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Palladium(II)-catalyzed Suzuki–Miyaura Reactions of Arylboronic Acid with Aryl Halide in the Presence of Aryl-Ferrocenyl-Phosphines

A.T. Khabiyev* and B.S. Selenova

Kazakh National Technical University named after K.I. Satpaev,
2 Satpaev str., 050013, Almaty, Kazakhstan

Abstract

This study examined investigation of catalytic activity of aryl-ferrocenyl-phosphine (2-methoxyphenyl diferrocenyl phosphine (cat. 1), 2-tert-butyloxyphenyl diferrocenyl phosphine (cat. 2), 2-methoxynaphtyl diferrocenyl phosphine (cat. 3), 1,1'-bis(diphenylphosphino) ferrocene (cat. 4), phenyl diferrocenyl phosphine (cat. 5)) ligands with palladium salts as precursors in Suzuki–Miyaura reaction. Suzuki–Miyaura reaction is one of the important cross-coupling reactions and extremely powerful in forming C–C bonds. Aryl-ferrocenyl-phosphine ligands confer unprecedented activity for these processes, allowing reactions to be performed at low catalyst levels, to prepare extremely hindered biaryls and to be carried out, in general, also for reactions of aryl chlorides by temperature 100 ºC and pressure 1 atm. Sterically demanding and strongly Lewis-basic ferrocene-based phosphines are water- and oxygen-resistant. The Suzuki–Miyaura reaction is also an important reaction in the ground and fine organic synthesis, in the production of drugs and intermediates. To analyze the conversion of halogen aryl compounds the ^{1}H NMR spectroscopy was used. The advantage of Suzuki–Miyaura reaction in comparison with other cross-coupling reactions (Kumada-, Heck-, Heck-Carbonylation-, Murahashi-, Sonogashira-, Negishi-, Stille-reaktion, etc.) is in the usage of low toxic, water- and oxygen-insensitive thermostable organoboron compounds. As boronic acid was used phenylboronic acid and as weak base – potassium phosphate. Catalyst, precursor and weak base were dissolved in toluene. All reactions were performed under an atmosphere of nitrogen or argon. The catalytic cycle of Suzuki–Miyaura reaction typically includes three main steps: oxidative addition of the haloaromatic to catalytic active palladium (0) species, transmetalation, and reductive elimination of the product under back formation of catalytically active species. All used catalysts showed good activity with aryl bromides and weak activity with aryl chlorides.

Keywords: ferrocene, palladium catalysts, C,C-cross-coupling reactions, Suzuki–Miyaura reaction, homogeneous catalyses.

Introduction

Recently palladium catalysts and C,C-cross-coupling reactions find application in synthesis of various chemicals in pharmaceutical and electronic industry, in petrochemistry, in generation of liquid crystals [1], solar cells [2], etc. An example of such application is large–scale production of 2-cyano-4-methylbiphenyl [3] – an intermediate in the synthesis of antagonist angiotensin II [4], synthesis of liquid–crystal compounds [5], antibiotics, for instance vancomycin [6]. With these catalysts it is possible to construct large molecules from small. In 2010 specialists from pharmaceutical company GlaxoSmithKline (GSK) published a work, where they calculated, that 17% of all "medical" reactions are catalyzed by palladium catalysts [7]. It should be noted that not only heterogeneous catalysts are widely used in the chemical and petroleum industries, but also homogeneous metal complex catalysts. They characterized by high selectivity and enable to create cost-effective and environmentally friendly processes. In several cases homogeneous metal complex catalysts have significant advantages over homogeneous catalysts.

Among diverse C,C-cross-coupling reactions it is necessary to single out Suzuki–Miyara reaction, representing a combination of aryl- or vinyl boronate

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* Corresponding author. E-mail: alibek1324@mail.ru

with aryl halides. Due to the high thermo-stability, low sensitivity to water and oxygen and low toxicity of boronic acids in Suzuki–Miyara reaction in comparison with Li-, Mg-, Al- and Zn- organometallic substances it is possible to use different functional groups and synthesize large amount of various organic substances.

Suzuki–Miyara reaction usually carried out by temperature 100 ºC and pressure 1 atm. Sterically demanding and strongly Lewis-basic ferrocene-based phosphines are of the highest significance in the Suzuki–Miyaura catalytic reaction [8-9]. Kinetic of this reaction as well as computational investigations have shown that these ligands accelerate the oxidative addition, which is believed to be the rate determining step [10-11].

All catalysts represented in this paper showed good activity with aryl bromides and weak activity with aryl chlorides. This phenomenon is explained by the difference in the strength of the chemical bond C-Cl (96 kcal·mol^{-1}) and C-Br (81 kcal·mol^{-1}) [12].

Experimental

All reactions were performed under an atmosphere of nitrogen or argon using standard Schlenk techniques. Phenyl boronic acid (157 mg, 1.3 mmol), potassium phosphate tribasic (636.81 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 ºC. 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 (Aluminum Oxide 90 Acidic) with a particle size of 90 µm (standard, Merck KGaA) or silica with a particle size of 40-60 µm (230-400 mesh (ASTM), Becker) was used for column chromatography. All reagents (bromoaryls, bromochlorides, palladium acetate, potassium phosphate tribasic, 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 ^{1}H NMR spectroscopy. The ^{1}H 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) down field from tetramethylsilane with the solvent as reference signal (^{1}H NMR: $CHCl_3$, δ 7.26; $^{13}C\{^{1}H\}$ NMR: $CDCl_3$, δ 77.00). Interpretation of ^{1}H NMR spectra was performed with the help of MestReNova computer program and shown in Table 1. Five aryl-ferrocenyl-phosphine ligands (2-metoxyphenyl-, 2-tretbutyloxyphenyl-, 2-metoxynaphtyl-, phenyl-dipherrocenyl phosphine and 1,1'-diphenylphosphin ferrocene) were prepared according to procedures published at the Chemnitz University of Technology [13].

Results and Discussion

5 aryl-ferrocenyl-phosphine catalysts for Suzuki–Miyaura reaction (2-methoxyphenyl diferrocenyl phosphine (cat. 1), 2-tert-butyloxyphenyl diferrocenyl phosphine (cat. 2), 2-methoxynaphtyl diferrocenyl phosphine (cat. 3), 1,1'-bis(diphenylphosphino) ferrocene (cat. 4), phenyl diferrocenyl phosphine (cat. 5)) ligands with palladium salts as precursors) 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).

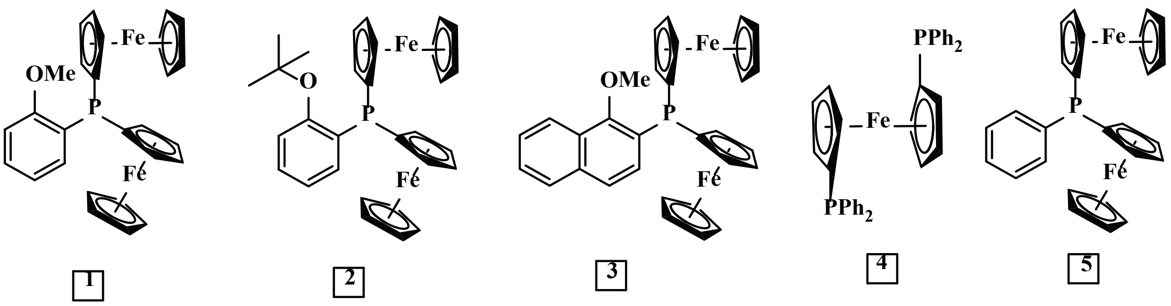


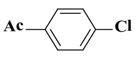
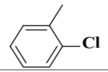
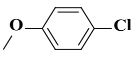
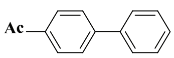
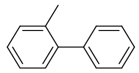
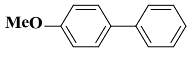
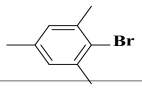
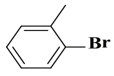
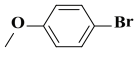
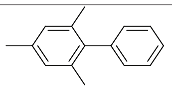
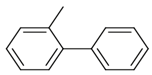
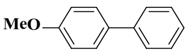
Fig. 1. Catalysts for Suzuki–Miyara reaction (1-5).

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

Figure 2 shows catalytic activity of catalyst 1 – 2-metoxyphenyl dipherrocenylphosphine 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 (99.5 %) > a (96 %) > e (91,4 %) > d (79.1 %) > b (4.6 %) > c (3.4 %). The following series of catalytic conversion can be explained on the basis of the structure of aryl halides. Bromoaryls as mentioned above due to the weaker chemical bond of C-Br than C-Cl are more active substances in the Suzuki-Miyara reaction. Among bromoaryls 4-bromoanisole is more active than 2-bromotoluene and 2-bromomesitilene. 2-bromotoluene is more active than 2-bromomesitilene. This phenomenon can be explained by analyzing the structure of bromoaryls. 4-bromoanisole contains in its composition methoxy-group in para-position which is capable to activate brom. 2-bromotoluene and 2-bromomesitilene contains in its composition one and two methyl-group respectively. Methyl-group causes steric hindrance in the formation of a complex with the catalyst and reduces the activity of the catalyst in Suzuki–Miyara reaction. The similar situation is observed by chloroaryls. 4-chloroacetophenone is more active than 2-chlorotoluene and 4-chloroanisole, because it contains in its composition acetyl-group in para-position which is capable to activate chlor. 2-chlorotoluene and 4-chloroanisole are inactive in Suzuki–Miyara reaction. In 2-chlorotoluene methyl-group probably causes steric hindrance in the formation of a complex with the catalyst and in 4-chloroanisole methoxy-group is not sufficiently active to activate chlor.

Table 1

^{1}H NMR signals of methyl group of initial compound and product

Initial compound-aryl chloride			
Structure			
Name	4-chloroacetophenone	2-chlorotoluene	4-chloroanisole
Signal of methyl group	2.48	2.30	3.68
Conventional sign	a	b	
Product			
Structure			
Name	4-acetyl-1,1’-biphneyl	2-methyl-1,1’-biphenyl	4-metoxy-1,1’-biphenyl
Signal of methyl group	2.53	2.18	3.75
Initial compound-aryl bromide			
Structure			
Name	2-bromomesitilene	2-bromotoluene	4-bromoanisole
Signal of methyl group	2.27 (6H), 2.13 (3H)	2.30	3.68
Conventional sign	d	e	f
Product			
Structure			
Name	2,4,6-trimethyl-1,1’-biphenyl	2-methyl-1,1’-biphenyl	4-metoxy-1,1’-biphenyl
Signal of methyl group	1.9 (6H), 2.23 (3H)	2.18	3.75

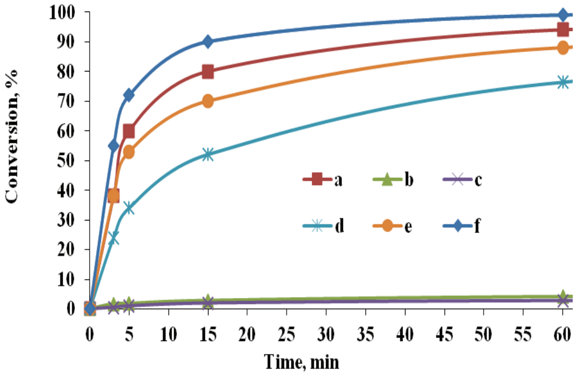


Fig. 2. The conversion of aryl halogenides a–f in Suzuki – Miyaura reaction with the usage of catalyst 1.

From Fig. 3 it can be seen that the catalytic activity of catalyst 2 – 2-tretbutyloxyphenyl dipherrocenylphosphine 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–Miyara reaction was built after analyzing the results of experiments: f (98.5 %) > a (98.5 %) > e (91.1 %) > b (18.4 %) > c (3.4 %) > d (1.8 %). In comparison with catalyst 1, catalyst 2 contains 2-tretbutyloxy-group instead 2-metoxy-group. 2-tretbutyloxy-group of catalyst 2 causes steric hindrance in the formation of a complex with three methyl-groups of 2-bromomesitilene. As a result, the activity of 2-bromomesitilene with catalyst 2 is the lowest.

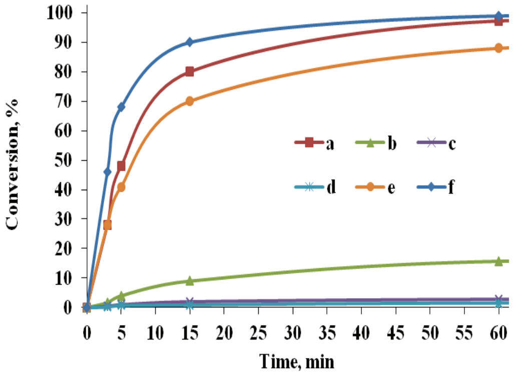


Fig. 3. The conversion of aryl halogenides a–f in Suzuki–Miyaura reaction with the usage of catalyst 2.

4-bromoanisole shows the highest conversion for catalyst 3 – 2-metoxynaphtyl-dipherrocenylphosphine 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–Miyara reaction: f (99.3 %) > a (97.2 %) > e (92.3 %) > d (79.6 %) > b (6.1 %) > c (3.3 %). Explanation of such activity is analogous to the explanation of the activity of catalyst 1 – 2-metoxyphenyl dipherrocenylphosphine.

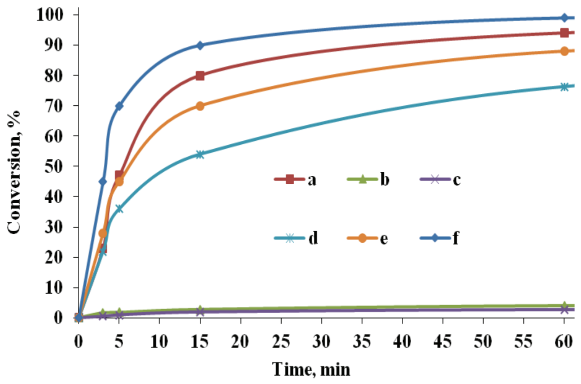


Fig. 4. The conversion of aryl halogenides a–f in Suzuki – Miyaura reaction with the usage of catalyst 3.

The highest catalytic activity depicted in Fig. 5 is observed for 4-bromoanisole with the usage of catalyst 4-phenyl-dipherrocenylphosphine. 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 (99.7 %) > a (95 %) > e (92 %) > d (82 %) > b (6.3 %) > c (3.2 %). Explanation of such activity is analogous to the explanation of the activity of catalyst 1 – 2-metoxyphenyl dipherrocenylphosphine.

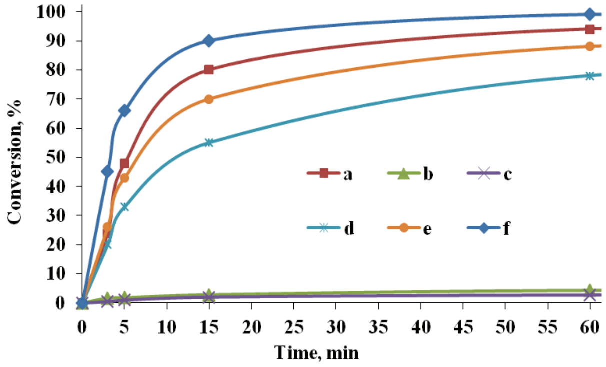


Fig. 5. The conversion of aryl halogenides a–f in Suzuki – Miyaura reaction with the usage of catalyst 4.

Figure 6 shows the catalytic activity of catalyst 5 – 1,1'-diphenylphosphinferrocene. 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 (99.4 %) > a (96 %) > e (92.3 %) > d (79.7 %) > b (6.4 %) > c (3.7 %). Explanation of such activity is analogous to the explanation of the activity of catalyst 1 – 2-metoxyphenyl dipherrocenylphosphine.

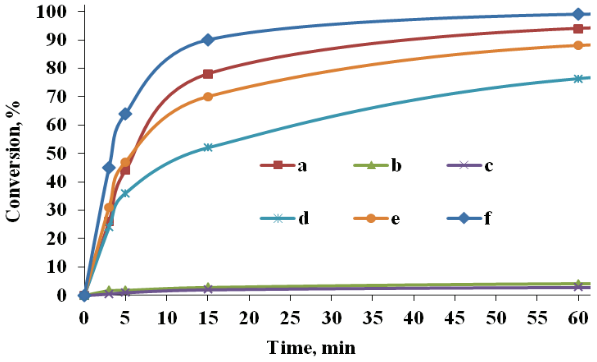


Fig. 6. The conversion of aryl halogenides a–f in Suzuki–Miyaura reaction with the usage of catalyst 5.

Conclusion

All aryl-ferrocenyl-phosphine catalysts (1-5) showed 100% reaction yield within 24 hour with aryl bromides. As it can be seen from Figs. 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 convenient 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 naphtyl (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.

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