



Investigation of Catalytic Activity and Kinetics of a Pd/Biphenyl-based Phosphine System in the Ullmann Cross-coupling of *Para*-substituted Aryl Bromides

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Catalytic activity of a Pd/biphenyl based- phosphine system in the Ullmann cross-coupling reaction of various para-substituted aryl bromides were investigated. The results showed that the bulky electron-rich phosphine efficiently modify the electronic and steric properties of palladium center and promote the cross-coupling reaction. Mechanistic study using the Hammett correlation reveals that electron-withdrawing substituents decrease the electron density at the palladium center and decrease the rate of oxidative-addition step such that this step will become the rate determining step (rds). On the other hand, electron-donating groups increase the rate of oxidative-addition step such that the reductive-elimination step will become the rds.

Keywords: Ullmann cross-coupling, Palladium catalyst, Phosphine, Hammett correlation, Mechanistic study

INTRODUCTION

The Ullmann coupling of aryl halides catalyzed by Pd(0) is one of the simplest route to achieve biaryls from corresponding aryl halides [1-9]. There are some proposed mechanisms for the Ullmann coupling which are different in some mechanistic details particularly the oxidation states of palladium in catalytic cycle. Among them, $0 \rightarrow 2 \rightarrow 4$ mechanism is the most generally accepted mechanism [10,11]. It involves a consecutive double oxidative addition of aryl halide on Pd(0) which leads to a Pd(IV) species. Bulky electron rich ligands such as phosphines increase the electron density on Pd, thus facilitate oxidative addition step [12,13]. They also control the steric environment of metallic center and affect on the contribution of these double consecutive oxidative addition steps on overall rate constants [14-16]. Pd(IV) intermediates are very unstable and readily convert into Pd(II) *via* the reductive elimination, the rate of which is usually increased by the coordination of bulky ligands to the palladium center. A terminal reducing agent is required to regenerate Pd(0) from Pd(II) in order to

make the reaction catalytic (Scheme 1) [17-20].

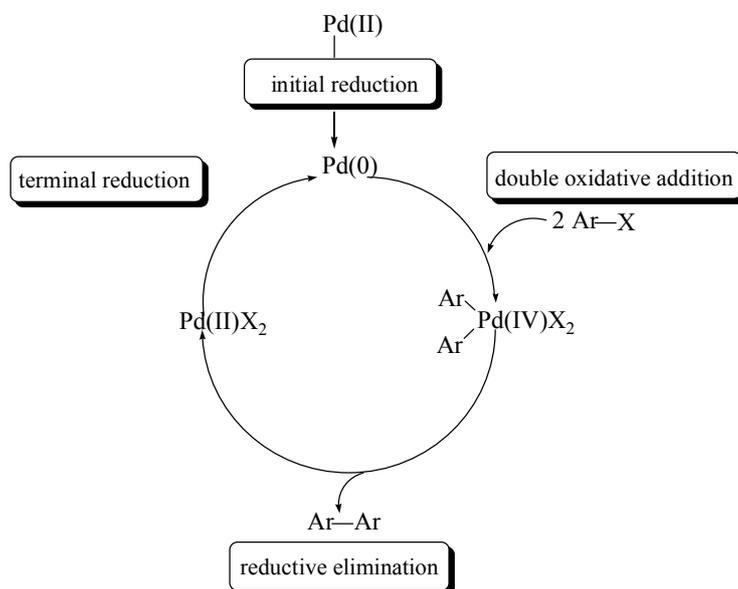
In contrast to other alternative coupling routes, it does not involve transmetallation step which makes it very useful for kinetics studies. This benefit will be enhanced by employing 4-substituted aryl halides which have no steric effect on coupling reaction center.

We have already investigated the catalytic activity of a Pd/biphenyl based-phosphine system in the Ullmann homocoupling reaction of various aryl bromides [21]. Biphenyl-based phosphines are bulky electron-rich ligands which stabilize metal-center by an arene-Pd interaction [22,23] and modify its electronic and steric properties. They have been employed in many cross-coupling reactions including Heck, Suzuki [24], Sonogashira, Negishi [25], amination [26,27] and α -arylation of carbonyl-containing compounds [28]. Herein, we reported the Ullmann cross coupling reactions of same catalytic system to gain further mechanistic information about the contribution of elementary steps in the overall rate of reaction.

EXPERIMENTAL

All chemicals were purchased from Fluka and Merck

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Scheme 1. General catalytic cycle for the Ullmann palladium-catalyzed coupling of aryl halides

companies and used without any further purification. 2-diphenylphosphino-2'-methylbiphenyl was prepared according to previously published procedure [29]. ^1H NMR spectra were recorded on a Bruker Avance 200 MHz spectrometer. ^{13}C NMR spectra were recorded on a Bruker Avance 100 MHz spectrometer. Thin layer chromatography was done on precoated silica gel Fluorescent 254 nm (0.2 mm) on aluminum plates. Gas chromatography was done using a Varian CP-3800 (column: CP-Sil 8 CB fused silica capillary column). All of the Ullmann reactions were carried out under an inert atmosphere of nitrogen. A cylinder of inert gas, fitted with a pressure regulator and needle valve is used as the source of inert gas. The apparatus setup involves an inlet for inert gas flow and an outlet for the unobstructed flow of the gas through a bubbler containing mineral oil.

General Procedure for the Cross-Coupling of Aryl Halides

A reaction tube was charged with two aryl halides, each (2.5 mmol), Et_3N (7.5 mmol), $\text{Pd}(\text{OAc})_2$ (0.2 mol%), phosphine (0.4 mol%) and 10 ml of DMF under a dry nitrogen atmosphere and the resulting mixture was heated at 100°C for 24 h. After extraction with diethyl ether

(3×20 ml) the combined organic layer was dried over MgSO_4 . The solvent was evaporated and the biphenyl product was characterized by ^1H NMR spectroscopy.

RESULTS AND DISCUSSION

The kinetic study of cross-coupling reactions is very important but is difficult due to wide variety of reactants involved in the reaction. On the other hand, most of catalytic cycles are very similar and involve similar elementary steps such as oxidative addition and reductive elimination. Studying the kinetics of the Ullmann coupling reactions is easier than other catalytic cycles because it involves only aryl halides as starting reactants. Therefore, the Ullmann coupling reaction can be considered as a suitable model for investigating the kinetics of other coupling reactions. Despite of many valuable researches on the cross-coupling reactions, almost all of them have focused on the presentation of new and efficient methods for the synthesis rather than the kinetic study.

Kinetic studies of catalytic cycles should be able to answer two basic questions, which mechanism is more likely and which step in the catalytic cycle is the slowest and rate-limiting step? To answer the first question, a

competitive reaction using equimolar amounts of 4-iodobenzene and 4-bromoanisole was performed to investigate the contribution of $0 \rightarrow 2$ and $0 \rightarrow 2 \rightarrow 4$ electron transfer mechanisms. Since, aryl iodides are more nucleophile than the corresponding aryl bromides, biphenyl is the only coupling product if $0 \rightarrow 2 \rightarrow 4$ is the main mechanism. However, in $0 \rightarrow 2$ mechanism, both homo and cross coupling products should be observed [10]. In our preliminary tests, no cross-coupling product was observed indicating a $0 \rightarrow 2 \rightarrow 4$ mechanism should be responsible.

To answer the second question, the steps of overall mechanism were first carefully analyzed. The first oxidative addition step requires the oxidation of electron-rich Pd(0) into Pd(II) while the second oxidation step is carried out from relatively electron-poor Pd(II) to Pd(IV). In addition, Pd(II) intermediate is more crowded than the initial Pd(0) precursor due to addition of an aryl and a halide ligands. Therefore, the first oxidation step was unlikely to be the rate determining step (rds) and was excluded. The terminal reduction step of Pd(II) to Pd(0) was also excluded since it is independent of the kind of aryl halide. This leaves the second oxidative addition and reductive elimination steps as possible candidates for the rate limiting step.

We used Hammett correlation to continue mechanistic study. The electronic property of para substitution effects on the rate of reaction. Electron donating groups enhance the oxidative addition step rate while electron withdrawing groups increase the reductive elimination step rate. The Hammett correlation can be considered as:

$$\frac{\log k_{RR'}}{\log k_{RR}} = \rho \sigma_p \quad (1)$$

where $k_{RR'}$ is related to the cross coupling of R and R' substituted aryl halide and k_{RR} is related to the homocoupling reaction of R substituted aryl halide. σ_p is the Hammett substituent constant [30,31] and ρ is the reaction constant. If the second oxidative addition is the rate limiting step, the rate should be increased by increasing the σ_p and therefore, the reaction constant, ρ , should be positive while if the reductive elimination is the rate limiting step, the rate should be decreased by increasing the σ_p and therefore, the reaction constant, ρ , should be negative. Since the turn over frequency is a measure of rate of reaction, the Eq. (1) can be

rewritten as:

$$\log TOF_{RR'} = \log TOF_{RR} + \rho \sigma_p \quad (2)$$

where $TOF_{RR'}$ is the turn over frequency of the cross-coupling reaction of R and R' substituted aryl halide and TOF_{RR} is the turn over frequency of homocoupling reaction of R substituted aryl halide. ρ can be obtained from the slope of the Hammett plot of $\log TOF_{RR'}$ against σ_p .

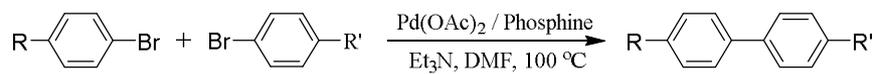
Using the optimized reaction conditions obtained for the homocoupling system [21], we investigated the cross-coupling reactions of various para-substituted aryl bromides. The results were shown in Table 1.

Mechanistic studies of Ullmann cross-coupling reaction of para-substituted aryl halides. Table 1 shows substituents on para position of aryl halides have great effect on the reaction yield. We used the corresponding turn over frequencies to investigate the effect of para-substituents on the rate and mechanism of the Ullmann cross-coupling reactions.

Figures 1a-f shows the plot of $\log TOF$ vs. the σ_p for all studied different aryl halides. These linear free energy relationships yield the corresponding reaction constant (ρ) for these aryl halides. All Figures involve two separate linear correlation with different slope signs.

The straight lines at the right-hand sides of Hammett graphs (with $\rho > 0$) show that the second oxidative-addition of aryl halide to Pd is the rate-limiting step. Less electron-withdrawing substituents (less positive σ_p) have higher reaction rate since the palladium center has more electron density. By increasing the rate of oxidative-addition step, the rate of this step will eventually be more than reductive elimination step and in this moment, the reductive elimination step will be rate limiting step. This change in mechanism led to change in reaction constant sign which is shown in the left-hand sides of Hammett graphs (with $\rho > 0$). For all studied aryl bromides but bromobenzene, this change in slope takes place at $\rho = 0$. It means that the rate of oxidative addition and reductive-elimination steps of cross-coupling of these aryl halides with bromobenzene are similar. In the case of bromobenzene itself (Fig. 1d), this similarity takes place at methyl substituent.

The highest reaction constant ρ -value were obtained for NH_2 and NO_2 substituents which means that the reaction

Table 1. The Hammett Parameters Calculated for Various *Para*-substituted Aryl Bromides

Entry	<i>R</i>	<i>R'</i>	$\sigma_p(R)$	<i>logTOF</i>	ρ
1	NH ₂	OMe	-0.27	1.53	
2	NH ₂	Me	-0.17	1.58	0.63
3	NH ₂	H	0.0	1.70	
4	NH ₂	COMe	0.55	1.51	-0.50
5	NH ₂	NO ₂	0.78	1.30	
6	OMe	NH ₂	-0.66	1.53	
7	OMe	Me	-0.17	1.72	0.41
8	OMe	H	0.0	1.81	
9	OMe	COMe	0.55	1.65	-0.33
10	OMe	NO ₂	0.78	1.54	
11	Me	NH ₂	-0.66	1.58	
12	Me	OMe	-0.27	1.72	0.33
13	Me	H	0.0	1.79	
14	Me	COMe	0.55	1.70	-0.24
15	Me	NO ₂	0.78	1.60	
16	H	NH ₂	-0.66	1.70	0.27
17	H	OMe	-0.27	1.81	
18	H	Me	-0.17	1.79	-0.08
19	H	COMe	0.55	1.74	
20	H	NO ₂	0.78	1.72	

Table 1. Continued

21	COMe	NH ₂	-0.66	1.51	
22	COMe	OMe	-0.27	1.65	0.37
23	COMe	Me	-0.17	1.70	
24	COMe	H	0.0	1.74	
25	COMe	NO ₂	0.78	1.48	-0.34
26	NO ₂	NH ₂	-0.66	1.30	
27	NO ₂	OMe	-0.27	1.54	0.63
28	NO ₂	Me	-0.17	1.60	
29	NO ₂	H	0.0	1.72	
30	NO ₂	COMe	0.55	1.48	-0.48

^aReaction condition: bromobenzene (2.5 mmol), aryl halide (2.5 mmol), Pd(OAc)₂ (0.2 mol%), phosphine (0.4 mol%), NEt₃ (7.5 mmol), DMF (10 ml), 100 °C, 5 h, N₂.

rate for 4-bromoaniline and 1-bromo 4-nitrobenzene is very susceptible to the electronic property of para-substituents of cross-coupling reactant. This susceptibility is very significant for the right-hand side of 4-bromoaniline plot wherein, the rds is reductive-elimination step. and for the left-hand side of 1-bromo 4-nitrobenzene plot wherein the rds is the second oxidative-addition step. The least slope belongs to un-substituted bromobenzene which reveals the similar contribution of both reductive-elimination and oxidative-addition steps.

CONCLUSIONS

Mechanistic study using the Hammett correlation reveals that both reductive-elimination step and the second-oxidative addition steps are very important in rate of the Ullmann cross-coupling reactions. Electron-withdrawing substituents decrease electron density at the palladium center and decrease the rate of oxidative-addition step such that this step will become the rds. On the other hand,

electron-donating groups increase the rate of oxidative-addition step such that the reductive-elimination step will become the rds.

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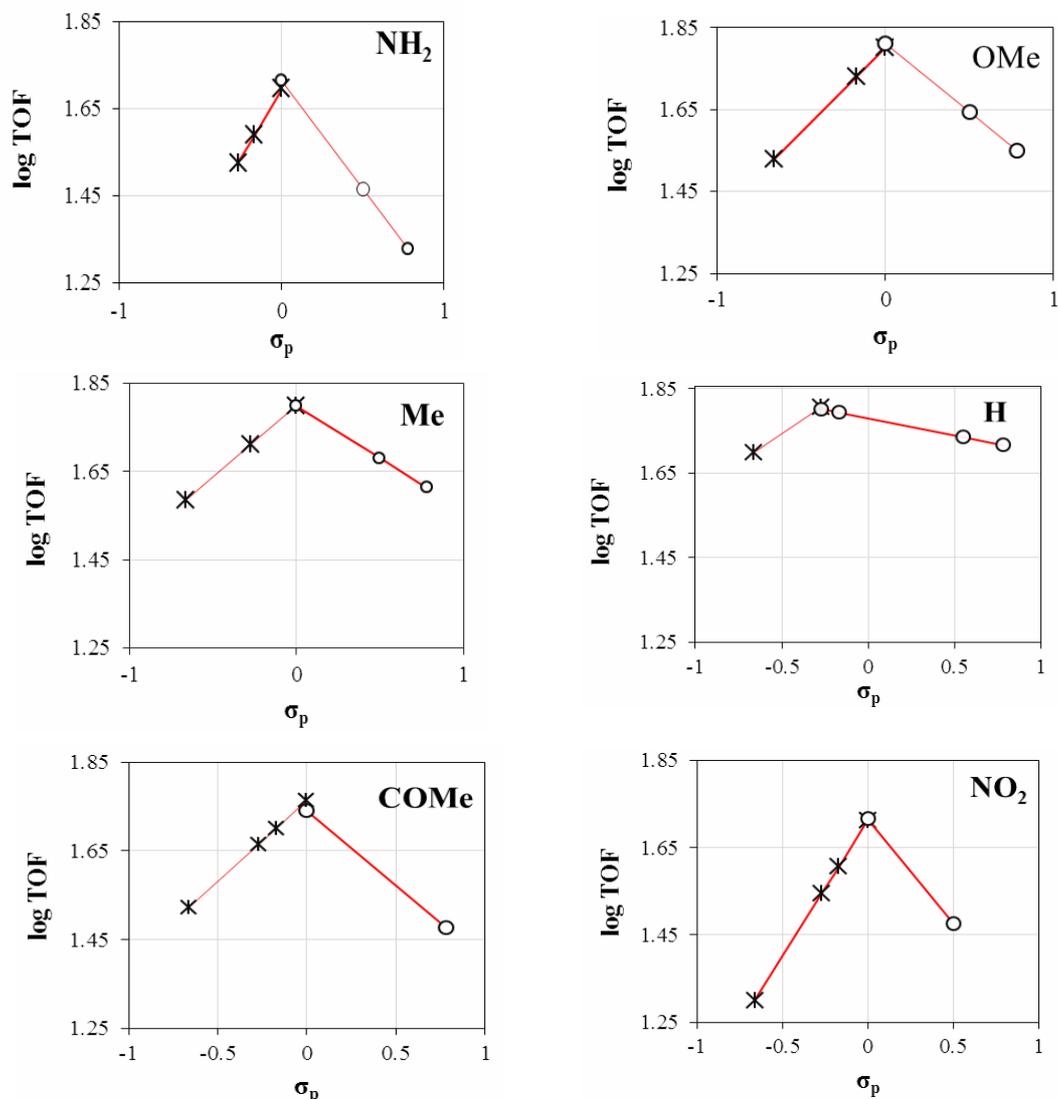


Fig. 1. The plots of $\log TOF$ vs. σ_p for all studied different aryl halides.

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