibbs free energies calculated at 298 K and 1 atm of pressure. Frequency calculations were used to characterize the structures either as a ground state (zero negative frequencies) or as a transition state (exactly one negative frequency). Intrinsic reaction coordinate (IRC) calculations were performed for transition states to ensure they connect the correct reactant and product. In the case of the radical delocalization process, the potential energy surface (PES) around the transition state (TS) is limiting and necessary for the “spontaneous initiation” element of the mechanism.

The mechanism proposed here may also be applicable to other biaryl cross-coupling reactions involving arylmetal reagents and could be envisioned as an S$_{RN1}$ reaction with an additional π-Lewis acid to stabilize the π-RA independent of the reacting Grignard reagent. Finally, this mechanistic understanding of the reaction can provide a starting point for the asymmetric synthesis of chiral biaryl systems, a class of compounds that has found intense interest in the past few years.

**EXPERIMENTAL SECTION**

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very flat so IRC calculations were unsuccessful. However, manual distortion along the imaginary mode in either direction followed by full optimization led to the correct reactant and product. For the PES in Figure 2, a series of constrained optimizations were performed, where the C1−I distance was constrained. Only the electronic energy is reported for these calculations.

**ASSOCIATED CONTENT**

**Supporting Information**
Details of the computational methods used, additional references and the complete ref 46, additional analysis as referred to in the text, and coordinates of the characterized stationary points are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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**Notes**
The authors declare no competing financial interest.

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