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Synthesis and Catalytic Properties of Palladium Complex with Histamine Scaffold

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Abstract

In catalytic transformations, electronic s-donor properties are signifcantly affected by the presence of the heterocyclic skeleton Among heterocyclic skeletons, imidazole is among the most preferred in catalyst chemistry. In addition, the application of palladium complexes in sp2-sp2 carbon-carbon bond formation reactions has been successful. For this purpose, in the study, palladium complex carrying histamine moiety was systematically prepared to catalyze the Suzuki-Miyaura cross coupling reaction of bromobenzene with arylboronic acids to form biaryls in the presence of NaOH as base. All synthesized compound and palladium complex were fully characterized by Fourier Transform Infrared (FTIR) and ^{1}H- and ^{13}C-NMR spectroscopies. As a result of the investigation of the optimum conditions for the Suzuki-Miyaura cross coupling reaction, was determined that it was 30 minute, 82°C, NaOH as the base, and IPA-H_2O as the solvent. The presence of the bulky ditertbutyldicarbonate group, which is connected via the N atoms of the histamine skeleton in the structure, and the binding of Pd metal were determined by blanck test experiments to show that it affects the catalytic activity. As a result of the catalytic experiments, it was determined that the synthesized palladium complex was moderately effective in the Suzuki-Miyaura cross-coupling reaction.

Keywords: Palladium, Ionic liquid, Catalysis

1. Introduction

Carbon-carbon bond formation reactions with the help of palladium catalysis have become a frequently used method in organic synthesis [1-3]. In fact, the use of organopalladium complex as a catalyst won the Nobel Prize in Chemistry in 2010. Today, palladium complexes are widely used as catalysts [4,5]. Especially in recent years, many synthetic methods have been developed due to the numerous applications of palladium catalysts in various natural products, agrochemicals and pharmaceutical products, as well as in the preparation of advanced materials on both laboratory and industrial scales [6-10].

The interaction of organoboron reagents with aryl halides to form biaryl derivatives, the palladium-catalyzed traditional Suzuki-Miyaura cross-coupling reaction, has emerged as a powerful tool in organic synthesis in the last few years. The main purpose here is to ensure the formation of sp^2-sp^2 carbon-carbon bonds. However, considering most of the Suzuki Miyaura cross coupling reactions, it cannot effectively convert aryl chlorides, which are among the cheapest and easily available aryl halides [11,14].

Although phosphine-based ligands have been used to improve the catalytic conversion in cross-coupling reactions, N-heterocyclic carbene (NHC) ligands have recently attracted attention in light of many positive properties such as relatively high thermal stability and moisture. The electronic σ-donor properties of NHCs are significantly affected by the presence of the heterocyclic skeleton [15-21].

Although N-aryl classification comparison has been extensively studied in the studies conducted to date, studies on modification of the NHC-derived backbone are quite limited [22]. It is thought that the steric effects in the structure positively affect the catalytic transformations because such a modification will greatly

increase the steric and electronic capabilities of the palladium center [23,24]. In 2012, Zhou and co-workers synthesized acenaphthoimidazolylidene palladium complexes. They reported that they synthesized highly effective and general catalysts for sterically hindered Suzuki-Miyaura cross-coupling reactions in excellent yields using low catalyst loadings under mild reaction conditions. The high catalytic activity of these Pd complexes they synthesized emphasized that in addition to the concept of "flexible steric bulk", the σ-donor properties of the NHC ligands are also important for accelerating the transformations [25]. Glorius et. al. introduced a unique family of N-heterocyclic carbenes derived from bioxazolines (IBiox) for application in transition metal catalysis. The ligands in the scaffold are electron-rich, sterically demanding and have limited flexibility. Their activity was investigated in Suzuki-Miyaura cross-coupling of sterically hindered aryl chlorides and boronic acids. For the first time, tetraortho-substituted biaryls with methyl and larger ortho-substituents were synthesized from aryl chlorides using the Suzuki-Miyaura method [26]. Organ et. al. summarized recent advances with the PEPPSI style of Pd–NHC catalysts in aryl aminations and aryl sulfinations from both applications and mechanistic standpoints [27]. Lough et al synthesized a series of N-heterocyclic carbene catalysts in large volumes and evaluated their catalytic transformations in the Suzuki-Miyaura reaction. They concluded that the cyclopentyl-substituted catalyst was nearly inactive, suggesting that “flexible bulk” was required to support these transformations [28]. In a study by our group in 2018, a series of piperidoimidazolinium salts with different chain lengths (butyl, octyl, dodeacyl, octadeacyl) and their Pd–N-heterocyclic carbene complexes with pyridine were synthesized and characterized using elemental analysis and spectroscopic methods. The effects of these ligands on catalyst activation and the performance of the complexes were investigated in Suzuki–Miyaura reactions of arylboric acid with aryl chlorides. The complex with the ligand with the longest chain length was found to be the most active. The results showed that the alkyl chain length of piperidoimidazolin-2-ylidene controls the distribution and composition of the nanoparticles and affects the catalytic activity [29]. In a study conducted in 2021, a series of azolium salts containing benzothiazolium, benzimidazolium and imidazolium bearing CN-substituted benzyl moiety and their palladium complexes were synthesized. The synthesized palladium complexes were systematically prepared to catalyze the acylative Suzuki–Miyaura coupling reaction of acyl chlorides with arylboronic acids to form benzophenone derivatives in the presence of potassium carbonate as a base and to catalyze the conventional Suzuki–Miyaura coupling reaction of bromobenzene with arylboronic acids [30].

In this context, we prepared the NHC precursor and its palladium complex, which has histamine as its main scaffold, to investigate whether it would be useful for the Suzuki-Miyaura cross-coupling reaction. The reaction of interest was carried out under mild conditions and moderate catalytic conversions were obtained.

2. Materials and Methods

2.1. Chemicals

Reagents used in the synthesis are dichloromethane (Sigma Aldrich), dioxane (Sigma Aldrich), tetrahydrofuran (Sigma Aldrich), dimethyl sulfoxide (Riedel-de Haen), Boc_2O (Merck); Histamine (Precious Metals Online), $PdCl_2$ (Sigma Aldrich) were commercially purchased.

2.2. Instrumentations

^1H NMR and ^{13}C NMR spectra were recorded on a Varian AS 400 Mercury instrument. $CDCl_3$ were used as solvents. Chemical shifts are given in ppm relative to TMS; linkage constants (*J*) in Hz. FTIR spectra were recorded on a Perkin Elmer Spectrum 100 series. Analyses were performed with a gas chromatograph from Agilent Model 7820A Series, equipped with HP ECD detector systems. The analytical column used was a DB-5-MS column (30 m × 250 μm I.D. and film thickness 0.25 μm). Helium and nitrogen (99.99%) were used as carrier and make-up gas, respectively. The GC split valve was closed for 5 min., and helium was used as carrier gas with a flow rate of 15.0 mL min^{-1}. The flow rate of carrier gas was adjusted at 1.0 mL min^{-1}. The oven temperature program will be 50 °C for 5 minutes, increasing to 150 °C at 25 °C min^{-1}, increasing to 220 °C at 10 °C min^{-1}, and increasing to 280 °C at 5 °C min^{-1} will be released, the total running time is set to be 33 min. At the end of the analysis the fiber was cleaned by inserting it into the GC injection port for 15 min at 250 °C. The SPME holder for manual sampling was obtained from Supelco (Bellefonte, PA, USA).

General procedure for Suzuki cross-coupling reaction

A two-necked 25.0 ml flask fitted with a reflux condenser and septum was charged with aryl bromide (1.0 mmol), phenylboronic acid (1.0 mmol), NaOH (0.5 mmol) and the catalyst (0.5 mol%) in IPA–H_2O mixture (2 ml, 1:1). The mixture was heated to 82 °C at 30 min. under an air. For catalytic conversion monitoring, a small amount of sample was periodically withdrawn by syringe and conversion was analyzed by GC chromatography.

2.3. Synthesis of Ligand and its Palladium Complex

2.3.1. Synthesis and characterization of compound 1

Histamine dihydrochloride and Boc_2O (ditertbutyldicarbonate) were mixed in a mixture of dioxane and water in a balloon at room temperature for

24 hours. The amino group in its structure is protected by the Boc_2O (ditertbutyldicarbonate) structure. At the end of the reaction, dioxane and water were removed from the medium by simple distillation, and the remaining white solid was dried under vacuum. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (s, 1 H, NC*H*N), 7.13 (s, 1 H, N-C*H*), 3.41 (d, J = 8 Hz, 2 H, CH_2) 2.72 (t, J = 8 Hz, 2 H, CH_2), 1.60 (s, 9 H, C-(CH_3)$_3$), 1.43 (s, 9 H, C-(CH_3)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.2, 134.9, 79.3, 40.3, 28.4, 27.5. FT-IR (KBr disk, cm^{-1}): 3084, 2923, 2849, 2477, 1624, 1525, 1473, 1436, 1236, 1148, 1110, 1088, 1029, 956, 905, 852, 805, 730, 517.

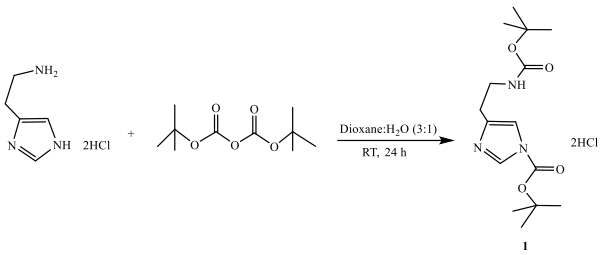
2.3.2. Synthesis and characterization of complex Pd1

1 and bisacetonitrile palladium dichloride were refluxed in dichloromethane at 39 °C under gas for 24 hours. At the end of the reaction, the solvent was removed by simple distillation. Then, a yellow solid was obtained. The complex **Pd1** was isolated by column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 2 H, NC*H*N), 7.19 (s, 2 H, N-C*H*), 7.40 (s, 2 H, N-C*H*), 5.00 (s, 2 H, N*H*), 3.93 (d, J = 8 Hz, 4 H, CH_2) 3.35 (t, J = 8 Hz, 4 H, CH_2), 1.61 (s, 18 H, C-(CH_3)$_3$), 1.44 (s, 18 H, C-(CH_3)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.0, 144.9, 140.2, 138.2, 115.1, 87.7, 79.3, 39.1, 28.4, 27.7, 15.2. FT-IR (CsI disk, cm^{-1}): 3393, 3151, 2975, 2932, 1774, 1706, 1595, 1495, 1371, 1323, 1304, 1276, 1245, 1147, 1060, 1041, 1009, 952, 868, 841, 800, 789, 679, 606, 538, 492, 464, 428.

3. Results and Discussion

3.1. Synthesis of the azolium salt (1) and Pd(II) complex

Compound **1** was prepared by a one-pot reaction by histamine dihydrochloride with Boc_2O (ditertbutyldicarbonate) in a dioxane-water mixture at room temperature for 24 hours. The general synthesis route of the ligand is given in scheme 1. The compound was obtained as a white solid in 79% yield and exhibited good solubility in polar solvents. It was characterized by ^{1}H-NMR, ^{13}C-NMR and Fourier transform infrared (FT-IR) spectroscopies. The C_2–H resonance, NC*H*N peak of the imidazolium salt, was observed at δ = 8.00 ppm as a sharp singlet in the ^{1}H NMR spectrum. Additionally, there are C-(CH_3)$_3$ signals corresponding to a total of 18 protons at 1.60 and 1.43 ppm as evidence of the binding of the Boc_2 group to histamine. In the ^{13}C NMR spectrum (**1**) the chemical shift of NC*N* sp^2 carbon atoms appears at 156.2 ppm. In the high frequency region of the IR spectrum, a symmetric band of moderate intensity was observed at 3084 cm^{-1} due to the overlap of N-H group vibrations with hydrogen-bonded vibrations, and at 2923 cm^{-1} for C-H group vibrations. As for the vibrations of C=O and C-O groups, a strong band was observed at 1423 cm^{-1} and 1148 cm^{-1}, respectively.



Scheme 1 Synthesis route to the compound **1**.

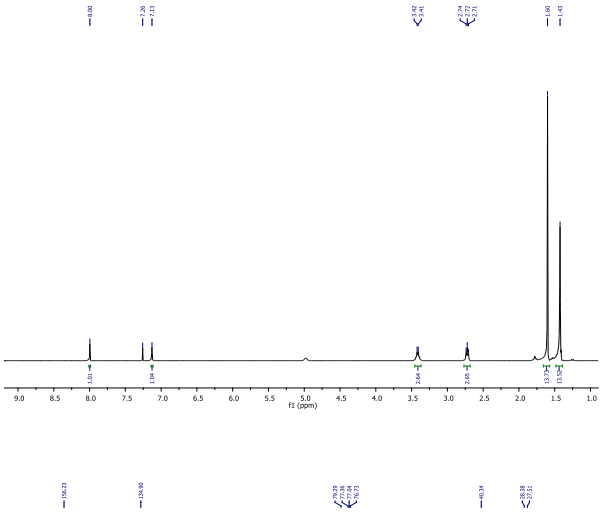
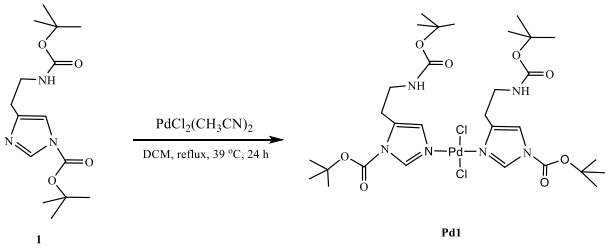


Figure S1. ^{1}H and ^{13}C NMR spectrums of compound **1** ($CDCl_3$).



Scheme 2 Synthesis route to the complex **Pd1**.

Celal Bayar University Journal of Science
Volume 20, Issue 3, 2024, p 40-46
Doi: 10.18466/cbayarfbe.1513027

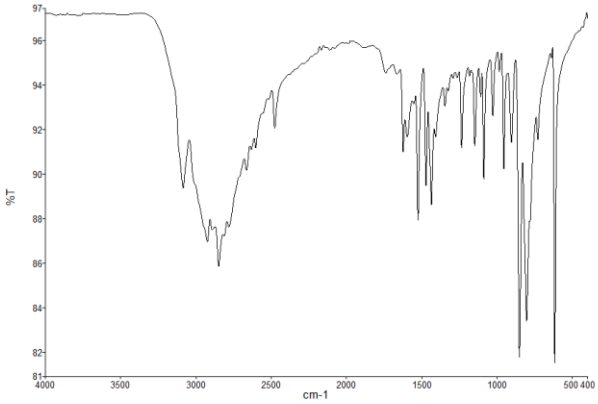
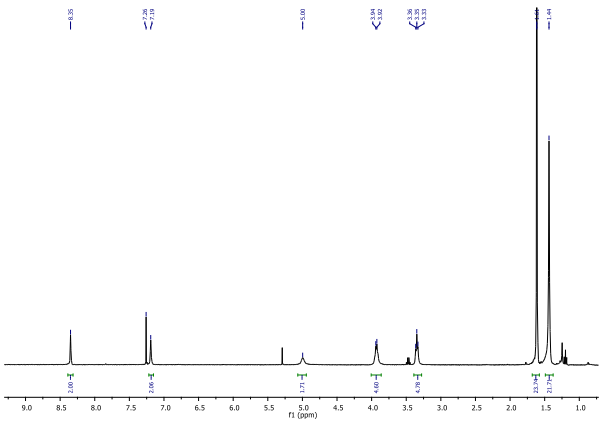


Figure S2. FT-IR spectrums of compound **1**.

The new palladium complex (**Pd1**) was obtained by refluxing in dichloromethane in the presence of bis(acetonitrile)palladium dichloride overnight (Scheme 2). The synthesized palladium complex was obtained in 66% yield as a yellow solid with good solubility in polar solvents and resistant to air and moisture. It was characterized by ^{1}H-NMR, ^{13}C-NMR and Fourier transform infrared (FT-IR) spectroscopies. After binding to palladium metal, the C_2-H resonance, the NC*H*N peak of the imidazolium salt, was observed at δ = 8.35 ppm as a sharp singlet in the ^{1}H NMR spectrum. The reason for the shift to the high ppm low area observed here is due to the change in electron density and the shielding effect due to the bonding of palladium metal. This shift is evidence of the bonding of palladium to us. Unlike compound **1**, medium intensity peaks were observed between 468 cm^{-1} and 424 cm^{-1}, which are defined as the fingerprint region of Pd-Cl bonds in the **Pd1** complex.



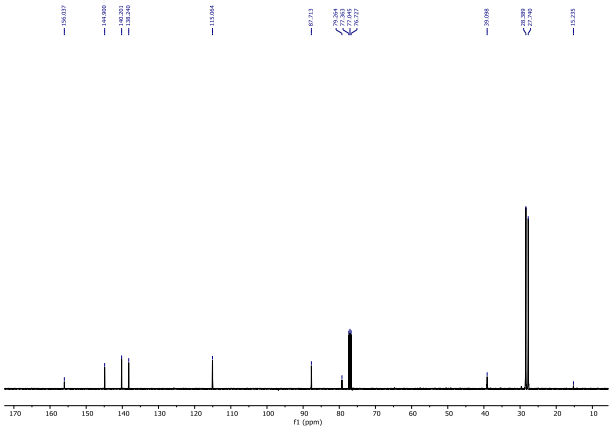


Figure S3. ^{1}H and ^{13}C NMR spectrums of compound **Pd1** ($CDCl_3$).

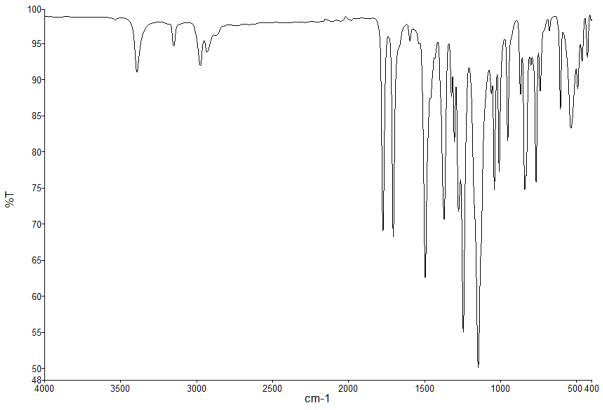


Figure S4. FT-IR spectrums of complex **Pd1**.

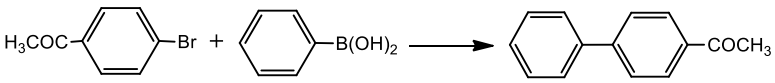
To look into the effect of the palladium complex on the Suzuki–Miyaura cross-coupling reaction, a model reaction was produced using 4-bromoacetophenone (1 mmol), phenyl boronic acid (1.5 mmol), and KOH (0.5 mmol). Conversions were determined by the GC. In optimization studies, the appropriate solvent system was determined as 2 mL (1:1, IPA-H_2O). In this catalytic cycle, the role of IPA was to dissolve aryl bromides and the role of water was to activate phenyl boronic acid and the base. Although weak bases such as $NaHCO_3$ and K_2CO_3 were used, the reaction was carried out efficiently (Table 1, entries 9, 6). Although KO^{t}Bu was a strong base, the reaction did not produce effective results (Table 1, entry 10). The best efficiency was achieved in Cs_2CO_3 and NaOH (Table 1, entries 7, 5). However, due to the price of Cs_2CO_3, substrate experiments were conducted with NaOH. Using only 2-propanol as the solvent negatively affected the catalytic conversion (Table 1, entry 1). A blank test was performed to investigate the effect of the presence of the catalyst. No product formation was observed in the reaction medium without addition of catalyst (Table 1, entry 4). Reducing the

Celal Bayar University Journal of Science
Volume 20, Issue 3, 2024, p 40-46
Doi: 10.18466/cbayarfbe.1513027

catalyst loading into the catalytic cycle negatively affected the efficiency (Table 1, entry 2).

Evaluation of the substrate scope of the reaction of various phenylboronic acids with various bromoacetophenone derivatives under optimized reaction conditions was carried out (Table 2). Bearing electron-withdrawing or electron-donating substituents in the para and ortho positions, such as 4-CH_3, 4-tert-butyl, 4-Br, 4-F, 4-CF_3, 2-CF_3, 2-CH_3 and 4-F-3-COH converted into a large number of arylboronic acid-related target products (Table 2, entries 1-13). Results in the range of 47-88% were found in the obtained catalytic conversions. Aryl bromides formed from 4-CH_3, 4-OCH_3, 4-NO_2 and 4-CHO in the para position gave 4-methyl-biphenyl, 4-methoxybiphenyl 4-nitrobiphenyl and 4-carbaldehydebiphenyl products in yields of 64%, 65%, 63% and 59%, respectively (Table 2, entries 1-4). Also, different aryl phenyl boronic acids were studied. Phenyl boronic acids formed from these substituents 4-CH_3, 4-Br and 4-*t*-Bu in the para position gave the products 1-(4'-methyl-[1,1'-biphenyl]-4-yl)ethan-1-one, 1-(4'-bromo-[1,1'-biphenyl]-4-yl)ethan-1-one and 1-(4'-tertbutoxy-[1,1'-biphenyl]-4-yl)ethan-1-one in good yields of 69%, 59% and 65%, respectively (Table 4, entries 5, 6, 13). The effect of CH_3 group in the ortho and meta positions of aryl phenyl boronic acid was investigated. As a result of the catalytic cycle, phenyl boronic acids formed from 2-CH_3 and 3-CH_3 gave 1-(2'-methyl-[1,1'-biphenyl]-4-yl)ethan-1-one and 1-(3'-methyl-[1,1'-biphenyl]-4-yl)ethan-1-one products with good yields of 57% and 60%, respectively (Table 4, entries 7, 8). The effect of CF_3 group in para and ortho positions of aryl phenyl boronic acid was investigated. As a result of the catalytic cycle, phenyl boronic acids formed from 4-CF_3 and 2-CF_3 gave 1-(4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)ethan-1-one and 1-(2'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)ethan-1-one products with good yields of 77% and 71%, respectively (Table 4, entries 9, 10). In addition, the increase of the CH_3 group in phenyl boronic acid was observed with a yield of 73% to 1-(2',5'-dimethyl-[1,1'-biphenyl]-4-yl)ethan-1-one (Table 4, entry 11).

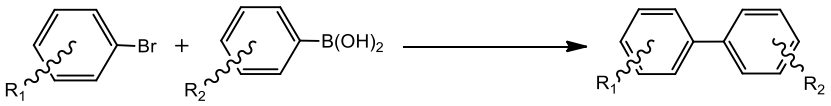
Table 1. Screening of reaction conditions in the Suzuki-Miyaura cross-coupling reaction.



Entry	Cat. (%mol)	Solvent	Base	Yield (%)
1	0.5	IPA	NaOH	76
2	0.2	IPA	NaOH	54
3	0.5	IPA–H_2O	NaOH	88
4	-	IPA–H_2O	NaOH	trace
5	0.5	IPA–H_2O	KOH	66
6	0.5	IPA–H_2O	K_2CO_3	75
7	0.5	IPA–H_2O	Cs_2CO_3	95
8	0.5	IPA–H_2O	Na_2CO_3	35
9	0.5	IPA–H_2O	$NaHCO_3$	67
10	0.5	IPA–H_2O	KO^{t}Bu	55
11[b]	0.5	IPA–H_2O	NaOH	37
12[c]	0.5	IPA–H_2O	NaOH	52

[a] Reaction conditions: 4-bromoacetophenone (1.0 mmol), phenyl boronic acid (1.0 mmol), base (0.5 mmol), IPA-H_2O = 1:1 (2.0 ml), 82°C, 30 min. [b] $PdCl_2(NCCH_3)_2$ (0.5 mol %). [c] **1** (0.5 mol %).

Table 2. Effects of substrate for Suzuki-Miyaura Cross-Coupling reaction



Entry	R_1	R_2	Yield (%)	TON/TOF
1	4-CH_3	H	64	128/256
2	4-$COCH_3$	H	65	130/260
3	4-NO_2	H	63	126/252
4	4-CHO	H	59	118/236
5	4-$COCH_3$	4-CH_3	69	138/276
6	4-$COCH_3$	4-Br	59	118/236
7	4-$COCH_3$	2-CH_3	57	114/228
8	4-$COCH_3$	3-CH_3	60	120/240
9	4-$COCH_3$	4-CF_3	77	154/308
10	4-$COCH_3$	2-CF_3	71	142/284
11	4-$COCH_3$	2,5-Me	73	146/292
12	4-$COCH_3$	4-F,3-COH	47	94/188
13	4-$COCH_3$	4-t-Bu	65	130/260

Reaction conditions: Aryl bromide (1.0 mmol), phenyl boronic acid (1.0 mmol), cat. **Pd1** (0.5 mol %), NaOH (0.5 mmol), IPA-H_2O=1:1 (2.0 ml), 82 ^oC, 30 min., TON = [yield]/[cat.], TOF = [TOF]/[h].

4. Conclusion

As a result, a series of studies were conducted to systematically examine the effect of the palladium complex bearing the histamine group on the Suzuki-Miyaura cross-coupling reaction. The structure of the synthesized complex and compound was elucidated with ^1H-^{13}C NMR and fourier transform infrared (FTIR) spectroscopies. Different base, solvent and catalyst loadings were investigated to reach optimum conditions in the reaction. Blanck test experiments were conducted to investigate the effect of the catalyst on the catalytic transformation. In these experiments, it was determined that the transformation remained at 37% when only $PdCl_2(NCCH_3)_2$ was added to the reaction medium as a catalyst. In addition, the addition of ligand to the reaction medium gave the transformation only as 52%. These experiments clearly demonstrated the effect of the **Pd1** catalyst we synthesized. At the end of the experiments, the optimum conditions were determined as 30 minutes, 82 °C, NaOH as base and 0.5 catalyst loading. As a result of the derivatization, efficiencies between 47-88% were obtained. It was observed that the groups in the para-position gave the desired final products with better yields compared to the groups in the meta- and ortho- positions. These obtained catalytic transformations provide a good basis for further studies.

Acknowledgement

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Author's Contributions

Hayati Türkmen: Determination of the topic, interpretation of the results and preparation of the draft were carried out.

Sinem Çakır: Performed the experiment and wrote the publication

Ethics

There are no ethical issues regarding the publication of this study.

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