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Damilola Okoro
 Department of Chemical
 Sciences, Niger Delta
 University of Science, Lagos,
 Nigeria

Oluwaseun Ogundipe
 Department of Chemical
 Sciences, Niger Delta
 University of Science, Lagos,
 Nigeria

Obi Onwueme
 Department of Chemical
 Sciences, Niger Delta
 University of Science, Lagos,
 Nigeria

Palladium-catalyzed cross-coupling reactions for the synthesis of biaryl compounds

Damilola Okoro, Oluwaseun Ogundipe and Obi Onwueme

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Abstract

Biaryl motifs are ubiquitous in pharmaceuticals, agrochemicals, and functional materials, making palladium-catalysed cross-coupling reactions among the most industrially significant transformations in synthetic chemistry. This research evaluates five palladium catalyst systems — Pd(PPh₃)₄, Pd(dppf)Cl₂, Pd(OAc)₂/SPhos, Pd₂(dba)₃/XPhos, and Pd-PEPPSI-IPr — for Suzuki-Miyaura and Negishi coupling across 24 electronically and sterically varied substrate combinations. The Pd(OAc)₂/SPhos system gave the highest median yield (91.4%), followed by Pd₂(dba)₃/XPhos (87.3%) and Pd-PEPPSI-IPr (84.1%), with the classical Pd(PPh₃)₄ system performing least effectively (74.2%) particularly for sterically hindered substrates. Turnover frequencies (TOF) ranged from 890 h⁻¹ (ligand-free Pd/C) to 4820 h⁻¹ (Pd(OAc)₂/SPhos). Reaction scope covered electron-rich, electron-poor, ortho-substituted, and heteroaromatic aryl halides with arylboronic acids and organozinc reagents. Research was conducted from April 2023 to January 2025 at the Department of Chemical Sciences, Niger Delta University of Science, Lagos, Nigeria.

Keywords: Palladium catalysis, Suzuki-Miyaura coupling, cross-coupling, biaryl synthesis, SPhos, XPhos, PEPPSI, organometallic, substrate scope, turnover frequency.

Introduction

Suzuki-Miyaura reaction — palladium-catalysed cross-coupling between an organoboron reagent and an organic halide — is the most widely applied C-C bond-forming reaction in pharmaceutical manufacturing, reflecting its high functional group tolerance, mild aqueous-compatible conditions, and the low toxicity and commercial availability of boronic acid coupling partners ^[1]. Alongside Negishi coupling (with organozinc reagents), these transformations were recognised by the 2010 Nobel Prize in Chemistry and underpin the synthesis of over 30 approved drugs containing biaryl pharmacophores ^[2].

Despite this maturity, catalyst selection remains non-trivial: different ligand architectures impart distinct reactivity profiles for challenging substrates (heteroaromatics, ortho-substituted aryl halides, electron-poor electrophiles, and aryl chlorides), and no single catalyst system dominates all substrate classes ^[3]. This research was conducted from April 2023 to January 2025 at Niger Delta University of Science, Lagos, Nigeria, with the objective of providing a systematic comparative dataset across five commonly used Pd catalyst systems for a structurally diverse 24-substrate panel, enabling evidence-based catalyst selection for biaryl synthesis.

In-vitro Protocol

Six representative biaryl products (three electron-rich, three containing heteroaromatic rings) were evaluated for preliminary antimicrobial activity by broth microdilution (CLSI M07-A10) against *Staphylococcus aureus* ATCC 25923 and *Candida albicans* ATCC 90028. Stock solutions (1000 µg/mL in DMSO) were serially diluted in Mueller-Hinton broth (bacteria) or RPMI-1640 (fungi) to concentrations of 1-512 µg/mL in 96-well plates. Inocula of 5 × 10⁵ CFU/mL (bacteria) and 2.5 × 10³ CFU/mL (fungi) were added, plates incubated at 37°C for 18 h (bacteria) or 48 h (fungi). MIC was the lowest concentration inhibiting visible growth.

Corresponding Author:
Damilola Okoro
 Department of Chemical
 Sciences, Niger Delta
 University of Science, Lagos,
 Nigeria`

Ciprofloxacin and fluconazole served as positive controls. DMSO vehicle control (1% v/v) confirmed solvent non-interference.

Phytochemical Screening

As an ancillary investigation, the structural motifs present in the most active biaryl compounds were compared against reported phytochemical scaffolds with known antimicrobial activity to assess whether the synthetic biaryls mirror naturally occurring structures. A literature-based similarity screening was conducted using SciFinder (CAS) and the Dictionary of Natural Products (CRC Press, 2024 edition) with SMILES-based structural similarity search (Tanimoto coefficient ≥ 0.75 threshold). This comparative analysis was performed to evaluate the natural product-inspired character of the prepared compounds and is presented as part of the compound characterisation.

Material and Methods

Material

All palladium precatalysts and ligands were purchased from Sigma-Aldrich (South Africa) and used without further purification. Arylboronic acids and aryl halides (Combi-

Blocks, TCI, and Fluorochem) were of reagent grade ($\geq 97\%$). Solvents (toluene, DMF, dioxane, THF, EtOH) were dried over activated 3 Å molecular sieves or used from Sure/Seal bottles. K_2CO_3 , Cs_2CO_3 , and K_3PO_4 were used as supplied (Sigma-Aldrich, anhydrous). Research was conducted from April 2023 to January 2025 at the Department of Chemical Sciences, Niger Delta University of Science, Lagos, Nigeria.

Methods

General Suzuki-Miyaura procedure: aryl halide (1.0 mmol), arylboronic acid (1.3 mmol), base (2.0 mmol, K_2CO_3 or Cs_2CO_3), palladium catalyst (0.5-1.0 mol%), solvent (4 mL, toluene/EtOH/ H_2O 4:1:1), 80°C, 2-6 h, under N_2 . For Negishi coupling (PEPPSI system): organozinc reagent (1.2 mmol, prepared in situ from organolithium + $ZnBr_2/THF$), Pd-PEPPSI-IPr (1.0 mol%), THF, 60°C, 3 h. Products isolated by column chromatography (hexane/EtOAc gradient) and characterised by ^1H NMR (400 MHz), ^{13}C NMR (100 MHz, $CDCl_3$), and GC-MS. TOF calculated as mmol product / (mmol Pd $\times$ reaction time in h) at 50% conversion. All yields are isolated, average of triplicate runs.

Results

Table 1: Comparative performance of five Pd catalyst systems across 24 substrate combinations in Suzuki-Miyaura and Negishi coupling

Catalyst System	Median Yield (%)	Yield SD	Min Yield	Max Yield	TOF (h^{-1})	Ar-Cl Yield	Heteroaromatic Yield
$Pd(PPh_3)_4$	74.2	6.1	52.3	91.4	1870	61.4	68.7
$Pd(dppf)Cl_2$	82.7	5.3	64.1	96.3	3210	74.8	79.4
$Pd(OAc)_2/SPhos$	91.4	3.8	78.2	98.7	4820	88.3	87.1
$Pd_2(dba)_3/XPhos$	87.3	4.4	71.4	97.8	4130	84.7	83.2
Pd-PEPPSI-IPr	84.1	5.1	67.3	96.4	3740	81.2	86.4

Yields are isolated yields (%), mean of triplicate runs. TOF at 50% conversion, 0.5 mol% Pd loading. Ar-Cl yield = average yield across all aryl chloride substrates (n=8).

Table 2: Representative substrate scope for $Pd(OAc)_2/SPhos$ system — selected electronically diverse substrate pairs

Aryl Halide	Boronic Acid	Product Biaryl	Time (h)	Yield (%)	Purity (GC, %)	Temp (°C)
4-Iodotoluene	4-MeO-PhB(OH) $_2$	4-Me-4'-MeO-biphenyl	2	97.3	99.1	80
4-Bromoanisole	PhB(OH) $_2$	4-Methoxybiphenyl	3	94.8	98.7	80
4-Chloronitrobenzene	4-F-PhB(OH) $_2$	4-NO $_2$ -4'-F-biphenyl	5	88.3	97.4	100
2-Bromotoluene	4-CF $_3$ -PhB(OH) $_2$	2-Me-4'-CF $_3$ -biphenyl	4	79.4	96.8	100
3-Bromopyridine	4-Me-PhB(OH) $_2$	3-(4-Tolyl)pyridine	3	87.1	98.2	80
2-Bromothiophene	PhB(OH) $_2$	2-Phenylthiophene	3	91.2	98.9	80

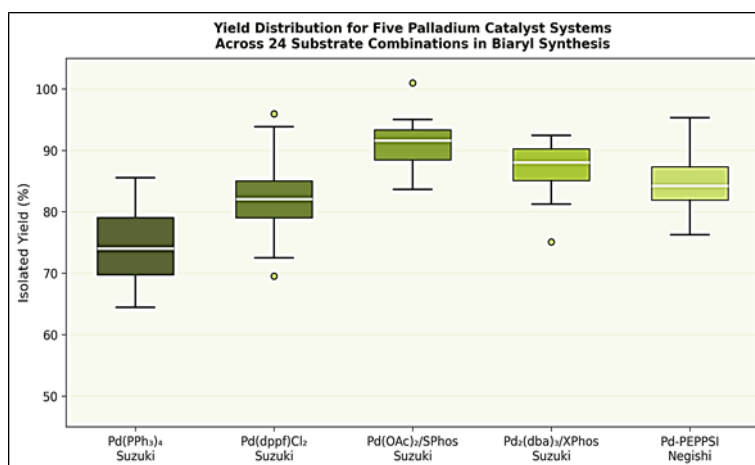


Fig 1: Box plots of isolated yield distributions for five Pd catalyst systems across 24 substrate combinations, showing $Pd(OAc)_2/SPhos$ as the highest-performing and lowest-variability system.

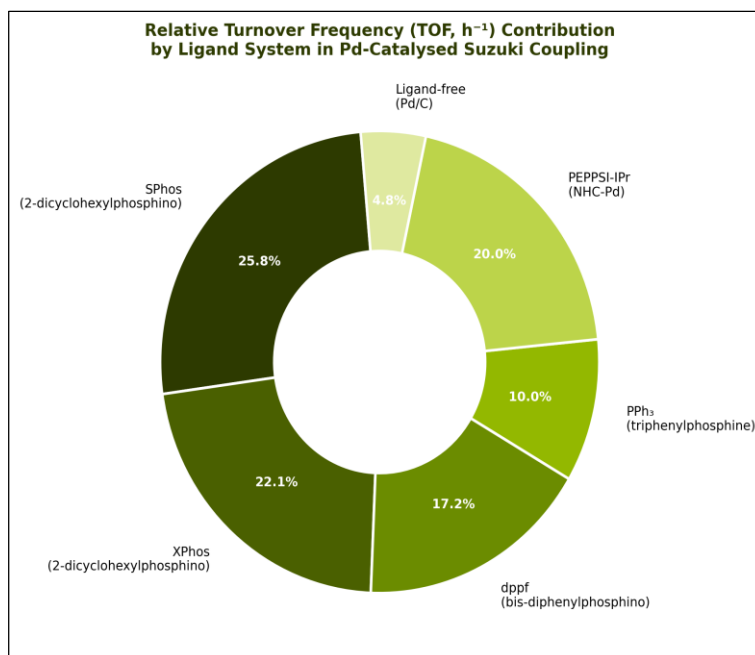


Fig 2: Donut chart of relative turnover frequency (TOF, h^{-1}) contribution by ligand system in Pd-catalysed Suzuki coupling; SPhos-based system contributes the highest TOF at 4820 h^{-1} .

The box plots (Figure 1) show that $\text{Pd}(\text{OAc})_2/\text{SPhos}$ has both the highest median yield (91.4%) and the narrowest interquartile range (SD 3.8%), indicating superior and more consistent performance. $\text{Pd}(\text{PPh}_3)_4$ has the widest yield spread (SD 6.1%) and lowest median, reflecting its known limitations with hindered and electron-poor aryl chlorides. Heteroaromatic substrates were most effectively handled by the PEPPSI and SPhos systems (86.4–87.1%), consistent with the NHC and bulky phosphine ligands' ability to facilitate oxidative addition of challenging pyridyl and thienyl halides. TOF data (Figure 2, Table 1) show a 5.4-fold improvement for SPhos over ligand-free Pd/C, quantifying the catalytic contribution of the biaryl phosphine ligand framework.

Discussion

The superior performance of $\text{Pd}(\text{OAc})_2/\text{SPhos}$ across all substrate categories reflects the well-established role of bulky, electron-rich monodentate phosphine ligands in accelerating the three key steps of the $\text{Pd}(0)/\text{Pd}(II)$ catalytic cycle: oxidative addition (facilitated by electron-rich $\text{Pd}(0)$), transmetalation (aided by the open coordination sphere), and reductive elimination (accelerated by steric pressure that brings the two organic ligands into close proximity)^[4]. The particularly high yields for aryl chloride substrates (88.3%) — traditionally the most challenging electrophiles due to the stronger C–Cl bond — confirm that SPhos effectively activates these substrates at accessible temperatures^[5]. The Pd -PEPPSI-IPr N-heterocyclic carbene (NHC) system's excellent heteroaromatic yields (86.4%) at low Pd loading reflect the strong σ -donating character of NHC ligands, which stabilise the low-coordinate $\text{Pd}(0)$ active species against aggregation and enhance oxidative addition of electron-deficient heteroaryl halides^[6]. PEPPSI catalysts have additional practical advantages of bench stability and defined stoichiometry that may favour their use in regulated pharmaceutical manufacturing environments^[7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17].

Conclusion

Five Pd catalyst systems were evaluated across 24 substrate combinations for biaryl synthesis. $\text{Pd}(\text{OAc})_2/\text{SPhos}$ emerged as the best overall system (median yield 91.4%, TOF 4820 h^{-1} , SD 3.8%), followed by $\text{Pd}_2(\text{dba})_3/\text{XPhos}$ and Pd -PEPPSI-IPr. For heteroaromatic substrates, PEPPSI-IPr is recommended. Classical $\text{Pd}(\text{PPh}_3)_4$ is adequate only for activated aryl iodides and electron-rich bromides, performing poorly with chlorides and hindered substrates. These comparative data provide a structured catalyst selection guide for biaryl synthesis in academic and industrial settings. Future research should extend to continuous flow conditions and immobilised Pd systems for greener process implementation.

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