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FULL PAPER

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Xantphos-ligated palladium dithiolates: An unprecedented and convenient catalyst for the carbonylative Suzuki–Miyaura cross-coupling reaction with high turnover number and turnover frequency

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Xantphos- and dithiolate-ligated macrocyclic palladium complexes as an efficient and stable catalyst for the carbonylative Suzuki–Miyaura cross-coupling reaction have been synthesized. The catalysts were characterized by ^{1}H-nuclear magnetic resonance (NMR), CHNS (carbon, hydrogen, nitrogen, and sulfur) analysis, melting point analysis, and ^{31}P-NMR spectroscopy. Several sensitive functional groups (e.g., $-NO_2$, –F, –Cl, –Br, $-NH_2$, and –CN) on the aromatic ring were well tolerated in the carbonylative Suzuki–Miyaura coupling reaction. The present palladium complexes produce six times higher turnover number (TON) and five times higher turnover frequency (TOF) compared with conventional homogeneous palladium precursors. Maximum TONs in the range of 10^5 to 10^6 and TOF in the range of 10^4 to 10^5 could be generated by a very low amount of catalyst loading (10^{-5} mol%).

KEYWORDS
biaryl ketone, carbonylation, homogeneous catalyst, palladium dithiolate, xantphos

1 | INTRODUCTION

Biaryl ketones are recognized as an important synthetic target because of their participation in a variety of useful organic transformations. Formation of these ketones is an important structural building block in the synthesis of natural products, pharmaceuticals, pesticides, photosensitizers, and advanced organic materials (Figure 1).[1–5] The synthesis of biaryl ketones by noncarbonylative approaches is well documented in the literature.[6–13]

The most convenient and traditional method for the synthesis of biaryl ketones involves Friedel–Crafts acylation reaction. However, this method requires an overstoichiometric amount of Lewis acid and suffers from compatibility issues with many substrates containing deactivating groups. It also generates waste such as aluminum salts, leading to poor atom economy. By contrast, carbonylative Suzuki–Miyaura cross-coupling of an aryl halide and organoboron aryl compounds over a Pd catalyst in the presence of a suitable base offers an alternative

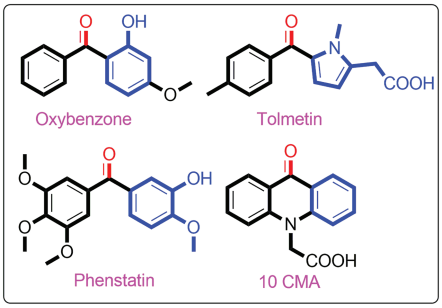


FIGURE 1 Examples of pharmaceutically active biaryl ketone

route for the synthesis of biaryl ketones, and hence is widely applied. The aforementioned reaction has unique features such as readily accessible and stable substrates, functional groups tolerance, broad substrate scope, and the phenyl boronic acids (provide nucleophilic source for this reaction) are easy to handle, nontoxic, and moisture, air and thermally stable. Recently, Fe- and Ni-catalyzed carbonylative cross-coupling between aryl halides and phenyl boronic acid with carbon monoxide has been reported for the synthesis of biaryl ketones.[14–17] Several studies have used homogeneous and heterogeneous palladium catalysts in this reaction.[18–28] However, many of these catalytic systems require high catalyst loading, with some even using active aryl iodides, thus limiting their large-scale application. By contrast, the presence of excess amounts of π-acidic CO as compared with the catalytic quantities of palladium lowers the rate of oxidative addition of metal with aryl halide. Sometimes, CO aggregation of palladium also leads to catalytically inactive species. Hence, to resolve this issue, it is necessary to design a new catalyst that can minimize the aforesaid drawbacks and provide good catalytic activity in the carbonylation reaction; however, designing such a catalyst remains a challenging task.

Recently, there has been an increasing interest in the development of palladacycle chemistry and significant advances have been made, especially on their application as an organometallic catalyst.[29–33] This was attributed to the ability of palladacycle complexes to achieve high activity at parts per million (ppm) level, remain thermally stable in various catalytic applications, and remain recyclable with a proper solvent system. Herrmann et al.[34] developed tri(*o*-tolyl)phosphine cyclopalladacycles and employed them in the study of Heck and Suzuki reaction way back in 1995. Afterwards, several research work into this field has been rapidly progressed for the development of series of nitrogen,[35–38] phosphorous,[39–43] sulfur,[44,45] and oxygen[46] derived palladium catalysts which were used for the carried out C-C and C-heteroatom bond forming a reaction to provided high TON and TOF. In 2003, Grigg and co-workers[47] successfully synthesized isoindolinone using *in situ* palladium nanoparticles generated from palladacycle complex in the presence of CO. Fairlamb and co-workers[31] used Bedford catalyst along with Bis (diphenylphosphino)ferrocene (dppf) to study alkoxy and aminocarbonylation reaction in 2007. Others employed Herrmann palladacycle as the catalyst in carbonylation[48] and aminocarbonylation[49] reactions using solid $Mo(CO)_6$ as a CO surrogate. Buchwald et al.[50] employed xantphos-ligated Pd catalyst at low temperatures for the aminocarbonylation (hetero) of aryl bromide in 2014. Bhanage and co-workers[51–53] reported carbonylative Suzuki reaction with palladium chalcogenolate complexes and Bedford catalyst and carbonylative Sonogashira reaction with oxime palladacycle in 2014, 2015, and 2016, respectively. We have recently developed supramolecular co-ordination complexes of palladium(II) made from bridging dithiolates with two *cis* positions blocked by dppe[54] and xantphos ligands.[55] These sulfur-based ligands were little explored due to their propensity to form insoluble polymeric products and the misbelief as catalyst poison. It is noteworthy that the new macrocyclic complexes are easy to synthesize and highly stable, and showed excellent catalytic activity in Suzuki[54,55] and Heck[56] C–C coupling reactions at very low concentrations. Encouraged by these results, in this work, we used xantphos-ligated Pd dithiolate complexes as catalysts to investigate carbonylative Suzuki–Miyaura reactions. Catalyst **1** {$[Pd_2(xantphos)_2(4,4'\text{-}SC_{12}H_8S)]_2(OTf)_4$ (**II**)} and catalyst **2** {$[Pd(xantphos)(1,4\text{-}SC_6H_4SH)]_2(OTf)_2$ (**I**) and $[Pd_2(xantphos)_2(1,4\text{-}SC_6H_4S)]_2(OTf)_4$ (**II**)} (Figure 2)[55] were chosen for the coupling reaction of aryl iodides with phenyl boronic acids in the presence of gaseous CO. The optimization studies with respect to various reaction parameters, the synthesis of biaryl ketones by coupling different aryl iodides with boronic acids, low catalyst loading, activity of present palladium macrocycles compared with traditional Pd catalysts, and

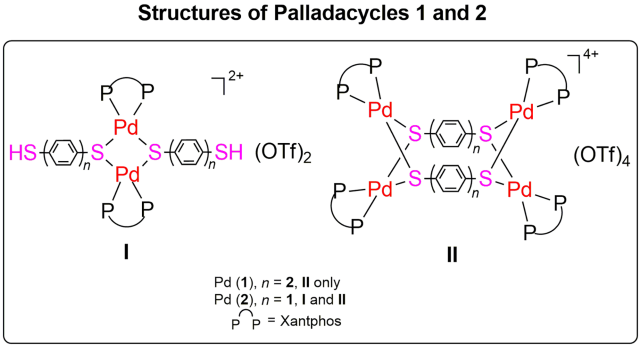


FIGURE 2 Structures of palladium catalysts **1** and **2**

gram scale-up synthesis of benzophenone, etc. will be discussed herein.

2 | EXPERIMENTAL

2.1 | Materials

All the chemicals and solvents were purchased from different reputed commercial sources (Sigma Aldrich, Alfa Aesar, Lobha Chemicals and S.D. fine chemicals) and were used without further purification. Carbon monoxide (cylinder) was purchased from Rakhangi Gas Services (Mumbai) with 99.99% purity. The Pd catalysts **1** and **2** were prepared according to the literature method and are provided in main manuscript.[55] The progress of the reaction was monitored by gas chromatography (GC) and GC–mass spectrometry (MS) and thin-layer chromatography using Merck silica gel 60 F254 plates. The products were visualized with a 254-nm UV lamp. The GC–MS-QP 2010 instrument [Rtx-17, 30 m × 25 mm inner diameter, film thickness (*df*) = 0.25 μm; column flow 2 ml min^{-1}, 100 to 240 °C at 10 °C min^{-1} rise] was used for the mass analysis of the products. The products were purified by column chromatography using 100–200-mesh silica gel. Elemental analysis for C, H, N, and S (CHNS analysis) was performed on a Carlo Erba EA-1110 CHNS Analyser. The ^{1}H-nuclear magnetic resonance (NMR) spectra were recorded at 500 MHz in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard. The ^{13}C-NMR spectra were recorded at 125 MHz in $CDCl_3$. Chemical shift was detected in parts per million (ppm) using TMS as an internal standard, with *J* (coupling constant) value recorded in Hertz. The ^{1}H-NMR spectra of the catalysts were recorded on Bruker and Varian NMR spectrometers operating at 300 and 500 MHz, respectively, with chemical shifts relative to internal acetone-d_6 and methanol-d_4 peak (δ 2.05 and 3.31). ^{19}F{^{1}H} and ^{31}P{^{1}H}-NMR spectra were recorded on a Bruker NMR spectrometer operating at 376 and 121 MHz, respectively, and ^{13}C{^{1}H}-NMR spectra were recorded on a Varian NMR spectrometer operating at 201 MHz.

2.2 | Catalyst preparation and its characterization

Catalyst 2 {[Pd(xantphos)(1,4-SC_6H_4SH)]$_2$($OTf)_2$ (**I**) and [Pd_2(xantphos)$_2$(1,4-SC_6H_4S)]$_2$($OTf)_4$ (**II**)} was prepared as follows: To a 5 ml acetone solution of 1,4-benzenedithiol (5.4 mg, 0.038 mmol), 5 ml acetone solution of [Pd(xantphos)($OTf)_2$] (75.2 mg, 0.076 mmol) was added. A wine-red solution mixture results which was stirred for 4 hr. The solvent was then evaporated in vacuum, and the red residue was washed with diethyl ether and extracted with acetone (3 × 5 ml). Finally, diethyl ether (10 ml) was added to yield a red colored solid of **catalyst 2** (48.1 mg, 0.024 mmol, 65%) with melting point > 230 °C (dec). Analytical calculation for **I**·$(H_2O)_2$ $C_{92}H_{74}F_6O_8P_4Pd_2S_6(H_2O)_2$: C, 55.64; H, 3.96; S, 9.67%; calculation for **II**·$(H_2O)_4$ $C_{172}H_{136}F_{12}O_{16}P_8Pd_4S_8(H_2O)_4$: C, 56.00; H, 3.93; S, 6.95%; found: C, 55.11; H, 3.75; S, 9.98%. ^{1}H-NMR (300 MHz, acetone-d_6): δ 1.50 (s, 6H, CH_3), 1.97 (s, 6H, CH_3), 5.60 (br s, 4H, C_6H_4), 6.88 (br s, 12H, *p*-H of PPh_2 + CHCHCH), 7.39 (m, 20H, *m*-H of PPh_2+ CPCHCH), 7.66 (br s, 16H, *o*-H of PPh_2), 7.92 (br s, 4H, CHCHCC), ^{1}H-NMR (500 MHz, CD_3OD): δ 1.50 (s, 6H, CH_3), 1.97 (s, 6H, CH_3), 5.53 (br s, 8H, C_6H_4), 6.84 (br s, 12H, *p*-H of PPh_2 + CHCHCH), 7.29 (m, 20H, *m*-H of PPh_2 + CPCHCH), 7.59 (br s, 16H, *o*-H of PPh_2), 7.90 (br s, 4H, CHCHCC), ^{31}P{^{1}H}-NMR (121 MHz, acetone-d_6): δ 4.3 (br, s), 7.9 (br, s) in about 1:1 ratio. The ^{31}P-NMR spectrum of catalyst is shown in Figure S1.

Catalyst 1 {[Pd_2(xantphos)$_2$(4,4′-$SC_{12}H_8S$)]$_2$($OTf)_4$ (**II**)} was prepared similar to **catalyst 2**, using [Pd(xantphos)($OTf)_2$] (75.1 mg, 0.076 mmol) and 4,4′-biphenyldithiol (8.3 mg, 0.038 mmol) to yield the title complex as a red solid (50.3 mg, 0.013 mmol, 70%) with melting point > 230 °C (dec). Analytical calculation for **Catalyst 1** $C_{184}H_{144}F_{12}O_{16}P_8Pd_4S_8$: C, 58.63; H, 3.85; S, 6.81; found: C, 58.60; H, 3.82; S, 6.94%. ^{1}H-NMR (300 MHz, acetone-d_6): δ 1.62 (s, 6H, CH_3; another peak due to the methyl group merged with the solvent peak at δ 2.05 ppm), 5.89 (d, $^{3}J_{HH}$ = 7.8 Hz, 4H, *o*-H, $C_{12}H_8$), 6.32 (d, $^{3}J_{HH}$ = 7.8 Hz, 4H, *m*-H, $C_{12}H_8$), 7.09 (br s, 4H, CHCHCH), 7.22 (br s, 8H, *p*-H of PPh_2), 7.30–7.49 (m, 20H, *m*-H of PPh_2 + CPCHCH), 7.53 (t, $^{3}J_{HH}$ = 6.9 Hz, 16H, *o*-H of PPh_2), 7.97 (d, $^{3}J_{HH}$ = 7.8 Hz, 4H, CHCHCC), ^{1}H-NMR (500 MHz, CD_3OD): δ 1.56 (s, 6H, CH_3), 2.01 (s, 6H, CH_3), 5.84 (d, $^{3}J_{HH}$ = 8.0 Hz, 4H, *o*-H, $C_{12}H_8$), 6.22 (d, $^{3}J_{HH}$ = 8.0 Hz, 4H, *m*-H, $C_{12}H_8$), 7.01 (br s, 4H, CHCHCH), 7.14 (br s, 8H, *p*-H of PPh_2), 7.31–7.44 (m, 20H, *m*-H of PPh_2 + CPCHCH), 7.53 (t, $^{3}J_{HH}$ = 7.5 Hz, 16H, *o*-H of PPh_2), 7.89 (d, $^{3}J_{HH}$ = 7.5 Hz, 4H, CHCHCC), ^{13}C{^{1}H}-NMR (201 MHz, acetone-d_6): δ 23.4 (s, CH_3), 38.7 (s, CCH_3), 117.6 (d, $^{1}J_{PC}$ = 45.1 Hz, CP of $C_{15}H_{12}O$), 127.4 (s, *o*-C of $C_{12}H_8$), 127.9 (s, CH of $C_{15}H_{12}O$), 130.3 (s, *m*-C of $C_{12}H_8$), 130.5 (s, CH of $C_{15}H_{12}O$), 130.8 (s, *m*-C of C_6H_5), 131.8 (s, CS of $C_{12}H_8$), 132.9 (d, $^{1}J_{PC}$ = 71.6 Hz, CP of C_6H_5), 134.2 (s, *o*−/*p*-C of C_6H_5), 134.7 (s, CH of $C_{15}H_{12}O$), 137.6 (s, CC of $C_{12}H_8$), 139.0 [s, CCC (CH_3) of $C_{15}H_{12}O$], 157.4 (s, CO of $C_{15}H_{12}O$), ^{19}F{^{1}H}-NMR (376 MHz, acetone-d_6): δ −78.7 (s), ^{31}P{^{1}H}-NMR

(121 MHz, acetone-d_6): δ 9.1 (s). Figure 2 shows structures of catalysts **1** and **2**.

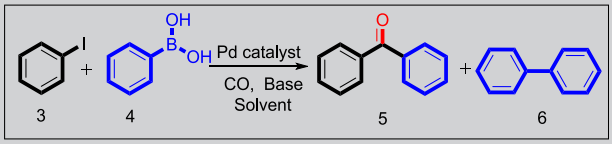
2.3 | Preparation of stock solution of the catalyst

Initially, we prepared the stock solution of the catalyst by dissolving the complex in acetonitrile solvent, and various catalyst concentrations (10^{-1} to 10^{-5} mol%) were prepared. First, to prepare 1 mol% of catalyst, 9.75 mg complex was weighed and dissolved into 1 ml acetonitrile (solvent). Afterward, we prepared 10^{-2}, 10^{-3}, 10^{-4}, and 10^{-5} mol% solutions by successive dilution from stock solution using acetonitrile. No special precautions were taken for the preparation of stock solution, and the catalyst was weighed and handled in air as it is air stable.

2.4 | General procedure for synthesis of biaryl ketone by carbonylative Suzuki–Miyaura reaction

In a typical procedure, 100-ml autoclave was charged with iodobenzene (0.5 mmol), aryl boronic acid (0.75 mmol), and K_2CO_3 (1.5 mmol) with 10 ml anisole as a solvent. Then, 0.1 mol% of Pd "**2**" (catalyst) was added and the autoclave was closed tightly with a clamp. Next, the autoclave was flushed with nitrogen gas three times. The autoclave was then pressurized with CO (0.3 MPa) and heated at 100 °C for 8 hr. The reaction mixture was stirred with a mechanical stirrer at 500 rpm. After completion of the reaction, the autoclave was cooled down to room temperature and the remaining CO was vented carefully and the reactor was opened. The reaction mixture was quenched with water and the product extracted with ethyl acetate (3 × 15 ml). The organic solvent was evaporated by a

TABLE 1 Screening of optimal reaction condition[a]



Entry number	Pd precursor	Base	Solvent	CO pressure (bar)	Time (hr)	Conversion[b] (%)	Selectivity[b] 5:6
1	Pd (**1**)	K_2CO_3	Anisole	5	8	85	85:15
2	Pd (**2**)	K_2CO_3	Anisole	5	8	96	94:6
3	Pd (**2**)	Na_2CO_3	Anisole	5	8	80	87:13
4	Pd (**2**)	K_3PO_4	Anisole	5	8	83	89:11
5	Pd (**2**)	Cs_2CO_3	Anisole	5	8	73	80:20
6	Pd (**2**)	K_2CO_3	Toluene	5	8	60	85:15
8	Pd (2)	K_2CO_3	Dimethylformamide	5	8	66	65:35
9	Pd (**2**)	K_2CO_3	CH_3CN	5	8	45	49:51
10	**Pd (2)**	**K_2CO_3**	**Anisole**	**3**	**8**	**97**	**96:4**
11	Pd (**2**)	K_2CO_3	Anisole	1	8	70	88:12
12	Pd (**2**)	K_2CO_3	Anisole	3	6	83	83:17
13	Pd (**2**)	K_2CO_3	Anisole	3	4	66	69:31
14[c]	Pd (**2**)	K_2CO_3	Anisole	3	8	98	95:5
15[d]	Pd (**2**)	K_2CO_3	Anisole	3	8	85	90:10
16[e]	Pd (**2**)	K_2CO_3	Anisole	3	8	50	80:20

[a]**Optimized reaction condition**: **3** (0.5 mmol), **4** (0.7 mmol), catalyst (0.1 mol%), base (1 mmol), solvent (10 ml), 100°C.

[b]Conversion and selectivity based on iodobenzene and calculated by GC and GC–MS.

[c]120 °C.

[d]80 °C.

[e]60 °C.

GC, gas chromatography; MS, mass spectrometry.

rotary evaporator to obtain the crude product, which was further purified by column chromatography (silica gel, 100–200-mesh size), with petroleum ether–ethyl acetate as the eluent to afford a pure product. The products were confirmed by GC–MS and ^{1}H- and ^{13}C-NMR spectroscopic analysis.

3 | RESULTS AND DISCUSSION

To achieve our goal, iodobenzene (**3**) and phenyl boronic acid (**4**) were chosen as model substrates as shown in Table 1. Initially, we have investigated the use of palladium catalysts **1** and **2** in the synthesis of biaryl ketone. It is noteworthy that catalyst **1** exists exclusively as a tetranuclear (**II**) macrocyclic Pd complex, whereas catalyst **2** is composed of both dinuclear (**I**) and tetranuclear (**II**) Pd complexes in solution.[55] In the experimental study, first, iodobenzene (0.5 mmol) was reacted with phenyl boronic acid (0.7 mmol) using the Pd catalysts **1** and **2** (0.1 mol%), respectively, with K_2CO_3 (1 mmol) as the base under a CO atmosphere in 10 ml anisole at 100 °C for 8 hr. The results showed that Pd catalyst **2** was more active than Pd catalyst **1** (Table 1, Entry 1); thus, further optimization was performed using only the former (Table 1, Entry 2). Second, the base study was performed using Na_2CO_3, K_3PO_4, and Cs_2CO_3 as inorganic bases (Table 1, Entries 3–5), which resulted in 80%, 83%, and 73% conversion of iodobenzene, respectively, with good selectivity. It was observed that replacing of K_2CO_3 the conversion of the iodobenzene was brought down. However, K_2CO_3 acted as an effective base, which enabled efficient conversion of iodobenzene (97%) as well as good selectivity (Table 1, Entry 10). Furthermore, we studied the influence of various solvents on the model reaction. The effect of different solvents, such as toluene (60%), dimethylformamide (66%), CH_3CN (45%), and anisole (97%) was screened (Table 1, Entries 6–10). Among these, anisole was found to be an excellent solvent for the proposed protocol and thus further optimization was performed only using anisole (Table 1, Entry 10). We then investigated the effect of CO (gas) pressure on the model reaction (Table 1, Entries 10–11). When CO pressure decreases from 0.5 to 0.3 MPa, no significant conversion of iodobenzene was observed; however, upon further lowering the CO pressure from 0.3 to 0.1 MPa, both conversion of iodobenzene and selectivity decreased. Thus, the study of CO pressure indicates that 0.3 MPa is enough to ensure effective reaction progress. The reaction time was optimized by performing the reaction for different periods, ranging between 4 and 8 hr (Table 1, Entries 10, 12, and 13). When we reduced the reaction time from 8 to 6 hr, conversion was also reduced from 97% to 83%. Only 66% conversion of iodobenzene was observed for 4-hr reaction time (Table 1, Entry 13). Thus, based on this result, 8 hr was found to be sufficient for reaction completion with good conversion and selectivity. Finally, variation of temperature revealed that conversion and selectivity remained the same when the temperature was raised from 100 to 120 °C (Table 1, Entry 14). However, upon decreasing the temperature from 80 °C or 60 °C, conversion of iodobenzene also reduced (Table 1, Entries 15 and 16). Thus, the temperature study indicated that 100 °C was optimum for the complete conversion of iodobenzene.

We then aimed to achieve high TON and TOF by reducing the catalyst loading (Table 2). We started the experiment by initially loading 10^{-1} mol% of palladium, which gave a product yield of 97% with TON and TOF of 9.70×10^2 and 1.21×10^2, respectively (Table 2, Entry 1). Although catalyst loading of 10^{-2} mol% and 10^{-3} mol % did not present any significant changes in the product yields, both TON and TOF were amplified to 9.70×10^3 and 9.50×10^4 for the former and 1.21×10^3 and 1.18×10^4 for the latter, respectively (Table 2, Entries 2 and 3). Inspired by this result, we further decreased the catalyst loading to 10^{-4} mol%. Although the yield of product was 45% in this case, the TON increased to 4.50×10^5 (Table 2, Entry 4). With the aim of increasing the yield of product, we performed the reaction with 10^{-4} mol% catalyst loading at 120 °C for 8 hr; however, this reaction yielded only 50% of ketone, with TON and TOF estimated as 5.00×10^5 and 6.25×10^4, respectively (Table 2, Entry 5). Finally, the reactor was charged with 10^{-5} mol% of catalyst, but this gave only 10% yield of the expected product, although the TON was very high (1.00×10^6; Table 2, Entry 6).

TABLE 2 Effect of catalyst loading on the reaction[a]

Entry number	Pd (2) mol%	Yield[b] (%)	TON	TOF (hr^{-1})
1	10^{-1}	97	9.70×10^2	1.21×10^2
2	10^{-2}	97	9.70×10^3	1.21×10^3
3	$\mathbf{10^{-3}}$	**95**	$\mathbf{9.50 \times 10^4}$	$\mathbf{1.18 \times 10^4}$
4	10^{-4}	45	4.50×10^5	5.62×10^4
5[c]	10^{-4}	50	5.00×10^5	6.25×10^4
6	10^{-5}	10	1.00×10^6	1.25×10^5

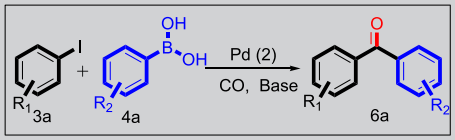
[a]**Optimized palladium loading**: **3** (0.5 mmol), **4** (0.7 mmol), K_2CO_3 (1 mmol), anisole (10 ml), 100 °C, 8 hr, CO (0.3 MPa).

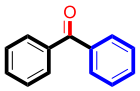
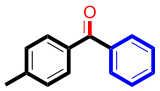
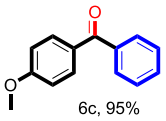
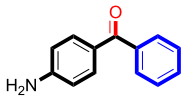
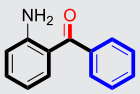
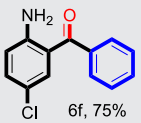
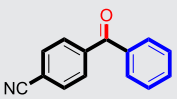
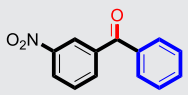
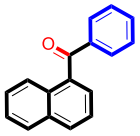
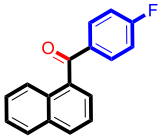
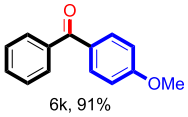
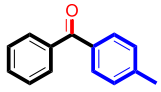
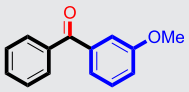
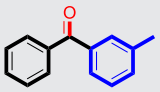
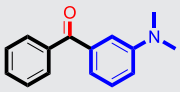
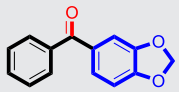
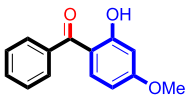
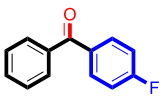
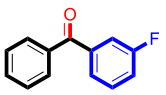
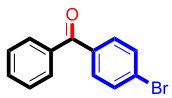
[b]Yield determined by GC and GC-MS.

[c]120 °C.

GC, gas chromatography; MS, mass spectrometry; TOF, turnover frequency; TON, turnover number.

TABLE 3 Scope of the palladium catalyst for the synthesis of biaryl ketone[a]



 6a, 95% TON: 9.50×10^4 TOF: 1.18×10^4	 6b, 93% TON: 9.3×10^4 TOF: 1.16×10^4	 6c, 95% TON: 9.50×10^4 TOF: 1.18×10^4	 6d, 81% TON: 8.10×10^4 TOF: 1.01×10^4
 6e, 78% TON: 7.80×10^4 TOF: 9.7×10^3	 6f, 75% TON: 7.5×10^4 TOF: 9.3×10^3	 6g, 90% TON: 9.00×10^4 TOF: 1.12×10^4	 6h, 80% TON: 8.00×10^4 TOF: 1.00×10^4
 6i, 82% TON: 8.2×10^4 TOF: 1.02×10^4	 6j,85% TON: 8.50×10^4 TOF: 1.06×10^4	 6k, 91% TON: 9.10×10^4 TOF: 1.13×10^4	 6l, 86% TON: 8.60×10^4 TOF: 1.07×10^4
 6m,85% TON: 8.50×10^4 TOF: 1.06×10^4	 6n,84% TON: 8.40×10^4 TOF: 1.05×10^4	 6o,73% TON: 7.30×10^4 TOF: 9.12×10^3	 6p,63% TON: 6.30×10^4 TOF: 7.87×10^3
 6q, 74% TON: 7.40×10^4 TOF: 9.2×10^3	 6r, 70% TON: 7.00×10^4 TOF: 8.7×10^3	 6s, 71% TON: 7.10×10^4 TOF: 8.8×10^3	 6t, 69% TON: 6.90×10^4 TOF: 8.6×10^3

[a]**Reaction condition**: **3a** (0.5 mmol), **4a** (0.7 mmol), catalyst (10^{-3} mol%), K_2CO_3 (1 mmol), anisole (10 ml), 100 °C, 8 hr, CO (0.3 MPa).

GC, gas chromatography; MS, mass spectrometry; TOF, turnover frequency; TON, turnover number.

Under optimized reaction conditions, we next applied the developed protocol for the synthesis of substituted benzophenone by carbonylative coupling of a range of aryl iodides with phenyl boronic acid (Table 3). Overall, the reactions progressed smoothly and tolerated a wide variety of functional groups. Simple iodobenzene and phenyl boronic acid coupled smoothly under the developed protocol and produced excellent yield (95%) of the desired product (**6a**) with TON of 9.50×10^4. The electron-donating substituent bearing aryl iodide was then smoothly converted into the corresponding ketone. Donating groups such as *p*-Me, *p*-OMe, *p*-NH_2, and *o*-NH_2 on iodobenzene were successfully transformed into respective ketones **6b**–**6e** with TON ranging from 9.3×10^4 to 7.8×10^4 and TOF from 1.16×10^3 to 9.7×10^3. Furthermore, disubstituted iodobenzene such as *o*-NH_2 and *p*-Cl were also coupled with phenyl boronic acid to yield ketone **6f** with TON of 7.5×10^4. Next, electron-withdrawing functionalities such as *p*-CN and *m*-NO_2 also produced ketones **6g** and **6h** in good yield with TONs of 9×10^4 and 8×10^4, respectively. Likewise, a fused-ring 1-iodonaphthalene was smoothly reacted with phenyl boronic acid and 4-F-phenyl boronic acid to yield the corresponding ketones **6i** and **6j**, with TONs of 8.2×10^4 and 8.5×10^4, respectively. Next, we explore the current protocol could be work by using substituted phenyl boronic acid. Electron-donating groups such as *p*-OMe, *p*-Me, *m*-OMe, *m*-Me, and *m*-N$(Me)_2$ could be successfully coupled with aryl iodide, which gave corresponding ketones **6k**, **6l**, **6m**, **6n**, and **6o** with high TONs (range 9.10×10^4 to 7.30×10^4) and TOFs

TABLE 4 Comparative study of palladium catalysts **1** and **2** with conventional palladium precursors[a]

Entry number	Pd precursor	Yield	TON[b]	TOF (hr)
1	$Pd(OAc)_2$	21	2.10×10^4	2625
2	$PdCl_2$	13	1.30×10^4	1625
3	$PdCl_2(PPh_3)_2$	18	1.80×10^4	2250
4	Pd **1**	83	8.30×10^4	10,375
5	**Pd 2**	**95**	$\mathbf{9.50 \times 10^4}$	**11,875**

[a]**Reaction condition**: **3** (0.5 mmol), **4** (0.7 mmol), catalyst (10^{-3} mol%), base (1 mmol), anisole (10 ml), 100 °C, 8 hr, CO (0.3 MPa).

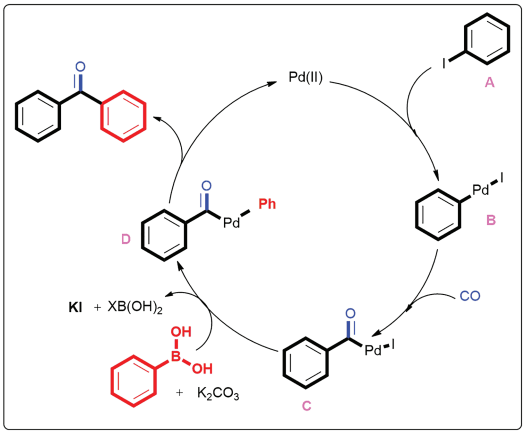
[b]Yield calculated by GC and GC-MS.

GC, gas chromatography; MS, mass spectrometry; TOF, turnover frequency; TON, turnover number.

(range 1.13×10^4 to 9.12×10^3). Further, 3,4-(methylenedioxy)phenylboronic acid was also reacted with aryl iodide to produce ketone **6p** with TON 6.30×10^4. Next, oxybenzone (**6q**) was successfully synthesized, an important molecule in medicinal chemistry, which can be used as a sunscreen agent as it protects the skin from harmful effects of the sun.[57,58] Moreover, halogenated biaryl ketones (**6r–6t**) were synthesized using the aforesaid protocol with yield range of 69%–71% and TONs from 6.9×10^4 to 7.1×10^4.

Furthermore, we tested the efficiency of catalyst **2** for the gram scale-up synthesis of benzophenone. The catalytic activity of catalyst **2** was slightly reduced for gram scale-up to 5 mmol (1.02 g) with 87% benzophenone yield achieved.

Next, we compared various conventional palladium precursors with the present palladium thiolate complexes **1** and **2** with respect to TON and TOF (Table 4). Iodobenzene (**3**) and phenyl boronic acid (**4**) were chosen as reacting substrates for the synthesis of biaryl ketone. In the comparative study, both catalysts **1** and **2** demonstrated superior catalytic activity than conventional palladium precursors. Commercially available Pd precursors such as $Pd(OAc)_2$, $PdCl_2$, and $PdCl_2(PPh_3)_2$ gave very poor yield and generated low TONs (2.10×10^4 to 1.80×10^4; Table 4, Entries 1–3). However, catalyst **2** showed slightly higher activity in comparison to catalyst **1**, which is attributed to the higher stability of the latter. Catalyst **2** comprises both tetranuclear (**II**) and dinuclear (**I**) complexes in solution in almost equal proportions, as demonstrated by ^{31}P-NMR spectra, whereas catalyst **1** only exists as **II**. In a previous work, we have estimated the stability of **II** (−870 kcal/mol), which is −435 kcal/mol higher than that of **I** (−435 kcal/mol), as evaluated by density functional theory calculation.[55] Similarly, the stability of **II** in **1** was found to be −872 kcal/mol. The same trend was also observed in the case of Suzuki–Miyaura C–C coupling



SCHEME 1 Plausible reaction mechanism of palladium thiolate-catalyzed carbonylative Suzuki–Miyaura cross-coupling reaction

reactions.[55] The thermal stability of the catalysts was evaluated by thermogravimetric analysis. The thermogravimetric curves indicated that both catalysts are stable enough in solid state, and the decomposition phase starts after 320 and 305 °C, respectively, for catalyst **1**[55] and **2** (Figures S2 and S3 in electronic supplementary information (ESI)). Overall, the palladium complexes provided an excellent yield of the expected products with TONs of up to 8.30×10^4 to 9.50×10^4 achieved (Table 4, Entries 4 and 5). Based on these results, it can be concluded that catalyst **2** exhibits superior activity in terms of TON and TOF, which are sixfold and fivefold more than conventional palladium precursors, respectively.

The mechanism of carbonylative Suzuki–Miyaura cross-coupling reaction with palladium complexes is shown in Scheme 1. Initially, aryl iodide (A) is subjected to oxidative addition with palladium (0) species to form intermediate B. Then, CO (gas) co-ordinates with palladium to form species C. Next, in the presence of a base (K_2CO_3), phenyl boronic acid undergoes transmetalation with palladium species to give species D. Subsequently, reductive elimination of palladium occurs for the synthesis of benzophenone. The high

TABLE 5 Recycled study of the catalyst[a]

Entry number	Recycle run	Yield[b] (%)
1	Fresh catalyst	95
2	First recycle	93
3	Second recycle	92
4	Third recycle	65

[a]**This catalyst shows better activity than other one**: **3** (0.5 mmol), **4** (0.7 mmol), catalyst (1 mol%), base (1 mmol), anisole (9 ml), water(1 ml), 100 °C, 8 hr, CO (0.3 MPa).

[b]Yield calculated by GC and GC-MS.

GC, gas chromatography; MS, mass spectrometry.

activity of Pd complexes can be attributed to the wide bite angle (110°) and flexible coordination behavior (97°–133°) of xantphos.[59] As the cycle produces the intermediate Ph–Pd–COPh before the production of the benzophenone Ph_2CO, the increase in bite angle (i.e., P–Pd–P) can diminish the Ph–Pd–COPh angle, thus speeding up the reductive elimination process, as observed in C–C coupling reactions.[60]

We next evaluated the recycle ability of the catalyst. For this purpose, we used iodobenzene and phenyl boronic acid as model substrates for the synthesis of benzophenone. Initially, the reactor was charged with the starting materials and catalyst, and then solvent (9 ml) and water (1 ml) were added. The reactor was then pressurized with 0.3 MPa of CO and stirred at 450 rpm for 8 hr. After completion of the reaction, the reactor was cooled down to room temperature and the remaining CO was vented carefully. The reaction mixture was quenched with water and the product was extracted with ethyl acetate. The collected water was then evaporated under vacuum and the product dried in an oven. The dried catalyst was used for next recycle by charging of reactor with starting material. The results showed that up to the second run no significant difference was observed in the yield of benzophenone (Table 5). However, after the third run, the yield of benzophenone drastically reduced to 65%. The residue of the catalyst obtained after the third run was characterized as single-phase Pd_4S by powder X-ray diffraction pattern (Figure S4 in ESI and JCPDS File No. 73-1387), which may explain the decreased yield of benzophenone. It is noteworthy that Pd nanoparticles were observed in the case of Suzuki coupling reactions using the same catalyst.[55] The reaction condition is also responsible for the transformation of Pd complex participating in different catalytic cycles.[61]

4 | CONCLUSION

In conclusion, xantphos-ligated macrocyclic palladium dithiolate complexes were explored for synthesizing biaryl ketone by carbonylation. The catalysts synthesized were a source of highly active Pd species which allowed the reaction to be performed under mild reaction conditions and much lower catalyst loadings in comparison with commercially available palladium sources in organic solvents. Furthermore, the catalyst maintained its catalytic activity up to gram-scale levels with only marginal reduction in the yield of the product. The catalyst synthesized exhibited high TON (1.00×10^6) and TOF (1.25×10^5). Furthermore, the palladium thiolate complexes could tolerate a wide range of substrate scope with the effective electronic factor.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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