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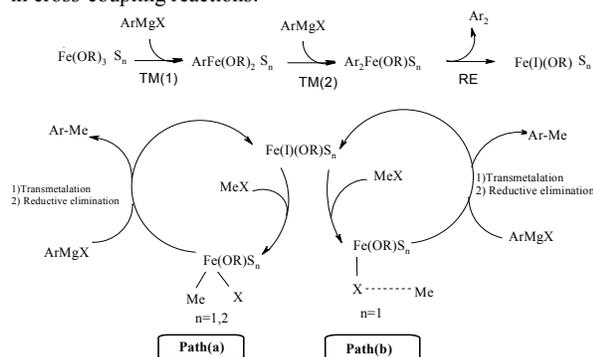
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New Insights into Mechanism of Iron-Catalyzed Cross-Coupling Reactions[†]

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Abstract The mechanism of the iron-catalyzed cross-coupling of alkyl halides with aryl Grignard reagents is studied by a combination of GC monitoring and DFT calculation. Herein, we investigate two possible reaction pathways, the regular Oxidative Addition (OA) pathway and Atom Transfer (AT) pathway, that might occur in the rate-limiting step. The computational studies revealed that the AT pathway performs energetically easier than the regular OA pathway.

The use of transition metal catalysis to form new carbon-carbon bonds has emerged as a powerful tool in organic synthesis.^{1,2} Transition metal-catalyzed cross-couplings have made great progress and have been used in a vast number of applications, but the use of palladium, nickel, zinc, and copper is generally expensive and these metals are toxic. Recently, the interest in iron-catalyzed coupling reactions has increased significantly because of its environmentally benign character, low cost, and low toxicity.³⁻⁵ Kochi initially suggested an Fe(I) species as a potential intermediate in the iron-catalyzed cross-coupling reaction that is converted to Fe(III) through oxidative addition. Subsequently, transmetalation and reductive elimination processes reproduce the active Fe(I) catalyst.⁶⁻¹⁰ On the other hand, Furstner and co-workers suggested the involvement of Fe(-II)/Fe(0) species, due to the low activity of used Fe(I) complexes containing Cp ligands.¹¹ Here, we describe how the reaction could be controlled by Fe(I) as a lowest kinetically reasonable oxidation state in iron-catalyzed cross-coupling reactions. Furthermore, we demonstrate the mechanistic role of Fe(I) species in cross-coupling reactions.¹²



Scheme 1. Proposed mechanisms for Oxidative addition (path a) and Atomic transfer (path b) pathways with one and/or two coordinated solvents.

Our recent studies and computations on precatalytic stages of Fe(I) species in iron-catalyzed cross-coupling reactions showed that formation of Fe(I) complex occurred before rate-limiting step.^{12,13} Subsequently, the current study investigates possible reaction pathways that might occur during the rate-limiting step and not during the stages that might have happened prior to that step. Moreover, we believe the active catalyst is an Fe(I) species that undergoes a fairly standard catalytic cycle involving oxidative addition or atomic transfer and transmetalation, in either order, followed by a reductive elimination (scheme 1).¹³

To allow for an in-depth study, the investigation of two possible paths for the rate-limiting step has been proposed: regular oxidative addition (OA) and atom transfer (AT) paths. Subsequently, we demonstrate the most important path for the production of Fe(III) from the active catalyst Fe(I) in theoretical study and GC monitoring.

However, investigation of radical mechanism pathway can be excluded in the proposed catalytic cycle. Regarding the contribution of radical intermediates, no product was detected by GC. In fact, the cross-coupling products had already been formed before any radicals recombined with iron.¹⁴

The active catalyst Fe(I) is produced from a precursor complex, FeX_3 . One of the requirements of transmetalation is an available lone pair on the -X group to coordinate the incoming metal; this coordination should involve a stronger bond to the metal than to the iron. Frequently, for C-C couplings using palladium, oxygen ligands can activate the palladium catalyst in the coupling reaction. The use of hydroxide ligands in palladium catalyst has been reported, but using hydroxides in iron catalysts would cause precipitation as ferric hydroxide. Here, we have prepared an iron alkoxide as a safe catalyst and used it for C-C cross-coupling. The aim of this study was to investigate model reactions for the two different paths of cross-coupling: OA and AT. We reveal insights into the mechanism for C-C couplings based on the iron catalyst used, the experimental conditions, and detailed computational investigations at the DFT level. The iron alkoxide was used as a transition metal catalyst and reduced to an active catalyst by Grignard reagents.¹⁵

We assumed that the reaction is first order¹³ and the kinetic dependence on all reagents and catalysts (iron ethoxide and iron methoxide) is the same as the dependence on phenyl magnesium bromide. The iron alkoxide was prepared by mixing ferric chloride and the appropriate sodium alkoxide in toluene, and after concentrating the resulting precipitate was dissolved in dry tetrahydrofuran (THF) with dodecane as an internal standard. It should be noted that the precipitate has moderate solubility in THF and a saturated solution was prepared. Cyclohexyl bromide was added in aliquots to a mixture of phenyl magnesium bromide and iron alkoxide under inert conditions (N_2) and the cross-coupling product formation was followed by GC (Fig. 1).

Nevertheless, in the presence of oxygen, the reaction mixture might be oxidized through the reaction of oxygen with low-valent aryl iron species.¹⁶

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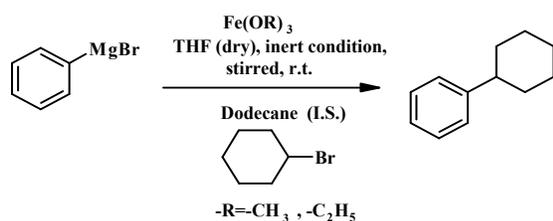


Figure 1 Iron-catalyzed cross coupling

The concentration of the product was determined for samples withdrawn from the reaction mixture before each addition of cyclohexyl bromide at constant time intervals. Both of the experimentally studied catalysts, iron ethoxide and iron methoxide, showed mechanistic similarities. It is expected that the transmetalation process can be followed by either OA (path a) or AT routes (path b) (Scheme 1). From our previous work, using Hammett studies and modeling, we believe that in the rate limiting step, the oxidation state of the catalytically active iron species is Fe(I).¹³

Accordingly, figure 2 shows the change in the phenylcyclohexane concentration during the cross-coupling reaction, measured by GC. First, the active catalyst Fe(I) was formed by the reduction of iron alkoxide by phenylmagnesium bromide. The gentle positive slope of the plotted line during the initial phase indicates a low concentration of phenylcyclohexane in the vessel (A..B plot, Fig.2). After repeated additions of cyclohexyl bromide to the reaction vessel, the slope became linear, representing the lower bound of the final concentration of phenylcyclohexane as a cross-coupling product (B-C plot, Fig.2). We focused on the linear phase, during which the reaction could have been controlled by the OA or AT mechanism. Thus, we measured the concentration of phenylcyclohexane by GC and conducted computational modeling to interpret the mechanism in the linear region. Evidently, after transmetalation and reductive elimination had occurred, the cross-coupling product was formed (Scheme 1). The final region of the graph represents a deactivation phase in which all the substrates and the active catalyst Fe(I) were consumed to produce the coupling product (C---D plot, Fig.2).

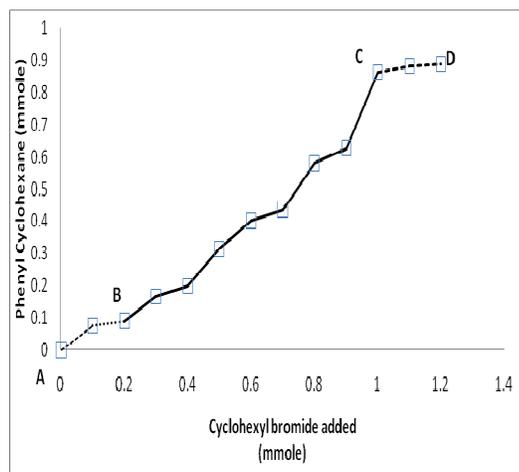


Figure 2 Phenyl cyclohexane formation on titration with iron alkoxide

To obtain reliable results in the experimental and theoretical studies, all experiments were performed under inert conditions.

Monoaryl and diaryl iron alkoxides were prepared by the initial two transmetalations (TM1 and TM2) and were stabilized by (*n*) solvent molecule(s) (Scheme 1).

Consequently, the third transmetalation (TM3) generated the active catalyst Fe(I) and biphenyl as a homo-coupling product. However, the current experimental and theoretical studies are not focused on transmetalation, but on the following process, which may occur either via OA (path a) or AT routes (path b). Nevertheless, in the presence of oxygen, the reaction mixture might be oxidized through the reaction of oxygen with low-valent aryl iron species.¹⁶

To investigate the proposed mechanism rationally and to clarify details about the degree of solvation, both the proposed mechanisms in Scheme 1 (path (a) and path (b)) were modeled using DFT calculations. According to our theoretical results, the reaction pathway was affected energetically by the number of coordinated solvent molecules (Fig. 3, Table 1).

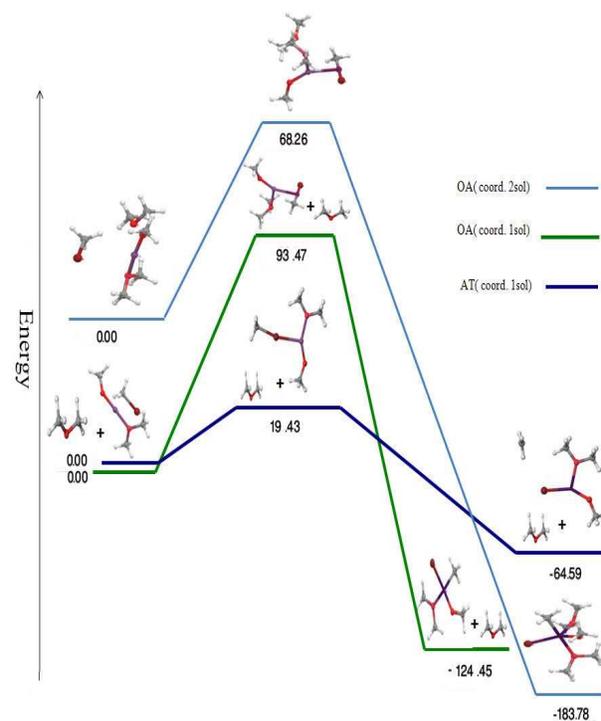


Figure 3: Oxidative Addition and Atom transfer pathways with one or two coordinated solvents by using PBF model calculated at UB3LYP/ LACVP* with relative energies in kJ.mole⁻¹.

Two possible complexes with different numbers of coordinated solvents were suggested for the OA pathway, (Fe(I)(OR)S₁ and Fe(I)(OR)S₂), both of which are also possible for the AT pathway. However, the calculations were performed based on both complexes for the OA pathway, whereas the preferred complex coordinated only one solvent in the AT pathway. The latter case suggests that further solvent makes it difficult to find accurate force constants and frequencies due to instability in geometry. To facilitate calculation of the stability of the complexes and the feasible pathways, the phenylmagnesium halide and ferric alkoxide that were used experimentally were modeled by methyl bromide and ferric methoxide (Fig.3). Oxidative addition of an alkyl bromide to linear Fe(I)(OCH₃)S₁ or planar Fe(I)(OCH₃)S₂ leads to complexes with tetrahedral or trigonal bipyramidal molecular geometry, respectively.

The one possible pathway of atom transfer gives a tri-coordinated complex, Fe(I)(OCH₃)₃Br. This means that the formation of this complex involves a transition state in which formation of the iron-bromide bond occurs simultaneously with the breakage of the carbon-halide bond.

Table 1. Absolute Energies (E_{ab}) and Relative Energies (E_{re}) including ZPE corrections for the species of the proposed paths, with coordinated (n) explicit solvent molecules by using PBF model calculated at UB3LYP/LACVP* in kJ.mol⁻¹. The value of E for each reactant is set at zero and relative energies are calculated accordingly. (1 Hartree=2625.5 kJ).

Species	Oxidative Addition (Path a, n=1)		Oxidative Addition (Path a, n=2)		Atomic Transfer (Path b, n=1)	
	E_{ab}	E_{re}	E_{ab}	E_{re}	E_{ab}	E_{re}
Reac.	-1579441.99	0.00	-1579393.15	0.00	-1579441.46	0.00
T.S.	-1579348.52	93.47	-1579377.40	68.26	-1579422.04	19.43
Prod.	-1579566.44	-124.45	-1579576.94	-183.78	-1579506.05	-64.59

In fact, breaking of the carbon-halide bond in the AT pathway leads to two possible complexes, with either the methyl group or the halide included in the Fe(I) complex. The calculation showed that the complex formed including the methyl group is much higher in energy, and therefore is not shown in Fig. 3. Interestingly, the activation energy for the suggested AT pathway was lower than the pathways proposed for OA (Table. 1). The activation energies for the proposed OA pathways were calculated as 93.47 kJ.mol⁻¹ and 68.26 kJ.mol⁻¹, when one or two explicit solvent molecules coordinate to iron complex. Although the activation energy for AT pathway, was found 19.43 kJ.mol⁻¹, when one explicit solvent molecule coordinates to complex. Fig. 3 shows that the AT pathway can be considered most rapid in the presence of mono-solvated iron methoxide and methyl bromide; this effect is rationalized by atom transfer to form a complex with one halide bound to iron. This result indicates that the transfer of a halide atom from alkyl halide to the iron for the AT pathway occurs more efficiently than formation of the tetrahedral or trigonal bipyramidal complexes necessary for the OA pathways.

Experimental Section

Experimental details can be found in the Electronic Supplementary Information (ESI). The calculations were performed using the Jaguar 8.0 from Schrödinger.¹⁷ All species were computed at Becke's three-parameter hybrid exchange functional with the correlation functional of Lee, Yang, Parr (B3LYP) in combination of LACVP* basis set. To improve the accuracy in similarity between theoretical and experimental results, we have done the calculations made in a comparative manner and used the empirical dispersion correction method developed by Grimme and coworkers, DFT-D3 (zero damping).¹⁸ To assess the performance of this approach, the reasonable unrestricted B3LYP (UB3LYP) instead of B3LYP method has been used. This method was preferred, because it is less common to find any significant spin contamination in DFT calculations, especially when unrestricted Kohn-Sham orbitals are utilized. All geometries were optimized in gas phase, with explicit solvent molecules modeled by dimethyl ether (DME) and thermodynamic corrections to the free energy were found from frequency calculations at the optimized structures. Energies in solvent were calculated using the PBF (Poisson Boltzmann Finite element) solvation model at the optimized gas phase geometries.¹⁹ The final free energies were obtained by addition of thermodynamic correction (including zero point energy correction) from the frequency calculation to the energies in solvent. The number of solvents that stabilize the complex models was suggested and each species optimized. Reaction paths were followed by QRC in order to confirm transition states related to corresponding minimums. Frequency calculations were carried out to determine the thermodynamic properties of stationary species. For the minimum and transition state structures, real frequency

values and imaginary frequency values were accepted, respectively. In our DFT calculations, the $\langle S^2 \rangle$ values were investigated after each calculation and, if the value of $\langle S^2 \rangle$ differed from $s(s+1)$ by more than a few percent above the theoretical expectation, a restricted open shell wave function was calculated and used as an initial guess in the unrestricted calculation.

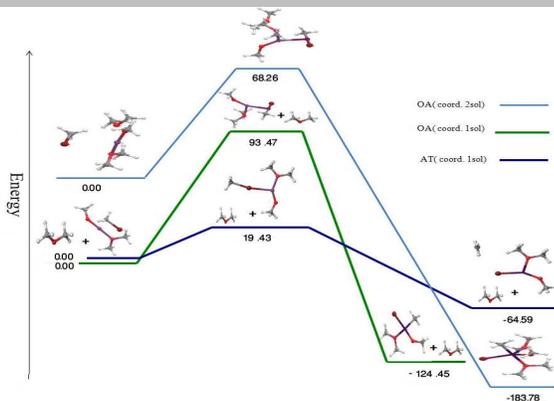
Conclusions

In summary, the reaction paths in the iron-catalyzed cross-coupling reaction between an alkyl halide and phenyl magnesium bromide in the presence of ferric alkoxide has been investigated by DFT calculations and experiments. The iron-mediated coupling of an aryl Grignard reagent with an iron alkoxide leads to an Fe(I) oxidation state under inert conditions. The resulting Fe(I) complex undergoes a reaction with the alkyl halide leading to the cross-coupling product. This rate-limiting step can proceed through the OA or AT pathway. The computational studies indicate that the activation energy for the AT pathway is lower than that for the OA pathway. The relative energies of these pathways depend on the number of solvent molecules included in the complex models and on the method of cleavage of the carbon-halide bond in the AT pathway. The lowest energy pathway was obtained when a mono-solvated complex was formed and atom transfer led to Fe(I)(OCH₃)₃Br. We wish to demonstrate that iron alkoxide would be useful as an environmentally benign catalyst for C-C cross-coupling.

Keywords: · Oxidative Addition (OA) · Atom Transfer (AT) · cross-coupling reactions · iron alkoxide · reaction mechanisms

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The computational studies on the mechanism of the iron-catalyzed cross-coupling revealed that the AT pathway performs energetically easier than the regular OA pathway.



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