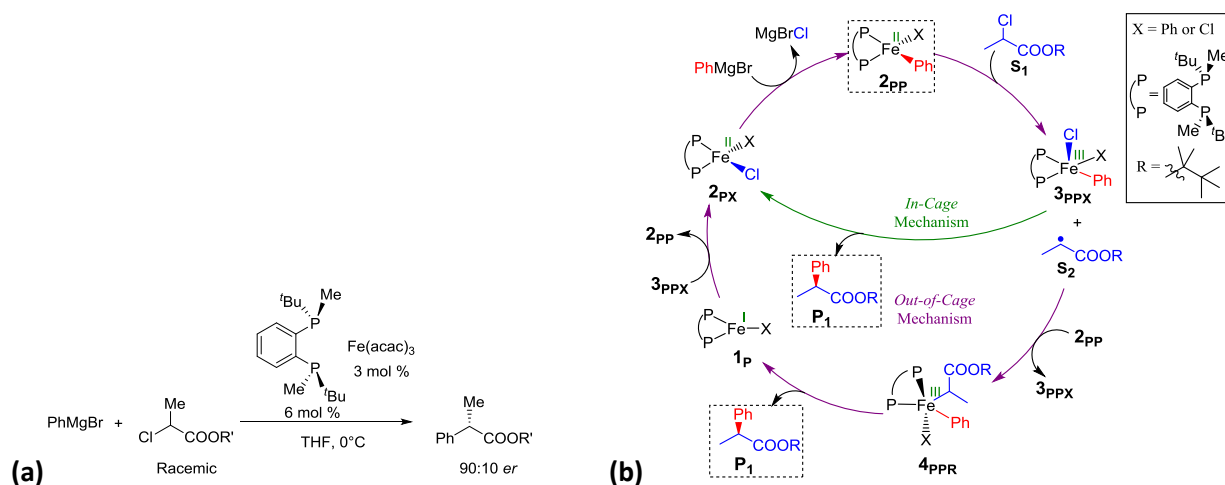


Computational Insights on the Mechanism and the Origin of Enantioselectivity in Fe-catalyzed Cross-Coupling Reaction

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Introduction: The development of methods for generation of chiral compounds is of great significance due to its pharmaceutical importance. Transition metals are used in homogenous catalysis for a variety of transformations, including cross-coupling reactions and formation of asymmetric compounds. The developments of new methods involving non-toxic and readily available metals for coupling reactions are increasing nowadays, Fe is very important in this regard.¹ The mechanistic understanding of Fe-catalyzed reactions is important for further development in this field. Recently, M. Nakamura and coworkers have reported the first Fe-catalyzed enantioselective cross-coupling reaction (Scheme 1a).² They proposed that the reaction proceed through an *out-of-cage* mechanism (Scheme 1b). On the basis of radical probe studies a radical pathway was proposed. The mechanism of the reaction is not established, and there is no clear understanding of the origin of enantioselectivity.



Scheme 1. (a) Fe-catalyzed enantioselective cross-coupling reaction. (b) The proposed *in-cage* and *out-of-cage* mechanisms (nomenclature given in scheme for X = Ph).

Methods: The AFIR method as implemented in GRRM program is used to explore potential energy surface of the reaction. The DFT methods are used for calculation using Gaussian 09 program. The optimization of stationary points and computation of energies are done at PCM_{THF}/B3LYP-D3BJ/SDD(Fe,Br);6-31+G**(O, P, Cl, Mg);6-31G*(C,H) level of theory.

Results and Discussion: We studied the thermodynamics of generation of proposed active Fe(II) species from reagents. We found that the energy of Fe(I) and Fe(II) species differ only by a small amount (2.7 kcal/mol). Among the different possible species, it is found that for Fe(I) (**1_P**), Fe(II) (**2_{PP}**) and Fe(III) (**3_{PPX}**, **4_{PPR}**), the lowest energy spin states are quartet, quintet, and quartet respectively.

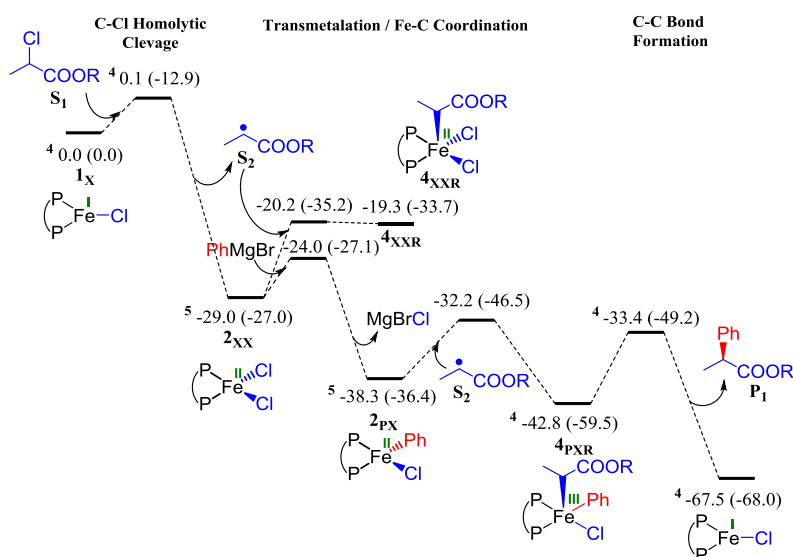
The reaction starting from lowest energy Fe(II) species [Fe(PP*)Ph₂] (**2_{PP}**) is less likely, as the activation barrier for biphenyl formation is less from the corresponding Fe(III) species (**3_{PPX}** and **4_{PPR}**) in comparison to forward reaction through the *in-cage* or *out-of-cage* mechanisms (Scheme 1b). It is in agreement with the experimental finding which requires slow addition of Grignard reagent. The C-C coupling from **3_{PPX}** is found to have higher activation barrier than coupling from **2_{PP}** (Scheme 1b). Hence, the reaction through *in-cage* mechanism is less likely in comparison to *out-of-cage* mechanism. The activation barrier for C-Cl activation through other lower energy Fe(II) species, [Fe(PP*)PhCl] is high (24.0 kcal/mol). Hence, the reaction through Fe(II) species is less probable. As the reaction involves Fe(I), Fe(II) and Fe(III) species, we also considered C-Cl activation from Fe(I) and Fe(III) species. Interestingly, the activation barrier for the C-Cl activation by Fe(I) is very low.

The most probable mechanism, according to our calculation, is given in Scheme 2. The active species for C-Cl activation is Fe(I), not Fe(II) as proposed in the literature. Activation barrier for the transmetalation is low and it converts **2_{XX}** to lower energy intermediate **2_{PX}**. Lower concentration of Grignard reagent diminishes the possibility of further conversion of **2_{PX}** to **2_{PP}** via transmetalation.

The C-C coupling occurs through Fe(II) intermediate (**2_{PX}**) as proposed by M. Nakamura and coworkers. It occurs by the inner sphere mechanism. Both Fe-C bond formation and C-C bond formation step could be enantioselectivity determining. We found that C-C bond formation is enantioselectivity determining.

References

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Scheme 2. The Free energy profile for preferable mechanism based on computational results in Fe-catalyzed coupling reaction.