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Feasibility of the Suzuki-Miyaura Cross-Coupling on a Model System†

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A density functional theory study at the level of B3LYP/6-311 G (d,p) is carried out on the Suzuki-Miyaura cross-coupling of aryl chlorides and arylboronic acids, in this work. The results on the structure parameters are in good agreement with the experimental findings in some aspects. However, discrepancies still arise in reasonable range. A static analysis of the reactants is obtained through the calculation in order to explain the feasibility of reaction in stereo-hindrance and electronic effect.

Key Words: Suzuki-Miyaura, Cross-coupling.

INTRODUCTION

Palladium-catalyzed Suzuki-Miyaura cross-coupling reaction between organoboron compounds and other various organic electrophiles[1], which is tolerant to extremely sensitive functional groups such as ester, aryl halides and arene diazonium tetrafluoroborate salts[2] *etc*., is one of the most important methods for the formation of C-C bonds[3,4] for the syntheses of natural products and pharmaceutical agents[5] in mild condition, even in water[6]. This reaction has been subjected in several experimental investigations to determine its reliable and widely applications in organic syntheses[7-9] and the 2010 chemistry Nobel prize was awarded for it (eqn. 1)[10].

$$\mathrm{R{-}B(OH)_2 + R'X \xrightarrow[base]{[Pd]} RR' + XB(OH)_2}$$

The mechanism of the Suzuki-Miyaura cross-coupling reaction has been reported massively, even though is still not fully understood (Fig. 1). Fig. 1 schematically presents the whole catalytic cycle when the reaction proceed. The progress of cross-coupling reaction mainly consists of three steps[11], (I) Oxidative addition, (II) transmetalation and (III) reductive elimination. The oxidative addition and reductive elimination are so common in transition-metal catalyzed reactions that the related researches are well explainable[12,13]. Or possibly the whole catalytic-cycle process of the cross-coupling reaction has been investigated with computational methods almost[14-24]. Nevertheless, the investigation on the spontaneousness, heat effect and the characteristic of these reactions is carried out rarely and comparatively less study is known about the feasibility of the reaction on a model system supported by experiment.

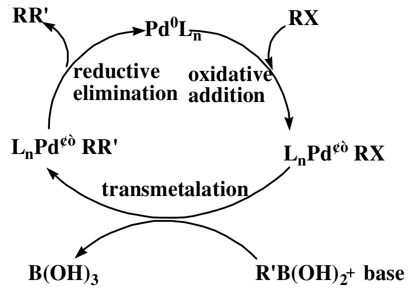

Fig. 1. n = 1,2

In this work, we use density functional theory to investigate the feasibility of the Suzuki-Miyaura cross-coupling reaction on a classic synthesis for Suzuki biaryl, aryl chlorides and aryl boronic acids, of which high synthetic interest and versatility are believed to proceed well documented[25,26]. And the catalyst is not on the carpet in our calculation because of the specific structure of the palladium complexes are undefined.

EXPERIMENTAL

To investigate the feasibility of the Suzuki-Miyaura reaction depicted in eqn. 2, the specific structure of catalyst we chose was not definite. However, the synthesis catalyzed by the palladium complexes was remarkable and the results regarding conversion and selectivity were maximal, K_2CO_3 and PEG-400 as base and solvent, respectively. The reactions were carried out at 140 ºC with I_2 and TBAB (entries **2a**, **2b**) as the additive.

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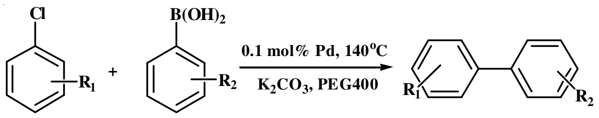
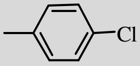
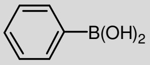
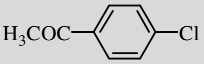
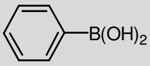
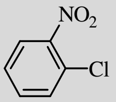
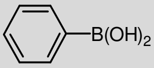
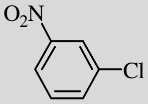
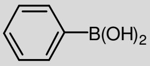
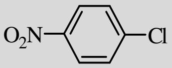
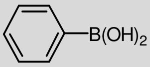


As can be seen from Table-1, a range of aryl chlorides and aryl boronic underwent the reaction in good to yield and different location of the group R$_1$ had effect on the yield. In all cases, the isolated yield was part of excellent ranging from 57 to 97 %. All reactions conducted on 0.5 mmol scale in 2 mL of solvent using 0.2 equiv. I$_2$ or 1.0 equiv. TBAB (entries **2a**, **2b**) as additive.

TABLE-1
SUBSTRATE SCOPE OF THE SUZUKI CROSS-COUPLING REACTION OF ARYL CHLORIDES WITH ARYLBORONIC ACIDS[a]

Entry	Aryl chlorides	Phenylboronic acid	t (h)	Yield (%[b])
1			48	64
2a			48	57[c]
2b			48	97[c]
2c			48	63
2d			25	90

a) Reaction conditions: chlorobenzene (0.5 mmol), arylboronic acid (1.5 equiv.), base (K$_2$CO$_3$, 2.0 equiv.), additive (I$_2$, 0.2 equiv.), PEG-400 (2 mL), temperature (140 °C); b) Isolated yield; c) Additive (TBAB, 1.0 equiv.)

Computational details: All calculations were performed with the Gaussian 98[27] software at the B3LYP/6-311 G (d, p) level, by means of DFT[28-30]. The geometries of the reactants and products were fully optimized without symmetry restriction normally. The analysis in the stability of molecular geometries above, evaluating of the thermal and entropic contributions, which were needed to derive the enthalpies, H$_{298}$ and Gibbs free enthalpies, G$_{298}$, at 298.15 K, were obtained through the calculation of vibration frequency in the rigid-rotor harmonic-oscillator approximation. Due to its high accuracy and convincing results, this method became up to our grade level of calculating.

RESULTS AND DISCUSSION

Fig. 2 showed the geometrical structures of the reactants and products, which were optimized involved in the reaction, the reaction enthalpies Δ_rH, the Gibbs free energies of reaction Δ_rG and the charge of all atoms calculated at the B3LYP 6-311 G (d, p) level of theory listed below Table-2.

In the Table-2, the Δ_rG and the Δ_rH of all the series of the reaction were less than zero, therefore, the Suzuki-Miyauya reaction on this model might take place spontaneously, without any catalysts and were exothermic. From the charge of atoms specially focused on the C-3, it was fact that the lower the negative charge density, the higher reactivity the reaction. It confirmed that the reaction was electrophilic substitution one according to the mechanism we mentioned before.

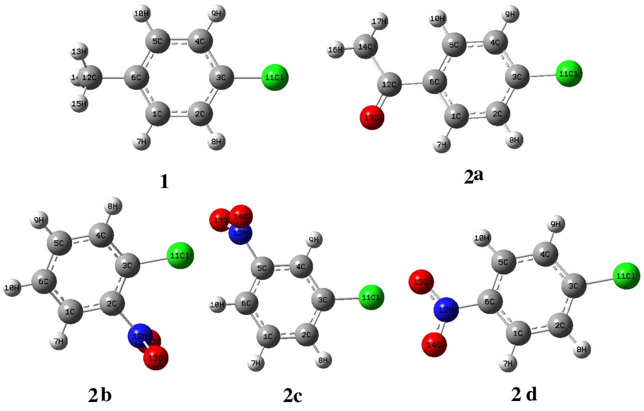
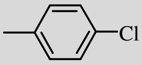
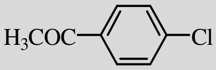
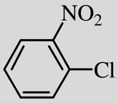
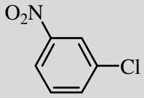
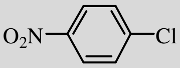


Fig. 2. Structures of reactants optimized by B3LYP 6-311 G (d, p) are shown. Colour code: C gray, N blue, O red, Cl green.

TABLE-2
PROPERTIES OF REACTANTS IN THERMODYNAMIC FUNCTION

Entry	Aryl chlorides	Δ_rH (kJ mol^{-1})	Δ_rG (kJ mol^{-1})	C-3 Charge (au[a])
1		-104.004	-96.0832	-0.215565
2a		-112.568	-110.809	-0.189809
2b		-122.624	-121.655	-0.169609
2c		-118.247	-116.735	-0.210852
2d		-110.279	-116.425	-0.178788

Reactivity comparison

Entry 1 and entry 2b: Obviously we summarized that the details of calculation of **1** (*p*-chloro toluene) and **2b** (*o*-nitro chloro benzene) agreed with the results of experiment well, relatively, the larger Δ_rG and 64 % yield of **1** compared to the less Δ_rG and 97% yield of **2b**. As it known, stereohindrance and electronic effect played a great role in progress of the reaction, but which one dominated the progress was not well understood. So we summed up that *p*-chloro toluene had the methyl in the position of -*p*, so the stereo-hindrance decreased relatively, but couldn't be ignored and also prevented the progress. On the other hand, the electronic effect promoted the reaction readily, on account of electronic rich of methyl. Everything taken into account, in contrary to the calculation and experiment, electronic effect was more important in the reaction than the stereohindrance. Effective persuasive messages were obtained when considered the **2b** in the two effects, also the *o*-nitro chloro benzene had the nitro in the *ortho* position, so the influence of stereo-hindrance is more and the progress proceeded hardly in theory. But the *o*-nitro promoted the reaction because of decreasing the electronic density of C-3 as a *meta*-position directing group. So, the electronic effect was still in the highest light rather than the stereo-hindrance effect.

Entries 1, 2a, 2b and 2c: It was proved that there was nothing else byproduct came up but only what was expect. So after 48 h the whole progresses of the reaction in entries **1, 2a, 2b** and **2c** completed but different level of yields obtained. We confirmed through the charge C-3 was the higher the electronic charge of C-3, the higher reactivity of the reaction had, for example, the charge of C-3 of **1**, **2a, 2c** were -0.2156 au, -0.1898 au and -0.2109 au, respectively. All of them were higher than -0.1696 au, the charge C-3 of **2b**, in accord with the related isolated yield, 64, 57, 63 and 97 %, respectively. And so did the related magnitudes of $\Delta_r G$, were -96.0832 kJ mol^{-1}, -110.809 kJ mol-1, -118.247 kJ mol^{-1} of **1, 2a, 2c** and the smallest -122.624 kJ mol^{-1}of **2b**. The results of experiment corresponded with the calculation.

Entries 2a and 2d: The charge of C-3 in **2a** was -0.1898 au compared with -0.1788 au of C-3 in **2d**, on the basis of the discussion of B, **2d** would get more reactivity in the progress than **2a** in yield, which fitted the experiment well, 90 % in 25 h of **2d** than 57 % in 48 h of **2a**. The $\Delta_r G$ of each of them also satisfied us in experiment and calculation, -110.809 kJ mol^{-1} of **2a** than -116.425 kJ mol^{-1} of **2d**.

Conclusion

In summary, the calculation of this computational study with B3LYP/6-311 G (d, p) DFT fits the results of present experiment well in some aspects. Although it is just an analysis in static state through the thermodynamic function and the charge on the optimized geometry, not in dynamics through the kinetics of the reaction.

The electronic effect plays a great role in Suzuki-Miyauya reaction on this kind model but not the stereo-hindrance effect and it is suggested that the result of this kind reaction in case of no catalyst in it. This work gives us a piece of information in advancing the Suzuki-Miyauya reactivity in aspects of choosing aryl chlorides with different kinds of substitutent groups.

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