[Article]

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铁催化芳基格氏试剂的联芳交叉偶联的反应机理

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摘要: 利用密度泛函理论(DFT)计算研究了 $[\text{Fe}(\text{MgBr})_2]$ 催化的邻氯苯乙稀与溴代苯基镁反应生成联芳化合物的交叉偶联反应的机理. 研究了两个机理. 机理A包括三个基本步骤: (I) 氧化 $[\text{Fe}(\text{MgBr})_2]$ 生成 $[\text{Ar}-\text{Fe}(\text{MgBr})]$, (II) 加成产生 $[\text{Ar}-(\text{phenyl})-\text{Fe}(\text{MgBr})_2]$, (III) 还原消除回到 $[\text{Fe}(\text{MgBr})_2]$. 机理B不形成 $[\text{Ar}-\text{Fe}(\text{MgBr})]$. 在第一步, 溴代苯基镁在 $[\text{Cl}-\text{Mg}-\text{Br}]$ 离解形成 $[\text{Ar}-\text{Fe}(\text{MgBr})]$ 之前直接进攻氧化加成后的中间体. 考虑溶剂效应后, 机理B优于机理A. 无论机理A还是机理B, 整个催化循环过程的决速步骤都是 $[\text{Ar}-(\text{phenyl})-\text{Fe}(\text{MgBr})_2]$ 的还原消除再生催化剂 $[\text{Fe}(\text{MgBr})_2]$ 的步骤, 使用导体极化连续模型(CPCM)方法计算其在四氢呋喃溶剂中的吉布斯自由能(ΔG_{sol})是 $82.98 \text{ kJ} \cdot \text{mol}^{-1}$.

关键词: 铁催化剂; 联芳; 交叉偶联; 反应机理; 密度泛函理论

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Reaction Mechanism for the Iron-Catalyzed Biaryl Cross-Coupling of Aryl Grignard Reagents

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Abstract: Mechanisms for the $[\text{Fe}(\text{MgBr})_2]$ catalyzed cross-coupling reaction between *ortho*-chlorostyrene and phenylmagnesium bromide to form biaryl were studied using density functional theory (DFT) calculations. We investigated two mechanisms. Cycle A included three basic steps: (I) oxidation of $[\text{Fe}(\text{MgBr})_2]$ to obtain $[\text{Ar}-\text{Fe}(\text{MgBr})]$, (II) addition to yield $[\text{Ar}-(\text{phenyl})-\text{Fe}(\text{MgBr})_2]$, and (III) reductive elimination to return to $[\text{Fe}(\text{MgBr})_2]$. Cycle B did not form $[\text{Ar}-\text{Fe}(\text{MgBr})]$. In the first step, phenylmagnesium bromide attacks the intermediate of the oxidative addition directly before $[\text{Cl}-\text{Mg}-\text{Br}]$ dissociates to form $[\text{Ar}-\text{Fe}(\text{MgBr})]$. The catalytic Cycle B is favored over the catalytic Cycle A when considering the solvent effect. The rate-limiting step in the overall catalytic cycle for both Cycle A and Cycle B is the reductive elimination of $[\text{Ar}-(\text{phenyl})-\text{Fe}(\text{MgBr})_2]$ to regenerate the catalyst $[\text{Fe}(\text{MgBr})_2]$, where the Gibbs free energy in solvent tetrahydrofuran (THF), ΔG_{sol} , is $82.98 \text{ kJ} \cdot \text{mol}^{-1}$, as determined using the conductor polarized continuum model (CPCM) method.

Key Words: Iron catalyst; Biaryl; Cross-coupling; Reaction mechanism; Density functional theory

1 Introduction

Transition metal-catalyzed cross-coupling reactions are of utmost importance for the formation of carbon-carbon as well as carbon-heteroatom bonds. In general, palladium and nickel catalysts dominate this field, such as, Negishi,^{1,2} Suzuki,^{3,4} Heck,^{5,6}

Stille,^{7,8} and Kumada-Corriu^{9–11} reactions. The biaryl compounds are very important intermediates in modern organic synthesis and pharmaceutical products.¹² Palladium- and nickel-catalyzed cross-coupling reactions are among the most versatile methods for the synthesis of biaryl compounds. Suzuki-Miyaura reactions between

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arylboronic acids and aryl halides are widely applied because of their especially mild conditions and excellent compatibility with many functional groups.^{13–16} However, palladium and nickel catalysts are limited by the high price or considerable toxicity, especially for industrial processes. Iron-catalyzed cross-coupling reactions have become increasingly important in the construction of complex molecular frameworks in the last few decades due to their high efficiency, cheapness, non-toxicity, and the environmental health of the simple iron salt precatalysts.^{17–20} The complex, air-sensitive ligands are also not required and the mild reaction conditions tolerate various functional groups.

Furstner *et al.*^{21,22} reported a lot of highly selective iron-catalyzed cross-coupling reactions of aryl halides with alkyl magnesium halides and the iron-catalyzed cross-coupling reactions have matured into a class of effective carbon-carbon as well as carbon-heteroatom bond-forming reactions.^{23–27} In general, the iron-catalyzed biaryl syntheses from aryl Grignard species and aryl halides are proved unselective.^{22,28–30} For example, Hatakeyama *et al.*^{31,32} reported a method which requires a special precatalyst combination of iron(II) fluoride and a carbene ligand and also needs the generation of the catalytically active species in a prior step to improve the selectivity.

Later, von Wangelin *et al.*³³ paid attention to many papers^{34,35} about the rich coordination abilities of olefins with iron in low oxidation states and proposed a new method of activation for olefin-substituted aryl chlorides. The sequential olefin coordination at the catalyst and haptotropic migration could affect C—Cl bond activation of chlorostyrenes.³⁶ They had reported an efficient iron-catalyzed biaryl synthesis where the reaction of aryl Grignard species with chlorostyrenes proceeded under mild reaction conditions in the presence of iron(III) tris(acetylacetonate) [Fe(acac)₃] as precatalyst.³⁶

The theoretical understanding of the reaction mechanisms of the transition metal-catalyzed processes may shed light on how to design more powerful catalysts and how to control the catalysis process. However, the mechanisms of the iron-catalyzed reactions remain rather obscure. Kochi,³⁷ Furstner,^{20,22} Bogdanovic,³⁸ Norrby,³⁹ *et al.* have reported some mechanisms of iron-catalyzed cross-coupling reactions of Grignard reagents. Our group⁴⁰ have investigated the mechanisms of iron-catalyzed cross-coupling reactions of alkyl Grignard reagents using density functional theory calculations.

The catalyzed cycles start from the inorganic Grignard reagent [Fe(MgX)₂], where X=Br or I. [Fe(MgX)₂] consists of two magnesium atoms and one iron center that are connected *via* two covalent intermetallic bonds. It was generally used to explain many of the experimental results by Furstner *et al.*^{20–22} where the initial [Fe(MgX)₂] is formed from the iron precatalyst and RMgX. The mechanism is through Fe(–II) and Fe(0) catalytic cycle, where the iron center is Fe(–II) in [Fe(MgX)₂], and Fe(0) in [R–Fe(MgX)] and [R–(R)–Fe(MgX)₂]. The multiplicity of Fe is set as 1. As far as we know, detailed theoretical studies concerning the [Fe(MgX)₂] catalyzed biaryl cross coupling processes of aryl

Grignard reagents have not yet been performed, although the experimental results involving iron-catalyzed cross-coupling of aryl Grignard reagents have recently been reported.^{41,42}

Here, we select one typical reaction in the experimental work of Gulak and von Wangelin³⁶ as an example, which is depicted in Scheme 1, in order to gain insight into the mechanisms of iron-catalyzed cross-coupling reactions of aryl Grignard reagents. The experimental reaction was carried out in tetrahydrofuran (THF)/*N*-methyl-2-pyrrolidone (NMP) using Fe(acac)₃ (5%, molar fraction) as the precatalyst. Fe(acac)₃ reacts with R-MgBr to yield the inorganic Grignard reagent [Fe(MgBr)₂], which is readily soluble in THF. Our thorough theoretical investigation is applied to [Fe(MgBr)₂] catalyzed cross-coupling reaction between *ortho*-chlorostyrene [Cl-Ph-vinyl] and phenylmagnesium bromide [PhMgBr] using density functional theory (DFT) calculations with the B3LYP method.^{43–48}

We will study two mechanisms. One mechanism is named as Cycle A with forming [Ar-Fe(MgBr)] in the catalytic cycle and another mechanism is named as Cycle B without forming [Ar-Fe(MgBr)] in the catalytic cycle. Our theoretical studies will answer the questions: Which catalytic cycle is favored? Which step is the rate-determining step in the whole catalytic cycle? Is it possible to lower the energy barrier when considering the solvent effect? Answers to these questions will improve the understanding of iron-catalyzed cross-coupling of aryl Grignard reagents.

2 Computational methods

All DFT calculations were performed using the Gaussian 03 program⁴⁹ with the B3LYP hybrid functional.^{43–48} The 6-311++G(*d*, *p*) basis set was used for C, H, Cl, Br, and Mg.^{50,51} The SDD quasi-relativistic pseudopotential and associated basis set was used for iron.⁵² All equilibrium structures of the gas phase geometries were fully optimized without any symmetry restriction and then the vibrational frequencies analysis was performed to ensure that the local minima had zero imaginary frequencies and the transition state had exactly one. The solvent effect was calculated using the conductor polarized continuum model (CPCM) method⁵³ with the UFF radii on the gas-phase optimized geometries. The polarizable continuum model (PCM) is a commonly used method in computational chemistry to model solvation effects. It models the solvent as a polarizable continuum, rather than individual molecules, which has two popular types: dielectric PCM (DPCM) and conductor-like PCM (CPCM). Both the electronic and nonelectronic free energies in solution were added to the gas-phase Gibbs free energies to obtain the solution Gibbs free energies in THF, ΔG_{sol} .⁴⁰ All the solution-phase free energies reported in the paper

Scheme 1 Iron-catalyzed cross-coupling reaction between *ortho*-chlorostyrene and phenylmagnesium bromide

correspond to the reference state of $1 \text{ mol} \cdot \text{L}^{-1}$, 298 K.

3 Results and discussion

3.1 Catalytic Cycle A with forming [Ar-Fe(MgBr)]

The catalytic cycle A is similar as the mechanistic proposal of Furstner *et al.*,²² which is outlined in Fig.1. It includes three basic steps: (I) oxidation of $[\text{Fe}(\text{MgBr})_2]$ to obtain $[\text{Ar-Fe}(\text{MgBr})]$, (II) addition with phenylmagnesium bromide to yield $[\text{Ar}(\text{-phenyl})\text{-Fe}(\text{MgBr})_2]$, and (III) reductive elimination to return to $[\text{Fe}(\text{MgBr})_2]$. The cycle A includes three transition states (TS_1 , TS_2 , TS_3). The fully optimized structures of the reactant R_1 , the catalyst CA, the complex **2**, the transition state TS_1 , the intermediates **3** and **4**, and the product P_2 are shown in Fig.2. The fully optimized geometries of the reactant R_2 , the complex **5**, the transition states TS_2 , TS_3 , the intermediate **6**, and the final product P_1 are shown in Fig.3. The values of the bonding distances (the unit is nm) are also given in Figs.2 and 3.

(I) oxidation of $[\text{Fe}(\text{MgBr})_2]$ to obtain $[\text{Ar-Fe}(\text{MgBr})]$. The approach of R_1 toward the catalyst CA, $[\text{Fe}(\text{MgBr})_2]$, leads to the formation of a complex **2**. From **2**, after passing through a transition state TS_1 , the intermediate **3** of oxidative addition is obtained. In the optimized geometry of **2** (see Fig.2), the iron atom is above the center of the phenyl and is far from the $^1\text{C}-\text{Cl}$ bond. The distances of $^1\text{C}-\text{Fe}$ and $\text{Cl}-\text{Fe}$ are 0.207 and 0.342 nm, respectively. Then in the transition state TS_1 , the chlorine atom approaches toward ^2Mg atom around the iron center departing from ^1C atom. The distance of $\text{Cl}-\text{Fe}$ is 0.239 nm. It becomes 0.224 nm in the optimized geometry of **3**, accompanying with the formation of $\text{Cl}-^2\text{Mg}$ bond (0.242 nm, see Fig.2). At the same time, the distance of $\text{Fe}-^2\text{Mg}$ increases from 0.253 nm in the optimized structure of **2** to 0.260 nm in the optimized structure of

Fig.2 Fully optimized structures of the reactant R_1 , the catalyst CA, the intermediates **2**, **3**, **4**, the transition state TS_1 , and the product P_2 .

The unit of the distance is nm. C: cyan, H: white, Fe: red, Mg: ochre, Br: pink, Cl: green. Colors refer to the web version of this article.

3 because of the bonding of Cl atom with the ^2Mg atom and the interaction of Cl atom with Fe atom. The weakening process of the bonding of $\text{Fe}-^2\text{Mg}$ is beneficial for the further reaction, i.e., the covalent intermetallic bonding of $\text{Fe}-^2\text{Mg}$ breaks and the molecule P_2 dissociates from **3** to form the intermediate **4**, $[(\text{BrMg})\text{-Fe}(\text{-Ph-vinyl})]$. The bond distances of $^1\text{C}-\text{Fe}$ and $\text{Fe}-^1\text{Mg}$ in the optimized structure of **4** are 0.189 and 0.245 nm, respectively.

(II) Addition of another reactant phenylmagnesium bromide R_2 to **4** yields the intermediate **6**, $[\text{Ar}(\text{-Ph-})\text{-Fe}(\text{MgBr})_2]$. After the intermediate **4** is formed, the approach of R_2 toward **4**, leads to the formation of a complex **5**. From **5**, passing through a three-membered-ring transition state TS_2 , the intermediate **6** is formed. From the fully optimized structures of **5**, TS_2 and **6** shown in Fig.3, it can be seen that the $\text{Fe}-^2\text{Mg}$ distance is 0.267 nm in TS_2 , compared to that of 0.277 nm in **5**. The distance of $\text{Fe}-^2\text{C}$ also decreases from 0.439 nm in **5** to 0.354 nm in TS_2 , so that it is easy for atom ^2C to attack Fe atom in TS_2 , leading to the formation of a $\text{Fe}-^2\text{C}$ bond to obtain the intermediate **6**. The bond distance of $\text{Fe}-^2\text{C}$ in **6** is 0.189 nm.

(III) Finally, reductive elimination of **6** to return to the catalyst

Fig.1 Outline of the iron-catalyzed cross-coupling reaction mechanism for the product P_1 from *ortho*-chlorostyrene R_1 and phenylmagnesium bromide R_2 .

Fig.3 Fully optimized structures of the reactant R_2 , the intermediates 5, 6, the transition states TS_2 , TS_3 , and the final product P_1

The unit of the distance is nm. C: cyan, H: white, Fe: red, Mg: ochre, Br: pink, Cl: green. Colors refer to the web version of this article.

CA, $[Fe(MgBr)_2]$. This process passes through the third transition state TS_3 to form the product P_1 , [Ph-Ph-vinyl] and to regenerate the original catalyst CA. From the fully optimized structures of 6, TS_3 , and P_1 shown in Fig.3, the 2C and 1C atoms in TS_3 go closer to 0.179 nm from 0.287 nm in 6 and finally the bond of $^2C-^1C$ is formed in P_1 (0.149 nm).

The electronic energy profiles for the whole catalytic cycles for iron-catalyzed cross-coupling reaction between *ortho*-chlorostyrene and phenylmagnesium bromide are depicted in Fig.4, where the summation of the electronic energies of the reactant R_1 and the catalyst CA is set as zero energy.

From Fig.4, it can be seen that the energy barrier from the complex 2 to the first transition state TS_1 is 106.11 $\text{kJ} \cdot \text{mol}^{-1}$. The energy value needed for the process in which the molecule P_2 , $[Cl-Mg-Br]$, dissociates from the intermediate 3 to form the intermediate 4 is 115.16 $\text{kJ} \cdot \text{mol}^{-1}$. It refers to the breaking of the strong covalent intermetallic bonding of $Mg-Fe$. This could be offset by the large exothermicity ($-139.64 \text{ kJ} \cdot \text{mol}^{-1}$) process forming the intermediate 3 from 2. The transition state connecting 3 and 4 has not been found after many attempts. The energy barrier of TS_2 from 5 to form a stable structure 6 [Ar-(phenyl)- $Fe(MgBr)_2$] is small (4.87 $\text{kJ} \cdot \text{mol}^{-1}$).

The energy barrier of TS_3 to form the final product P_1 from the intermediate 6 when releasing the catalyst CA through the reductive elimination is 96.47 $\text{kJ} \cdot \text{mol}^{-1}$. This process is needed to break two $Fe-C$ bonds. In all, the energy barriers for the steps of $2 \rightarrow 3$, $3 \rightarrow 4$ and $6 \rightarrow CA + P_1$ are closer and the step of $3 \rightarrow 4$ is the

Fig.4 Electronic energy profiles for the overall catalytic cycles of the iron-catalyzed cross-coupling reaction

rate-limiting step in the whole catalytic cycle of the mechanism of Cycle A for the gas calculation.

3.2 Catalytic cycle B without forming $[Ar-Fe(MgBr)]$

Considering that the required electronic energy for the process in which the molecule P_2 , $[Cl-Mg-Br]$ dissociates from the intermediate 3 to form the intermediate 4 is very high by 115.16 $\text{kJ} \cdot \text{mol}^{-1}$ (see Fig.4), it could be possible that there is another way to lower the energy barrier, namely if phenylmagnesium bromide (R_2) attacks the intermediate 3 directly before the formation of 4, $[Ar-Fe(MgBr)]$. Our previous calculations⁴⁰ about $[Fe(MgBr)_2]$ catalyzed cross-coupling reaction between 4-chlorobenzoic acid methyl ester and *n*-hexylmagnesium bromide have proved that the new path is easier than the catalytic cycle A with forming $[Ar-Fe(MgBr)]$. We did the similar calculations for the reaction between *ortho*-chlorostyrene and phenylmagnesium bromide. The catalytic cycle is named as cycle B, which is also shown in Fig.1.

From Fig.1, it can be seen that the reactant R_2 firstly approaches toward the intermediate 3 to form the complex 7. From 7, after passing through one transition state TS_4 , an intermediate 8 is formed. The fully optimized structures of 7, TS_4 and 8 in the gas phase are shown in Fig.5. Then the molecule P_2 dissociates from the intermediate 8 to yield 6. In the optimized geometry of 7, the distance of $Cl-^3Mg$ is 0.245 nm. The $Cl-^3Mg$ bond length becomes longer to 0.264 nm compared to that of 0.242 nm in 3, which means that the Cl atom is now linked to the 3Mg atom. The distance of Cl with Fe also becomes longer to 0.241 nm, compared to that of 0.224 nm in 3. The distances of $Fe-^3Br$ and $Fe-^3Mg$ are 0.250, 0.345 nm, respectively. Next, the atom 3Br in 7 rotates around the 3Mg atom to bring the atom 2C close to the Fe atom, so that the atom 2C can attack the Fe center easily. In the optimized structure of the transition state TS_4 , the distance of atom 2C from the Fe atom is 0.258 nm. It becomes shorter to 0.201 nm in the optimized structure of 8, which is close to the value of 0.189 nm in the optimized structure of 6 (see Fig.3). The distances

Fig.5 Fully optimized structures of the intermediates 7, 8 and transition state TS_4 for the Cycle B

The unit of the distances is nm. C: cyan, H: white, Fe: red, Mg: ochre, Br: pink, Cl: green. Colors refer to the web version of this article.

of $^2C-^3Mg$ and $Fe-^3Mg$ become longer to 0.225, 0.316 nm in **8**, compared to those of 0.210, 0.264 nm in TS_4 , respectively. It is beneficial for the process in which the molecule P_2 dissociates from the intermediate **8** to yield **6**.

The electronic energy profile from the intermediate **3** to the intermediate **6** for Cycle B is also depicted in Fig.4. From Fig.4, it can be seen that the energy barrier to pass over the transitional state TS_4 is only 55.21 $\text{kJ}\cdot\text{mol}^{-1}$, which is much smaller than 115.16 $\text{kJ}\cdot\text{mol}^{-1}$ required when the molecule P_2 , $[Cl-Mg-Br]$ dissociates directly from the intermediate **3** before another reactant R_2 attacks. However, the energy needed for the process when the molecule P_2 , $[Cl-Mg-Br]$ dissociates from the intermediate **8** to form **6** is very high, i.e., 138.57 $\text{kJ}\cdot\text{mol}^{-1}$. It looks that the Cycle B is not favored than Cycle A for the gas phase calculations, which is different from the previous calculations about $[Fe(MgBr)_2]$ catalyzed cross-coupling reaction between *n*-hexylmagnesium bromide and 4-chlorobenzoic acid methyl ester.⁴⁰

3.3 Solvent effect

All of the above results are calculated in the gas phase. According to our previous study about $[Fe(MgBr)_2]$ catalyzed cross-coupling reaction between 4-chlorobenzoic acid methyl ester and *n*-hexylmagnesium bromide,⁴⁰ the CPCM method is suitable to calculate the solvent effect for the iron-catalyzed cross-coupling reactions of alkyl Grignard reagents. Now we used the same CPCM method to investigate the solvent effect for the $[Fe(MgBr)_2]$ catalyzed cross-coupling reaction between *ortho*-chlorostyrene

and phenylmagnesium bromide. In order to clarify whether the solvent effect can play a significant role in the process, we compare the Gibbs free energies ΔG_g and the Gibbs free energies in THF solution, ΔG_{sol} for the overall catalytic cycles of two mechanisms (Cycle A and Cycle B), which are shown in Fig.6. The former is depicted as the solid line and the latter is drawn as the dashed line.

From Fig.6, it can be seen that the solvent effect is very obvious for the steps of dissociating P_2 from **3** to form **4** in the Cycle A or from **8** to obtain **6** in the Cycle B. $\Delta G_{sol}(3 \rightarrow 4)$ is $-55.94 \text{ kJ}\cdot\text{mol}^{-1}$ compared that $\Delta G_g(3 \rightarrow 4)$ is 67.02 $\text{kJ}\cdot\text{mol}^{-1}$. Similarly, $\Delta G_{sol}(8 \rightarrow 6)$ is $-17.00 \text{ kJ}\cdot\text{mol}^{-1}$ compared that $\Delta G_g(8 \rightarrow 6)$ is 86.69 $\text{kJ}\cdot\text{mol}^{-1}$. The solvent effect is exothermic.

The solvent effect causes large changes of the ΔG values for the processes of $(3 \rightarrow 4)$ in the Cycle A and of $(8 \rightarrow 6)$ in the Cycle B. As far as we know, the solute is placed in a cavity in the solvent using CPCM method. The free energy of solvation was calculated from the surface charges of the solute and their interactions with the solvent.^{40,54} In general, the solvent effect is large for the dissociation processes because the gas phase calculations strongly favor the formation of clusters and make dissociation reactions more difficult than in condensed phases.^{40,54-56} For example, Schubert and Papai⁵⁷ has reported that the solvent effect was large for the process of dissociation of a PMe_3 ligand in the C—C coupling. Other calculations reported by Castellani *et al.*⁵⁸ also showed that the solvent effect can change the dissociation energy value from 332.31 $\text{kJ}\cdot\text{mol}^{-1}$ in the gas phase to 168.45 $\text{kJ}\cdot\text{mol}^{-1}$ within the toluene solvent for the process of dissociation of $\mu\text{-CH}_3$ contact ion-pair.

We can see that the energy barrier ΔG_{sol} from **4** through **5** to TS_2 in THF solvent during the process from **3** to **6** for Cycle A is 39.76 $\text{kJ}\cdot\text{mol}^{-1}$. However, the energy barrier ΔG_{sol} from **7** through TS_4 to **8** in THF solvent during the process from **3** to **6** for Cycle B is

Fig.6 Gibbs free energy in gas phase (ΔG_g , solid line) and Gibbs free energies in THF solution (ΔG_{sol} , 298 K, dashed line) for the overall catalytic cycles

only $7.74 \text{ kJ} \cdot \text{mol}^{-1}$, which is smaller than that of Cycle A. So the catalytic Cycle B without forming $[\text{Ar-Fe}(\text{MgBr})]$ is favored over the catalytic Cycle A with forming $[\text{Ar-Fe}(\text{MgBr})]$ when considering the solvent effect, this conclusion keeps line with our previous study.⁴⁰

For the other steps from **2** to TS_1 and **6** to TS_3 , the solvent effect is also large, where the $\Delta G_{\text{sol}} (\text{2} \rightarrow \text{TS}_1)$ in THF is $68.90 \text{ kJ} \cdot \text{mol}^{-1}$ compared to $\Delta G_{\text{g}} (\text{2} \rightarrow \text{TS}_1)$ in the gas phase ($96.98 \text{ kJ} \cdot \text{mol}^{-1}$) and the $\Delta G_{\text{sol}} (\text{6} \rightarrow \text{TS}_3)$ in THF is $82.98 \text{ kJ} \cdot \text{mol}^{-1}$ compared to $\Delta G_{\text{g}} (\text{6} \rightarrow \text{TS}_3)$ in the gas phase ($105.63 \text{ kJ} \cdot \text{mol}^{-1}$). It can be seen that the solvent effects can lower the energy barrier. These variations can be clearly seen in Fig.6.

In all, the rate-limiting step in the whole catalytic cycles for both Cycle A and Cycle B is the reductive elimination of **6** to form P_1 when the catalyst CA is re-generated, where the ΔG_{sol} is $82.98 \text{ kJ} \cdot \text{mol}^{-1}$ in THF solvent using the CPCM method. The conclusion is the same as our previous study about $[\text{Fe}(\text{MgBr})_2]$ catalyzed cross-coupling reaction between 4-chlorobenzoic acid methyl ester and *n*-hexylmagnesium bromide.⁴⁰ The CPCM method has been widely used to study the solvent effect for transition metal-catalyzed cross-coupling reactions.^{59,60}

4 Conclusions

Our studies reported the first theoretical investigation of $[\text{Fe}(\text{MgBr})_2]$ catalyzed cross-coupling reaction between *ortho*-chlorostyrene and phenylmagnesium bromide using DFT calculations. We studied two mechanisms. One is named as Cycle A with forming $[\text{Ar-Fe}(\text{MgBr})]$ in the catalytic cycle. It includes three basic steps: (I) oxidation of $[\text{Fe}(\text{MgBr})_2]$ to obtain the intermediate **4**, $[\text{Ar-Fe}(\text{MgBr})]$, (II) addition to yield the intermediate **6**, $[\text{Ar}(\text{-phenyl})\text{-Fe}(\text{MgBr})_2]$ and (III) reductive elimination to return to the catalyst CA, $[\text{Fe}(\text{MgBr})_2]$. Another is named as Cycle B without forming $[\text{Ar-Fe}(\text{MgBr})]$ in the catalytic cycle. In the first step, the phenylmagnesium bromide R_2 attacks the intermediate **3** directly to form a new intermediate **7** before the molecule P_2 $[\text{Cl-Mg-Br}]$ dissociates to form the intermediate **4**, $[\text{Ar-Fe}(\text{MgBr})]$.

The solvent effects can lower the energy barrier. The catalytic Cycle B without forming $[\text{Ar-Fe}(\text{MgBr})]$ is favored over the catalytic Cycle A with forming $[\text{Ar-Fe}(\text{MgBr})]$ when considering the solvent effect. The rate-limiting step in the whole catalytic cycles for both Cycle A and Cycle B is the reductive elimination of **6** to form P_1 when the catalyst CA is re-generated, where the ΔG_{sol} is $82.98 \text{ kJ} \cdot \text{mol}^{-1}$ in THF solvent using the CPCM method.

Supporting Information: Detailed molecule coordinates of all optimized structures and the calculated energy values are included. This information is available free of charge *via* the internet at <http://www.whxb.pku.edu.cn>.

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铁催化芳基格氏试剂的联芳交叉偶联的反应机理

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Reaction Mechanism for the Iron-Catalyzed Biaryl Cross-Coupling of Aryl Grignard Reagents

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Table S1 The calculated values of electronic energy ΔE , zero-point energy correction ΔZPE , relative enthalpy ΔH , relative entropy ΔS , Gibbs free energy ΔG_g and Gibbs free energy in solution THF, ΔG_{sol} , (298 K) for the overall catalytic cycles

	ΔE	ΔZPE	ΔH	ΔS	ΔG_g	ΔG_{sol}
CA+R ₁	0.0	0.0	0.0	0.0	0.0	0.0
2	-194.86	3.89	-191.29	-202.44	-130.93	-102.81
TS ₁	-88.75	-1.93	-90.29	-188.96	-33.95	-33.91
3	-334.50	2.21	-330.98	-182.14	-276.68	-209.52
4+P ₂	-219.34	-2.25	-220.91	-37.75	-209.66	-265.46
5	-304.52	0.39	-300.85	-187.53	-244.94	-246.48
TS ₂	-299.65	-0.16	-298.78	-217.91	-233.82	-225.70
6	-327.85	-0.06	-324.56	-188.99	-268.21	-265.50
TS ₃	-231.38	-1.66	-232.66	-235.05	-162.58	-182.52
P ₁	-228.50	5.07	-223.43	-28.76	-214.86	-279.08
7	-478.91	4.40	-470.71	-344.70	-367.94	-256.24
TS ₄	-423.70	5.37	-417.37	-400.05	-298.09	-251.37
8	-466.42	4.34	-458.52	-347.54	-354.90	-248.50

The unit of relative entropy ΔS is J mol⁻¹ K⁻¹ and all other energy units are kJ mol⁻¹.

The full optimized geometries:

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Molecule CA

Fe	0.00000000	0.00000000	2.39143900
Mg	0.00000000	1.80703100	0.64199400
Mg	0.00000000	-1.80703100	0.64199400
Br	0.00000000	-3.42084500	-1.10836100
Br	0.00000000	3.42084500	-1.10836100

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Molecule R1

C	-2.43269000	-0.39722900	0.06258200
C	-1.68006100	0.77226000	0.06810700
C	-0.29244700	0.69870800	-0.01148100
C	0.38882900	-0.52752200	-0.09408900
C	-0.40606900	-1.68779300	-0.10913700
C	-1.79061000	-1.63199800	-0.02673500
H	-3.51338500	-0.34030500	0.12070700
H	-2.15931300	1.74045100	0.13605100
H	0.08404600	-2.64860800	-0.21165300
Cl	0.60142500	2.21999400	0.01874800
C	1.85691900	-0.60188900	-0.17813600
H	2.35150500	0.27713600	-0.57704500
C	2.60777000	-1.63761500	0.20677600
H	2.18751900	-2.52972700	0.65824400
H	3.68495300	-1.61229600	0.09406200
H	-2.36941200	-2.54808600	-0.04640200

21

Molecule 2

Fe	-0.22599900	-0.80855000	-0.04218800
Mg	2.19780300	-0.13650200	-0.20441100
Mg	-0.42584500	1.69799200	-0.27804900
Br	-1.15323900	3.96895000	-0.21581700
Br	4.58083200	-0.14123000	-0.08717100
Cl	-2.23562900	-3.01635200	-1.70262500
C	-1.58389600	-2.36833800	-0.19657800
C	-2.27011100	-1.31459100	0.47977500
C	-0.34587000	-2.90845900	0.23469300
C	-1.57469700	-0.76202500	1.59458000
C	0.29510000	-2.35537000	1.35988200
H	0.10898700	-3.70896600	-0.33285800
C	-0.32944400	-1.27168900	2.02494500
H	-2.00914800	0.07869300	2.12046900
H	1.23650200	-2.75768900	1.71094400
C	-3.59384400	-0.82662200	0.06639400
H	-3.85455600	-0.98345600	-0.97394200
C	-4.47861700	-0.23932600	0.87695000
H	-4.29814500	-0.09511100	1.93648000
H	-5.43002100	0.11030000	0.49559000
H	0.18706100	-0.77303200	2.83508500

21

Molecule TS1

Fe	-0.44150300	-0.52235500	-0.00618500
Mg	2.07663700	-1.12766400	-0.19803600
Mg	0.73392700	1.67571900	-0.12513400
Br	1.19725000	4.00018200	-0.00803700
Br	4.18034600	-2.23498000	-0.29193400
Cl	-1.34540500	-1.62822600	1.90529800
C	-2.24171100	-0.53853500	0.42565200
C	-3.31194200	-1.10071800	-0.33115000
C	-2.10019000	0.86281800	0.66724000
C	-4.10721100	-0.17567000	-1.00086600
C	-3.00225100	1.73716200	0.00084100
H	-1.61783300	1.21939500	1.56907500
C	-3.96099000	1.21957900	-0.84168600
H	-4.85583900	-0.54401700	-1.69328000
H	-2.95717200	2.80178800	0.20253400
C	-3.48201200	-2.55490700	-0.45148700
H	-2.63345400	-3.15447900	-0.13901400
C	-4.58873900	-3.18123300	-0.86299200
H	-5.49313000	-2.65132000	-1.14097200
H	-4.62358800	-4.26221800	-0.91936100
H	-4.64038600	1.88221000	-1.36451100

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Molecule 3

Fe	0.25998700	-1.49542400	-0.31805900
Mg	-2.23390100	-0.80140800	-0.08035500
Mg	0.30721800	1.02905000	-0.20092800
Br	0.38831400	3.36750500	-0.55627900
Br	-4.38492200	0.08705800	0.33448800
Cl	-1.35728400	-3.04247500	-0.33022900
C	1.83167300	-0.57383300	0.50757400
C	1.78700500	-0.20780900	1.87351700
C	3.11475800	-0.69446900	-0.10560000
C	2.94439300	0.01678900	2.61746900
H	0.82806800	-0.12421900	2.38016400
C	4.26688600	-0.42938100	0.64690100
C	4.18522500	-0.08706800	1.99333100
H	2.87650300	0.28316900	3.66596900
H	5.24020100	-0.47570800	0.17176800
C	3.20399100	-1.09606200	-1.52245700
H	2.28855000	-0.96130400	-2.09953300
C	4.26198700	-1.62288800	-2.14630100
H	5.20102000	-1.81708400	-1.64014900
H	4.21326900	-1.88849900	-3.19522500

H	5.09250300	0.11364500	2.55191300
18			
Molecule 4			
Fe	0.87212000	2.18614400	-0.28289300
Mg	-1.11905800	0.77019000	-0.09162300
Br	-3.08482300	-0.56116400	0.08174900
C	1.33816000	-0.17504000	-1.81541700
C	1.80121500	-1.46102700	-2.08268100
H	0.98992100	0.43219400	-2.64840400
C	2.24818900	-1.76835100	0.26775600
C	2.25979800	-2.25849600	-1.03365600
H	1.80991100	-1.83729600	-3.09984600
H	2.63060600	-2.38896800	1.07067800
C	1.75758700	0.03421600	1.93959000
H	1.74171500	1.12035500	2.03471000
C	1.73764400	-0.68250900	3.06836300
H	1.72307400	-1.76690100	3.06746200
H	1.72497600	-0.19771900	4.03706100
H	2.63107800	-3.25780000	-1.23068200
C	1.77927300	-0.47734100	0.55513900
C	1.32331700	0.36436000	-0.50534500
3			
Molecule P2			
Mg	0.00000000	0.00000000	-0.69375300
Cl	0.00000000	0.00000000	-2.88562500
Br	0.00000000	0.00000000	1.63944700
13			
Molecule R2			
Mg	0.72792400	-0.00028900	-0.00001100
Br	3.08433800	0.00005500	-0.00003400
C	-1.35077400	-0.00029800	0.00024700
C	-2.09211900	-1.19845500	0.00014900
C	-2.09158500	1.19818900	0.00015000
C	-3.48792200	-1.20387900	-0.00006300
H	-1.58387500	-2.16001500	0.00027800
C	-3.48739900	1.20424100	-0.00006300
H	-1.58294200	2.15954300	0.00027800
C	-4.18928000	0.00034000	-0.00018800
H	-4.02636300	-2.14607200	-0.00012900
H	-4.02541000	2.14668000	-0.00013000
H	-5.27386200	0.00057000	-0.00037600
31			
Molecule 5			

C	4.40816600	1.21746500	-0.99558200
C	3.13503000	0.74273800	-1.30572200
C	1.97909600	1.19812000	-0.62663100
C	2.15378500	2.17830100	0.39850100
C	3.44502700	2.62854400	0.70969900
C	4.55886300	2.15964800	0.01955100
H	5.27255900	0.84080000	-1.53011400
H	3.04237900	-0.00637900	-2.08739000
H	3.57787300	3.34438700	1.51314500
Mg	1.26101100	-0.92217300	0.12396000
Br	2.42524900	-2.90023400	-0.54538300
Fe	0.28425300	0.96559800	-1.48898000
Mg	-1.77911800	-0.17912900	-0.02878200
Br	-0.46344800	-1.05916400	2.00421800
C	-3.84587400	0.03784300	-0.33285700
C	-4.77314200	-0.27080100	0.68216400
C	-4.38456200	0.50385200	-1.54823700
C	-6.14997900	-0.12564100	0.49959000
H	-4.42632500	-0.63817200	1.64564600
C	-5.75887900	0.65353500	-1.74493100
H	-3.72607700	0.75840600	-2.37688000
C	-6.64648800	0.33823600	-0.71755700
H	-6.83391100	-0.37534700	1.30474300
H	-6.13654900	1.01369900	-2.69687900
H	-7.71526500	0.45180800	-0.86444000
C	0.97673900	2.73432200	1.09434600
H	0.11891600	2.06994000	1.17235200
C	0.87035100	3.96108500	1.61445800
H	-0.03689400	4.27745200	2.11493100
H	1.67164000	4.68929900	1.55120800
H	5.54651200	2.51963500	0.28503400

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Molecule TS2

C	3.53020400	2.27829400	-1.42446400
C	2.34050500	1.56280700	-1.52817900
C	1.37890100	1.55650000	-0.49049800
C	1.66789200	2.31321000	0.68663100
C	2.88274800	3.00851400	0.78382200
C	3.80112400	2.99711700	-0.26018600
H	4.24903200	2.25764600	-2.23557700
H	2.16132700	0.98797100	-2.43284600
H	3.11623400	3.55288800	1.69210200
Mg	1.28952800	-0.81616600	-0.07580900

Br	2.99824500	-2.19773000	-1.02326100
Fe	-0.41479700	1.02448500	-0.85435400
Mg	-1.72064900	-0.96016600	0.37065500
Br	-0.05043500	-2.07846000	1.86095100
C	-3.63044900	-0.30317300	-0.22359300
C	-4.59279600	0.21869600	0.66508600
C	-3.98161300	-0.31139900	-1.58945600
C	-5.82943900	0.69127900	0.22434900
H	-4.38838000	0.25622200	1.73286800
C	-5.21614500	0.15948900	-2.04345500
H	-3.28726600	-0.70365500	-2.33070400
C	-6.14389500	0.66288600	-1.13436100
H	-6.54843800	1.07976500	0.93872400
H	-5.45299500	0.13167400	-3.10233600
H	-7.10422300	1.02978300	-1.48018700
C	0.66425700	2.37496900	1.76569600
H	-0.04935500	1.54976700	1.78235300
C	0.53165400	3.32565900	2.69630600
H	-0.24604300	3.26523100	3.44793700
H	1.18082700	4.19334300	2.73739700
H	4.73640000	3.53628800	-0.16000800

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Molecule 6

C	-1.92562100	2.68568000	-2.29598400
C	-1.40000800	1.44302000	-1.95285000
C	-1.22477100	1.05359800	-0.60557100
C	-1.55761600	2.01229500	0.39267500
C	-2.06660300	3.27200500	0.03675500
C	-2.26068200	3.60416000	-1.29845400
H	-2.06480900	2.94398100	-3.34013900
H	-1.12113400	0.75999900	-2.75287400
H	-2.32998500	3.97815800	0.81661400
Mg	0.93037600	1.29924300	0.15902600
Br	2.58286100	3.01118800	0.26897100
Fe	-0.68959000	-0.78345900	-0.25551300
Mg	1.95627400	-1.53249800	-0.18091100
Br	3.59744200	-3.25220600	-0.27115700
C	-2.43002300	-1.47435200	0.02188100
C	-3.52992600	-1.50869700	-0.85242300
C	-2.48215100	-2.26715500	1.18225400
C	-4.62554200	-2.32709500	-0.58702300
H	-3.53590000	-0.88941800	-1.74474700
C	-3.57802800	-3.09267100	1.45139500

H	-1.65788500	-2.25300900	1.89835800
C	-4.65024100	-3.12102300	0.56329100
H	-5.46606300	-2.34697600	-1.27308700
H	-3.59599100	-3.70145700	2.34916500
H	-5.50701900	-3.75354900	0.76732700
C	-1.31653200	1.64852400	1.81220500
H	-1.65578700	0.65771200	2.10987100
C	-0.70613500	2.42622100	2.71681100
H	-0.33848500	3.41649800	2.46780300
H	-0.56017900	2.09137500	3.73738600
H	-2.66455300	4.57427900	-1.56300200

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Molecule 7

C	-2.85401600	-3.68829300	-1.81723800
C	-2.03799900	-2.56694200	-1.67938200
C	-1.92656400	-1.85797300	-0.46166300
C	-2.73518700	-2.30872400	0.61825000
C	-3.56870300	-3.42643200	0.47131100
C	-3.61995900	-4.11888000	-0.73512800
H	-2.89742400	-4.21812600	-2.76227400
H	-1.46679000	-2.24540300	-2.55187700
H	-4.16177800	-3.76344300	1.31434400
Mg	-2.77859000	0.25750200	-0.02701800
Br	-4.80762800	1.48019200	-0.31973300
Mg	2.93539300	-0.37644700	-0.06178300
Br	0.92540500	-0.92896200	1.37015800
Fe	-0.44907000	-0.59102000	-0.69346400
Cl	1.42066600	0.47721700	-1.78136700
Mg	-0.24670200	1.94810700	-0.35060600
Br	0.60971800	4.05514200	0.32016200
C	4.99693800	-0.64077800	-0.05630400
C	5.66151600	-1.27252400	1.01336200
C	5.80348500	-0.20185100	-1.12485000
C	7.04529000	-1.45668800	1.02043000
H	5.09861900	-1.63499800	1.87071400
C	7.18812300	-0.37971600	-1.12903600
H	5.35467500	0.29534100	-1.98189800
C	7.81252200	-1.00933000	-0.05375800
H	7.52368700	-1.94714100	1.86220200
H	7.77829400	-0.02682500	-1.96874200
H	8.88818700	-1.14918000	-0.05242500
C	-2.71226900	-1.54520200	1.89616200
H	-1.73232700	-1.35852100	2.32711800

C	-3.79859400	-1.05729200	2.51129700
H	-3.71584300	-0.50022600	3.43775500
H	-4.79767300	-1.19720500	2.11150000
H	-4.25814400	-4.98969500	-0.83150200

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Molecule TS4

C	-3.14165600	2.76441600	-0.31393100
C	-2.38942800	1.62179400	-0.56505100
C	-1.34290800	1.19043200	0.28482900
C	-1.06230700	2.02676200	1.40576900
C	-1.83551500	3.17447300	1.66116900
C	-2.87113400	3.54086500	0.81340900
H	-3.94143500	3.04491700	-0.99074100
H	-2.64306900	1.03205500	-1.44274100
H	-1.61928400	3.77092300	2.54057900
Mg	0.83488300	1.78955800	-0.34998100
Br	1.75136600	3.85690700	-1.13035100
Mg	-1.00604600	-3.02982800	0.08056900
Br	0.38699600	-2.00415100	1.84035900
Fe	-0.49462100	-0.47398900	-0.35270100
Cl	0.43402500	-2.47712100	-1.71734100
Mg	2.08481800	-0.97156400	-0.41792100
Br	4.37315600	-1.61187800	-0.27607100
C	-2.68230400	-1.84053500	-0.35907100
C	-3.58891300	-1.46194400	0.65708900
C	-3.17685400	-1.81929400	-1.68378100
C	-4.89372300	-1.06744100	0.37298900
H	-3.26282300	-1.45052400	1.69371900
C	-4.48065300	-1.42154200	-1.98076100
H	-2.52774400	-2.10743600	-2.50745100
C	-5.33988200	-1.04424000	-0.94927100
H	-5.56108200	-0.77110000	1.17525900
H	-4.82624300	-1.40648100	-3.00914100
H	-6.35427200	-0.73297900	-1.17435100
C	0.09810300	1.72190000	2.28173900
H	0.21774100	0.68660900	2.58351900
C	1.00712400	2.62309800	2.68065900
H	1.83608400	2.33684600	3.31803900
H	0.95675600	3.66444800	2.37923900
H	-3.45960200	4.42635600	1.02457900

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Molecule 8

C	-1.77290400	-3.89697200	-1.12412200
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C	-1.31713700	-2.58437800	-1.24130200
C	-0.91342600	-1.82605300	-0.11956600
C	-1.00616400	-2.45874700	1.15583000
C	-1.48119100	-3.77471000	1.26417000
C	-1.85642400	-4.49234600	0.13445200
H	-2.07559100	-4.44688700	-2.00831400
H	-1.25863000	-2.14658500	-2.23601100
H	-1.57577900	-4.23285900	2.24270100
Mg	-2.67959400	-0.36986900	-0.15967800
Br	-5.02994100	-0.73270000	-0.18935400
Mg	3.07262800	0.59928700	-0.07151900
Br	5.28483500	1.06242500	0.59096600
Fe	-0.01209500	-0.07520200	-0.19731900
Cl	1.22077700	2.09377300	-0.11750100
Mg	-1.37804500	2.31728300	-0.08555300
Br	-2.06445000	4.59060500	-0.03818200
C	1.67735100	-1.08486100	-0.59878100
C	2.35740200	-2.03333400	0.20609700
C	2.19964500	-0.91653500	-1.91382700
C	3.42941500	-2.78950400	-0.27583400
H	2.01843500	-2.20607500	1.22287600
C	3.26277000	-1.68506400	-2.40739200
H	1.73497800	-0.19781000	-2.58941600
C	3.87902100	-2.62511800	-1.58557600
H	3.91731300	-3.50586200	0.37608300
H	3.60919300	-1.53903800	-3.42481100
H	4.71126400	-3.21180900	-1.95575400
C	-0.56154300	-1.69195300	2.33331400
H	-0.55828900	-0.60310700	2.19939000
C	-0.16203800	-2.15886100	3.52099300
H	0.13626400	-1.48590800	4.31565500
H	-0.12024900	-3.22028200	3.74037700
H	-2.23170500	-5.50399700	0.23525300

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Molecule TS3

C	-2.71171500	1.19240000	-2.44366000
C	-1.91933400	0.16530800	-1.96912700
C	-1.73024000	-0.08151700	-0.56999600
C	-2.41629700	0.80822400	0.33360900
C	-3.23998400	1.82536300	-0.18238700
C	-3.39438700	2.02539800	-1.54585000
H	-2.80860400	1.34770100	-3.51248400
H	-1.41717100	-0.48343800	-2.68414300

H	-3.76699500	2.46484900	0.51650100
Mg	0.26123000	1.31309300	0.10709200
Br	0.65078300	3.65670600	0.32521300
Fe	-0.01122900	-1.08833700	-0.34097200
Mg	2.58255500	-0.76109600	-0.22044300
Br	4.94443500	-1.13057600	-0.16874700
C	-1.79050200	-1.82898700	-0.19721600
C	-2.82221200	-2.54739000	-0.82600400
C	-1.23435200	-2.34191100	0.98561100
C	-3.26500900	-3.73848200	-0.26272500
H	-3.27773000	-2.16764200	-1.73349900
C	-1.66155000	-3.54656400	1.54366700
H	-0.41564900	-1.78086700	1.49329500
C	-2.69572200	-4.23762600	0.91689200
H	-4.06005900	-4.29359200	-0.74838300
H	-1.19934800	-3.93623900	2.44359700
H	-3.05663600	-5.16819200	1.33889300
C	-2.23268100	0.68250900	1.79300100
H	-2.18598100	-0.32858100	2.18775600
C	-2.11003300	1.70795800	2.64646400
H	-2.09999600	2.74047800	2.31446100
H	-2.00156500	1.53502800	3.71090300
H	-4.03227100	2.82066000	-1.91137000

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Molecule P1

C	-2.89976200	0.59634600	0.07172700
C	-1.50692700	0.77544400	-0.00588300
C	-0.68383300	-0.37730400	0.02089200
C	-1.28842800	-1.64006000	0.07096900
C	-2.67110300	-1.79354700	0.11845900
C	-3.48321200	-0.66320200	0.12850200
H	-3.53452500	1.47650000	0.06526800
H	-0.65092100	-2.51693500	0.09871700
H	-3.10539200	-2.78585800	0.16366500
C	0.80907000	-0.33375600	0.04496900
C	1.55405700	-0.90172000	-0.99558800
C	1.49428500	0.21561600	1.13680600
C	2.94818100	-0.90745900	-0.95470000
H	1.03654400	-1.32967600	-1.84728900
C	2.88531900	0.20468100	1.18155500
H	0.93012100	0.65165700	1.95328600
C	3.61823300	-0.35364700	0.13372600
H	3.50854600	-1.34497000	-1.77362900

H	3.39879000	0.62942600	2.03713700
H	4.70186200	-0.35941600	0.16831400
C	-1.03904800	2.16989900	-0.14534200
H	-1.75930000	2.90485500	0.20918400
C	0.08425600	2.63279800	-0.70227300
H	0.85186300	1.98869800	-1.10979800
H	0.25777400	3.70105200	-0.76657400
H	-4.56189200	-0.75986400	0.17880000