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Regioselective C-H arylation of imidazoles employing macrocyclic palladium(II) complex of organoselenium ligand

Sunil Kumar[1], Sohan Singh[1], Jitendra Gadwal, Parvesh Makar, Hemant Joshi*

ISC Laboratory, Department of Chemistry, School of Chemical Sciences and Pharmacy, Central University of Rajasthan, NH-8, Bandarsindri, Ajmer, Rajasthan 305817, India

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ABSTRACT

In this report we have presented synthesis of a new air stable bidentate selenium ligand (**L1**) by the reaction of 1,8-bis(2-(chloromethyl)phenoxy)octane with sodium salt of diphenyl diselenide. The reaction of bidentate selenium ligand (**L1**) with $Pd(CH_3CN)_2Cl_2$ in acetonitrile under reflux conditions resulted nineteen membered ring macrocyclic palladium(II) complex. The structure of ligand precursors, ligand, and macrocyclic palladium(II) complex were authenticated by using ^1H, $^{13}C\{^1H\}$ NMR spectroscopy and elemental analysis. The repeated attempts to obtain single crystals of macrocyclic palladium(II) complex were unsuccessful probably due to long flexible aliphatic chain in the molecule. The air and moisture stable, thermally robust macrocyclic palladium(II) complex was employed as catalyst to catalyze the regioselective arylation reaction of imidazole derivatives. The reaction works efficiently without any need of inert atmosphere. The current protocol works under mild reaction conditions with exclusive C-5 regioselectivity. Excellent yields (~73–95%) were obtained by using only 1.5 mol% of **C1**, with wide range of derivatives and large functional group tolerance. Homogeneous nature of catalysis process was confirmed with the help of mercury and triphenylphosphine poisoning tests. Further, the catalyst can be reused with significant loss (22%) in the efficiency.

1. Introduction

In the last two decades organoselenium ligands have made an appearance as privileged class of ligand moieties due to their strong soft donor abilities, air and moisture stable nature, low cost syntheses, higher sigma donation properties, and similar catalytic properties with respect to carbene and phosphine based ligands [1]. Several metal complexes of these ligands have been reported as efficient catalysts for various organic transformations like Heck coupling, Suzuki-Miyaura coupling, C-H activation, oxidation of alcohols, N-alkylation reaction, transfer hydrogenation, and many more reactions as discussed in the recent review articles [2]. Palladium when coordinates with organoselenium ligands, the selenium of ligand donates its sigma electrons to palladium center which in turn increase the sigma electron density on palladium center and helps palladium center to ease the oxidative addition step in catalysis. This results in greater yield of products in catalysis [1,2]. Considering these distinctive characteristic of organoselenium coordinated palladium complexes, it was decided to synthesize a new class of bidentate macrocyclic palladium(II) complex of organoselenium ligand and explore its catalytic potential for regioselective C-H arylation of imidazoles with aryl bromide derivations.

The heterocyclic molecules containing nitrogen atom are among the elite class of molecules due to their wide range of applications in natural products, agrochemicals, biologically active molecules, pharmaceuticals, and in material science [3]. Among the class of nitrogen containing heterocycles, imidazole and its derivatives has gained extensive attention due to the plethora of pharmaceutically active molecules and drugs [4]. The regioselective C-H bond arylation of imidazole is one among the important protocol for the syntheses of such imidazole derivatives [5]. The arylation reaction is more favored to C-2 and C-5 positions as compared to C-4 position of imidazoles [6]. In order to activate C-2 position, strong base (sodium or potassium tert-butoxide) with copper salts are used whereas to activate C-5 position, bases like pivalate or acetate with polar solvent were used. The regioselective C-5 arylation of imidazole reported earlier was mostly catalyzed by palladium based catalysts with *N*-heterocyclic carbene or phosphine ligands [5,7–9]. Recently palladium complexes of organochalcogen ligands were used as efficient catalyst for regioselective arylation of imidazoles [1b–d]. The advantages of such catalytic systems over the phosphine and carbene based ligand systems are, (i) the ligand and

* Corresponding author.
E-mail address: hemant.joshi@curaj.ac.in (H. Joshi).
[1] These authors contributed equally.

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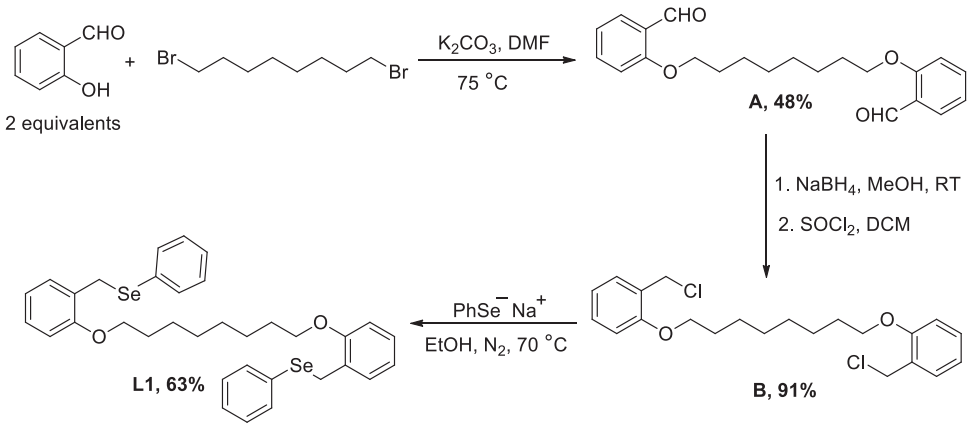
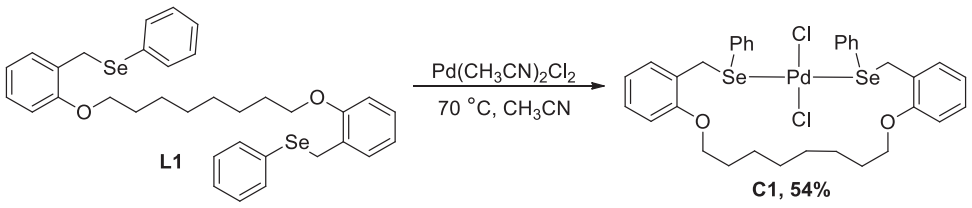


Scheme 1. Synthesis of bidentate organoselenium ligand.



Scheme 2. Synthesis of macrocyclic Pd(II) complex.

complexes are air and moisture stable, (ii) low or comparative catalyst loading, (iii) higher C-5 selectivity of arylated products, (iv) wide substrate scope with large functional group tolerances, (v) mild reaction conditions, and (vi) no need of inert atmosphere to catalyze the reaction.

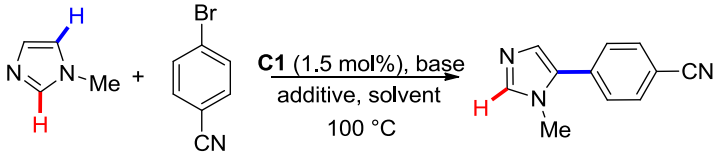
2. Results and discussion

The organoselenium ligand and macrocyclic palladium(II) complex were synthesized as shown in Schemes 1 and 2. The new organoselenium ligand, and macrocyclic palladium(II) complex were characterized with the help of ^{1}H, ^{13}C{^{1}H} NMR spectroscopy, and elemental analysis. First, the ligand precursor 2,2′-(octane-1,8-diylbis(oxy))dibenzaldehyde (**A**) was synthesized by the reaction of two equivalents of salicylaldehyde with 1,8-dibromooctane in presence of K_2CO_3 and DMF solvent. The ligand precursor **A** was isolated as white solid in 48% yield. The formation of ligand precursor **A** was confirmed by ^{1}H, and ^{13}C{^{1}H} NMR spectrum. The ^{1}H NMR spectrum of **A** shows characteristic singlet peak at 10.51 ppm due to aldehyde group, whereas the triplet at 4.07 ppm is due to OCH_2 group. The ^{13}C{^{1}H} NMR spectrum shows a characteristic peak at 189.8 ppm due to carbonyl group and other peaks agree with the structure proposed in Scheme 1. The ligand precursor **A** was then taken in MeOH (15 mL) and reacted with 2.2 equivalents of solid $NaBH_4$ to give ligand precursor ((octane-1,8-diylbis(oxy))bis(2,1-phenylene))dimethanol (**A′**). The ligand precursor **A′** was isolated as white solid in 92% yield. In the ^{1}H NMR spectrum of **A′**, the aldehydic singlet peak which was at 10.51 ppm in **A** has disappeared and a new singlet at 4.72 ppm appeared due to conversion of CHO to CH_2OH. This was further confirmed by ^{13}C{^{1}H} NMR spectrum of **A′** which also shows disappearance of carbonyl carbon peak and confirm reduction of aldehyde to corresponding alcohol. The ^{1}H NMR of **A′** shows characteristic broad singlet of OH at 2.51 ppm in the proton NMR. Further, **A′** was subjected to chlorination reaction with $SOCl_2$ in dry DCM to give 1,8-bis(2-(chloromethyl)phenoxy)octane (**B**) as yellow solid in 91% yield. In the ^{1}H NMR of **B**, the CH_2Cl singlet appeared at 4.68 ppm which was 0.04 ppm shielded with respect to CH_2OH due to less electronegativity of chlorine as compared to oxygen. The ligand precursor **B** in next step reacts with sodium salt of diphenyl diselenide in EtOH to give organoselenium ligand (**L1**) as yellow liquid in 63% yield (Scheme 1). The ^{1}H NMR spectrum of bidentate selenium ligand (**L1**) shows shielding of 0.52 ppm in $SeCH_2$ peak appearing at 4.16 ppm as singlet, which confirms binding of less electronegative selenium to the ligand substituting more electronegative chlorine. The peaks in ^{13}C{^{1}H} NMR spectrum of **L1** are in agreement with its structure proposed in Scheme 1. The ligand showed good solubility in common organic solvents like CH_3CN, $CHCl_3$, CH_2Cl_2, THF, MeOH, EtOAc, EtOH, DMF, and DMSO whereas it is sparingly soluble in non-polar solvents like pentane, hexane etc.

Next, to synthesize the macrocyclic palladium(II) complex of organoselenium ligand, the selenium ligand **L1** was reacted with $Pd(CH_3CN)_2Cl_2$ precursor in acetonitrile. The nineteen membered ring containing macrocyclic palladium complex was isolated as dark red solid in 54% yield. The macrocyclic complex was characterized with the help of ^{1}H and ^{13}C{^{1}H} NMR spectroscopy. The ^{1}H NMR of **C1**, shows a singlet at 4.69 ppm which was deshielded by 0.53 ppm with respect to free ligand and confirms coordination of ligand with palladium precursor. The ^{13}C{^{1}H} NMR spectrum of **C1** is in agreement with its structure proposed in Scheme 2. The repeated attempts to obtain the single crystals of macrocyclic palladium(II) complex were unsuccessful probably due to long flexible aliphatic chain in the molecule. The macrocyclic palladium(II) complex showed good solubility in common organic solvents like CH_3CN, $CHCl_3$, CH_2Cl_2, THF, DMF, and DMSO whereas it is insoluble in solvents like pentane, hexane etc.

Macrocyclic palladium(II) complex catalyzed regioselective arylation of imidazoles. The substituted imidazole derivatives make an important class of privileged scaffolds due to their extensive applications in industrial synthesis of polymers, functional materials, pharmaceuticals, natural products, and medicinal chemistry [4]. Considering the importance of these compounds, many researchers reported new catalytic systems for their syntheses [7–

Table 1
Optimization of reaction conditions for macrocyclic palladium(II) complex catalyzed regioselective arylation of imidazole[a]



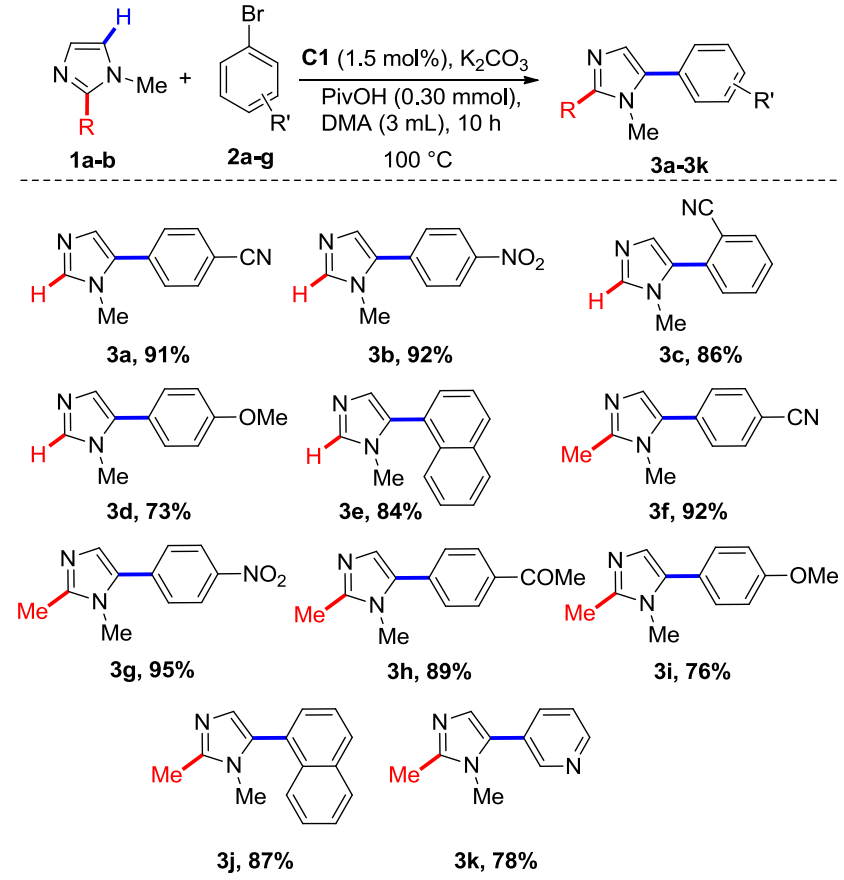
1a **2a** **3a**

Entry No.	Base	Solvent (3 mL)	Additive	Yield[b] (%)
1	-	DMA	-	nd
2	K_2CO_3	DMA	-	nd
3	K_2CO_3	DMA	$PhCO_2H$	11
4	K_2CO_3	DMA	PivOH	91
5	Na_2CO_3	DMA	PivOH	46
6	Cs_2CO_3	DMA	PivOH	26
7	KOH	DMA	PivOH	42
8	NaOH	DMA	PivOH	38
9	t-BuOK	DMA	PivOH	17
10	t-BuONa	DMA	PivOH	12
11	KOAc	DMA	PivOH	26
12	NaOAc	DMA	PivOH	21
13	K_2CO_3	DMF	PivOH	81
14	K_2CO_3	DMSO	PivOH	nd
15	K_2CO_3	THF	PivOH	13
16	K_2CO_3	1,4-dioxane	PivOH	24
17	K_2CO_3	Toluene	PivOH	17
18[c]	K_2CO_3	DMA	PivOH	93
19[d]	K_2CO_3	DMA	PivOH	78
20[e]	K_2CO_3	DMA	PivOH	62
21[f]	K_2CO_3	DMA	PivOH	53
22[g]	K_2CO_3	DMA	PivOH	nd

[a] Reaction conditions: 4-bromobenzonitrile (1.0 mmol), *N*-methyl imidazole (1.2 mmol), additive (0.30 mmol), base (2.0 mmol), solvent (3 mL), temperature (100 °C), time (10 h), under open air conditions
[b] Isolated yield.
[c] **C1** (2.0 mol%).
[d] **C1** (1.0 mol%).
[e] Reaction time (6 h).
[f] Temp (60 °C).
[g] Control experiment without catalyst.

9]. Most of the earlier reported catalysts are based on sterically bulky phosphine, and NHC ligands coordinated metal complexes. In most cases, these ligand systems are known to be air and moisture sensitive and cannot be used in open air conditions which limits usage of these catalysts. To overcome this issue, the air and moisture insensitive organoselenium ligated palladium complexes serve as better alternatives [1b-d]. Intrigued with these earlier reports, we planned to explore the catalytic potential of macrocyclic palladium(II) complex of organoselenium ligand for regioselective arylation of imidazole derivatives. A reaction between 4-bromobenzonitrile (**2a**) and *N*-methyl imidazole (**1a**) was selected as model reaction for optimizing reaction conditions (Table 1). First we carried out a reaction between **1a** and **2a**, in presence of **C1** (1.5 mol%) in DMA (3 mL) without base and additive, there was no conversion to desired coupled product **3a** and starting materials recovered as it is (Table 1, entry 1). Next, a similar reaction was performed as entry 1, in presence of K_2CO_3 without additive, which does not result in coupled product **3a** (Table 1, entry 2). After, when benzoic acid was used as an additive under similar reaction conditions as entry 2, it resulted in 11% yield of **3a** (Table 1, entry 3). The reaction under the similar conditions as entry 3 but with pivalic acid (PivOH) as an additive instead of benzoic acid, resulted in 91% yield of coupled product **3a** (Table 1, entry 4). This shows that PivOH as an additive is crucial for the reaction as it takes part in proton shuttle during C-H bond cleavage [10]. The high steric hindrance and pK_a value of PivOH (5.03) in comparison to benzoic acid (4.20) helps in achieving greater yields of **3a**. The proton NMR spectrum confirms arylation at C-5 position of imidazole and no C-2 arylated product was observed during the reaction. Next, different bases like Na_2CO_3, Cs_2CO_3, KOH, NaOH, t-BuOK, t-BuONa, KOAc, and NaOAc were screened (Table 1, entries 4-12) for the arylation reaction under similar reaction conditions as discussed in entry 4. The bases Na_2CO_3 and Cs_2CO_3 resulted in 46 and 26% yield of **3a** respectively (Table 1, entries 5 and 6). Moderate yields (38-42%) of **3a** were achieved with KOH and NaOH (Table 1, entries 7 and 8). Other bases like t-BuOK, t-BuONa, KOAc, and NaOAc were not found suitable for the arylation reaction and resulted poor yields of **3a** (12-26%, Table 1, entries 9-12). With the best reaction condition in hand (Table 1, entry 4), we screened various solvents like DMF, DMSO, THF, 1,4-dioxane, and toluene for the arylation reaction. DMF resulted in 81% yield of **3a** (Table 1, entry 13), whereas reaction did not work with DMSO (Table 1, entry 14). Solvents like THF, 1,4-dioxane, and toluene resulted in poor conversion of **3a** (Table 1, entries 15-17). Among all the screened bases and solvents K_2CO_3 and DMA found best suitable for the arylation reaction (Table 1, entry 4) and hence used for further catalysis studies. Next, suitable catalyst loading for optimum conversion was screened (Table 1, entries 18 and 19). Upon increasing the catalyst loading to 2.0 mol%, the yield of **3a** increased slightly (93%, Table 1, entry 18). A lower yield of 78% was isolated when 1.0 mol% of **C1** was used (Table 1, entry 19). When reaction under the conditions as discussed in entry 4 was stopped after 6 h, the conversion lowered to 62% (Table 1, entry 20). Upon decreasing the reaction temperature to 60 °C, the conversion of **3a** dropped to

Table 2
Substrate scope for macrocyclic palladium(II) complex catalyzed arylation of imidazole[a]

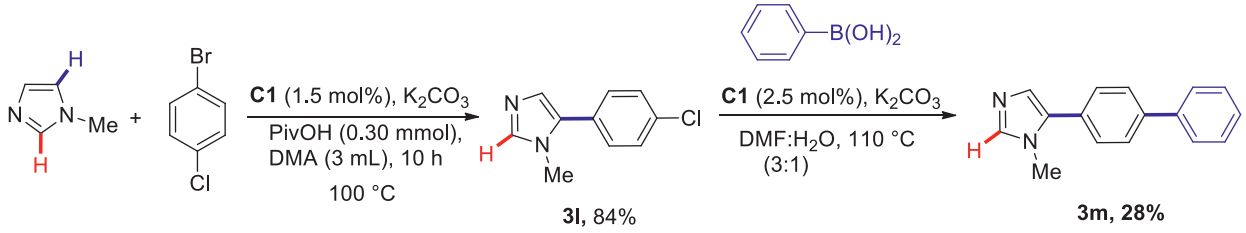


53% (Table 1, entry 21). A control experiment without the macrocyclic Pd(II) catalyst (**C1**) resulted no conversion of desired product **3a** (Table 1, entry 22).

The best optimized condition among all the screened conditions is N-methyl imidazole (1.2 mmol), aryl bromide (1.0 mmol), PivOH (0.3 mmol), K_2CO_3 (2.0 mmol), with 2.0 mol% **C1** for 10 h at 100°C to achieve maximum yield of **3a** (Table 1, entry 18). A catalyst loading of 1.5 mol% was chosen for further studies of substrate scope as it gave comparative yield with lower catalyst loading (Table 1, entry 4). We were fascinated to see that no C-2, C-4 arylated and homocoupled products were detected during the arylation reaction.

Next, with the best screened conditions in hand (Table 1, entry 4), we explored the substrate scope for structurally divergent aryl bromides and imidazole derivatives (Table 2). The results suggested that a wide range of structurally divergent aryl bromide substrates with deactivated, electron withdrawing, and electron donating functional groups like naphthyl, cyano, nitro, $COCH_3$, methoxy, and pyridine can be activated using this protocol with excellent yields (73–95%, Table 2, entries **3a**-**3k**) and greater regioselectivity towards C-5 arylation. The electron withdrawing groups (cyano and nitro) at para position of aryl bromide upon reaction with *N*-methyl imidazole resulted in excellent yield (91–92%) of C-5 arylated products **3a** and **3b** (Table 2). Whereas the electron withdrawing group (cyano) at ortho position of aryl bromide resulted in slight lower yield (86%) of C-5 arylated product **3c** (Table 2). When electron donating group on para position of aryl bromide (-OMe) was tested for the arylation reaction, it resulted in lower yield (73%) of arylated product **3d** (Table 2) as compared to electron withdrawing groups. The sterically bulky deactivated derivative 1-bromonaphthalene resulted in excellent yield (84%) of arylated product **3e** (Table 2). Next, we performed arylation reactions of 1,2-dimethyl-1*H*-imidazole with the aryl bromide derivatives (Table 2, entries **3f**-**3k**). The reaction with deactivated, electron withdrawing, and electron donating derivatives went smoothly with slightly higher yields as compared to *N*-methyl imidazole derivative. The reaction with heterocyclic derivative (3-bromopyridine) was also proceed smoothly resulting 78% yield of arylated product **3k** (Table 2). The arylated products like **3a** and **3e** are very important intermediates for useful bioactive molecules [5]. The current protocol suggests an easy one pot method for their high yield syntheses with greater C-5 regioselectivity. A comparison of current protocol with earlier reports is tabulated in supporting information (Table s1).

Imidazole substituted biaryl motifs are considered as an important intermediate for many functional and biologically active molecules [11]. Syntheses of such derivative is limited in literature as only few reports are available to date [8d]. We planned a sequential arylation and Suzuki-Miyaura coupling reaction for the synthesis of 5-([1,1′-biphenyl]-4-yl)-1-methyl-1*H*-imidazole (**3m**, Scheme 3). In first step, a regioselective arylation reaction of 1-methyl-1*H*-imidazole with 1-bromo-4-chlorobenzene was carried out under the optimum reaction conditions (Table 1, entry 4). The reaction resulted in 84% yield of **3l** (Scheme 3) which has a para chlorine functional group available. The compound **3l** in next step subjected to Suzuki-Miyaura coupling reaction with phenylboronic acid to give 5-([1,1′-biphenyl]-4-yl)-1-methyl-1*H*-imidazole (**3m**, Scheme 3) in 28% yield.



Scheme 3. Sequential arylation and Suzuki-Miyaura coupling reactions.

Further to gain insights about the nature of catalysis process, mercury and triphenylphosphine poisoning tests were conducted [12]. First we performed a reaction under standard reaction conditions (Table 1, entry 4) with excess amount of triphenylphosphine (5.0 mol%). The reaction resulted 88% yield of **3a** with no significant effect on the yield as compared to entry 4 (91%). Next, in a reaction same as entry 4 but with excess of mercury (Pd/Hg = 1/300) we observed 83% yield of **3a** (see experimental section for detailed procedure and results). Both these tests suggested that the reaction has negligible effect of mercury and triphenylphosphine poisoning which confirms homogeneous nature of arylation reaction. The reusability experiment gave 76% yield of **3a** with 22% loss of efficiency in the catalyst performance.

3. Conclusions

A new bidentate organoselenium ligand (**L1**) with long flexible aliphatic chain was synthesized by the reaction of 1,8-bis(2-(chloromethyl)phenoxy)octane and $PhSe^{-}Na^{+}$. Macrocyclic palladium(II) complex (**C1**) was synthesized by the reaction of $Pd(CH_3CN)_2Cl_2$ precursor with **L1** in acetonitrile. The air and moisture stable **C1** and **L1** were characterized with the help of ^{1}H, $^{13}C\{^{1}H\}$ NMR spectroscopy, and elemental analysis. The new macrocyclic Pd(II) complex was used as catalyst for regioselective arylation of imidazole with aryl bromide derivatives. The protocol resulted in exclusive C-5 arylated product, no C-2, C-4 arylated or homocoupling products were observed during the reaction. The catalyst works efficiently (73–95%) with only 1.5 mol% loading of **C1**, covering broad substrate scope. The protocol showed excellent tolerance towards many functional groups like -CN, $-NO_2$, $-COCH_3$, and -OMe. The protocol was also applied to sequential arylation and Suzuki-Miyaura coupling reaction and showed good conversions in both the reactions. The mercury and triphenylphosphine poisoning tests do not affect the yield of reactions and suggested homogeneous nature of catalysis process. The catalyst can be reused with significant loss in the efficiency.

4. Experimental section

General. The reactions for the synthesis of ligand precursors (**A** and **B**), ligand (**L1**), and macrocyclic complex (**C1**) were carried out using standard Schlenk line techniques. The catalytic arylation of imidazole with aryl bromide derivatives was carried out in a pressure tube under open air conditions. HPLC grade solvents like DMF, EtOAc, Hexane, MeOH, DCM, EtOH, DMA, DMSO, THF, 1,4-dioxane, and toluene were used as received. Salicylaldehyde (Spectrochem), 1,8-dibromooctane (Spectrochem), K_2CO_3 (Spectrochem), $NaBH_4$ (Spectrochem), $SOCl_2$ (Spectrochem), Diphenyl diselenide (Spectrochem), *N*-methyl imidazole (Sigma Aldrich), 1,2-dimethyl-1*H*-imidazole (Sigma Aldrich), $CDCl_3$ (Sigma Aldrich), Na_2SO_4 (EMD), and $PdCl_2$ (Sigma Aldrich) were used as received. The reagents for arylation reaction were purchased from local vendors and used as received. Bruker 400 MHz instrument was used to record ^{1}H and $^{13}C\{^{1}H\}$ NMR spectrums of compounds at ambient temperature. The NMR solvent peaks are referenced as: (δ, ppm): ^{1}H, $CHCl_3$ (7.26); $^{13}C\{^{1}H\}$, $CDCl_3$ (77.00). Elemental analyses were carried out with a Perkin–Elmer 2400 Series-II C, H, N analyzer.

Synthesis of 2,2′-(octane-1,8-diylbis(oxy))dibenzaldehyde (A). A single neck round bottom flask was charged with salicylaldehyde (2.44 g, 20.00 mmol), 1,8-dibromooctane (2.72 g, 10.00 mmol), and K_2CO_3 (2.79 g, 20.20 mmol) in DMF (20 mL). The mixture was heated with stirring for 8 h at 75 °C. The progress of reaction was monitored by TLC and after maximum conversion to product, the reaction mixture was cooled to room temperature and extracted with ethyl acetate and cold water (3 * 20 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4 and concentrated using rotary evaporator. The residue was washed with cold hexane and dried under high vacuum to give **A** (1.69 g, 4.77 mmol, 48%) as white solid. Anal. Calcd for $C_{22}H_{26}O_4$ (354.4394): C, 74.55; H, 7.39. Found: C, 74.49; H, 7.34.

NMR ($CDCl_3$, δ/ppm): **^{1}H** (400 MHz) 10.51 (s, 1H), 7.82 (d, J = 6.0 Hz, 1H), 7.52 (t, J = 7.6 Hz, 1H), 7.02 – 6.96 (m, 2H), 4.07 (t, J = 6.4 Hz, 2H), 1.89 – 1.82 (m, 2H), 1.52 – 1.49 (m, 2H), 1.43 – 1.40 (m, 2H); **$^{13}C\{^{1}H\}$** (100 MHz) 189.8 (s), 161.5 (s), 135.9 (s), 128.1 (s), 124.8 (s), 120.4 (s), 112.5 (s), 68.4 (s), 29.2 (s), 29.0 (s), 25.9 (s).

Synthesis of ((octane-1,8-diylbis(oxy))bis(2,1-phenylene))dimethanol (A′). The ligand precursor **A** (1.42 g, 4.00 mmol) was taken in MeOH (10 mL) and cooled to 0 °C. Solid $NaBH_4$ (0.318 g, 8.4 mmol) was added to the reaction mixture in small portions over the time of thirty minutes and solution was allowed to reach room temperature. The mixture was stirred at room temperature for 8 h. The similar workup as **A**, gave ligand precursor **A′** (1.321 g, 3.68 mmol, 92%) as white solid. Anal. Calcd for $C_{22}H_{30}O_4$ (358.4712): C, 73.71; H, 8.44. Found: C, 73.76; H, 8.39.

NMR ($CDCl_3$, δ/ppm): **^{1}H** (400 MHz) 7.31 – 7.26 (m, 2H), 6.98 – 6.89 (m, 2H), 4.72 (s, 2H), 4.05 (t, J = 6.4 Hz, 2H), 2.51 (bs, 1H, OH), 1.89 – 1.82 (m, 2H), 1.54 – 1.43 (m, 4H); **$^{13}C\{^{1}H\}$** (100 MHz) 156.9 (s), 129.1 (s), 128.8 (s), 128.6 (s), 120.5 (s), 111.0 (s), 67.8 (s), 62.2 (s), 29.2 (2 × s), 26.1 (s).

Synthesis of 1,8-bis(2-(chloromethyl)phenoxy)octane (B). The ligand precursor **A′** (1.26 g, 3.50 mmol) was taken in dry DCM (10 mL). The $SOCl_2$ (3.6 mmol) was added dropwise to the reaction mixture and solution was allowed to stir at room temperature for 10 h. The progress of reaction was monitored by TLC and after maximum conversion to product, the reaction was neutralized with $NaHCO_3$. The similar workup as **A**, gave ligand precursor **B** (1.27 g, 3.21 mmol, 91%) as yellow solid. Anal. Calcd for $C_{22}H_{28}Cl_2O_2$ (395.3625): C, 66.83; H, 7.14. Found: C, 66.77; H, 7.09.

NMR ($CDCl_3$, δ/ppm): **^{1}H** (400 MHz) 7.37 – 7.28 (m, 2H), 6.96 – 6.88 (m, 2H), 4.68 (s, 2H), 4.03 (t, J = 6.4 Hz, 2H), 1.88 – 1.81 (m, 2H), 1.55 – 1.50 (m, 2H), 1.45 – 1.41 (m, 2H); **$^{13}C\{^{1}H\}$** (100 MHz) 156.8 (s), 129.1 (s), 128.8 (s), 128.6 (s), 120.4 (s), 110.9 (s), 67.8 (s), 62.2 (s), 29.2 (s), 26.0 (s).

Synthesis of 1,8-bis(2-((phenylselanyl)methyl)phenoxy)octane (L1). A 100 mL two necked round bottom flask was charged with diphenyl diselenide (0.468 g, 1.5 mmol) in EtOH (25 mL). The

mixture was stirred at 70 °C under N_2 atm. Ethanolic solution of $NaBH_4$ (0.121 g, 3.20 mmol) was added dropwise to the reaction mixture until it become colorless. Ligand precursor **B** (1.186 g, 3.00 mmol) was dissolved in 2 mL EtOH and added dropwise to this reaction mixture. The mixture was allowed to stir overnight under refluxing. The reaction mixture was cooled to room temperature and extracted with $CHCl_3$ and water (3 * 20 mL). The $CHCl_3$ layer was dried over anhydrous Na_2SO_4 and concentrated using rotary evaporator. The residue was washed with hexane and dried under high vacuum to give **L1** (1.21 g, 1.90 mmol, 63%) as yellow liquid. Anal. Calcd for $C_{34}H_{38}O_2Se_2$ (636.5843): C, 64.15; H, 6.02. Found: C, 64.23; H, 6.08.

NMR ($CDCl_3$, δ/ppm): **^{1}H** (400 MHz) 7.65 – 7.63 (m, 1H), 7.52 – 7.50 (m, 2H), 7.32 – 7.24 (m, 2H), 7.21 – 7.18 (m, 2H), 7.07 – 7.06 (m, 1H), 6.85 – 6.81 (m, 2H), 4.16 (s, 2H), 3.98 (t, J = 5.2 Hz, 2H), 1.85 – 1.79 (m, 2H), 1.55 – 1.50 (m, 2H), 1.45 – 1.41 (m, 2H); **^{13}C{^{1}H}** (100 MHz) 156.6 (s), 133.6 (s), 130.0 (s), 129.1 (s), 128.7 (s), 128.2 (s), 127.7 (s), 127.0 (s), 120.0 (s), 111.3 (s), 67.9 (s), 29.3 (s), 29.27 (s), 27.1 (s), 26.1 (s).

Synthesis of macrocyclic palladium(II) complex C1. A round bottom single necked flask was charged with **L1** (0.636 g, 1.00 mmol), $Pd(CH_3CN)_2Cl_2$ (0.259 g, 1.00 mmol), and CH_3CN (10 mL). The mixture was stirred while refluxing overnight. The progress of reaction was monitored by TLC and after maximum conversion to product, the reaction mixture was cooled to room temperature and solvent was removed using rotary evaporator. The remaining residue was washed with hexane and dried under high vacuum to give **C1** (0.44 g, 0.54 mmol, 54%) as dark red solid. Anal. Calcd for $C_{34}H_{38}Cl_2O_2PdSe_2$ (813.9103): C, 50.17; H, 4.71. Found: C, 50.22; H, 4.76.

NMR ($CDCl_3$, δ/ppm): **^{1}H** (400 MHz) 7.64 – 7.63 (m, 1H), 7.37 (d, J = 4.4 Hz 1H), 7.32 – 7.28 (m, 5H), 6.96 – 6.89 (m, 2H), 4.69 (s, 2H), 4.05 (t, J = 5.2 Hz, 2H), 1.88 – 1.83 (m, 2H), 1.57 – 1.55 (m, 2H), 1.46 – 1.45 (m, 2H); **^{13}C{^{1}H}** (100 MHz) 156.8 (s), 131.5 (s), 130.4 (s), 129.9 (s), 129.1 (s), 127.7 (s), 125.8 (s), 120.3 (s), 111.6 (s), 68.6 (s), 41.7 (s), 29.2 (s), 29.1 (s), 25.9 (s).

General procedure for macrocyclic palladium complex catalyzed arylation of imidazole. A pressure tube was charged with aryl bromide (1.0 mmol), imidazole derivative (1.2 equiv.), base (2.0 equiv.), additive (0.30 mmol), and solvent (3 mL). The reaction mixture was stirred at 100 °C for 10 h under open air conditions. The progress of reaction was monitored by TLC and after maximum conversion to product, the reaction mixture was cooled to room temperature and extracted with ethyl acetate and cold water (3 * 20 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4 and concentrated using rotary evaporator. The residue was purified using silica gel column (1 × 12 cm) chromatography with CH_2Cl_2/MeOH (20:1 v/v) solvents. The products as isolated were then authenticated with the help of ^{1}H and ^{13}C{^{1}H} NMR spectroscopy and data are presented in SI.

Experimental procedure for macrocyclic palladium complex catalyzed arylation of imidazole. A pressure tube was charged with 4-bromobenzonitrile (0.182 g, 1.0 mmol, 67.0 equiv.), 1-methyl-1*H*-imidazole (0.098 g, 1.2 mmol, 80.0 equiv.), K_2CO_3 (0.276 g, 2.00 mmol, 133.3 equiv.), PivOH (0.031 g, 0.30 mmol, 20.0 equiv.), macrocyclic palladium complex **C1** (0.013 g, 1.5 mol%, 0.015 mmol, 1 equiv.), and DMA (3 mL). The reaction mixture was stirred at 100 °C for 10 h under open air conditions. The progress of reaction was monitored by TLC and after maximum conversion to product, the reaction mixture was cooled to room temperature and extracted with ethyl acetate and cold water (3 * 20 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4 and concentrated using rotary evaporator. The residue was purified using silica gel column (1 × 12 cm) chromatography with CH_2Cl_2/MeOH (20:1 v/v) solvents to get 4-(1-methyl-1*H*-imidazol-5-yl)benzonitrile (**3a**) as white solid (93 %).

Triphenylphosphine poisoning test. Following the general procedure for arylation reaction, a pressure tube was charged with 4-bromobenzonitrile (1.0 mmol), 1-methyl-1*H*-imidazole (1.2 mmol), K_2CO_3 (2.0 mmol), PivOH (0.30 mmol), and DMA (3 mL). Catalyst **C1** (1.5 mol%) and triphenylphosphine (5.0 mol%) were added to this reaction mixture and allowed to stir at 100 °C for 10 h. The analogues workup as general procedure gave 88% yield of **3a**.

Mercury poisoning test. Following the general procedure for arylation reaction, a pressure tube was charged with 4-bromobenzonitrile (1.0 mmol), 1-methyl-1*H*-imidazole (1.2 mmol), K_2CO_3 (2.0 mmol), PivOH (0.30 mmol), and DMA (3 mL). Catalyst **C1** (1.5 mol%) and mercury (Pd/Hg = 1/300) were added to this reaction mixture and allowed to stir at 100 °C for 10 h. The analogues workup as general procedure gave 83% yield of **3a**.

Procedure for Reusability Experiment. In a pressure tube (10 mL), 4-bromobenzonitrile (0.182 g, 1.0 mmol), 1-methyl-1*H*-imidazole (0.098 g, 1.2 equiv.), K_2CO_3 (0.276 g, 2.0 equiv.), PivOH (0.031 g, 0.3 equiv.), macrocyclic palladium complex **C1** (1.5 mol%), and DMA (3 mL) were stirred and heated on 100 °C for 10 h. After 10 h, the reaction mixture was cooled and 150 μL of reaction mixture was taken out and analyzed using ^{1}H NMR spectroscopy. Thereafter a fresh batch of 4-bromobenzonitrile (0.182 g, 1.0 mmol), 1-methyl-1*H*-imidazole (0.098 g, 1.2 equiv.), K_2CO_3 (0.276 g, 2.0 equiv.), PivOH (0.031 g, 0.3 equiv.), was added in the absence of **C1** and reaction was allowed to stir at 100 °C for another 10 h. The analysis of aliquot shows 76% conversion of desired coupled product **3a**.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2021.121907.

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