



INVESTIGATION OF THE ACTIVITY OF PALLADIUM CATALYSTS WITH ARYL-FERROCENYL-PHOSPHINE LIGANDS IN SUZUKI-MIYaura REACTION

A. T. KHABIYEV^{*a,b} and B. S. SELENOVA^a

^aKazakh National Technical University named after K. I. Satpaev, 22 Satpaev Str.,
Kz-050013 ALMATY, KAZAKHSTAN

^bChemnitz University of Technology, 62 Strasse der Nationen Str., D-09010 CHEMNITZ, GERMANY

ABSTRACT

This study examined investigation of the activity of palladium catalysts with aryl-ferrocenyl-phosphine ligands in Suzuki-Miyaura reaction. The conversion of halogen aryl compounds were analyzed by ¹H NMR spectroscopy. The advantage of Suzuki reactions in comparison with other cross-coupling reactions is in the usage of water- and oxygen-insensitive thermostable organoboron compounds. Phenylboronic acid was used as boronic acid and potassium carbonate as weak base. All used catalysts showed good activity with aryl bromides and weak activity with aryl chlorides.

Key words: Ferrocene, Palladium catalysts, C,C-cross-coupling reactions, Suzuki-Miyaura reaction, Homogeneous catalyses.

INTRODUCTION

Suzuki-Miyaura reaction with organoboron compounds (mainly boric acid) in the cross-coupling reactions have the advantage of high thermo-stability, low sensitivity to water and oxygen and low toxicity in comparison with other organometallic substances (for example, organozinc compounds in Negishi reaction or organotin compounds in Stille-Millstein reaction) and as a rule carried out by temperature 100°C and pressure 1 atm. It has an industrial scale in the pharmaceutical and fine chemicals. An example of such application is large-scale production of 2-cyano-4-methylbiphenyl – an intermediate in the synthesis of antagonist angiotensin II^{1,2}, synthesis of liquid-crystal compounds³, antibiotics, for instance vancomycin^{4,5}.

Sterically demanding and strongly Lewis-basic ferrocene-based phosphines are of the highest importance in the Suzuki-Miyaura catalytic reactions⁶⁻⁸. Kinetic of this reactions

* Author for correspondence; E-mail: alibek1324@mail.ru

as well as computational investigations have shown that these ligands accelerate the oxidative addition, which is believed to be the rate determining step⁹⁻¹⁵.

All catalysts represented in this paper showed good activity with aryl bromides and weak activity with aryl chlorides.

EXPERIMENTAL

All reactions were carried out under an atmosphere of nitrogen or argon using standard Schlenk techniques. Phenyl boronic acid (157 mg, 1.3 mmol), potassium carbonate (404 mg, 3 mmol), 0.5 mol % of applicable catalyst (1-5, fig. 1), precursor-palladium acetate (1.12 mg, 0.01 mmol) and internal standard-acetyl ferrocene (38 mg, 0.17 mmol) were dissolved in toluene. After addition of 1 mmol of the appropriate aryl bromide (2-bromotoluene, 2-bromomesitilene and 4-bromoanisole) or aryl chloride (2-chlorotoluene, 4-chloroacetophenone and 4-chloroanisole) the reaction mixture was stirred for 1 h at 100°C. Samples of 1 mL were taken after 3, 5, 15, 20, 30, and 60 min and chromatographed on silica gel or alumina with diethyl ether as eluent. Toluene and diethyl ether were purchased in Sigma-Aldrich and purified by distillation from sodium/benzophenone. Alumina with a particle size of 90 mm (standard, Merck KGaA) or silica with a particle size of 40-60 mm (230-400 mesh (ASTM), Becker) was used for column chromatography. All reagents (bromoaryls, bromochlorides, palladium acetate, acetylferrocene and deuterated chloroform) manufactured by Sigma-Aldrich, excepting the synthesized catalysts, were obtained from commercial suppliers and were used without further purification. All volatiles were evaporated under reduced pressure and the conversions were determined by ¹H NMR spectroscopy. The ¹H NMR spectra were recorded with a Bruker Avance III 500 spectrometer operating at 500.303 MHz in the Fourier transform mode. Chemical shifts are reported in δ (parts per million) downfield from tetramethylsilane with the solvent as reference signal (¹H NMR: CHCl₃, δ 7.26; ¹³C {1H} NMR: CDCl₃, δ 77.00). Interpretation of ¹H NMR spectra was performed with the help of MestReNova computer program and shown in Table 1. Five Suzuki-Miyaura catalysts (2-metoxypheyl-, 2-tretbutyloxyphenyl-, 2-metoxynaphtyl-, phenyl-dipherrocenylphosphine and 1,1'-diphenylphosphiniferrocene) were prepared according to procedures published at the Chemnitz University of Technology¹⁶.

RESULTS AND DISCUSSION

5 catalysts for Suzuki-Miyaura reaction were synthesized and studied in laboratories of the Department of Inorganic Chemistry at the Chemnitz University of Technology (Germany) and in the Laboratory of Engineering Profile at the Kazakh National Technical University (Fig. 1).

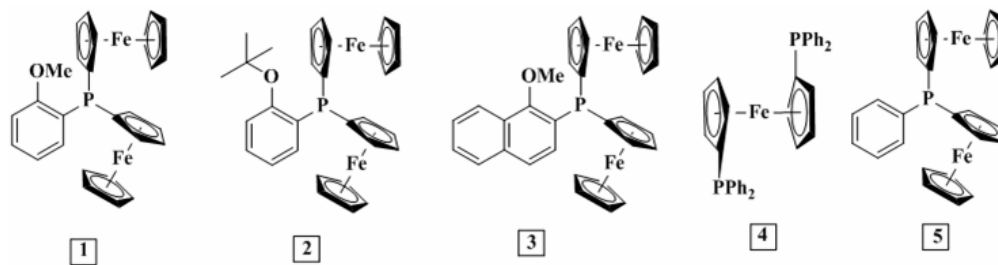


Fig. 1: Catalysts for Suzuki-Miyara reaction (1-5)

Each of the products (substituted biphenyls) and initial compound (halogenoaryls) contain easily analyzable hydrogen peak at methyl group in ^1H NMR spectra (Table 1). Internal standard – acetylferrocene with ^1H NMR signal of the methyl group at 4.08 was added to the original reaction mixture for more convenient and accurate calculation of the yield of products. Yield of the reaction was calculated by integration of the peaks corresponding to the protons of the methyl groups.

Table 1: ^1H NMR signals of methyl group of initial compound and product

	Structure and name of initial compound	Signal of methyl group of initial Compd.	Structure and name of product	Signal of methyl group of product
	1	2	3	4
a	 4-chloroacetophenone	2.48	 4-acetyl-1,1'-biphenyl	2.53
b	 2-chlorotoluene	2.30	 2-methyl-1,1'-biphenyl	2.18
c	 4-chloroanisole	3.68	 4-methoxy-1,1'-biphenyl	3.75
d	 2-bromomesitylene	2.27 (6H), 2.13 (3H)	 2,4,6-trimethyl-1,1'-biphenyl	1.9 (6H), 2.23 (3H)

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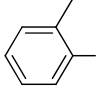
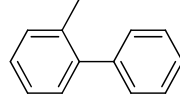
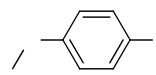
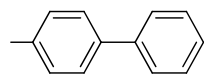
	Structure and name of initial compound	Signal of methyl group of initial compd.	Structure and name of product	Signal of methyl group of product
	1	2	3	4
e	 2-bromotoluene	2.30	 2-methyl-1,1'-biphenyl	2.18
f	 4-bromoanisole	3.68	 4-methoxy-1,1'-biphenyl	3.75

Fig. 2 shows catalytic activity of catalyst 1-2-methoxyphenyl diphferrocenylphosphine in the Suzuki-Miyara reaction. 4-bromoanisole has the highest conversion among various aryl halogenides. Catalyst 1 comprise the following series with respect to decreasing specific catalytic activity in the Suzuki-Miyara reaction: f (99.2 %) > a (95 %) > e (90 %) > d (76.3 %) > b (4.3 %) > c (2.7 %).

Br

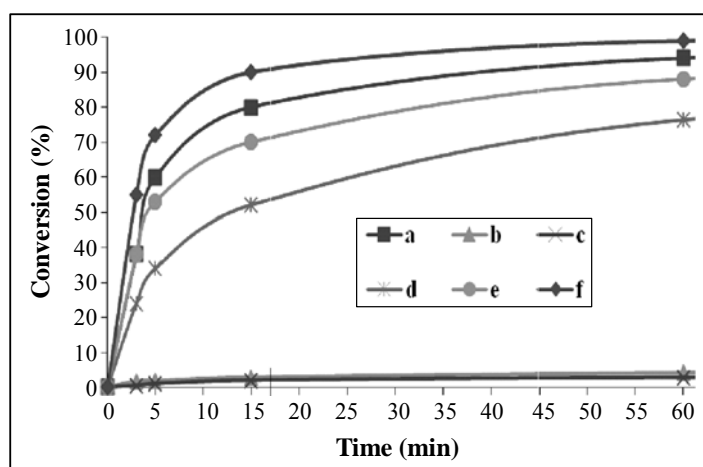


Fig. 2: The conversion of aryl halogenides a-f in Suzuki-Miyaura reaction with the usage of catalyst 1

From Fig. 3, it can be seen that the catalytic activity of catalyst 2-2-tretbutyloxyphenyl diphferrocenylphosphine shows lower conversion in comparison with catalyst 1 (Fig. 2). As well as for catalyst 1 4-bromoanisole has the highest conversion among various aryl halogenides. Furthermore, the following series with respect to decreasing specific catalytic

activity in the Suzuki-Miyaura reaction was built after analyzing the results of experiments: $f (99.6 \%) > a (97.3 \%) > e (92 \%) > b (15.7 \%) > c (2.9 \%) > d (1.5 \%)$.

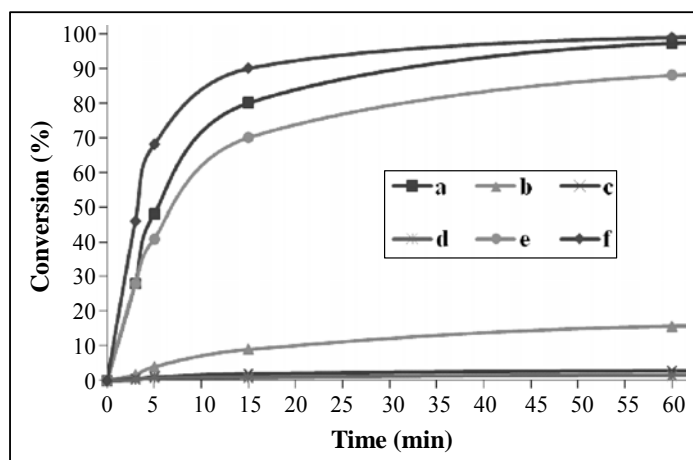


Fig. 3: The conversion of aryl halogenides a-f in Suzuki-Miyaura reaction with the usage of catalyst 2

4-bromoanisole shows the highest conversion for catalyst 3-2-metoxynaphthyl-diphenylphosphine in comparison with halogenoaryls a-f in Fig. 4. The result of activity of catalyst 3 is represented in following series with respect to decreasing specific catalytic activity in the Suzuki-Miyaura reaction: $f (99.3 \%) > a (96 \%) > e (91 \%) > d (76.3 \%) > b (4.4 \%) > c (2.8 \%)$.

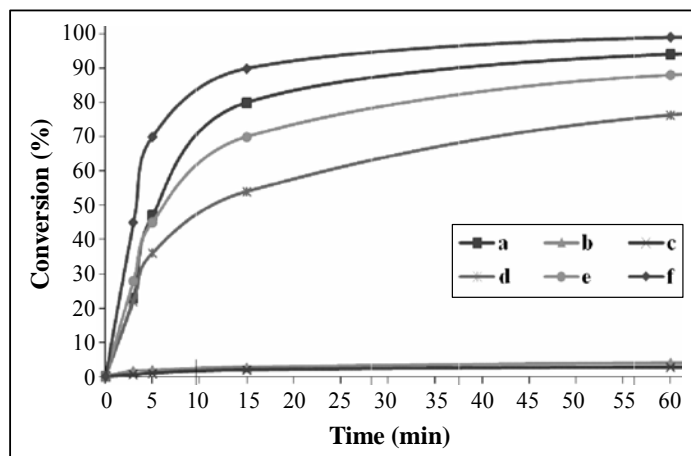


Fig. 4: The conversion of aryl halogenides a-f in Suzuki-Miyaura reaction with the usage of catalyst 3

The highest catalytic activity depicted in Fig. 5 is observed for 4-bromoanisole with the usage of catalyst 4-phenyl-dipferrocenylphosphine. As mentioned above, bromoaryls have a significantly higher activity than the aryl chlorides. Catalyst 4 comprise the following series with respect to decreasing specific catalytic activity in the Suzuki-Miyara reaction: f (99.1 %) > a (94.4 %) > e (89 %) > d (78 %) > b (4.2 %) > c (2.6 %).

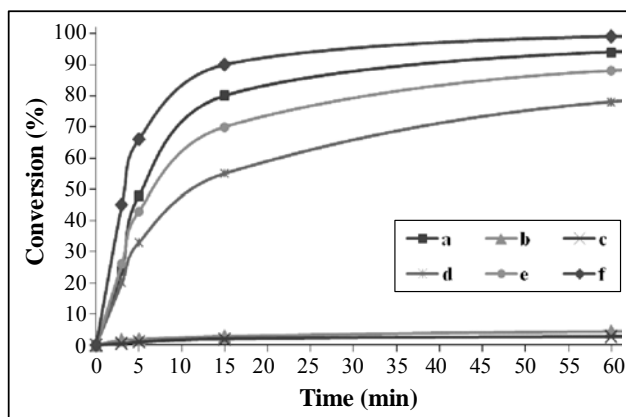


Fig. 5: The conversion of aryl halogenides a-f in Suzuki-Miyaura reaction with the usage of catalyst 4

Fig. 6 shows the catalytic activity of catalyst 5-1,1'-diphenylphosphiniferrocene. Conversion of 4-bromoanisole for catalyst 5 as well as for catalysts 1-4 is the highest among aryl halogenides a-f. The following series with respect to decreasing specific catalytic activity in the Suzuki-Miyara reaction was built after analyzing the results of experiments: f (99 %) > a (94 %) > e (88 %) > d (76.3 %) > b (4.1 %) > c (2.5 %).

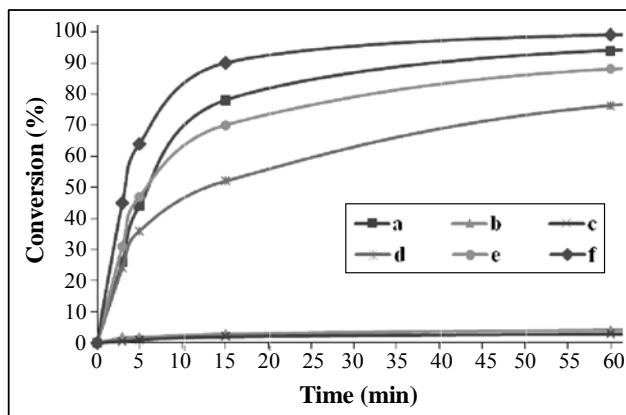


Fig. 6: The conversion of aryl halogenides a-f in Suzuki-Miyaura reaction with the usage of catalyst 5

CONCLUSION

As it can be seen from Figure 2-6, all compounds are catalytically active and the best catalyst for the Suzuki-Miyaura reaction is catalyst 2. Electron-rich phosphine ligands are best suitable in the Suzuki-Miyara reaction, which correlates with our results. The great variety and the low price of organic chlorides make them attractive for the application in industrial scale. However, often organic aryl-chlorides due to the relative high stability of the C-Cl bond exhibit low activity and as a result of poor performance are not used in the cross-coupling reactions. Catalytic activity of catalysts 1-5 in the Suzuki-Miyaura reaction with aryl halogenides a-f has the following series: cat. 2 > cat. 3 > cat. 1 > cat. 4 > cat. 5. All in situ generated phosphino palladium species showed moderate to high catalytic activity with aryl bromides (d-f) toward the formation of biphenyl derivatives. It was found that the diphosphine ferrocenyl species (cat. 4) were less active and productive than the catalysts based on diferrocenyl phosphines (cat. 1, cat. 2, cat. 3 and cat. 5). The diferrocenyl systems featuring phenyl (cat. 1, cat. 2 and cat. 5) and naphthyl (cat. 3) groups show a similar activity and productivity with conversions of 94-100% within 1 hour excepting chloroaryls. The most active among bromoaryls d-f is 4-bromoanisole and among chloroaryls is 4-chloroacetophenone. 4-bromoanisole contains an activating methoxy-located at the para-position and 4-chloroacetophenone-methyl carbonyl group. All catalysts (1-5) showed 100% reaction yield within 24 hour with aryl bromides.

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