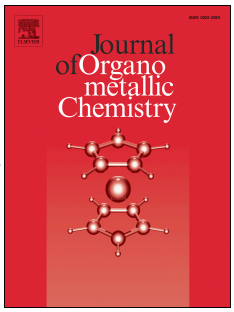

Arylation of heterocyclic compounds by benzimidazole-based N-heterocyclic carbene-palladium(II) complexes

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PII: S0022-328X(19)30519-4

DOI: https://doi.org/10.1016/j.jorganchem.2019.121076

Reference: JOM 121076

To appear in: *Journal of Organometallic Chemistry*

Received Date: 25 October 2019

Revised Date: 12 December 2019

Accepted Date: 13 December 2019

Please cite this article as: N. Sahin, N. Gürbüz, H. Karabıyık, H. Karabıyık, İ. Özdemir, Arylation of heterocyclic compounds by benzimidazole-based N-heterocyclic carbene-palladium(II) complexes, *Journal of Organometallic Chemistry* (2020), doi: https://doi.org/10.1016/j.jorganchem.2019.121076.

Arylation of Heterocyclic Compounds by Benzimidazole-based N-Heterocyclic Carbene-Palladium(II) Complexes

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Dedicated to 120 years Celebration of Professor Aleksandr Nikolaevich Nesmeyanov.

Abstract

Specific C-H bond can be activated for arylation using aryl halide without the aid of directing the group in the case of electron-rich heteroarenes. The ability to readily generate halo substituted arylated heteroarenes is important in organic chemistry since these species are important building blocks for biochemists. In this manuscript, we report the synthesis of PEPPSI type-novel benzimidazole-based N-heterocyclic carbene-palladium(II) complexes (**2a-e**). All of the new compounds were fully characterized by ^{1}H, $^{13}C\{^{1}H\}$ NMR and FT-IR spectra. The structures of **2c**, **2d**, and **2e** were determined by X-ray crystallography and the prepared complexes (**2a-e**) were investigated as catalysts for the direct arylation of 2-n-propylthiazole, 4,5-dimethylthiazole and 2-acetylthiophene with various aryl bromides. ~~And showed~~ High catalytic activity for arylation was seen reaction using only 0.5 mol% catalyst for 1 h.

Keywords: N-heterocyclic carbene, benzimidazole, PEPPSI, direct arylation, thiophenes, thiazoles.

1. Introduction

Both thiophene and thiazole derivatives have attracted attention due to their important biological activity. For example, the 2-arylthiophene derivative Canagliflozin is a drug used in the treatment of type 2 diabetes, and Duloxetine is used against major depressive disorder diabetes. Motapizone is used in the treatment of ~~against~~ platelet aggregation diabetes and Tiemonium and Penthienate are antimuscarinics [1-3]. Sulfathiazole is an antimicrobial drug,

Ritonavir is used as an antiretroviral drug. Abafungin is used an antifungal drug, and Bleomycine and Tiazofurin are antineoplastic drugs [4]. Some phenanthrothiazoles display interesting potential pharmacological activity [5] (Figure 1).

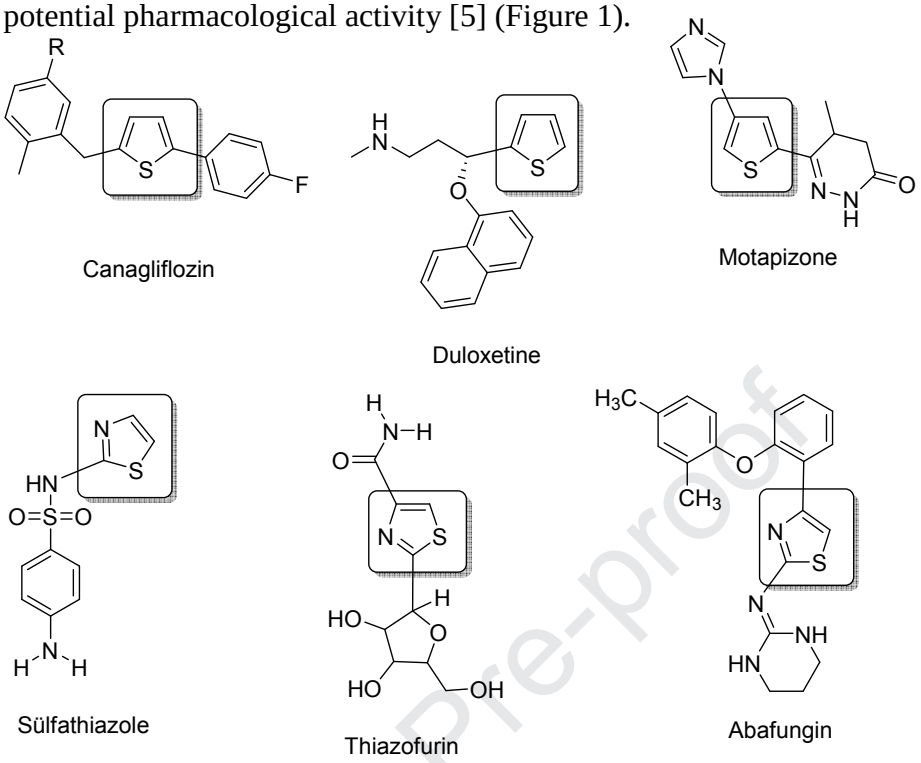


Figure 1. Examples of bioactive thiophene or thiazole derivatives.

Since they have such important biological activity, the discovery of more direct and selective procedures to synthesize arylated thiophene and thiazole derivatives is an important topic in synthetic organic chemistry. Classical methods for the synthesis of such compounds are metal-catalyzed cross-coupling reactions such as Suzuki-, Stille-, Negishi- or Kumada-type reactions [6-9]. However, such reactions require the pre-synthesis of organometallic derivatives and they produce stoichiometric amounts of metallic salts as byproducts which could be harmful in pharmaceutical, agrochemical, and related biological applications [10]. ~~Firstly,~~ In 1985-1992, Ohta et al. first reported the direct arylation of heteroaromatics with aryl halides using a C−H activation strategy through the cleavage of two C−H bonds, which is an environmentally and economically more attractive method using ~~in which~~ $Pd(PPh_3)_4$ ~~was used~~ as the catalyst and dimethylacetamide (DMAc) as the solvent [11-13]. Since then, palladium-catalyzed direct arylation has been successfully applied for the arylation of heterocycles such as arenes, thiophenes, indoles, indolizines, azoles, pyridines, and furans [14-19]. Although the heterocyclic compounds are arylated at positions C2, C3, C4 and C5, both experimental studies and computational studies have shown that predominantly, either

C2-arylated product or mixtures of C2- and C5-arylated products have been obtained. According to computational studies, the reason for this selectivity is the free energy of activation for C-H bonds [20, 21]. When the C2- and C5-positions are blocked, the C3- and C4-positions of heterocycles are arylated (Figure 2).

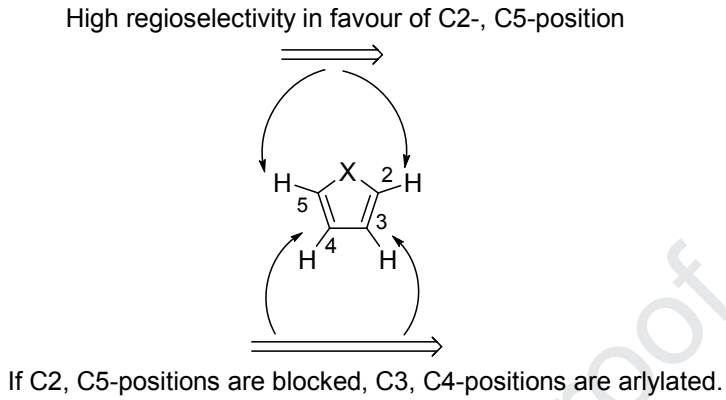


Figure 2. The most favourable positions of heterocycles for direct arylations.

Palladium complexes containing two halides, an unstable pyridine derivative and a bulky NHC ligand were defined as "**P**yridine **E**nhanced **P**recatalyst **P**reparation **S**tabilization and **I**nitiation" (PEPPSI) by Organ [22, 23]. In recent years some studies on the direct arylation reaction of PEPPSI type palladium-N-heterocyclic carbene (NHC) complexes have been published [24, 25]. These studies have shown that these complexes exhibit very good catalytic activity. PEPPSI complexes have gained real practical importance in numerous catalytic processes because of the ease of handling, and that they are air and moisture stable.

Allyl substituents on such ligand precursors are capable of coordinating to the metal centre leading to a coordination environment made up of sp^2-carbon donors [26, 27]. Inspired by this, we became interested in the coordination chemistry of N-heterocyclic carbenes bearing N-methallyl substituents. Herein, synthesis and characterization of methallyl substitued benzimidazole-based ligand precursors (**1a-e**) and their PEPPSI-type palladium-NHC complexes (**2a-e**) were described. These compounds were characterized using ~~by~~ spectroscopic techniques, and the structure of **2c**, **2d**, and **2e** were determined with ~~by~~ single-crystal X-ray diffraction. The catalytic activities of new Pd(II)-NHC complexes (**2a-e**) were also investigated and they showed good activity as catalysts in the direct arylation reaction.

2. Experimental

2. 1. Materials and measurements

All experiments were performed under argon in flame-dried glassware using standard Schlenk techniques. All reagents were purchased from Sigma Aldrich Co. (Dorset, UK). The solvents used were purified by distillation over the drying agents indicated and were transferred under argon. Melting points were determined using the Electrothermal 9100 melting point detection apparatus in capillary tubes and the melting points are reported as uncorrected values. Fourier transform infrared (FT-IR) spectra were recorded in the range of 400–4000 cm^{-1} on Perkin Elmer Spectrum 100 FT-IR. ^{1}H NMR and $^{13}C\{^{1}H\}$ NMR spectra were taken using a Bruker As 400 Mercury spectrometer operating at 400 MHz (^{1}H), 100 MHz ($^{13}C\{^{1}H\}$) in $CDCl_3$ with tetramethylsilane as the internal reference. ^{1}H peaks are labeled as singlet (s), doublet (d), triplet (t) and multiplet (m). Chemical shifts and coupling constants are reported in ppm and in Hz, respectively. Catalytic reactions were observed on an Agilent 6890 N GC system by GC-FID with an HP-5 column of 30 m length, 0.32 mm diameter and 0.25 μm film thickness. Column chromatography was performed using silica gel 60 (70–230 mesh). All the measurements were taken at room temperature for freshly prepared solutions.

2.2. Synthesis

All the compounds were prepared under argon gas atmosphere. Benzimidazole-based ligand precursors (**1a-e**) and their corresponding Pd(II)-NHC complexes **(2a-e)** were synthesized according to the literature [28]. Ligand **1a** and **1e** were published in our previous study [29, 30].

2.3. General procedure for the preparation ligand precursors (1a-e)

Benzimidazole (10 mmol) was added to a solution of NaH (10 mmol) in dry THF (30 mL), the mixture was stirred for 1 h at room temperature. β-Methallylchloride (10.1 mmol) was added dropwise ~~up~~on to the obtained solution and heated for 24 h at 60 ^{o}C. Then, the THF was removed under ~~the~~ vacuum. Dichloromethane (50 mL) was added ~~upon~~ to the solid. The mixture was filtered and the obtained clear solution was concentrated under vacuum. Then the solution was distilled and 1-(β-methallyl)benzimidazole was obtained. The 1-(β-methallyl)benzimidazole (1 mmol) and alkyl halide (1 mmol) were stirred in DMF (5 mL) for 24 h at 80 ^{o}C. White product was precipitated then after ~~following the~~ completion of the process, the solution was filtered, the solid was rinsed out with diethyl ether and dried under vacuum. The crude product was recrystallized from dichloromethane/diethyl ether.

2.3.1. 1-(β-Methallyl)-3-(4-methylbenzyl)benzimidazolium chloride, 1a

Yield: 82%, mp 195-197 °C; FT-IR $\nu_{(CN)}$: 1551 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.72 (s, 3H, $NCH_2C(CH_3)CH_2$), 2.23 (s, 3H, $CH_2C_6H_4$-4-CH_3), 4.90 (s, 1H, $NCH_2C(CH_3)CH_2$), 5.04 (s, 1H, $NCH_2C(CH_3)CH_2$), 5.21 (s, 2H, $NCH_2C(CH_3)CH_2$), 5.78 (s, 2H, $CH_2C_6H_4$-4-CH_3), 7.09 (d, 2H, Ar-*H*, *J* = 8 Hz), 7.31 (d, 2H, Ar-*H*, *J* = 8 Hz), 7.45-7.51, 7.53-7.55 and 7.59-7.61 (m, 4H, Ar-*H*), 11.74 (s, 1H, NC*H*N). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 19.7 ($NCH_2C(CH_3)CH_2$), 21.2 ($CH_2C_6H_4$-4-CH_3), 51.4 ($CH_2C_6H_4$-4-CH_3), 53.6 ($NCH_2C(CH_3)CH_2$), 116.1 ($NCH_2C(CH_3)CH_2$), 139.2 ($NCH_2C(CH_3)CH_2$), 113.7, 113.9, 127.1, 128.2, 128.3, 129.8, 130.0, 131.2, 131.7 and 137.5 (Ar-*C*), 144.0 (N*C*HN).

2.3.2. 1-(β-Methallyl)-3-(4-ter-butylbenzyl)benzimidazolium bromide, 1b

Yield: 89%, mp 190-192 °C; FT-IR $\nu_{(CN)}$: 1553 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.27 (s, 9H, $CH_2C_6H_4$-4-$C(CH_3)_3$), 1.80 (s, 3H, $NCH_2C(CH_3)CH_2$), 4.99 (s, 1H, $NCH_2C(CH_3)CH_2$), 5.13 (s, 1H, $NCH_2C(CH_3)CH_2$), 5.29 (s, 2H, $NCH_2C(CH_3)CH_2$), 5.86 (s, 2H, $CH_2C_6H_4$-4-$C(CH_3)_3$), 7.28 (d, 2H, Ar-*H*, *J* = 8 Hz), 7.45 (d, 2H, Ar-*H*, *J* = 8 Hz), 7.56-7.58, 7.66-7.71 (m, 4H, Ar-*H*), 11.60 (s, 1H, NC*H*N). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 19.9 ($NCH_2C(CH_3)CH_2$), 31.2 ($CH_2C_6H_4$-4-$C(CH_3)_3$), 34.7 ($CH_2C_6H_4$-4-$C(CH_3)_3$), 51.2 ($CH_2C_6H_4$-4-$C(CH_3)_3$), 53.6 ($NCH_2C(CH_3)CH_2$), 116.3 ($NCH_2C(CH_3)CH_2$), 137.4 ($NCH_2C(CH_3)CH_2$), 113.7, 113.9, 126.4, 127.2, 127.3, 128.0, 129.6, 131.3, 131.6 and 152.5 (Ar-*C*), 143.2 (N*C*HN).

2.3.3. 1-(β-Methallyl)-3-(2,4,6-trimethylbenzyl)benzimidazolium chloride, 1c

Yield: 87%, mp 226-227 °C; FT-IR $\nu_{(CN)}$: 1553 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.77 (s, 3H, $NCH_2C(CH_3)CH_2$), 2.29 (s, 3H, $CH_2C_6H_2$-2,4,6-$(CH_3)_3$), 2.32 (s, 6H, $CH_2C_6H_2$-2,4,6-$(CH_3)_3$), 4.89 (s, 1H, $NCH_2C(CH_3)CH_2$), 5.09 (s, 1H, $NCH_2C(CH_3)CH_2$), 5.30 (s, 2H, $NCH_2C(CH_3)CH_2$), 5.88 (s, 2H, $CH_2C_6H_2$-2,4,6-$(CH_3)_3$), 6.93 (s, 2H, Ar-*H*), 7.21 (d, 1H, Ar-*H*, *J* = 8 Hz), 7.44 (t, 1H, Ar-*H*, *J* = 8 Hz), 7.54 (t, 1H, Ar-*H*, *J* = 8 Hz), 7.66 (d, 1H, Ar-*H*, *J* = 8 Hz), 11.60 (s, 1H, NC*H*N). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 19.7 ($NCH_2C(CH_3)CH_2$), 20.2 and 21.1 ($CH_2C_6H_2$-2,4,6-$(CH_3)_3$), 47.4 ($CH_2C_6H_2$-2,4,6-$(CH_3)_3$), 53.5 ($NCH_2C(CH_3)CH_2$), 115.6 ($NCH_2C(CH_3)CH_2$), 137.6 ($NCH_2C(CH_3)CH_2$), 113.6, 113.8, 125.0, 127.0, 127.2, 130.2, 131.4, 131.7, 137.9 and 139.8 (Ar-*C*), 144.4 (N*C*HN).

2.3.4. 1-(β-Methallyl)-3-(2,3,5,6-tetramethylbenzyl)benzimidazolium chloride, 1d

Yield: 88%, mp 235-236 °C; FT-IR $\nu_{(CN)}$: 1557 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.69 (s, 3H, $NCH_2C(CH_3)CH_2$), 2.19 (s, 12H, CH_2C_6H-2,3,5,6-$(CH_3)_4$), 4.80 (s, 1H, $NCH_2C(CH_3)CH_2$), 5.01 (s, 1H, $NCH_2C(CH_3)CH_2$), 5.28 (s, 2H, $NCH_2C(CH_3)CH_2$), 5.83 (s,

2H, C*H*$_2$C$_6$H-2,3,5,6-(CH$_3$)$_4$), 7.01 (s, 1H, Ar-*H*), 7.21 (d, 1H, Ar-*H*, *J* = 8 Hz), 7.40 (t, 1H, Ar-*H*, *J* = 8 Hz), 7.46 (t, 1H, Ar-*H*, *J* = 8 Hz), 7.60 (d, 1H, Ar-*H*, *J* = 8 Hz), 11.29 (s, 1H, NC*H*N). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ (ppm): 16.1 (CH$_2$C$_6$H-2,3,5,6-(*C*H$_3$)$_4$), (19.7 (NCH$_2$C(*C*H$_3$)CH$_2$), 20.6 (CH$_2$C$_6$H-2,3,5,6-(*C*H$_3$)$_4$), 47.9 (*C*H$_2$C$_6$H-2,3,5,6-(CH$_3$)$_4$), 53.5 (N*C*H$_2$C(CH$_3$)CH$_2$), 115.5 (NCH$_2$C(CH$_3$)*C*H$_2$), 137.7 (NCH$_2$*C*(CH$_3$)CH$_2$), 113.7, 127.0, 127.2, 127.6, 131.5, 131.7, 133.6, 134.0 and 135.2 (Ar-*C*), 144.1 (N*C*HN).

2.3.5. 1-(β-Methallyl)-3-(2,3,4,5,6-pentamethylbenzyl)benzimidazoliumchloride, 1e

Yield: 84%, mp 201-202 ^{o}C; $\nu_{(CN)}$: 1556 cm^{-1}; ^{1}H NMR (399.9 MHz, CDCl$_3$) δ (ppm): 1.75 (s, 3H, NCH$_2$C(C*H*$_3$)CH$_2$), 2.29, 2.27 and 2.24 (s, 15H, CH$_2$C$_6$(C*H*$_3$)$_5$-2,3,4,5,6), 2.49 (s br, 2H, *H*$_2$O), 4.85 (s, 1H, NCH$_2$C(CH$_3$)C*H*$_2$), 5.06 (s, 1H, NCH$_2$C(CH$_3$)C*H*$_2$), 5.36 (s, 2H, NC*H*$_2$C(CH$_3$)CH$_2$), 5.87 (s, 2H, C*H*$_2$C$_6$(CH$_3$)$_5$-2,3,4,5,6), 7.33-7.29 (m, 2H, NC$_6$*H*$_4$N), 7.57-7.47 (m, 1H, NC$_6$*H*$_4$N), 7.84 (d, 1H, NC$_6$*H*$_4$N, *J* = 8 Hz), 11.04 (s, 1H, NC*H*N). ^{13}C{^{1}H} NMR (100.5 MHz, CDCl$_3$) δ (ppm): 17.0, 17.1 and 17.3 (CH$_2$C$_6$(*C*H$_3$)$_5$-2,3,4,5,6), 19.7 NCH$_2$C(*C*H$_3$)CH$_2$), 48.4 (*C*H$_2$C$_6$(CH$_3$)$_5$-2,3,4,5,6), 53.5 (N*C*H$_2$C(CH$_3$)CH$_2$), 115.3 (NCH$_2$C(CH$_3$)*C*H$_2$), 137.4 (NCH$_2$*C*(CH$_3$)CH$_2$), 113.7, 124.9, 127.0, 127.1, 131.5, 131.8, 133.6, 134.0 and 137.8 (NC$_6$H$_4$N and CH$_2$C$_6$(CH$_3$)$_5$-2,3,4,5,6), 143.8 (N*C*HN).

2.4. Preparation of Pd-NHC complex (2a-e)

Ligand precursors (**1a-e**) (1 mmol), PdCl$_2$ (1 mmol) and K$_2$CO$_3$ (5 mmol ~~and~~) (and excess of KBr for **2b)** in pyridine (5 mL) were stirred at 80 ^{0}C for 4 h. After the reaction was finished, pyridine was removed under vacuum. CH$_2$Cl$_2$ (10 mL) was added to the resulting solid mixture. The solution was filtered through a silica gel and celite layer ~~in order~~ to remove unreacted PdCl$_2$. The solvent in the reaction medium was removed under vacuum and dried. The crude product was crystallized in CH$_2$Cl$_2$/pentane and bright yellow Pd-NHC complexes (**2a-e**) were obtained.

2.4.1. Dichloro[1-(β-methallyl)-3-(4-methylbenzylbenzimidazole-2-ylidene]pyridine palladium(II), 2a

Yield: 76%, mp 158-160 ^{o}C; FT-IR $\nu_{(CN)}$: 1407 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 1.55 (s, 3H, NCH$_2$C(C*H*$_3$)CH$_2$), 2.32 (s, 3H, CH$_2$C$_6$H$_4$-4-C*H*$_3$), 5.11 (s, 1H, NCH$_2$C(CH$_3$)C*H*$_2$), 5.15 (s, 1H, NCH$_2$C(CH$_3$)C*H*$_2$), 5.58 (s, 2H, NC*H*$_2$C(CH$_3$)CH$_2$), 6.20 (s, 2H, C*H*$_2$C$_6$H$_4$-4-CH$_3$), 7.09-7.21 (m, 5H, Ar-*H*), 7.35 (t, 2H, Ar-*H*, *J* = 8 Hz), 7.41 (d, 1H, Ar-*H*, *J* = 8 Hz), 7.47 (d, 2H, Ar-*H*, *J* = 8 Hz), 7.77 (t, 1H, Ar-*H*, *J* = 8 Hz), 9.0 (tt, 2H, C$_5$*H*$_5$, *J* = 4 Hz, ^{2}*J* = 4 Hz). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ (ppm): 20.4 (NCH$_2$C(*C*H$_3$)CH$_2$), 21.2 (CH$_2$C$_6$H$_4$-4-*C*H$_3$), 53.0 (*C*H$_2$C$_6$H$_4$-4-CH$_3$), 55.0

(N*C*H_2C(CH_3)CH_2), 114.7 (NCH_2C(CH_3)*C*H_2), 137.9 (NCH_2*C*(CH_3)CH_2), 111.1, 111.5, 123.2, 124.5, 127.9, 129.5, 132.1, 134.9, 138.1, 139.4 and 151.3 (Ar-*C*), 164.6 (Pd-C_{carb}).

2.4.2. Dibromo[1-(β-methallyl)-3-(4-ter-butylbenzylbenzimidazole-2-ylidene]pyridine palladium(II), 2b

Yield: 71%, mp 147-149 ^oC; FT-IR $\nu_{(CN)}$: 1403 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.27 (s, 9H, $CH_2C_6H_4$-4-C(C*H*$_3$)$_3$), *J* = 8 Hz), 1.91 (s, 3H, NCH_2C(C*H*$_3$)CH_2), 5.14 (s, 1H, NCH_2C(CH_3)C*H*$_2$), 5.15 (s, 1H, NCH_2C(CH_3)C*H*$_2$), 5.54 (s, 2H, N*C*H_2C(CH_3)CH_2), 6.16 (s, 2H, C*H*$_2$$C_6H_4$-4-C($CH_3$)$_3$), 7.09-7.10 (m, 2H, Ar-*H*), 7.16-7.20 (m, 1H, Ar-*H*), 7.31-7.42 (m, 5H, Ar-*H*), 7.54 (d, 2H, Ar-*H*, *J* = 8 Hz), 7.75 (tt, 1H, Ar-*H*, *J* = 8 Hz, ^2J =4 Hz), 9.04 (tt, 2H, C_5H_5, *J* = 4 Hz, ^2J = 4 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 20.7 (NCH_2C(*C*H_3)CH_2), 31.3 ($CH_2C_6H_4$-4-C(*C*H_3)$_3$), 34.5 ($CH_2C_6H_4$-4-*C*(CH_3)$_3$), 53.5 (31.3 (*C*$H_2C_6H_4$-4-C(CH_3)$_3$), 55.5 (N*C*H_2C(CH_3)CH_2), 115.0 (NCH_2C(CH_3)*C*H_2), 137.9 (NCH_2*C*(CH_3)CH_2), 111.1, 111.6, 123.1, 124.5, 125.0, 125.7, 127.8, 131.9, 134.5, 135.1, 137.9, 139.2, 151.1 and 152.6 (Ar-*C*), 164.1 (Pd-C_{carb}).

2.4.3. Dichloro[1-(β-methallyl)-3-(2,4,6-trimethylbenzylbenzimidazole-2-ylidene]pyridine palladium(II), 2c

Yield: 76%, mp 206-207 ^oC; FT-IR $\nu_{(CN)}$: 1399 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.82 (s, 3H, NCH_2C(C*H*$_3$)CH_2), 2.26 (s, 9H, $CH_2C_6H_2$-2,4,6-(C*H*$_3$)$_3$), 5.01 (s, 1H, NCH_2C(CH_3)C*H*$_2$), 5.06 (s, 1H, NCH_2C(CH_3)C*H*$_2$), 5.52 (s, 2H, N*C*H_2C(CH_3)CH_2), 6.17 (s, 2H, C*H*$_2$$C_6H_2$-2,4,6-($CH_3$)$_3$), 6.41 (d, 1H, Ar-*H*, *J* = 8 Hz), 6.86-6.91 (m, 3H, Ar-*H*), 7.06 (t, 1H, Ar-*H*, *J* = 8 Hz), 7.30 (t, 3H, Ar-*H*, *J* = 8 Hz), 7.71 (tt, 1H, Ar-*H*, *J* = 8 Hz, ^2J = 4 Hz), 8.92 (tt, 2H, C_5H_5, *J* = 4 Hz, ^2J = 4 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 20.4 (NCH_2C(*C*H_3)CH_2), 20.8 ($CH_2C_6H_2$-2,4,6-(*C*H_3)$_3$), 21.1 ($CH_2C_6H_2$-2,4,6-(*C*H_3)$_3$), 50.2 (*C*$H_2C_6H_2$-2,4,6-(CH_3)$_3$), 54.9 (N*C*H_2C(CH_3)CH_2), 114.6 (NCH_2C(CH_3)*C*H_2), 138.1 (NCH_2*C*(CH_3)CH_2), 111.0, 111.5, 122.9, 123.2, 124.5, 127.6, 129.7, 134.6, 134.8, 138.5, 138.7, 139.5 and 151.3 (Ar-*C*), 164.4 (Pd-C_{carb}).

2.4.4. Dichloro[1-(β-methallyl)-3-(2,3,5,6-tetramethylbenzylbenzimidazole-2-ylidene]pyridinepalladium(II), 2d

Yield: 79%, mp 228-230 ^oC; FT-IR $\nu_{(CN)}$: 1407 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.90 (s, 3H, NCH_2C(C*H*$_3$)CH_2), 2.25 (s, 6H, CH_2C_6H-2,3,5,6-(C*H*$_3$)$_4$), 2.25 (d, 6H, CH_2C_6H-2,3,5,6-(C*H*$_3$)$_4$, *J* = 4 Hz), 5.07 (s, 1H, NCH_2C(CH_3)C*H*$_2$), 5.13 (s, 1H, NCH_2C(CH_3)C*H*$_2$), 5.59 (s, 2H, N*C*H_2C(CH_3)CH_2), 6.28 (s, 2H, C*H*$_2$$C_6H$-2,3,5,6-($CH_3$)$_4$), 6.44 (d, 1H, Ar-*H*, *J* =

8 Hz), 6.95 (t, 1H, Ar-*H*, *J* = 8 Hz), 7.08 (s, br, 1H, Ar-*H*), 7.13 (t, 1H, Ar-*H*, *J* = 8 Hz), 7.34-7.37 (m, 3H, Ar-*H*), 7.77 (tt, 1H, Ar-*H*, *J* = 8 Hz, ^{2}J = 4 Hz), 8.95 (tt, 2H, C_5H_5, *J* = 4 Hz, ^{2}J = 4 Hz). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 16.5 (CH_2C_6H-2,3,5,6-(CH_3)$_4$), 20.4 ($NCH_2C(CH_3)CH_2$), 20.6 (CH_2C_6H-2,3,5,6-(CH_3)$_4$), 50.7 (CH_2C_6H-2,3,5,6-(CH_3)$_4$), 54.9 ($NCH_2C(CH_3)CH_2$), 114.5 ($NCH_2C(CH_3)CH_2$), 138.1 ($NCH_2C(CH_3)CH_2$), 111.0, 111.4, 122.8, 123.2, 124.5, 130.6, 132.5, 134.3, 134.7, 135.0, 139.4 and 151.2 (Ar-*C*), 164.4 (Pd-C_{carb}).

2.4.5. Dichloro[1-(β-methallyl)-3-(2,3,4,5,6-pentamethylbenzylbenzimidazole-2-ylidene]pyridine palladium(II), 2e

Yield: 78%, mp 214-215 ^{o}C; FT-IR $\nu_{(CN)}$: 1395 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.90 (s, 3H, $NCH_2C(CH_3)CH_2$), 2.23 (s, 6H, CH_2C_6-2,3,4,5,6-(CH_3)$_5$), 2.31 (s, 9H, CH_2C_6-2,3,4,5,6-(CH_3)$_5$), 5.08 (s, 1H, $NCH_2C(CH_3)CH_2$), 5.13 (s, 1H, $NCH_2C(CH_3)CH_2$), 5.59 (s, 2H, $NCH_2C(CH_3)CH_2$), 6.30 (s, 2H, CH_2C_6-2,3,4,5,6-$(CH_3)_5$), 6.42 (d, 1H, Ar-*H*, *J* = 8 Hz), 6.93 (t, 1H, Ar-*H*, *J* = 8 Hz), 7.11 (t, 1H, Ar-*H*, *J* = 8 Hz), 7.34-7.37 (m, 3H, Ar-*H*), 7.77 (tt, 1H, Ar-*H*, *J* = 8 Hz, ^{2}J = 4 Hz), 8.97 (tt, 2H, C_5H_5, *J* = 4 Hz, ^{2}J = 4 Hz). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 16.9 (CH_2C_6-2,3,4,5,6-(CH_3)$_5$), 17.3 (CH_2C_6-2,3,4,5,6-(CH_3)$_5$), 17.5 (CH_2C_6-2,3,4,5,6-(CH_3)$_5$), 20.4 ($NCH_2C(CH_3)CH_2$), 51.4 (17.3 (CH_2C_6-2,3,4,5,6-(CH_3)$_5$), 55.0 ($NCH_2C(CH_3)CH_2$), 114.5 ($NCH_2C(CH_3)CH_2$), 138.0 ($NCH_2C(CH_3)CH_2$), 110.9, 111.6, 122.7, 123.1, 124.4, 127.9, 133.1, 134.6, 134.7, 134.8, 135.9, 139.5 and 151.2 (Ar-*C*), 164.2 (Pd-C_{carb}).

2.5. X-ray crystallography

Suitable single crystals of the complexes **2c-e** were selected for data collection performed on an Oxford Xcalibur Eos diffractometer using graphite monochromated MoK_α radiation (λ=0.71073 Å). Details of the data collection conditions and refinement processes are summarized in Table 1. The collected intensities of three crystals were corrected for Lorentz and polarization factors. Analytical absorption correction was performed by CrysAlisPro 1.171.38.41 software. Cell parameters were also determined by CrysAlisPro software [31]. Using Olex2 [32], the structures of **2c-e** were resolved with the ShelXT structure solution program using Intrinsic Phasing and refined with the ShelXL [33] refinement package using Least Squares minimization. All non-hydrogen atoms were refined anisotropically. All H atoms were positioned geometrically and refined using a riding model, fixing the aromatic C—H distances at 0.93 Å, methylene C—H distances (except for C16) at 0.97 Å, methyl C—H distances at 0.96 Å. C—H distances of double-bonded methylene C16 atom were fixed at

0.93 Å. U_{iso}(H) values were set to 1.2U_{eq} (1.5U_{eq} for the methyl group) of the parent atom. Molecular diagrams were created using *ORTEP*3 [34]. For complex **2c**, systematic absences and intensity statistics indicated non-centrosymmetric $P2_1$ space group. However, an inversion twin ~~has~~ occurred in the crystal structure of **2c**. The command TWIN −1 0 0 0 −1 0 0 0 −1 2 was ~~has~~ applied to the data and the crystal structure was refined as a two-component twin. After the final refinement, the Flack parameter was ~~is~~ 0.50(7).

Table 1. Crystal data and structure refinement parameters for complexes **2c-e**

	Complex **2c**	Complex **2d**	Complex **2e**
CCDC number	1883977	1883972	1883971
Chemical formula	$C_{26}H_{29}Cl_2N_3Pd$	$C_{27}H_{31}Cl_2N_3Pd$	$C_{28}H_{33}Cl_2N_3Pd$
Formula weight	560.82	574.89	588.87
Temperature (K)	294	304	304
Crystal system	Monoclinic	Triclinic	Monoclinic
Space group	*P* 2_1	*P* -1	*C* 2/c
Crystal size (mm^3)	0.21×0.13×0.09	0.40×0.35×0.23	0.60×0.50×0.30
Crystal shape/color	Prism/orange	Prism/orange	Prism/orange
a (Å)	8.4728(5)	8.5236(6)	24.9764(10)
b (Å)	17.0364(10)	11.3683(7)	8.4773(3)
c (Å)	17.5407(12)	14.4251(9)	25.3075(9)
α (°)	90	79.636(5)	90
β (°)	94.232(6)	84.577(5)	95.110(3)
γ (°)	90	70.601(6)	90
Volume ($Å^3$)	2525.0(3)	1296.00(15)	5337.1(3)
Formula *Z*	4 (*Z*'=2)	2	8
T_{min}, T_{max}	0.872, 0.925	0.762, 0.864	0.696, 0.793
F(000)	1144	587	2416
Calc. Density (g cm^{-3})	1.475	1.473	1.466
Abs. Coeff. μ (mm^{-1})	0.97	0.94	0.92
θ range (°)	3.002-2.502	3.194-26.367	3.233-25.681
Index ranges	$-9 \le h \le 10$	$-6 \le h \le 10$	$-30 \le h \le 20$
	$-20 \le k \le 20$	$-11 \le k \le 14$	$-9 \le k \le 10$
	$-20 \le l \le 20$	$-16 \le l \le 18$	$-24 \le l \le 30$
Measured refls	15662	6850	8848
Independent refls	8868	5236	5031
Observed refls	5979	4318	4086
No. of parameters	562	303	314
R_{int}	0.057	0.019	0.019
Goodness of Fit on F^2	1.01	1.04	1.03
R indices [$I>2\sigma(I)$]	R_1 = 0.067	R_1 = 0.038	R_1 = 0.037
	wR_2 = 0.148	wR_2 = 0.082	wR_2 = 0.103
$\Delta\rho_{max}$, $\Delta\rho_{min}$ ($eÅ^{-3}$)	2.16, −0.56	0.52, −0.51	0.55, −0.50
$(\Delta/\sigma)_{max}$	<0.0001	0.0004	0.002

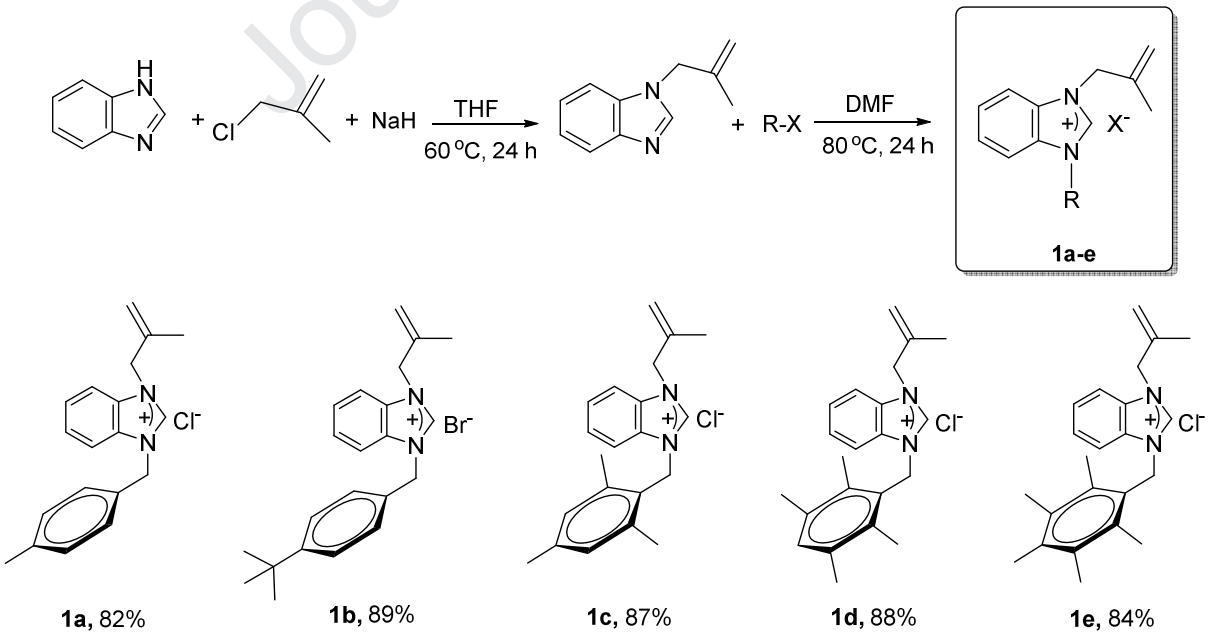
2.6. General Procedure for the Arylation Reaction

KOAc (1.0 mmol), aryl bromide derivatives (1.0 mmol), heteroaryl derivatives (2-n-propylthiazole, 4,5-dimethylthiazole and 2-acetylthiophene) (2.0 mmol), and Pd-NHC complexes **2a-e** (0.5 mol% or 1 mol%) were dissolved in N,N-dimethylacetamide (DMAc) (2 mL) in a small Schlenk tube under argon as described in the literature [35]. The reaction mixture was stirred at the ~~in~~ appropriate temperature for 1 h then ~~was~~ cooled to room temperature and the solvent was removed under vacuum. The obtained residue was purified by column chromatography (silica gel 60–120 mesh) ~~by~~ using diethyl ether/n-hexane (1:5) as eluent to afford the pure product. The purity of the compounds was checked by gas chromatography (GC) and gas chromatography-mass spectrometry (GC-MS). Conversions were calculated by taking into account the conversion of aryl bromides to products.

3. Results and Discussion

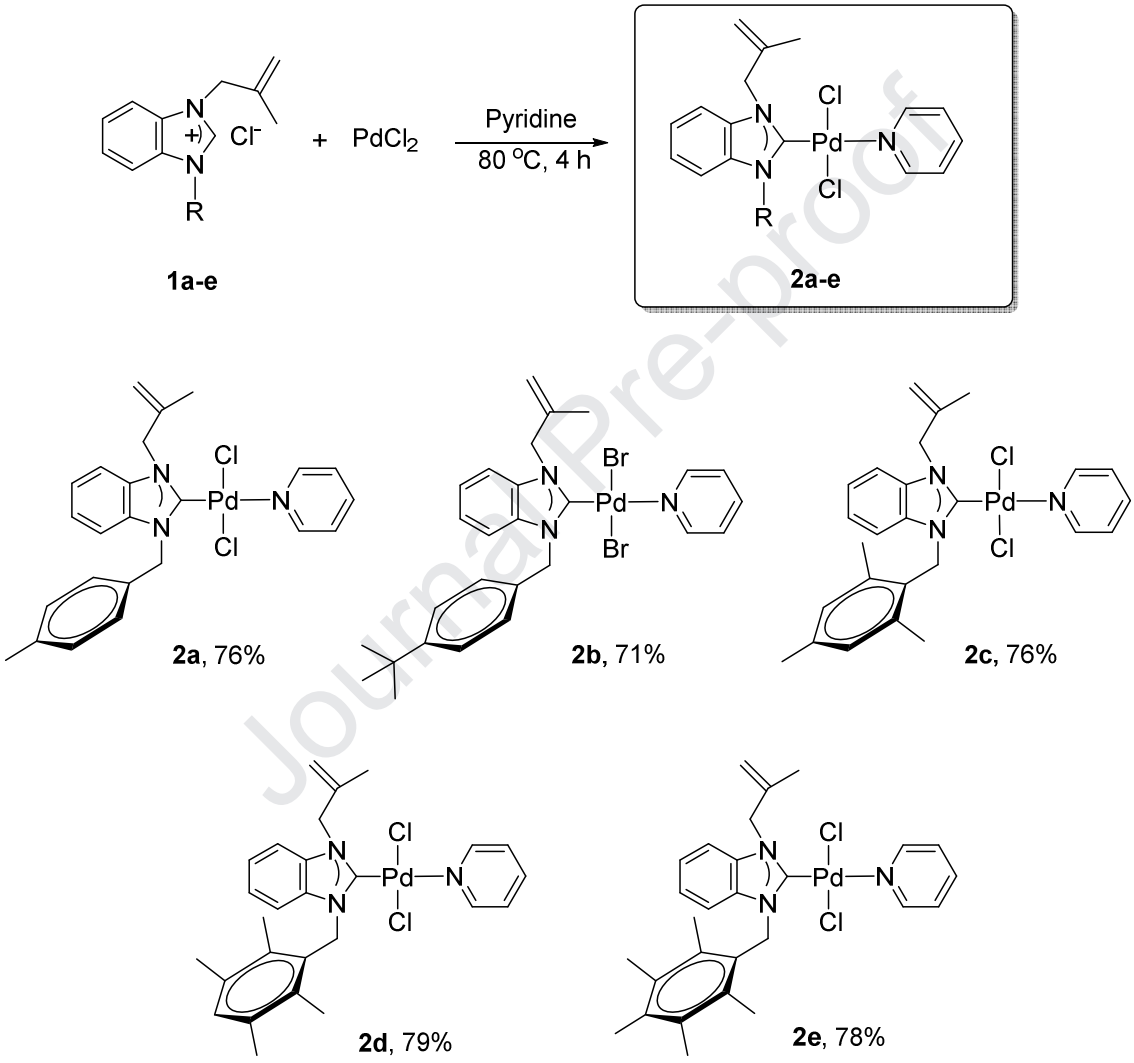
3.1. Synthesis and characterization of benzimidazole-based ligand precursors and their corresponding Pd-NHC complexes

The benzimidazole-based ligand precursors (**1a-e**) were prepared by reaction of 1-(β-methallyl)benzimidazole with 4-methylbenzyl chloride, 4-*ter*-butylbenzyl chloride, 2,4,6-trimethylbenzyl chloride, 2,3,5,6-tetramethylbenzyl chloride, and 2,3,4,5,6-pentamethyl chloride. These ligand precursors were prepared according to literature as shown in Scheme 1 [28, 36].



Scheme 1. Synthesis of benzimidazole-based ligand precursors (**1a-e**)

The synthetic route for the synthesis of Pd(II)-NHC complexes is shown in Scheme 2. Pd(II)-NHC complexes (**2a-e**) were synthesized from the reaction of $PdCl_2$, corresponding NHC ligands (**1a-e**) and K_2CO_3 in pyridine at 80 ^oC. The NHC ligands and Pd(II)-NHC complexes are air and moisture stable in the solid-state. All newly synthesized ~~all~~ compounds were characterized by FT-IR, ^1H NMR and $^{13}C\{^1H\}$ NMR spectroscopies. ~~Also,~~ For **2c**, **2d** and **2e** complexes were obtained as appropriate single crystals and the structure of these complexes ~~were~~ was elucidated in ~~by~~ X-ray diffraction studies.



Scheme 2. Synthesis of benzimidazole-based NHC-palladium(II) complexes **(2a-e)**

At the FT-IR spectra for all ligand precursors (**1a-e**), (CN) vibrations of benzimidazolium salts (**1a-e**) were assigned at around 1551-1557 cm^{-1}. These vibrations ~~at~~ in the Pd(II)-NHC complexes (**2a-e**) ~~have~~ were seen at around 1395-1407 cm^{-1}. The electropositive palladium center ~~which~~ pulls electron density towards itself and as a result, (CN) vibrations shift to the

lesser energy region in the complex by comparison ligand. These results are consistent with the literature [37, 38].

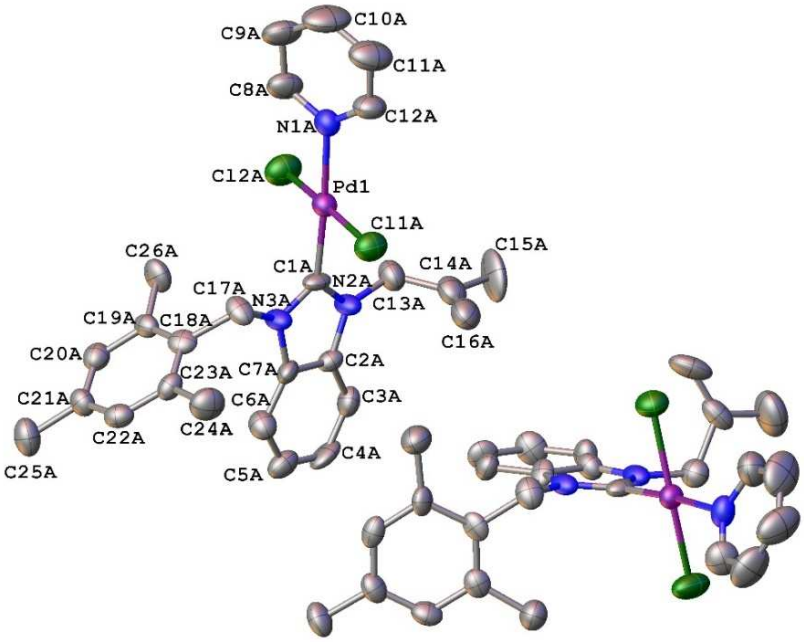
NMR spectra of all the compounds were analyzed in $CDCl_3$. In the ^1H NMR spectra, acidic protons (NC*H*N) for benzimidazolium salts (**1a-e**) were seen at 11.74, 11.60, 11.60, 11.29 and 11.04 ppm, respectively, as a characteristic sharp singlet. This acidic proton is lost when the complex is formed. ~~It was seen~~ The disappearance of acidic protons was seen in the ^1H NMR spectra of **2a-e** and this proves the of complex~~es~~ formation. Another evidence of complex formation, the carbene peak of N*C*N shifts much more to the downfield region compared to the corresponding ~~the~~ benzimidazolium salt. In the $^{13}C\{^1H\}$ NMR spectra, N*C*HN carbon peaks of ligand precursors (**1a-e**) were observed at 144.0, 143.2, 144.4, 144.1 and 143.8 ppm, respectively. After complex formation, N*C*N carbene resonance on the Pd(II)-NHC complexes (**2a-e**) which shifted much more to the downfield region was observed at 164.6, 164.1, 164.4, 164.4 and 164.2 ppm, respectively. These values are in agreement with reported data for similar PEPPSI type Pd(II)-NHC complexes [28]. Further ~~for more~~ details of complete NMR and FT-IR studies are given in supplementary information (Figure S1-S18).

3.2. Crystal structure description of 2c, 2d, and 2e complexes

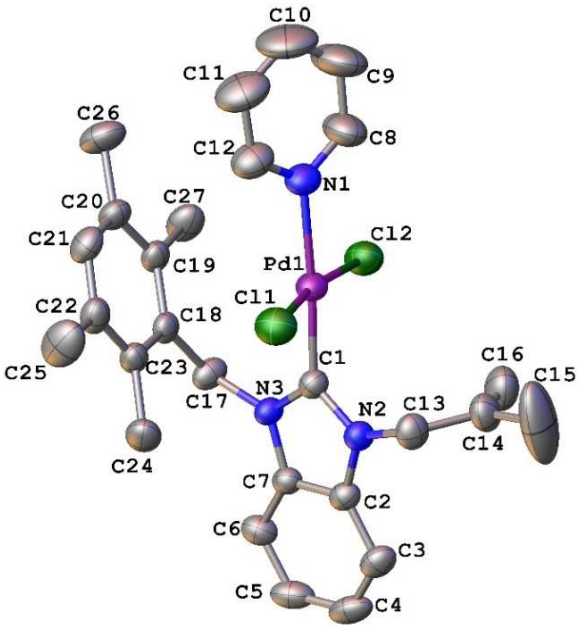
The crystal structures of three similar Pd-NHC complexes, **2c**, **2d** and **2e**, were determined ~~by~~ using the X-ray single-crystal diffraction technique. There are two symmetry independent molecules (referred to as mol**a** and mol**b**) in the asymmetric unit of the unit cell of **2c**. An ORTEP3 view of the asymmetric unit of **2c** is also given in Figure 3(a). Both the complexes **2d** and **2e** have one molecule in their asymmetric unit as shown in Figure 3(b)-3(c).

~~It is expected that~~ Palladium and its four coordination atoms are expected to form a square-planar geometry. The Pd1/Cl1/Cl2/C1/N1 coordination plane of **2c** and **2e** are slightly distorted from planarity. A maximum deviation of −0.028(1) Å for Pd1 atom is observed in **2e** and −0.083(7) Å for C1a in **2c**. This distortion is more pronounced in **2d** with a maximum deviation of 0.123(1)Å for Cl2 atom. C1—Pd—N1 and Cl1—Pd—Cl2 bond angles are expected to be linear. These values are in the range of 174.16(18)°-177.23(13)° for **2c** and **2e**. Similar values are observed in the literature [39-41]. A conspicuous deviation from linearity can be observed for **2d** due to Cl2—Pd1—Cl1 angle being ~~of~~ 170.77(3)°. The other bond angles in the coordination plane are almost perpendicular so as to adopt square geometry and in the of range 86.3(5)°-92.96(9)° for **2c**, **2d,** and **2e.** Selected bond distances, bond and torsion angles can be found in Table 2. The main geometric differences in the molecular structures of **2c**, **2d,** and **2e** are (i) the orientation of methyl-substituted benzene ring and, (ii)

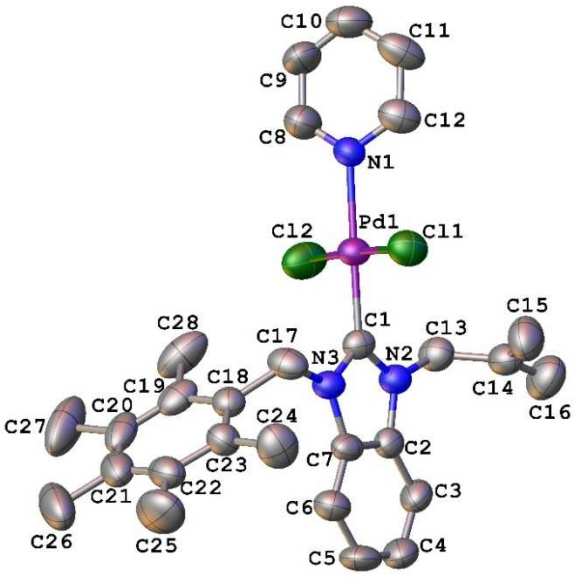
the conformation of aliphatic C13/C14/C15/C16 group. As shown in Figure 3(b)-(c), different orientations of methyl-substituted benzene rings arise from the rotation of the substituted benzene ring around the single C17—C18 and N3—C17 bonds. Torsion angles τ_1 (N3—C17—C18—C23) are −56.3(4)° for **2d** an110.5(4)° for **2e.**



(2a)



(2b)



(2c)

Figure 3. The asymmetric unit of **(a)** complex **2c**, **(b)** complex **2d**, **(c)** complex **2e** showing the atom-labelling scheme. Hydrogen atoms are omitted for clarity. Displacements ellipsoids are drawn at the 50% probability level. Mol**b** atoms of **2c** have not been labeled for clarity.

According to Newman projections on the C17—C18 bond, molecule **2d** and **2e** adapt to –sc(syn-clinal) conformations and +ac (anti-clinal), respectively. In the asymmetric unit of **2c** as shown in Figure 3(a), mol**a** and mol**b** having very similar bond distances are conformational isomers. Superimposition of mol**a** and mol**b** including H atoms can be seen in Figure 4. τ1 torsion angle is 113.0(14)° in mol**a**, while it is 63.8(19)° in mol**b**. They adapt to +ac and +sc conformations, respectively. Conformational differences of aliphatic substituents in each complex may predominantly ~~may~~ occur by virtue of rotations of related groups around the single C13—C14 bond. τ2 (N2—C13—C14—C15) torsion angle is −168.4(4)° in **2d**, whereas it is −47.4(5)° in **2e**. The corresponding values are 163.3(15)° and −167.5(15)° for mol**a** and mol**b**, respectively. Dihedral angles among the mean planes of coordination plane, benzimidazole, pyridine and C18/C23 rings of each molecule are also given in Table 2. The Pd—Cl, Pd—N1 and Pd—C1 bond distances given in Table 2 and the other bond distances are in ~~a~~ good agreement with similar Pd-NHC complexes in the literature [39-41]. In the absence of classical hydrogen bonds, crystal structures of **2c-e** are stabilized by weak intermolecular interactions. Figures and details of **2c**, **2d** and **2e** are given in the supplementary information file (Table S1, Figure S19-S21).

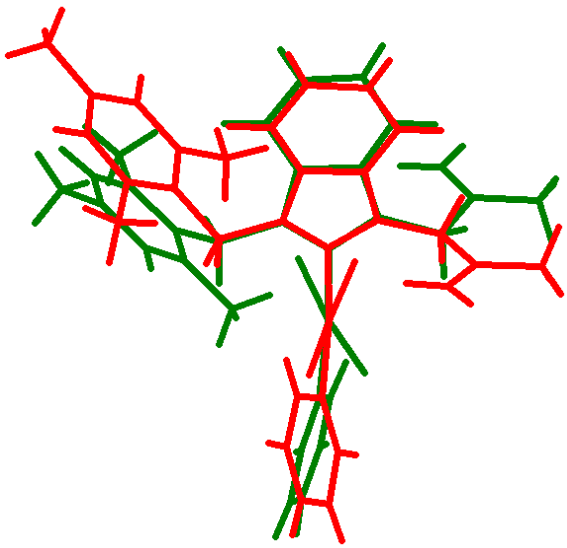


Figure 4. An overlay view of conformers mol**a** (green) and mol**b** (red) in the asymmetric unit of **2c.** The root-mean-square fit of atomic positions is 6.052×10^{-2} Å.

Table 2. Selected bond distances (Å), bond, torsion, and dihedral angles (°) of **2c-e**

	2c-mol**a**	**2c**-mol**b**	**2d**	**2e**
Bond Distances				
Pd—Cl1	2.284(5)	2.292(5)	2.317(9)	2.307(9)
Pd—Cl2	2.310(4)	2.302(4)	2.332(9)	2.289(1)
Pd—N1	2.120(13)	2.132(15)	2.122(3)	2.108(3)
Pd—C1	1.948(14)	1.928(16)	1.946(3)	1.954(3)
Bond and Torsion Angles				
Cl2—Pd1—Cl1	174.16(18)	174.59(19)	170.77(3)	176.32(4)
C1—Pd1—N1	175.0(6)	175.1(6)	175.62(11)	177.23(13)
N1—Pd1—Cl1	92.2(4)	91.2(4)	92.79(8)	92.96(9)
N1—Pd1—Cl2	92.8(4)	93.0(4)	92.67(8)	90.07(9)
C1—N2—C13—C14	103.8(18)	−106.7(17)	−96.1(4)	107.2(4)
C1—N3—C17—C18	152.8(14)	−138.9(15)	−42.3(4)	141.6(3)
N3—C17—C18—C19	−63.2(17)	−117.9(15)	126.1(3)	−73.3(4)
N2—C13—C14—C16	−20(2)	11(2)	12.6(6)	137.8(4)
Dihedral Angles				
A/*B*	73.7(3)	76.0(3)	72.47(5)	67.64(6)
A/*C*	35.4(6)	37.4(7)	29.65(17)	37.37(17)
B/*C*	71.7(5)	68.0(5)	78.18(12)	75.70(13)
B/*D*	84.2(3)	84.9(3)	77.72(9)	84.20(9)

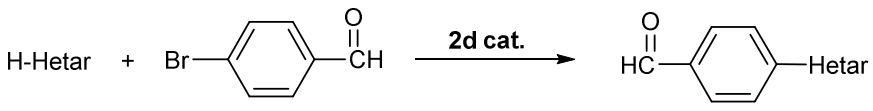
A, B, C, D in dihedral angles section denote coordination plane, benzimidazole ring, pyridine and C18/C23 rings, respectively.

3.3. Direct arylation of various heteroaromatic groups with aryl bromides using Pd(II)-NHC catalysts

Arylation at both C2 and C5 is also fairly common. The selectivity of arylation depends on the free energy of activation for C-H bonds [42]. Based on previous results on Pd-catalysed direct arylation, for this study, DMAc (N,N-dimethylacetamide) and KOAc (potassium acetate) were selected as the solvent and base [15, 35]. However, several attempts were made with a number of solvents and bases for this study. The reactions were performed at 100-150 ^{o}C under argon in the presence of **2d**. The results are summarized in Table 3. At direct arylation reaction of 2-*n*-propylthiazole, only C5-arylated product was obtained ~~due to~~ as it has a blocked C2-position. Coupling reactions of 2-*n*-propylthiazole with *p*-bromobenzaldeyhde were tested in the presence of different bases and solvents using 0.5 mol% or 1 mol% **2d** catalyst. The full conversion was obtained using DMAc as solvent and KOAc as base at 130 ^{0}C for 1 h (Table 3, entry 4). In this condition, when temperature

was reduced to 100 °C, the reaction yield was 76% (Table 3, entry 7); when time was shortened to 0.5 h, reaction yield was 100% (Table 3, entry 8); when the catalyst amount was decreased to 0.5 mol%, reaction yield was 94% (Table 3, entry 9). It was decided to reduce the amount of catalyst among the moderating conditions. For coupling of 2-acetylthiophene with *p*-bromobenzaldeyhde, the same reaction condition was found to be optimal (Table 3, entry 13). C5-position of C2-substituted 2-acetylthiophene ~~are~~ is reactive and mostly C5-arylated product was obtained. When the coupling reaction of 4,5-dimethylthiazole with *p*-bromobenzaldeyhde was tested ~~at~~ in the same conditions, only 16% coupling product was obtained (Table 3, entry 10), so the temperature was increased up to 150 °C and reaction yield ~~was~~ increased to 77% (Table 3, entry 11). C2-position of 4,5-dimethylthiazole was arylated because of blocked C4- and C5-positions. Although the amount of catalyst was decided to be 0.5 mol%, in later experiments, with 0.5 mol% catalyst for *p*-bromoanisole, ~~it was seen that~~ the reaction yield was seen to be low (Table 3, entry 14). Consequently, it was found that when the reaction was carried out in DMAc in the presence of KOAc at 130 °C for 1 h for arylation of 2-*n*-propylthiazole and 2-acetylthiophene, ~~for~~ with *p*-bromotoluene, *p*-bromobenzaldyehyde and 1-bromonaphthalene as aryl bromide ~~were used~~ 0.5 mol% Pd(II)-NHC catalyst was used and ~~for~~ with bromobenzene, *p*-bromoanisole and *p*-bromoacetophenone as aryl bromide, ~~were used~~ 1 mol% Pd(II)-NHC catalyst was used, and for arylation of 4,5-dimethylthiazole, ~~was used~~ 1 mol% catalyst was used for all aryl bromide. Palladium black formation was observed at the end of the reaction in all reactions. According to the literature inactive Pd(0) species is called Pd-black which allows the use of lower catalyst loadings [43, 44].

Table 3. Influence of the reaction conditions for the palladium-catalyzed direct arylation of heteroaromatic compounds with *p*-bromobenzaldeyhde.



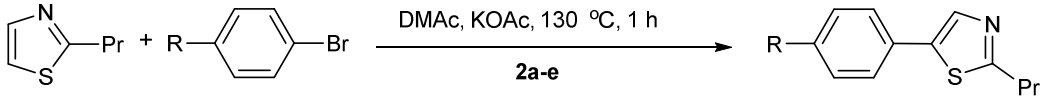
Entry	Heteroaromatic Derivatives	Solvent	Base	Cat. (mol%)	Temp. (°C)	Yield (%)
1	2-*n*-Propylthiazole	DMAc	NaOAc	1	130	43
2	2-*n*-Propylthiazole	DMAc	K_2CO_3	1	130	21
3	2-*n*-Propylthiazole	DMAc	Cs_2CO_3	1	130	0
4	2-*n*-Propylthiazole	DMAc	KOAc	1	130	100
5	2-*n*-Propylthiazole	DMF	KOAc	1	130	59
6	2-*n*-Propylthiazole	Toluene	KOAc	1	130	47
7	2-*n*-Propylthiazole	DMAc	KOAc	1	100	76

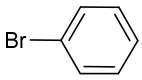
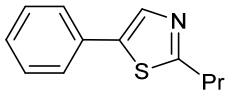
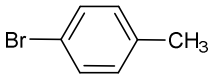
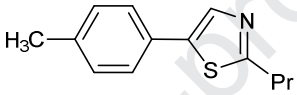
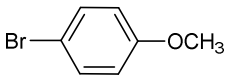
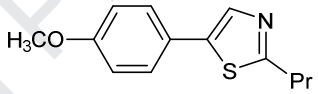
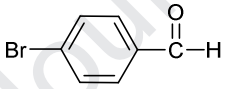
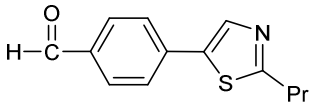
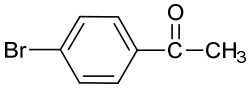
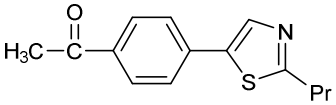
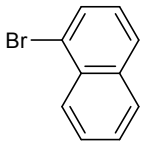
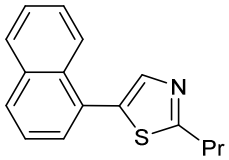
8	2-*n*-Propylthiazole	DMAc	KOAc	1	130	100[b]
9	**2-*n*-Propylthiazole**	**DMAc**	**KOAc**	**0.5**	**130**	**94**
10	4,5-Dimethylthiazole	DMAc	KOAc	1	130	16
11	**4,5-Dimethylthiazole**	**DMAc**	**KOAc**	**1**	**150**	**77**
12	2-Acetylthiophene	DMAc	KOAc	1	130	100
13	**2-Acetylthiophene**	**DMAc**	**KOAc**	**0.5**	**130**	**90**

[a]Conditions: Heteroaromatic compound (2.0 mmol), *p*-bromobenzaldehyde (1.0 mmol), base (2 mmol), solvent (2 mL), 1 h. b) 30 minutes. Product purity was checked by GC, conversions were calculated according to aryl bromide and the calibrations were based on decane.

Under ~~the~~ optimal conditions, direct arylation of 2-*n*-propylthiazole with various aryl bromides was examined and only the C5-arylated thiazole derivatives were obtained with good yields. When 2-*n*-propylthiazole was arylated with *p*-bromotoluene, *p*-bromobenzaldeyde and 1-bromonaphthalene, C5-arylated products were obtained ~~by~~ using only 0.5 mol% Pd(II)-NHC complexes (**2a-e**) as the catalyst that *p*-bromotoluene showed highest conversion in the range of 93-100% (Table 4, entries 6-10) and 1-bromonaphthalene showed lowest conversion in the range of 62-87% (Table 4, entries 26-30). In reactions using 0.5 mol% catalyst, it can be said that **2a** has the highest activity. Of the arylation reactions with bromobenzene, *p*-bromoanisole, and *p*-bromoacetophenone using 1 mol% catalyst, *p*-bromoanisole as an electron-rich aryl bromide gave 53% conversion lowest C5-arylated products with **2d** catalyst. (Table 4, entry 14). This is probably, this is because ~~of~~ the oxidative addition of *p*-bromoanisole to palladium appears to be slower than the oxidative addition of 2-*n*-propylthiazole. Again, **2a** showed the highest activity in reactions using 1 mol% catalyst. Although small differences in reactivities were observed for **2a-e** catalyst due to the similar nature of the NHC moieties, it can be said that the most effective catalyst in the direct arylation of 2-*n*-propylthiazole with aryl bromide is **2a**. **2a** catalyst gave 100% yield with bromobenzene, *p*-bromotoluene, *p*-bromoanisole, *p*-bromobenzaldehyde (Table 4, entries 1, 6, 11 and 16). For arylation reaction of 2-*n*-propylthiazole in the literature, the reaction temperature was 150 ^{o}C, and the catalyst was 1 mol%. When PEPPSI-type complex was used, reaction time 1 h [43], and when [$PdCl_2L_2$] type complex was used, reaction time was 20 h. [35]. In this study, reaction temperature was decreased to 130 ^{o}C, the catalyst amount was decreased to 0.5 mol% and reaction time was 1 h.

Table 4. Palladium(II)-NHC-catalyzed direct C5-arylation of 2-*n*-propylthiazole with aryl bromides.[a]

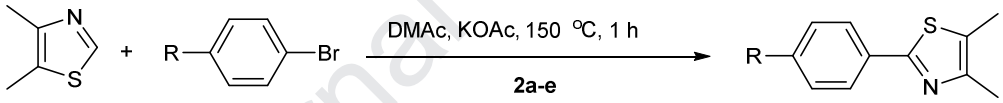


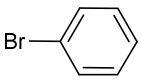
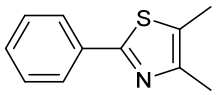
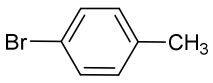
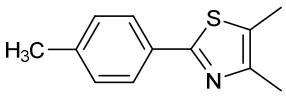
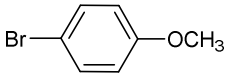
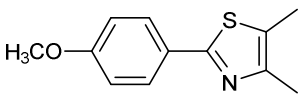
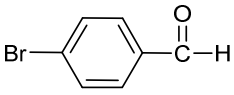
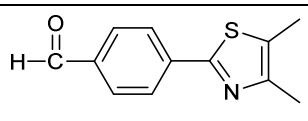
Entry	Cat.	Aryl bromide	Product	Conv. (%)	Yield (%)
1	**2a**			100	100
2	**2b**			100	100
3	**2c**			100	100
4	**2d**			99 49[b]	99 49[b]
5	**2e**			98	98
6	**2a**			100[b]	100[b]
7	**2b**			94[b]	94[b]
8	**2c**			100[b]	100[b]
9	**2d**			100 93[b]	100 93[b]
10	**2e**			100 100[b]	100 100[b]
11	**2a**			100	100
12	**2b**			79	79
13	**2c**			89	89
14	**2d**			53	53
15	**2e**			65	65
16	**2a**			100[b]	100[b]
17	**2b**			92[b]	92[b]
18	**2c**			71[b]	71[b]
19	**2d**			100 94[b]	100 94[b]
20	**2e**			100 81[b]	100 81[b]
21	**2a**			99	99
22	**2b**			96	96
23	**2c**			98	98
24	**2d**			93 54[b]	93 54[b]
25	**2e**			100	100
26	**2a**			87[b]	87[b]
27	**2b**			80[b]	80[b]
28	**2c**			62[b]	62[b]
29	**2d**			100 76[b]	100 76[b]
30	**2e**			100 67[b]	100 67[b]

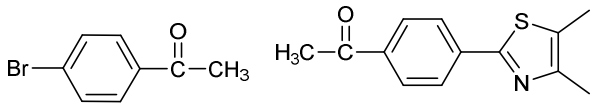
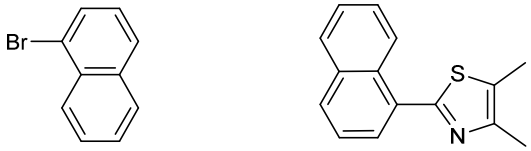
[a]Conditions: 2-n-propylthiazole (2.0 mmol), aryl bromide (1.0 mmol), Pd cat. (1 mol%), KOAc (2 mmol), N,N-dimethylacetamide (2 mL), 130 °C, 1 h. b) Pd cat. (0.5 mol%). Product purity was checked by GC, conversions were calculated according to aryl bromide and the calibrations were based on decane.

Next, direct arylation of 4,5-dimethylthiazole with various aryl bromides was investigated and mostly the C2-arylated thiazole derivatives were obtained due to C4- and C5-positions in blocked methyl groups. For all aryl bromides, ~~were used~~ 1 mol% Pd-NHC catalyst was used and the reaction was performed at 150 ^{0}C for 1 h. Arylation of *p*-bromotoluene gave full conversion with 100% yield with **2a-e** (Table 5, entries 6-10), and *p*-bromobenzene and *p*-bromoanisole gave high activities in the range of 60-100% (Table 5, entries 1-5, 11-15). ~~At~~ In the arylation reactions of *p*-bromobenzaldeyde, *p*-bromoacetophenone and 1-bromonaphthalene were obtained arylated products with the lowest yield in range of 3-57%. (Table 5, entries 16-30). The electron-deficient aryl groups such as *p*-bromobenzaldeyde, *p*-bromoacetophenone decreased the yield of C2-arylated products. On average, the **2b** catalyst showed the best activity. The 4,5-dimethylthiazole group has been rarely studied in the literature. As far as is known, while [$PdCl_2L_2$] type catalyst was used, PEPPSI type catalyst was not found for the arylation of 4,5-dimethylthiazole in the reports. Obtained results in this study are consistent with the literature [15, 45].

Table 5. Palladium(II)-NHC-catalyzed direct C2-arylation of 4,5-dimethylthiazole with aryl bromides.[a]



Entry	Cat.	Aryl bromide	Product	Conv. (%)	Yield (%)
1	**2a**			86	86
2	**2b**			94	94
3	**2c**			95	95
4	**2d**			100	100
5	**2e**			100	100
6	**2a**			100	100
7	**2b**			100	100
8	**2c**			100	100
9	**2d**			100	100
10	**2e**			100	83
11	**2a**			60	60
12	**2b**			100	100
13	**2c**			100	100
14	**2d**			73	73
15	**2e**			100	100
16	**2a**			28	28
17	**2b**			53	53
18	**2c**			24	24

19	**2d**		57	57
20	**2e**		36	83
21	**2a**		12	12
22	**2b**		22	22
23	**2c**		3	3
24	**2d**		18	18
25	**2e**		21	21
26	**2a**		77	77
27	**2b**		39	39
28	**2c**		28	28
29	**2d**		56	56
30	**2e**		34	88

[a]Conditions: 4,5-dimethylthiazole (2.0 mmol), aryl bromide (1.0 mmol), Pd cat. (1 mol%,), KOAc (2 mmol), *N*,*N*-dimethylacetamide (2 mL), 150 ^{o}C, 1 h. Product purity was checked by GC, conversions were calculated according to aryl bromide and the calibrations were based on decane.

When direct arylation of 2-acetylthiophene with various aryl bromides was investigated, similar results were obtained with arylation of 2-*n*-propylthiazole (Table 6). When 2-acetylthiophene was arylated with *p*-bromotoluene, *p*-bromobenzaldeyde and 1-bromonaphthalene, only 0.5 mol% Pd(II)-NHC complexes (**2a-e**) were used (Table 6, entries 6-10,16-20, 26-30). These arylbromides gave high conversion in the range of 80-100% with **2b** catalyst. **2d** catalyst showed lowest activity with 33% converison. When 2-acetylthiophene was arylated with bromobenzene, *p*-bromoanisole and *p*-bromoacetophenone, 1 mol%, Pd(II)-NHC complexes (**2a-e**) were used (Table 6, entries 1-5, 11-15, 21-25). **2b** catalyst provided highest conversion with these arylbromides in the range of 67-100%**,** and **2d** catalyst gave lowest conversion in the range of 49-100%. ~~Also~~ In addition, while from arylation of 2-acetylthiophene with *p*-bromotoluene, *p*-bromoanisole and 1-bromonaphthalene were obtained only C5-arylated products (Table 6, entries 6-10, 11-15, 26-30), with the other aryl bromide were obtained mostly C5-arylated product together with a trace of other position arylated products (Table 6, entries 1-5, 16-20, 21-25). However, with *p*-bromoanisole, ~~was obtained~~ the lowest arylated products were obtained (Table 6, entries 11-15). It was seen that more moderate conditions were presented for this reaction compared to previous studies in the literature which was used PEPPSI type catalyst [25]. In this study, the reaction temperature was decreased to 130 ^{0}C from 150 ^{0}C, the catalyst amount was decreased to 0.5 mol% from 1 mol%, and the reaction time was decreased to 1 h from 2 h compared to literature [25].

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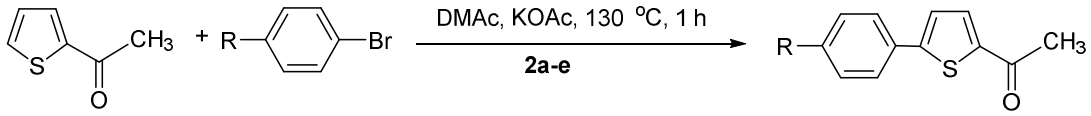
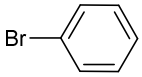
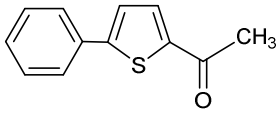
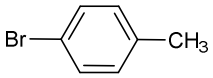
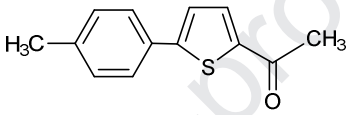
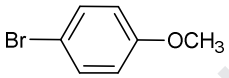
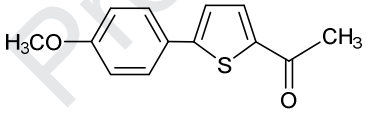
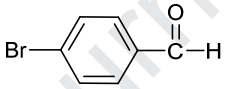
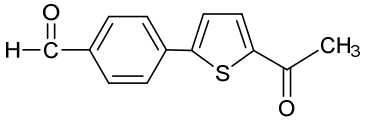
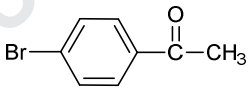
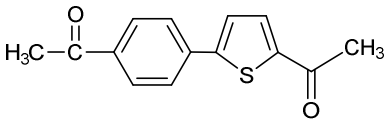
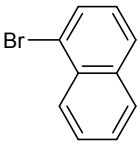
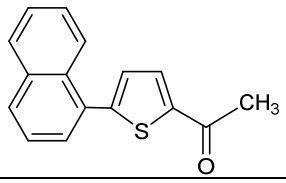
Table 6. Palladium(II)-NHC-catalyzed direct C5-arylation of 2-acetylthiophene with aryl bromides.[a]



Entry	Cat.	Aryl bromide	Product	Conv. (%)	Yield (%)
1	**2a**			100	91
2	**2b**			100	95
3	**2c**			95	89
4	**2d**			100	100
5	**2e**			100	100
6	**2a**			100[b]	91
7	**2b**			100[b]	100
8	**2c**			99[b]	99
9	**2d**			92[b]	92
10	**2e**			100[b]	100
11	**2a**			46	46
12	**2b**			67	67
13	**2c**			67	67
14	**2d**			49	49
15	**2e**			39	39
16	**2a**			68[b]	85
17	**2b**			88[b]	86
18	**2c**			84[b]	88
19	**2d**			33[b]	33
20	**2e**			97[b]	80
21	**2a**			94	80
22	**2b**			100	80
23	**2c**			94	82
24	**2d**			58	86
25	**2e**			100	81
26	**2a**			88[b]	88
27	**2b**			80[b]	80
28	**2c**			100[b]	100
29	**2d**			66[b]	66
30	**2e**			79[b]	79

[a]Conditions: 2-Acetylthiophene (2.0 mmol), aryl bromide (1.0 mmol), Pd cat. (1 mol%), KOAc (2 mmol), *N*,*N*-dimethylacetamide (2 mL), 130 °C, 1 h. b) Pd cat. (0.5 mol%). Product purity was checked by GC, conversions were calculated according to aryl bromide and the calibrations were based on decane.

4. Conclusion

In summary, ~~we have prepared~~ a series of benzimidazole-based ligand precursors were prepared (**1a-e**). These ligands were metallated with $PdCl_2$ in pyridine to give a new PEPPSI type palladium-NHC complex series (**2a-e**). All ligands and palladium complexes were

characterized using ^{1}H, $^{13}C\{^{1}H\}$ NMR and FT-IR spectroscopies. Crystal structure determination of **2c, 2d** and **2e** ~~were~~ was performed ~~by~~ using single-crystal X-ray diffraction method. ~~Aftermost~~, PEPPSI-type palladium-NHC complexes were used in the direct arylation of 2-*n*-propylthiazole, 4,5-dimethylthiazole and 2-acetylthiophene with various aryl bromides. These complexes proved to be highly active in the direct arylation reaction of 2-*n*-propylthizaole. In addition, it ~~has~~ was seen that he reaction conditions ~~are~~ were more moderate in terms of reaction temperature, time and quantity of catalyst amount.

Conflicts of interests

The authors have ~~are~~ no conflicts of interests to declare.

Acknowledgments

The authors thank the Scientific and Technological Research Institute of Turkey (TÜBITAK-BİDEB) the National Research Fellowship Programme for grants to N. Ş. Hande K. and Hasan K. acknowledge Dokuz Eylul University for the use of the Agilent Xcalibur Eos diffractometer (purchased under University Research grant No. 2010.KB·FEN.13).

Appendix A. Supplementary data

CCDC: 1883977, 1883971 and 1883972 and contain the supplementary crystallographic data for complexes **2c**, **2d** and **2e**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre by visiting www.ccdc.cam.ac.uk.

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Highlights

-Novel N-heterocyclic carbene ligands (NHC) and their PEPPSI type Pd(II)-NHC complexes have been synthesized.

- Structures of the complexes were determined by NMR, IR and X-ray spectroscopies.

-The complexes have been applied for the direct arylation of thiopene and thiazole derivatives with aryl bromide as a catalyst.

-Good to excellent coupling products have been obtained.

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All of the sources of funding for the work described in this publication are acknowledged below:

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The authors thank the Scientific and Technological Research of Turkey (TÜBITAK-BIDEB) the National Research Fellowship Programme for grants to N. Ş. Hande K. and Hasan K. acknowledge Dokuz Eylul University for the use of the Agilent Xcalibur Eos diffractometer (purchased under University Research grant No. 2010.KB·FEN.13).

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