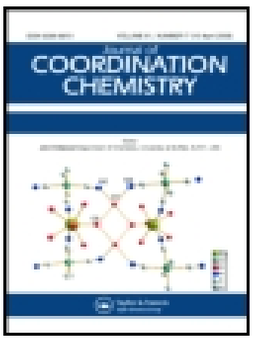


Journal of Coordination Chemistry

ISSN: 0095-8972 (Print) 1029-0389 (Online) Journal homepage: https://www.tandfonline.com/loi/gcoo20

Preparation and characterization of PEPPSI-palladium N-heterocyclic carbene complexes using benzimidazolium salts catalyzed by Suzuki-Miyaura cross coupling reaction and their bioactivities

L. Boubakri, K. Dridi, A. Sulaiman Al-Ayed, İ. Özdemir, S. Yasar & N. Hamdi

To cite this article: L. Boubakri, K. Dridi, A. Sulaiman Al-Ayed, İ. Özdemir, S. Yasar & N. Hamdi (2019): Preparation and characterization of PEPPSI-palladium N-heterocyclic carbene complexes using benzimidazolium salts catalyzed by Suzuki-Miyaura cross coupling reaction and their bioactivities, Journal of Coordination Chemistry, DOI: 10.1080/00958972.2019.1572886

To link to this article: https://doi.org/10.1080/00958972.2019.1572886

Preparation and characterization of PEPPSI-palladium N-heterocyclic carbene complexes using benzimidazolium salts catalyzed by Suzuki-Miyaura cross coupling reaction and their bioactivities

L. BOUBAKRI[1], K. DRIDI[2,3], A. SULAIMAN AL-AYED[2], İ. ÖZDEMIR[5], S. YASAR[5] and N. HAMDI*[1,2]

[1]Research Laboratory of Environmental Sciences and Technologies (LR16ES09), Higher Institute of Environmental Sciences and Technology, University of Carthage, Hammam-Lif, Tunisia
[2]Chemistry Department, College of Science and Arts, Qassim University, Al-Rass, Kingdom of Saudi Arabia
[3]Organic and Heterocyclic synthesis Laboratory, Chemistry Department, Faculty of Sciences, Elmanar University, Tunis, Tunisia
[4]Zoology Department, College of Science, King Saud University, P.O. Box 2455, Riyadh 11451, Saudi Arabia
[5]İnönü University, Faculty of Science and Art, Department of Chemistry, Malatya, Turkey

New palladium complexes were efficiently synthesized from the reaction of benzimidazolium salts **2a-e**, potassium carbonate (K_2CO_3) and palladium chloride ($PdCl_2$) in pyridine (for **3a-e**). The catalytic activity of these complexes in a catalytic system including palladium complexes and K_2CO_3 in DMF-H_2O was evaluated in Suzuki-Miyaura cross-coupling reactions of aryl bromides and chlorides with phenylboronic acid. Our novel complexes show excellent catalytic activities with high turnover numbers (TON) and high turnover frequencies (TOF) (*e.g.*, for the Suzuki-Miyaura reaction: TON up to 370 and TOF up to 123.3 h^{-1}). Both benzimidazolium salts **2a-e** and complexes **3** have been characterized using spectroscopic data and elemental analysis. The antimicrobial activity of the N-heterocyclic carbene palladium complexes **3a-e** varies with the nature of the ligands. Also, the IC_{50} values of both, complexes **(3a-e)** and benzimidazoles **2a-e**, have been determined. In addition, the new palladium complexes were screened for their antitumor activity. Complexes **3e** and **3d** exhibited the highest antitumor effect with IC_{50} values 6.85 µg/mL against MCF-7 and 10.75 µg/mL against T47D, respectively.

Keywords: Suzuki-Miyaura coupling; *N*-Heterocyclic carbene; Palladium(II) catalyst; Antimicrobial activity; Antitumor activity

1. Introduction

For the formation of carbon-carbon (C-C) bonds in the midst of organic halides and organoboron compounds, the palladium catalyzed Suzuki-Miyaura reaction is a very significant method [1, 2].

*Corresponding author. Email: naceur.hamdi@isste.rnu.tn

This reaction is harmonious with a broad range of functional groups, largely unaffected by the presence of water, and can proceed stereo- and regioselectively. Other advantages include the production of inorganic by-products that can be separated with ease from the reaction mixture, hence rendering the process suitable for use in industrial purposes as well as in a small-scale laboratory setting. For practical and economic reasons, the readily available aryl chlorides have generally been used as the substrates of choice for this coupling reaction [3]. However, there have been important endeavors in order to improve more reactive catalysts to facilitate the conversion of challenging aryl chlorides [4-6]. For this purpose, many substances have been investigated by various research groups, focusing especially on new catalyst structures and ligand modifications such as bulky and electron-rich phosphines [7], palladacycles [8, 9], and N-heterocyclic carbenes (NHCs), which provide highly reactive palladium-based carbon-carbon coupling catalysts due to their unique electronic and steric properties [10].

The complexes of the NHC have been synthesized with almost every transition metal [11-22]. Among these complexes, palladium-NHC complexes have come to the fore due to their success in cross-coupling reactions [23-25]. Although excellent progress has been made in mononuclear complexes [26-36], different type NHC-Pd complexes and their catalytic properties started to attract attention and awaken curiosity [37-39]. The NHC-Pd catalyzed cross-coupling reactions have increased in tendency over the past decade; palladium-catalyzed cross-coupling reactions represent over 60% of the carbon-carbon bond formation reactions used in medicinal chemistry [40-48].

The synthesis of biaryl compounds presents a unique challenge to chemists. In the traditional reactions of organic chemistry, no methods exist for the efficient coupling of two different aromatic groups in a single reaction. There are possible synthetic routes to make biaryls, but the ability to complete such a transformation quickly and efficiently *via* catalyst could be a potentially powerful tool for organic synthesis. Many developments utilizing homo-coupling and cross-coupling reactions have been presented in the past few decades. A great number of *in situ* generated NHC-Pd catalysts have been reported in Suzuki cross-coupling reactions [26, 27]. Herrmann reported the first Pd-NHC catalyst used for Suzuki cross-coupling reaction in 2002 [28]. Then, Pd-PEPPSI (pyridine-enhanced precatalyst preparation stabilization and initiation) type Pd-NHC complexes have been extensively developed by Organ and co-workers for the cross-coupling of challenging, aryl- and alkyl-electrophiles [29-36]. In particular,

our research group has achieved important improvements in Suzuki-Miyaura cross-coupling reactions using PEPPSI complexes [49].

Herein, we report: (i) the synthesis of Pd-PEPPSI-NHC complexes **3a-e** containing benzimidazole (**2a-e**) moiety, which were obtained from the reaction of N-alkylbenzimidazole with the addition of various alkyl halides, (ii) the structures of these compounds were characterized by spectroscopic methods (FT-IR, ^{1}H NMR, ^{13}C NMR and elemental analysis), (iii) the synthesized Pd-PEPPSI-NHC complexes **3a-e** were tested in Suzuki-Miyaura cross-coupling reactions of aryl bromides, and chlorides with phenylboronic acid; they exhibited excellent catalytic activity. In addition, their antimicrobial and antitumor activities were studied (scheme 1).

2. Results and discussion

The novel *N*,*N*-disubstituted 5,6-dimethylbenzimidazolium salts **2a-e** were synthesized in good yields of 89%-96% by reaction of *N*-substituted 5,6-dimethylbenzimidazoles **(A)**, **(B)** and **(C)**, with appropriate substituted benzyl halides in DMF at 70 °C for two days. The synthesis of the 1,3-dialkyl-5,6-dimethylbenzimidazolium salts **2a-e** is summarized in scheme 2.

The benzimidazolium salts **2a-e** were identified by spectroscopic data (including ^{1} H NMR, ^{13} C NMR and IR) and elemental analysis techniques.

The NC*H* N protons of benzimidazolium salts **2a-e** appeared as singlets at 11.58, 11.17, 11.54, 11.63 and 11.57 ppm, respectively. The value of δ[^{13}C{^{1}H}] NC*H*N in benzimidazolium salts **2a-e** was 152.8, 142.9, 141.8, 163.0 and 141.6 ppm, respectively. The benzylic proton signals $H_{1',1''}$ appeared at 5.67 and 5.76 ppm, respectively.

The aromatic protons of 5,6-dimethylbenzimidazolium salts **2a** were seen at *δ* between 6.94 and 7.37 ppm in the ^{1}H NMR spectrum. The carbene carbon chemical shift value belonging to 5,6-dimethylbenzimidazolium salts **2a** was observed at 152.8 ppm in the ^{13}C NMR spectra. $C_{1',1''}$ carbon was resonated at *δ* 51.8 and 51.4 ppm for **2a**.

Benzimidazolium salts **2a-e** were also characterized by FTIR spectroscopy in the range 4000-400 cm^{-1} to ensure their successful formation. In particular benzimidazolium salts **2a-e** exhibit a characteristic *ν*(C=N) band at 1566, 1547, 1566, 1670 and 1559 cm^{-1}, respectively.

M-NHC complexes can be synthesized by transmetallation from an Ag(I)-NHC salt [50] or direct metalation from the benzimidazoles salts via reaction with a metal salt and a base. The reaction of benzimidazolium salts **2a-e** with $PdCl_2$ in pyridine in the presence of K_2CO_3 afforded yellow palladium(II)-NHC complexes **3a** (96%), **3b** (95%), **3c** (98%), **3d** (89%) and **3e** (91%) in good yields. Complexes **3a-e** are air-stable solids and they are soluble in polar organic solvents (scheme 3).

The carbon-nitrogen band frequencies ν(C=N) for complexes **3a-e** were observed at 1613, 1597, 1614, 1612 and 1609 cm^{-1}, respectively, implying the coordination of imine nitrogen with palladium owing to the donation of electrons from nitrogen atom to the empty d-orbitals of the metal in complexes **3a-e** [51-53]. The ^1H NMR spectra of complexes **3** and **4** further supported the assigned structures.

The aromatic protons of complex **3b** appeared between 6.86 and 8.90 ppm. No signal corresponding to the iminium proton could be observed in the ^1H NMR spectra of complexes **3a-e**, confirming the formation of the NHC-Pd bonds. The NCN resonance of Pd-NHC complex **3b** appeared at 162.1 ppm. Only few examples of Pd-carbene complexes bearing benzimidazol-2-ylidene ligand for direct arylation of heteroaromatic compounds have been reported so far [54].

3. The Suzuki-Miyaura cross coupling reactions

The catalytic activities of PEPPSI complexes **3a-e** in Suzuki-Miyaura cross-coupling reaction were examined. The reaction was made at 80 °C in DMF/H_2O mixtures by using aryl bromides, chlorides and phenylboronic acid and base K_2CO_3. The solvents were used without any further purification in this coupling reaction.

In a typical catalytic experiment, the reactivity of 0.25 mol% loading of PEPPSI complexes **3** (0.25 mol%) in the presence of 4-chloroacetophenone (0.5 mmol) with phenylboronic acid (0.75 mmol) as a model reaction using the catalytic system (base (1 mmol)/solvent (6 mL)) (K_2CO_3/DMF/H_2O (1:1)). These reactions were carried out at 80 °C with reaction time limited to 3 h.

The Suzuki-Miyaura cross-coupling catalyzed by unsymmetrical and symmetrical palladium complexes **3** in the presence of the catalytic system: DMF/H_2O and K_2CO_3 is

presented in table 1. From table 1, we can say that the aryl chlorides having a donor group deactivate the formation of the corresponding complexes with respect to the oxidative addition whereas the attracting groups have an inverse effect. The best yields have been obtained during the coupling of activated aryl chlorides by attracting groups.

The results of the cross-coupling reactions of aryl bromides and chlorides with phenylboronic acid are given in table 1. From these results, we can say that 4-chloroacetophenone, 4-chloroanisole and 4-chlorotoluene react with phenylboronic acid to afford the corresponding compounds in moderate to goods yields (table 1, entries 1-15).

The synthesis of new heteroaryl in excellent yield in the presence of phenylboronic acid with pyridinic substrates is given in table 2. These results reveal that pyridine-containing palladium complexes **3a-e** were found to be the most active catalysts for Suzuki reaction in DMF/H_2O (1:1). These results show that the synthesized compounds have catalytic activity. Huang *et al.* also used aryl chlorides containing electron-rich, electron-poor and neutral groups in their study, but they obtained lower yields than us even though they conducted their experiments at higher temperature and longer period of reaction time [55]. All reactions afforded the corresponding biaryl compounds in high yields and under optimized conditions with excellent TON and TOF values (table 3).

The objective of this project was also to prepare carbene precursors that have sulfonate groups to make them soluble in water. The N-heterocyclic carbene ligand precursor (**4**) has been synthesized by adding sodium sulfonate bromide to a DMC solution of the 1-methyl-4,5-dihydro-1H-imidazole. Compound **4** is a white solid, soluble in water and DMSO, and insoluble in methanol and acetonitrile. Then the silver(I) complex (**5**) was prepared in water solution *via* deprotonation of **4** with Ag_2O (scheme 4).

The resonance of the NCHN proton of **4** in ^1H NMR was at 10.72 ppm in DMSO-d_6. The NCHN carbon of **4** resonates in the $^{13}C\{^1H\}$ NMR spectra at 155.5 ppm. C_2 carbon of silver(I)-NHC complex **5** resonates as two doublets at 185.2 and 187.3 ppm. The obtained silver N-heterocyclic carbene (Ag-NHC) complex **5** and the carbene precursor **4** will be interacted with [$PtCl_2$(COD)], [$PtCl_2(PR_3)_2]_2$ and [$AuCl(PPH_3)_3$] to afford new complexes; this work is under progress (scheme 5).

4. Antimicrobial activity studies for synthesized complexes

The results of the antimicrobials activities of palladium complexes **3** activity [56] against three used Gram-positive bacteria *Micrococcus luteus* LB 14110, *Staphylococcus aureus* ATCC 6538 and *Listeria monocytogenes* ATCC 19117 and Gram-negative bacteria *Salmonella Typhimurium* ATCC 14028 and *Pseudomonas aeruginosa* ATCC 49189 are presented in table 4. In table 4 it is shown that all complexes **3a-e** exhibit antimicrobial activity against one or more strains and is enhanced compared with the benzimidazoles **2**.

The minimal inhibitory concentrations (MICs) of PEPPSI palladium(II) complexes **3a-e** were determined against *Micrococcus luteus* LB 14110, *Listeria monocytogenes* ATCC 19117 and *Salmonella Typhimurium* ATCC 14028. The obtained results are given in table 5. Complex **3b** showed potentially higher broad-spectrum activity compared to all the other PEPPSI palladium(II) complexes.

5. Antitumor activity

The antitumor activity of synthesized PEPPSI palladium(II) complexes **3a-e** was tested *in vitro* against cancer human cell lines such as MDA-MB-231, MCF-7 and T47D. The results are summarized in table 6. All synthesized compounds showed good antitumor activity against MDA-MB-231, MCF-7 and T47D cell lines. The most active compounds are **3e** and **3d** against MCF-7 and T47D.

6. Conclusion

New unsymmetrically and symmetrically substituted benzimidazolium protic salts, which consist of inactive inorganic anion (Br-) and bioactive benzimidazolium cation, were synthesized in very high yields from a benzimidazole and different alkyl halides.

Pd-PEPPSI-NHC complexes **3a-e** were synthesized in good yields by the reaction of N,N-disubstituted benzimidazolium salts **2a-e** with $PdCl_2$ in the presence of K_2CO_3 as base in pyridine. The obtained compounds were identified by FT-IR, ^{1}H NMR and ^{13}C NMR spectroscopies and elemental analysis. Among the tested complexes, the PEPSSI complexes **3a-e** containing NHC ligands exhibited excellent catalytic activity. The palladium PEPSSI complexes **3a-e** presented enhanced antimicrobial activity compared with standard antibacterial. Some of them can act as practical use as antimicrobial agents. In addition, the PEPPSI palladium(II)

complexes **3a-e** showed good antitumor activity against MDA-MB-231, MCF-7 and T47D cell lines.

7. Experimental

All reactions for the preparation of benzimidazolium salts and palladium-(NHC)-PEPPSI complexes were carried out under air. $PdCl_2$, pyridine and solvents were purchased from Sigma-Aldrich and used as obtained. All solvents were purified and dried by the MBraun SPS 800 solvent purification system. Elemental analyses were performed by an Elementar Vario EL III Carlo Erba 1108. The melting points of the complexes and NHC precursors were determined using Stuart automatic melting point apparatus (SMP-40). IR spectra were recorded with a Perkin Elmer Spectrum 100 GladiATR FT/ IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO d_6 solutions operating on a Bruker Avance III HD 400/300 MHz NMR spectrometer and chemical shifts were reported relative to tetramethylsilane for ^{1}H and ^{13}C NMR spectra as standard. Column chromatography was performed using silica gel 60 (70–230 mesh). Solvent ratio is given as v/v. The products were characterized by GC (gas chromatography). Quantitative GC analyses were performed with a GC-2010 Plus gas chromatograph (SHIMADZU). GC conditions: The GC analyses were performed on a GC Agilent 7890B equipped with a HT 5 column (30 m, 0.25 mm i.d., 0.25 mm thickness). Conditions: injector and detector = 250 °C, gas = nitrogen at 1.57 mL/min, temperature = 80 °C, ramp of 5 °C/min up to 250 °C, and isotherm at 250 °C during 15 min. Calibration with dodecane as internal standard.

N-substituted benzimidazoles **A-C**, benzimidazolium salts (**2a-e**) and PEPPSI complexes (**3a-e**) were prepared according to the reported procedures [44]. Further experimental details and the NMR spectra assignment are provided in the Supplementary Material.

Acknowledgements

The authors gratefully acknowledge Qassim University, represented by the Deanship of Scientific Research, on the material support for this research under the number alrasscac2348-alrasscac-2018-1-14-S during the academic year 1940/2019AD".

References

[1] A. Suzuki. *J. Organomet. Chem.*, **576**, 147 (1999).

[2] N. Miyaura, A. Suzuki. *Chem. Rev.*, **95**, 2457 (1995).

[3] F. Rajabi, W.R. Thiel. *Adv. Synth. Catal.*, **356**, 1873 (2014).

[4] S. Akkoc, Y. Gok. *J. Coord. Chem.*, **66**, 1396 (2013).

[5] W. Huang, J. Guo, Y. Xiao, M. Zhu, G. Zou, J. Tang. *Tetrahedron*, **61**, 9783 (2005).

[6] M. Gholinejad, H.R. Shahsavari, M. Razeghi, M. Niazi, F. Hamed. *J. Organomet. Chem.*, **796**, 3 (2015).

[7] S.M. Wong, C.M. So, K.H. Chung, C.P. Lau, F.Y. Kwong. *Eur. J. Org. Chem.*, **2012**, 4172 (2012).

[8] S. Doherty, J.G. Knight, N.A.B. Ward, D.M. Bittner, C. Wills, W. McFarlaneet, W. Clegg, R.W. Harrington. *Organometallics*, **32**, 1773 (2013).

[9] G.R. Peh, E.A.B. Kantchev, J.C. Er, J.Y. Ying. *Chem. Eur. J.*, **16**, 4010 (2010).

[10] A. Akta, S. Akkoç, Y. Gök. *J. Coord. Chem.*, **66**, 2901 (2013).

[11] A.J. Arduengo III, R.L. Harlow, M.A. Kline. *J. Am. Chem. Soc.*, **113**, 361 (1991).

[12] W.A. Herrmann, M. Elison, J. Fisher, C. Köcher, G.R. Artus. *Angew. Chem. Int.*, **34**, 2371 (1995).

[13] N.M. Scott, S.P. Nolan. *Eur. J. Inorg. Chem.*, 1815 (2005).

[14] H.W. Wanzlick, E. Schikora. *Angew. Chem.*, **72**, 494 (1960).

[15] D. Bourissou, O. Guerret, F.P. Gabbaï, G. Bertrand. *Chem. Rev.*, **100**, 39 (2000).

[16] W.A. Herrmann. *Angew. Chem. Int. Ed.*, **41**, 1290 (2002).

[17] G.A. Grasa, M.S. Viciu, J. Huang, C. Zhang, M.L. Trudell, S.P. Nolan. *Organometallics*, **21**, 2866 (2002).

[18] S. Díez-González, S.P. Nolan. *Coord. Chem. Rev.*, **251**, 874 (2007).

[19] S. Díez-González, N. Marion, S.P. Nolan. *Chem. Rev.*, **109**, 3612 (2009).

[20] E.Ö. Karaca, M. Akkoç, E. Öz, S. Altin, V. Dorcet, T. Roisnel, N. Gürbüz, Ö. Çelik, A. Bayri, C. Bruneau, S. Yasar, I. Özdemir. *J. Coord. Chem.*, **70**, 1270 (2017).

[21] L. Boubakri, S. Yasar, V. Dorcet, T. Roisnel, C. Bruneau, N. Hamdi, I. Özdemir. *New J. Chem.*, **41**, 5105 (2017).

[22] L. Boubakri, L. Mansour, A.H Harrath, I. Özdemir, S. Yaşar, N. Hamdi. *J. Coord. Chem.*, **71**, 183 (2018); W.A. Herrmann, C.P. Reisinger, M. Spiegler. *J. Organomet. Chem.*, **557**, 93 (1998).

[23] W.A. Herrmann, V.P.W. Böhm, C.W.K. Gstöttmayr, M. Grosche, C.P. Reisinger, T. Weskamp. *J. Organomet. Chem.*, **617**, 616 (2001).

[24] A.C. Hillier, G.A. Grasa, M.S. Viciu, H.M. Lee, C. Yang, S.P. Nolan. *J. Organomet. Chem.*, **653**, 69 (2002).

[25] H. Ohta, T. Fujihara, Y. Tsuji. *Dalton Trans.*, 379 (2008).

[26] C.W.K. Gstottmayr, V.P.W. Böhm, E. Herdtweck, M. Grosche, W.A.A. Herrmann. *Angew. Chem. Int. Ed.*, **41**, 1363 (2002).

[27] M.S. Viciu, R.F. Germaneau, S.P. Nolan. *Org. Lett.*, **4**, 4053 (2002).

[28] W.A. Herrmann, M. Elison, J. Fischer, C. Köcher, G.R.J. Artus. *Angew. Chem. Int. Ed. Engl.*, **34**, 2371 (1995).

[29] G. Altenhoff, R. Goddard, C.W. Lehmann, F. Glorius. *Angew. Chem., Int. Ed.*, **42**, 3690 (2003).

[30] C.J. O'Brien, E.A.B. Kantchev, C. Valente, N. Hadei, G.A. Chass, A. Lough, A.C. Hopkinson, M.G. Organ. *Chem. Eur. J.*, **12**, 4743 (2006).

[31] P. Nun, J. Martinez, F. Lamaty. *Synlett*, 1761 (2009).

[32] A. Fürstner, G. Seidel, D. Kremzow, C.W. Lehmann. *Organometallics*, **22**, 907 (2003).

[33] O. Navarro, H. Kaur, P. Mahjoor, S.P. Nolan. *J. Org. Chem.*, **69**, 3173 (2004).

[34] Y. Han, H.V. Huynh, G.K. Tan. *Organometallics*, **26**, 6447 (2007).

[35] S.K. Yen, L.L. Koh, H.V. Huynh, T.S.A. Hor. *Chem. Asian J.*, **3**, 1649 (2008).

[36] D. Yuan, H.V. Huynh. *Organometallics*, **29**, 6020 (2010).

[37] N. Shang, S. Gao, C. Feng, H. Zhang, C. Wang, Z. Wang. *RSC Adv.*, **3**, 21863 (2013).

[38] S.D. Roughley, A.M. Jordan. *J. Med. Chem.*, **54**, 3451 (2011).

[39] T. Mizoroki, K. Mori, A. Ozaki. *Bull. Chem. Soc. Jpn.*, **44**, 581 (1971).

[40] R.F. Heck, J.P. Nolley. *J. Org. Chem.*, **37**, 2320 (1972).

[41] N. Miyaura, T. Yanagi, A. Suzuki. *Synth. Commun.*, **11**, 513 (1981).

[42] S. Mohanty, D. Suresh, M.S. Balakrishna, J.T. Mague. *Tetrahedron*, **64**, 240 (2008).

[43] A.W. Salman, R.A. Haque, S. Budagumpi, H.Z. Zulikha. *Polyhedron*, **49**, 200 (2013).

[44] L. Boubakri, A. Chakchouk-Mtibaa, H. Bilel, S. Yaşar, I. Özdemir, L. Mansour, L. Mellouli, N. Hamdi. *Molecules*, **22**, 420 (2017).

[45] S. Demir, I. Özdemir, B. Çetinkaya. *J. Organomet. Chem.*, **694**, 4025 (2009).

[46] S. Demir, I. Özdemir, O. Sahin, B. Çetinkaya, O. Büyükgüngör. *Synlett*, **3**, 496 (2010).

[47] N. Touj, N. Gürbüz, N. Hamdi, S. Yasar, I. Özdemir. *Inorg. Chim. Acta*, **478**, 187 (2018).

[48] F.E. Hahn, M.C. Jahnke. *Angew. Chem. Int. Ed.*, **47**, 3122 (2008).

[49] C.Y. Wang, Y.H. Liu, S.M. Peng, J.T. Chen, S.T. Liu. *J. Organomet. Chem.*, **692**, 3976 (2007).

[50] B. Çetinkaya, E. Çetinkaya, P.B. Hitchcock, M.F. Lappert, I. Özdemir. *J. Chem. Soc., Dalton Trans.*, 1359 (1997).

[51] B. Çetinkaya, I. Özdemir, M.N. Tahir, D. Ülkü. *J. Organomet. Chem.*, **561**, 7 (1998).

[52] B. Çetinkaya, B. Alıcı, I. Özdemir, C. Bruneau, P.H. Dixneuf. *J. Organomet. Chem.*, **575**, 187 (1999).

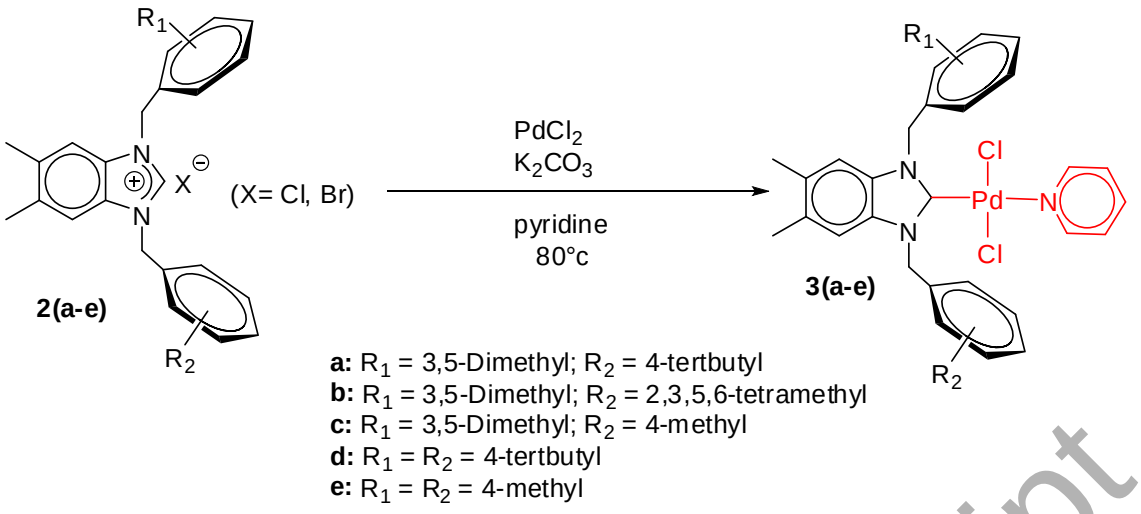
[53] B. Çetinkaya, B. Alıcı, I. Özdemir, C. Bruneau, P.H. Dixneuf. *Eur. J. Inorg. Chem.*, 29 (2000).

[54] K. Güven, E. Yücel, F. Cetintas. *Pharm. Biol.*, **44**, 79 (2006).

[55] W. Huang, J. Guo, Y. Xiao, M. Zhu, G. Zou, J. Tang. *Tetrahedron*, **61**, 9783 (2005).

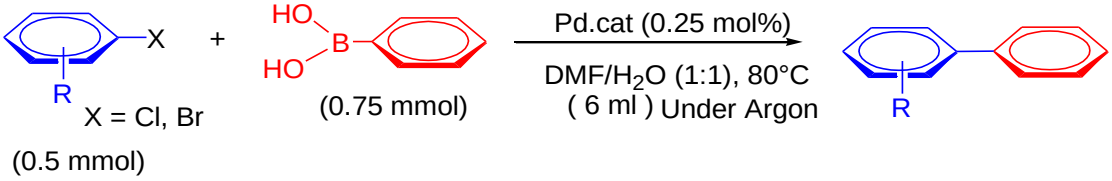
[56] National committee for clinical laboratory standard. referece method for broth dilution antifungal susceptibility testing of conidium-forming filamentous fungi. Proposed standard M38-P. National committee for clinical laboratory standard, Wayne (1998).

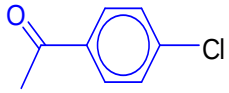
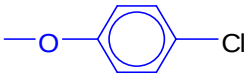
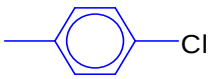
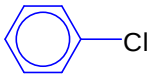
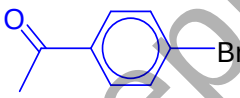
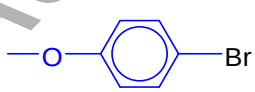
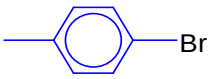
Graphical abstract



a: R_1 = 3,5-Dimethyl; R_2 = 4-tertbutyl
b: R_1 = 3,5-Dimethyl; R_2 = 2,3,5,6-tetramethyl
c: R_1 = 3,5-Dimethyl; R_2 = 4-methyl
d: $R_1 = R_2$ = 4-tertbutyl
e: $R_1 = R_2$ = 4-methyl

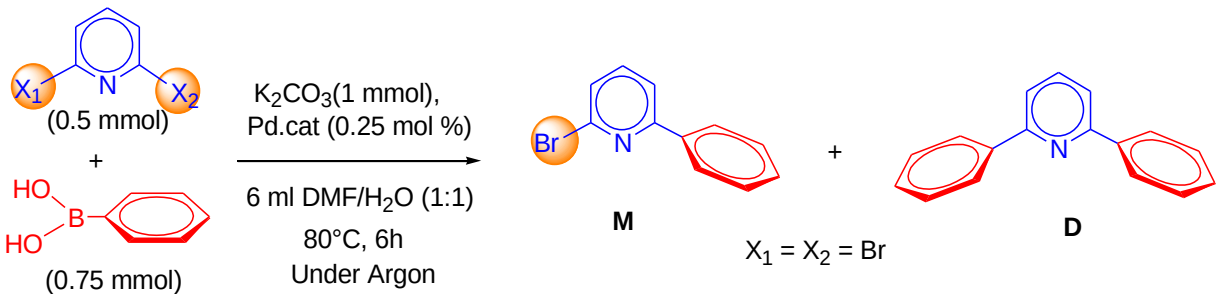
Table 1. The Suzuki-Miyaura cross coupling catalyzed by palladium complexes **3a-e**.

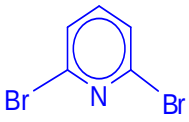


Entry	Substrates	[Cat]	Time (h)	Conversions (%) [a]
1		**3a**	3	95
2		**3b**	3	94
3		**3c**	3	95
4		**3d**	3	89
5		**3e**	3	96
6		**3a**	12	15
7		**3b**	12	19
8		**3c**	12	11
9		**3d**	12	10
10		**3e**	12	8
11		**3a**	12	9
12		**3b**	12	28
13		**3c**	12	29
14		**3d**	12	12
15		**3e**	12	18
16		**3a**	12	58
17		**3b**	12	96
18		**3c**	12	58
19		**3d**	12	49
20		**3e**	12	62
21		**3a**	3	100
22		**3b**	3	100
23		**3c**	3	100
24		**3d**	3	100
25		**3e**	3	100
26		**3a**	6	100
27		**3b**	6	100
28		**3c**	6	100
29		**3d**	6	100
30		**3e**	6	100
31		**3a**	6	100
32		**3b**	6	100
33		**3c**	6	100
34		**3d**	6	100
35		**3e**	6	100

[a] Conversions were determined by GC

Table 2. The Suzuki Coupling Reaction of phenylboronic acid with 2,6-dibromopyridine by catalyzed by palladium complexes **3**.

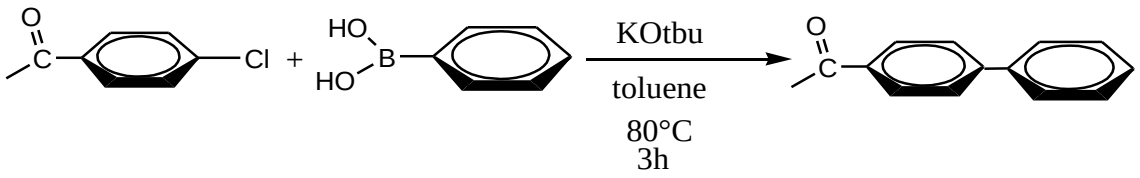


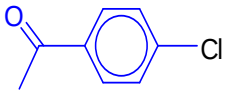
Entry	Substrate	[Cat] / (M/D) [a] ratio	Solvent	Base	Conversions (%)[b]
1		**3a**	DMF/H_2O	K_2CO_3	0/100
2		**3b**			0/100
3		**3c**			0/100
4		**3d**			0/100
5		**3e**			0/100

[a] (M/D): Monoarylated/Diarylated.

[b] Conversions were determined by GC.

Table 3. Suzuki Coupling Reactions[a].



Entry	Substrate	Cat (mol%)	TOF [b]	TON [c]	Conversions (%) [d]
1		**3a (0.2)**	123.3	370	74
2		**3b (0.5)**	53.3	160	80
3		**3c (0.5)**	46	138	69
4		**3d (0.2)**	63.33	190	95
5		**3e (0.5)**	62.66	188	94

[a] Reaction conditions: phenylboronic acid (0.75 mmol), parachloroacetophenone (0.5 mmol), Pd.cat (0.2 or 0.5 mol %), base (1 mmol), 6 mL solvent (1:1), 80 °C. Under argon.

[b] Turnover frequency in h^{-1} at 80 °C.

[c] Turnover number based on complexes **3**.

[d] Conversions were determined.

Table 4. The zone of inhibition (in mm) exhibited by PEPPSI palladium(II) complexes **3a-e** and benzimidazoles salts **2a-e**.

Compounds	Inhibition zone (mm)				
	LB14110	ATCC6538	ATCC19117	ATCC14028	ATCC49189
Complex 3a	18±0.5	16±1.1	20±0.4	20±0.4	25±0.1
Complex3b	23±0.2	17±0.5	16±1.5	24±0.4	25±0.3
Complex 3c	24±0.1	15±0.3	19±0.5	25±0.3	24±0.3
Complex 3d	25±0.3	15±0.3	16±0.3	30±0.1	26±0.2
Complex 3e	30±0.5	14±0.5	16±0.3	23±0.5	31±0.2
Salt 2a	17±0.5	13±1.1	18±0.4	18±0.4	23±0.1
Salt 2b	21±0.2	15±0.5	15±1.5	21±0.4	22±0.3
Salt 2c	22±0.1	14±0.3	17±0.5	22±0.3	21±0.3
Salt 2d	20±0.3	13±0.3	14±0.3	28±0.1	23±0.2
Salt 2e	25±0.5	14±0.5	13±0.3	21±0.5	27±0.2

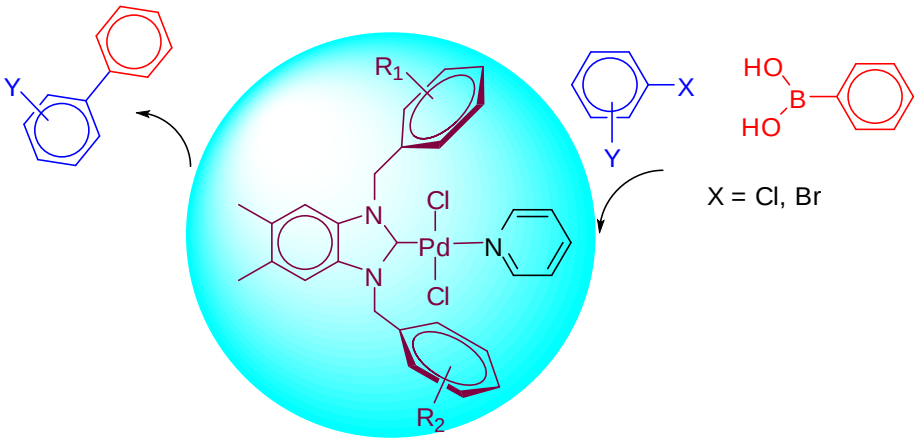
Table 5. Determination of the Minimum Inhibitory Concentrations (MICs) expressed in mg/mL of PEPPSI complexes **3a-e** and benzimidazoles salts **2a–e**.

Compounds	MIC (mg/mL)		
	LB14110	ATCC19117	ATCC14028
Complex 3a	0.039	1.25	2.5
Complex 3b	0.0192	0.078	1.25
Complex 3c	0.0195	1.25	2.5
Complex 3d	0.3125	2.5	2.5
Complex 3e	0.039	0.3125	2.5
Salt 2a	0.045	1.50	2.9
Salt 2b	0.0202	0.095	2.25
Salt 2c	0.0260	2.50	3.1
Salt 2d	0.4123	3.6	2.9
Salt 2e	0.052	0.6125	2.9
Ampicillin	0.0195	0.039	0.625

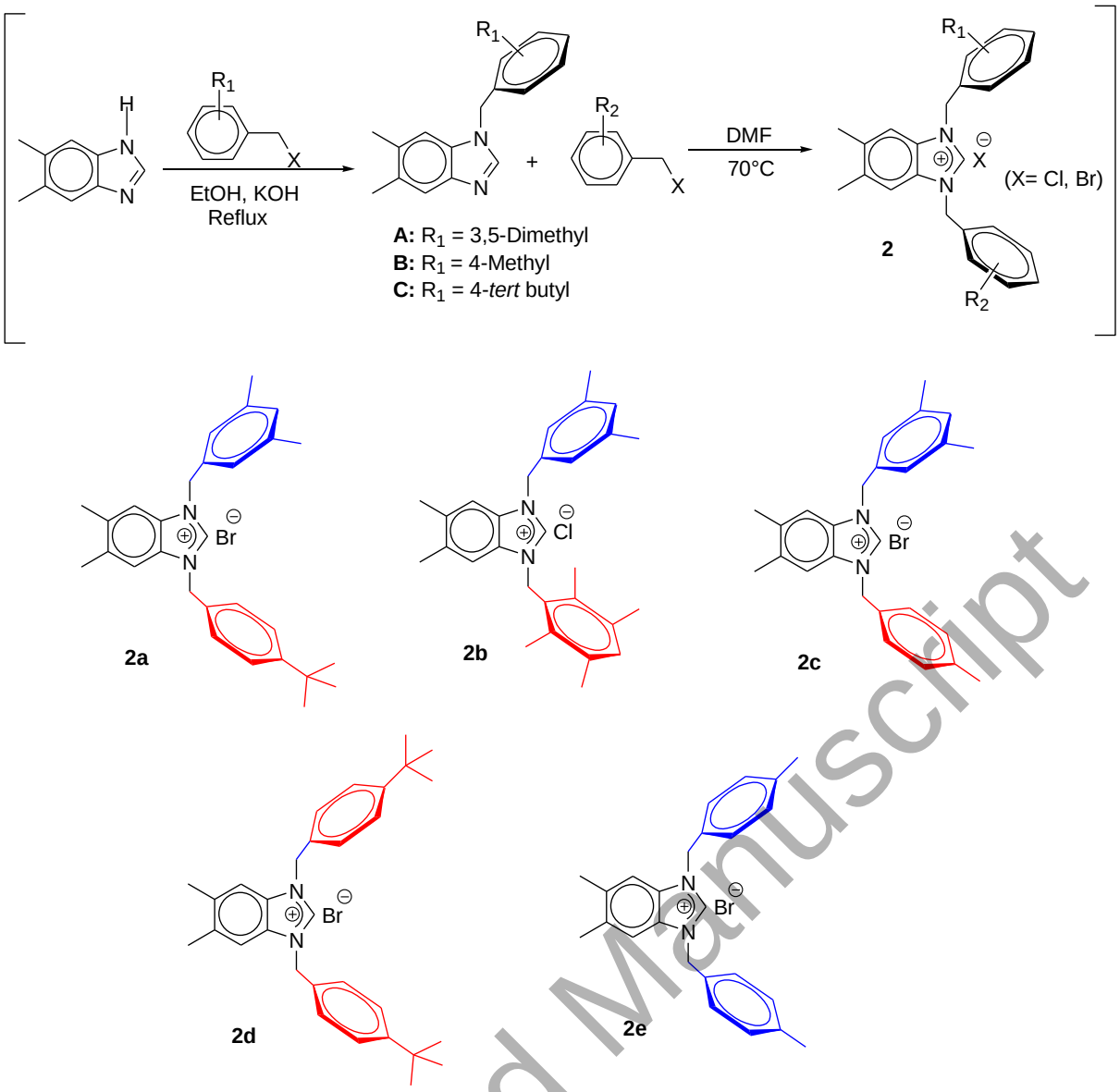
Table 6. Antitumor activity (IC_{50}, in μg/mL)[a] of compounds **3a-e**.

PEPPSI palladium(II) complexes 3a-e	MDA-MB-231	MCF-7	T47D
3a	19±1.30	18±2.0	22±1.30
3b	21.30±0.85	19.4±0.85	22.38±0.85
3c	9.45±2.75	18.50±2.75	12.50±2.75
3d	15.75±1.45	10.75±2.45	10.75±2.42
3e	8.85±1.20	6.85±1.30	16.96±1.30

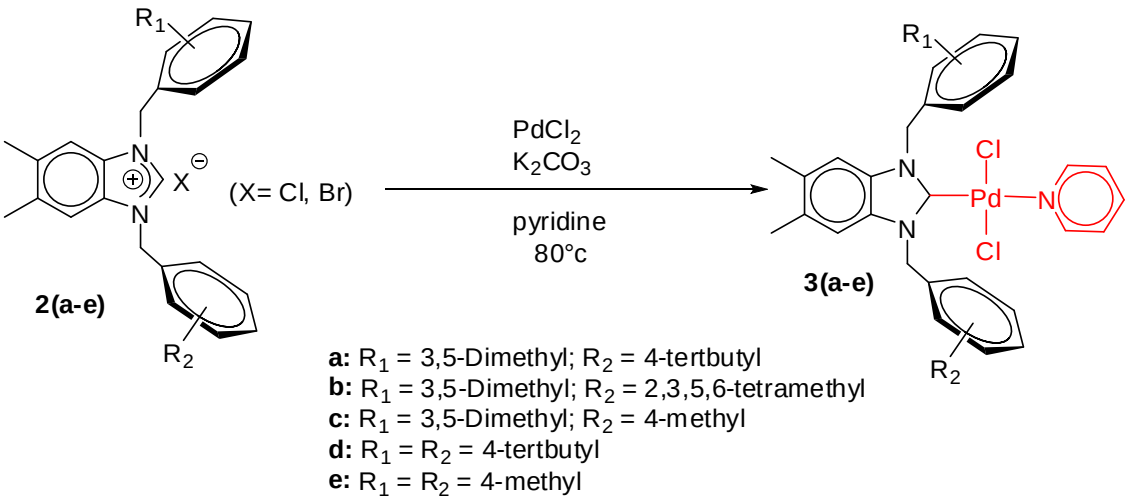
[a] The IC_{50} values represent an average of three independent experiments (mean ± SD).



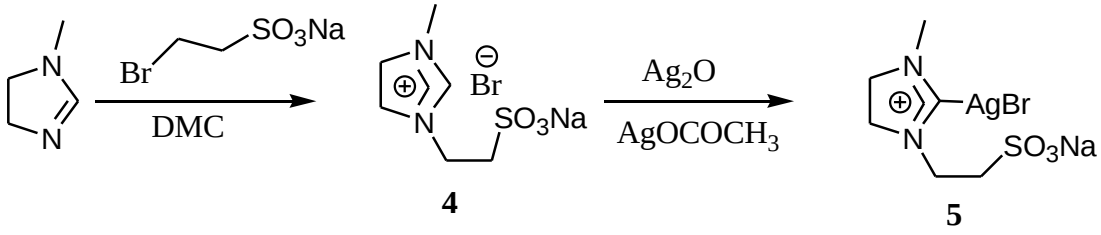
Scheme 1. Suzuki-Miyaura cross-coupling reactions of aryl bromides, and chlorides with phenylboronic acid.



Scheme 2. General preparation and structural formulae of benzimidazolium salts **2a-e**.

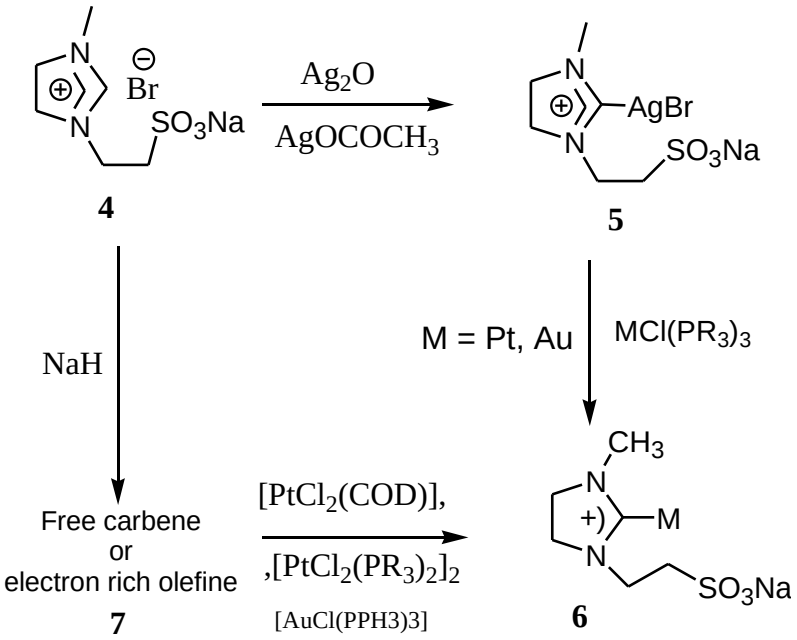


Scheme 3. General preparation of palladium complexes **3a-e**.



4 **5**

Scheme 4. Synthesis of silver(I) complex (**5**).



Scheme 5. Synthesis of metal-carbene complexes.