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Facile synthesis of NC(sp^3)O pincer palladium complexes and their use as efficient catalysts for Suzuki-Miyaura reaction of aryl bromides in aqueous medium

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ABSTRACT

Two NC(sp^3)O pincer palladium(II) complexes **3a-3b** were readily prepared in high yields in only two steps. Of the first step, catalytic hydrophosphination of 2-alkenoylpyridines and subsequent in situ phosphine oxidation produced the NC(sp^3)O pincer preligands **2a-2b**. The second step is palladation of the preligands **2a-2b** where $PdCl_2$ was used as the Pd source to afford the desired Pd pincers **3a-3b** via C(sp^3)-H bond activation. Single crystal X-ray diffraction analysis of complex **3a** unambiguously confirmed the NCO tridentate coordination mode of the complexes. The two complexes **3a-3b** were applied to catalyze the Suzuki-Miyaura reaction. Complex **3b** was found to be more efficient and exhibited very high activity in the Suzuki reaction of structurally diverse aryl bromides with arylboronic acids in aqueous ethanol under air. At a reaction temperature of 70 °C, a TON of up to 1.9×10^5 and a TOF of up to 9800 h^{-1} were achieved. At lower temperatures **3b** was still very active, giving a TON of up to 9.5×10^3 and a TOF of up to 3900 h^{-1} at room temperature.

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1 Introduction

Palladium(II) pincer complexes with monoanionic tridentate ligands have been extensively investigated and widely used as catalysts in organic transformations [1–13], ever since the independent pioneering works of Moulton and Shaw [14], van Koten and Noltes [15] in the late 1970s. Of particular significance, a broad variety of these complexes have been developed as effective catalysts for the Suzuki-Miyaura (SM) coupling reaction of aryl halides with arylboronic acids, providing a powerful tool for the construction of important biaryl compounds [13]. The first example of pincer Pd complex catalyzed SM coupling appeared in 2000 where Bedford and co-workers demonstrated that aryl-based bis(phosphinite) PCP pincer Pd complex **A** (X = TFA, Fig. 1) exhibited high activity with a turnover number (TON) of up to 1.9×10^5 in the reactions of aryl bromides [16]. This work inspired the subsequent development of many more pincer Pd catalysts (Fig. 1). As a result, besides bis(phosphinite) PCP pincers **A** [16–18] and **B** [19], bis(aminophosphine) PCP pincers [20–22] such as **C**, NCN pincers [23–26] such as bis(pyrazole) **D**, bis(thiazole) **E** and (oxazoline)(pyrazole) **F**, hybrid PCN pincers such as (phosphinite)(pyrazole) **G** [18], (phosphinite)(imine) **H** [27] and (aminophosphine)(pyrazole) **I** [28] as well as (imine)(thiophosphinite) NCS pincers **J** [29] were all successfully applied to the SM reaction. Among the reported pincer Pd catalysts, complex **C** showed extremely high activity with a TON of up to 10^6 and a turnover frequency (TOF) of up to 1.5×10^6 h^{-1} in the couplings of aryl bromides [20]. Furthermore, with a catalyst loading of 0.1 mol% of complex **C**, the coupling of non-activated chlorides such as chlorobenzene proceeded efficiently and afforded the desired coupled product in a reaction time as short as 1.5 h. Complex **B** was also able to accomplish the coupling of non-activated aryl chlorides, albeit with a relatively high catalyst loading (1 mol%) [19]. Importantly, complexes **C** [21], **D** [23], **E** [25] and **I** [28] performed very well when the reactions of aryl bromides were conducted in aqueous medium or in neat water.

In contrast to the wide applications of aryl-based pincer Pd complexes in catalysis such as in Suzuki reaction as described above, researches on the aliphatic pincer Pd complexes with C(sp^3)-Pd bonds are far less common [30–32]. In particular, those on unsymmetrical EC(sp^3)E′ Pd pincers remain scarce. This is partly because the synthesis of these complexes *via* C(sp^3)-H activation has been a considerable challenge. Additionally, unlike aromatic ligands, the appropriate aliphatic pincer preligands are usually difficult to obtain. To the best of our knowledge, there are only two reports on the use of EC(sp^3)E Pd pincers as catalysts for Suzuki reaction (Fig. 2). One is from Olsson and Wendt who

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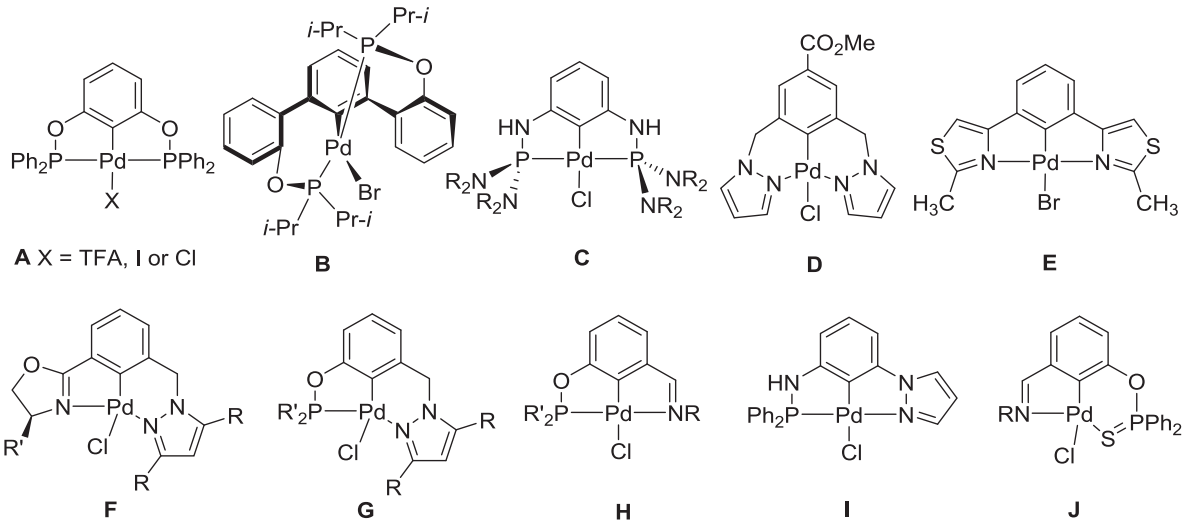


Fig. 1. Selected examples of aryl-based EC(sp^2)E and EC(sp^2)E′ pincer Pd catalysts for the Suzuki-Miyaura reaction.

Fig. 2. Reported aliphatic PC(sp^3)P pincer Pd catalysts for the Suzuki-Miyaura reaction.

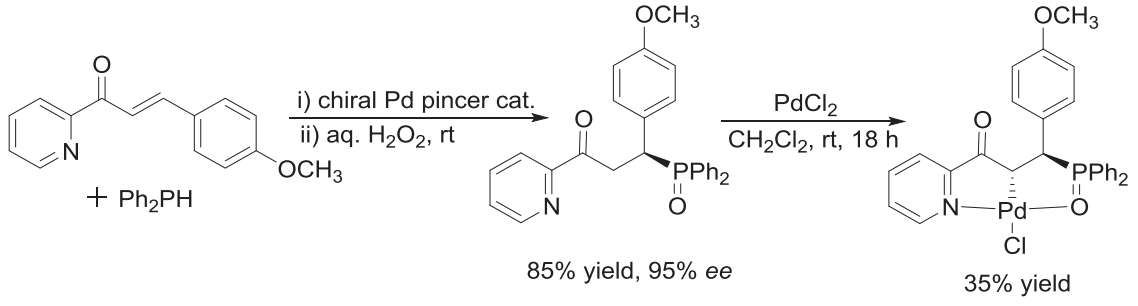
found that with the cyclohexyl-based PC(sp^3)P Pd pincer **K** as the catalyst a temperature as high as 160 °C was needed to achieve acceptable results [33]. The other report is by Frech and co-workers showing an adamantyl-based PC(sp^3)P Pd pincer **L** to be a more efficient catalyst, which worked well under much milder reaction conditions (in water/NaOH or toluene/K_3PO_4 at 100 °C) with a TON of up to 10^4 and a TOF of up to 4×10^4 h^{-1} for the coupling of various aryl bromides [34].

In our previously reported studies, we synthesized a wide variety of achiral and chiral pincer Pd complexes and explored their potentials in Pd-catalyzed organic transformations [18,26,27,35–45]. It was found that the achiral PCP complexes **A** (X = Cl), NCN′ complexes **F** as well as PCN complexes **G** and **H** were all effective catalysts for the Suzuki reaction of both aryl bromides and activated aryl chlorides even at a temperature as low as 40–50 °C [18,26,27,43]. In a more recent study on the chiral PCN pincer Pd catalyzed asymmetric hydrophosphination of 2-alkenoylpyridines, we discovered that phosphine oxide of the catalysis product was able to react with $PdCl_2$ in CH_2Cl_2 at room temperature to give a chiral NC(sp^3)O pincer Pd complex (Scheme 1) [46]. This procedure provides a direct and convenient method for the synthesis of rare and unsymmetrical EC(sp^3)E′ Pd pincers [47–49]. Unfortunately, the yield of the obtained chiral Pd pincer was rather modest. To further expand the chemistry and practical applications of aliphatic sp^3-carbometalated pincer Pd complexes, herein we report the synthesis of achiral NC(sp^3)O pincer Pd complexes **3a-3b** (Scheme 2) by modifying the procedure for the preparation of chiral NC(sp^3)O Pd pincer. The obtained Pd complexes **3** were applied to the Suzuki reaction of aryl bromides with arylboronic acids.

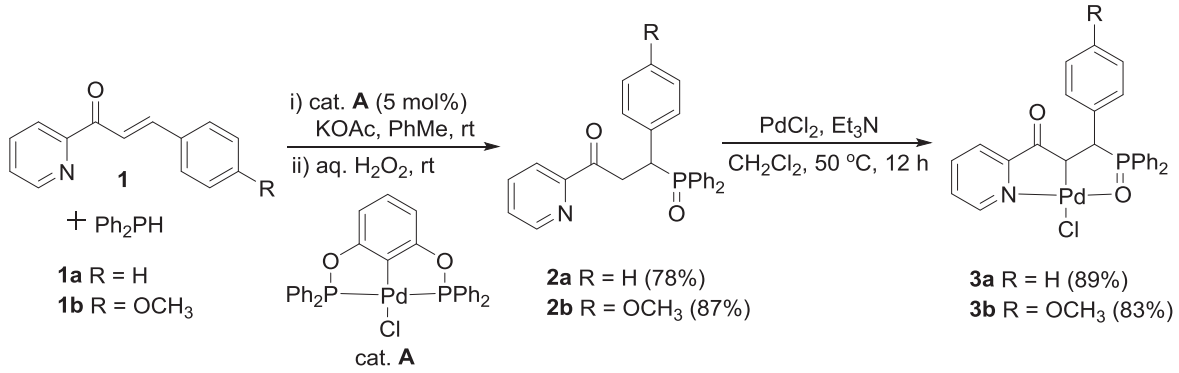
2. Results and discussion

2.1. Synthesis and characterization

As shown in Scheme 2, bis(phosphinite) PCP pincer Pd complex **A** (X = Cl) catalyzed hydrophosphination of 2-alkenoylpyridines **1a-1b** with diphenylphosphine was carried out in toluene at room temperature. Upon completion of the catalytic hydrophosphination, aqueous H_2O_2 was added directly to the reaction mixture to enable in situ phosphine oxidation and the pyridine-functionalized phosphine oxides **2a-2b** were thus obtained in 78 and 87% yields, respectively. Subsequently, the resulting NC(sp^3)O pincer preligands **2** reacted with $PdCl_2$ in the presence of Et_3N in CH_2Cl_2 at 50 °C where the desired C–H palladation of the preligands occurred efficiently to afford the NC(sp^3)O pincer Pd(II) complexes **3a-3b** in 89 and 83% yields, respectively. The overall yields of the two complexes reached ~70%. It is worthy to point out that all the materials and reagents employed in above synthetic procedure are either commercially available or can be easily synthesized. For example,



Scheme 1. Synthesis of a chiral NC(sp^3)O pincer Pd complex.



Scheme 2. Synthesis of achiral NC(sp^3)O pincer Pd complexes.

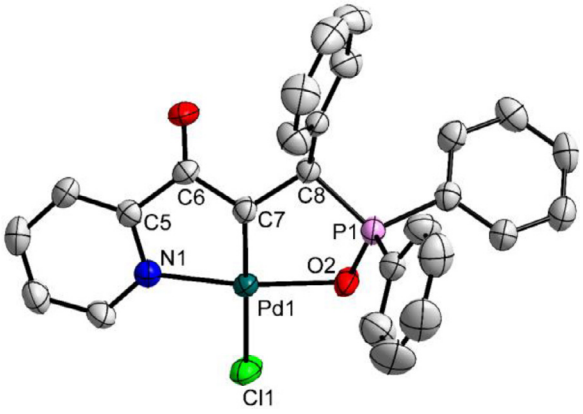


Fig. 3. Molecular structure of complex **3a** with ellipsoids drawn at the 50% probability level (hydrogen atoms are omitted for clarity).

Table 1
Selected bond lengths (Å) and angles (deg) for complex **3a**.

Complex	**3a**
Pd(1)-C(7)	2.030(4)
Pd(1)-N(1)	2.020(4)
Pd(1)-O(2)	2.063(3)
Pd(1)-Cl(1)	2.4034(12)
C(7)-Pd(1)-N(1)	83.52(15)
C(7)-Pd(1)-O(2)	86.39(13)
C(7)-Pd(1)-Cl(1)	177.28(11)
N(1)-Pd(1)-O(2)	169.83(13)
N(1)-Pd(1)-Cl(1)	95.94(10)
O(2)-Pd(1)-Cl(1)	94.09(8)

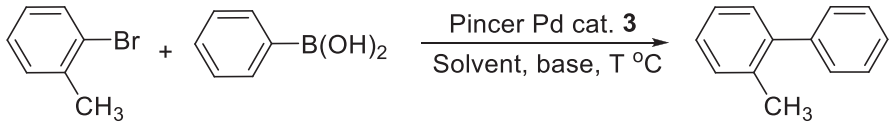
Table 2
Summary of crystal structure determination for complex **3a**.

Complex	**3a**
Formula	$C_{26}H_{21}ClNO_2PPd$
Mr	552.26
temp [K]	291(2)
wavelength [Å]	0.71073
cryst syst	orthorhombic
space group	Pbca
cryst size [mm]	0.2 × 0.16 × 0.16
a [Å]	11.528(3)
b [Å]	17.256(5)
c [Å]	23.198(4)
α [deg]	90.00
β [deg]	90.00
γ [deg]	90.00
V [Å^3]	4615.0(19)
Z	8
Dcalcd [g cm^{-3}]	1.590
μ [mm^{-1}]	1.013
θ range [deg]	2.942 to 26.369
index range	$-14 \le h \le 6$, $-21 \le k \le 13$, $-28 \le l \le 26$
no. of data collected	12,691
no. of unique data	4710
final R indices [I $>2\sigma$(I)]	$R_1 = 0.0427$
	$wR_2 = 0.0922$
R indices [all data]	$R_1 = 0.0629$
	$wR_2 = 0.1047$
F(000)	2224
Largest diff. peak/hole [e Å^{-3}]	1.410/−0.441

the Pd pincer catalyst **A** (X = Cl) for hydrophosphination was conveniently prepared via a one-pot phosphorylation/palladation reaction, that is, by simply mixing resorcinol, Ph_2PCl and $PdCl_2$ in the presence of Et_3N in refluxing toluene [18]. It is also interesting to note that through a pincer Pd complex catalyzed hydrophosphination reaction and the ensuing in situ phosphine oxidation, the pincer preligands **2** were produced in just one step with high efficiency. In the synthesis of pincer Pd complexes that are either sp^2-carbometalated or sp^3-carbometalated, preparation of the required pincer preligands via a catalyzed reaction is not very common. In addition, despite the fact that in the literature $Pd(OAc)_2$, $[PdCl_2(RCN)_2]$ (R = Ph or Me) and $[PdCl_2(COD)]$ are more often used as palladation reagent in the C–H activation step for the construction of Pd pincers, we have shown above that the desired C–H bond even a C(sp^3)-H bond activation can also be readily accomplished by using $PdCl_2$ as the Pd source. Taken together, the synthesis of complexes **3a-3b** is facile, convenient and high-yielding, which provides additional examples of rare and unsymmetrical EC(sp^3)E′ pincer Pd complexes.

The molecular structure of complex **3a** was unambiguously determined by single crystal X-ray diffraction analysis. The molecule is illustrated in Fig. 3. Selected bond lengths and bond angles are listed in Table 1. Details of crystal structure determination for complex **3a** are given in Table 2. Fig. 3 shows clearly that the pyridine-functionalized phosphine oxide **2a** acts as a NC(sp^3)O tridentate ligand when complexed with palladium, leading to the formation of the pincer Pd complex **3a**. The palladium atom features a distorted-square-planar geometry with tridentate coordination of the ligand **2a** via pyridine-N, the sp^3-C adjacent to carbonyl group and the phosphine oxide-O to the Pd(II) center and the chloride occupying the fourth coordination site. The two fused five-membered palladacycles are thus formed in which the two palladacycles both adopt envelope conformation. The Pd-C and Pd-O bond lengths in complex **3a** are 2.030(4) and 2.063(3) Å, respectively, which are slightly shorter than those in the related chiral NC(sp^3)O Pd complex [46]. While the Pd-N and Pd-Cl distances are slightly longer than those in the chiral complex [46]. All of the

Table 3
Suzuki coupling of 2-bromotoluene with phenylboronic acid catalyzed by the NC(sp^3)O pincer Pd(II) complexes **3**[a].



Entry	Cat. (mol%)	Solvent	Base	Temp. (°C)	Time (h)	Yield[b] (%)
1	**3b** (0.1)	EtOH	K_3PO_4	70	12	65
2	**3b** (0.1)	MeOH	K_3PO_4	70	12	56
3	**3b** (0.1)	Toluene	K_3PO_4	110	12	47
4	**3b** (0.1)	DMF	K_3PO_4	110	12	26
5	**3b** (0.1)	EtOH–H_2O[c]	K_3PO_4	70	12	98
6	**3b** (0.01)	EtOH–H_2O[c]	K_3PO_4	70	12	80
7	**3b** (0.01)	EtOH–H_2O[c]	K_3PO_4	70	24	79
8	**3b** (0.01)	EtOH–H_2O[c]	K_2CO_3	70	12	98
9	**3b** (0.01)	EtOH–H_2O[c]	K_2CO_3	70	6	98
10	**3b** (0.01)	EtOH–H_2O[c]	K_2CO_3	70	2	98
11	**3a** (0.01)	EtOH–H_2O[c]	K_2CO_3	70	2	85
12	**3b** (0.001)	EtOH–H_2O[c]	K_2CO_3	70	12	81
13	**3b** (0.001)	EtOH–H_2O[c]	K_2CO_3	70	24	92

[a] Reaction conditions: 2-bromotoluene (0.5 mmol), $PhB(OH)_2$ (0.6 mmol), pincer Pd cat. **3**, base (1.0 mmol), solvent (3.0 mL), under air. [b]Isolated yield. [c]EtOH–H_2O (v/v = 1:1, 3.0 mL).

bond angles around the Pd(II) center are comparable to those in the chiral complex [46] with the C-Pd-Cl and N-Pd-O angles being177.28(11)° and 169.83(13)°, respectively.

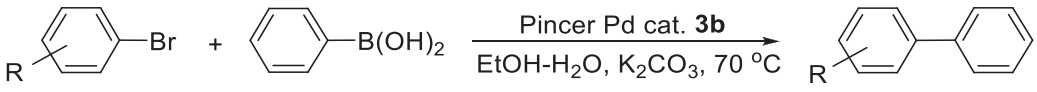
2.2. Catalytic properties of Pd complexes

At the outset the coupling of sterically hindered 2-bromotoluene with phenylboronic acid was chosen as a model to evaluate the catalytic potential of the obtained NC(sp^3)O pincer Pd complexes in the Suzuki reaction (Table 3). The desired coupled product was obtained in 65% yield after 12 h when the reaction was carried out with 0.1 mol% of complex **3b** as the catalyst in the presence of K_3PO_4 base in EtOH under air at 70 °C (entry 1). Changing the solvent from EtOH to MeOH, toluene or DMF (and also elevating the reaction temperature to 110 °C in the latter two solvents) did not afford better results (26–56% yields, entries 2–4). Pleasingly, the use of EtOH–H_2O mixture (1:1) as the solvent gave an excellent yield of 98% (entry 5). We then tried to reduce the loading of complex **3b**. When the catalyst loading was reduced to 0.01 mol%, the yields decreased dramatically to ~80% (entries 6 and 7). However, by replacing K_3PO_4 base with K_2CO_3, excellent yield (98%) was achieved again (entry 8). Furthermore, with K_2CO_3 as the base excellent yields were still obtained in a shorter reaction time such as in a time as short as 2 h (entries 9 and 10). Under the same conditions, complex **3a** showed a lower activity than complex **3b** (85%, entry 11 vs 98% yield, entry 10). Further reducing the catalyst loading of complex **3b** to 0.001 mol% resulted in an obviously decreased yield of 81% (entry 12 vs 8). Fortunately, prolonging the reaction time from 12 h to 24 h provided an excellent yield of 92% at this level of catalyst loading of 0.001 mol% (entry 13).

Based on the above results, the Suzuki coupling reactions of a variety of electronically and structurally diverse aryl bromides with phenylboronic acid were investigated with complex **3b** as the catalyst in the presence of K_2CO_3 base in EtOH–H_2O under air at 70 °C (Table 4). As shown in Table 4, complex **3b** exhibited very high activity with the TON value reached up to 1.9×10^5 and the TOF value up to 9800 h^{-1} in these couplings. With a catalyst loading of 0.01 mol%, both sterically hindered 2-bromotoluene and electronically deactivated 4-bromoanisole reacted smoothly with phenylboronic acid to deliver the desired products in excellent yields after only one hour (entries 1 and 2). When the catalyst loading was decreased to 0.001 mol%, the reactions of electronically deactivated 4–OCH_3- and 3–OCH_3-substituted aryl bromides, the activated 4-NO_2- bromide and the non-activated 4-CH_3- bromide as well as sterically hindered 2-CH_3-substituted aryl bromide all proceeded very well, affording the corresponding products in excellent yields after 24 h (entries 3,4,7,8 and also Table 3, entry 13). By contrast, in the case of 2-bromoanisole, a reactant both electronically deactivated and sterically hindered, a higher catalyst loading than 0.001 mol% was needed to achieve an excellent yield within 24 h (entries 5 and 6). On the other hand, for the 4-CH_3- and 4-CHO- aryl bromides, a catalyst loading as low as 0.0005 mol% was sufficient to ensure highly efficient couplings (entries 9 and 10). In comparison with aryl bromides, heteroaryl bromides were much less reactive. When 3-bromopyridine was subjected to the reaction with a catalyst loading of 0.01 mol%, the expected 3-phenylpyridine was obtained in only 63% yield after 24 h (entry 11).

The above data indicate that pincer Pd complex **3b** is a very efficient catalyst for the Suzuki couplings of aryl bromides with phenylboronic acid at 70 °C. This finding prompted us to investigate how well complex **3b** would perform catalytically at lower reaction temperature such as 50 °C and particularly at room temperature. In the literature the related such reports remain very few [26–28,43] and pincer Pd catalysts often exhibited low activity when the reactions were conducted at lower temperatures. For example, with 1 mol% of complex **B** (Fig. 1) as the catalyst the reaction of 2-bromotoluene with 4-tolylboronic acid in dioxane at 50 °C gave the coupled product in merely 45% yield after 20 h [19]. When 0.01 mol% of aliphatic adamantyl-based PC(sp^3)P Pd pincer **L** (Fig. 2) was used to catalyze the coupling of phenyl bromide with phenylboronic acid in water at 50 °C, 86% conversion into biphenyl could be achieved after 6 h. However, for the same reaction at room temperature only 2% conversion was observed after 6 h [34]. Therefore, development of effective pincer Pd catalysts for the Suzuki-Miyaura reaction at lower temperature is highly desirable. Thus, we conducted the following series of coupling reactions between aryl bromides and arylboronic acids, using complex **3b** as the catalyst at a reaction temperature of 50 °C (Table 5). We were pleased to find that complex **3b** also exhibited high activity at 50 °C with a TON of up to 9.9×10^3 and a TOF of up to 9900 h^{-1}. With a catalyst loading as low as 0.01 mol%, 2–bromo and 4-bromotoluene, 4–bromo, 3–bromo and 2-bromoanisole, 4-bromobenzaldehyde, 4-bromobenzonitrile, 1,3-dibromobenzene were all successfully coupled with phenylboronic acid or substituted phenylboronic acids to deliver the correspond-

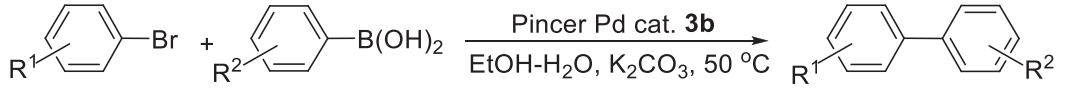
Table 4
Suzuki couplings of aryl bromides with phenylboronic acid at 70 °C catalyzed by the NC(sp^3)O pincer Pd(II) complex **3b**[a].



Entry	Cat. (mol%)	R	Time (h)	Yield[b] (%)	TON[c]	TOF[d] (h^{-1})
1	0.01	2-CH_3	1	95	9500	9500
2	0.01	4–OCH_3	1	98	9800	9800
3	0.001	4–OCH_3	24	99	99,000	4125
4	0.001	3–OCH_3	24	99	99,000	4125
5	0.001	2–OCH_3	24	76	76,000	3167
6	0.005	2–OCH_3	12	95	19,000	1583
7	0.001	4-NO_2	24	99	99,000	4125
8	0.001	4-CH_3	24	98	98,000	4083
9	0.0005	4-CH_3	24	96	192,000	8000
10	0.0005	4-CHO	24	92	184,000	7667
11[e]	0.01	–	24	63	6300	263

[a] Reaction conditions: ArBr (0.5 mmol), $PhB(OH)_2$ (0.6 mmol), pincer Pd cat. **3b**, K_2CO_3 (1.0 mmol), EtOH–H_2O (v/v = 1:1, 3.0 mL), 70 °C, under air. [b]Isolated yield. [c]TON: Turnover number. Defined as moles of product per mole of catalyst. [d]TOF: Turnover frequency. Defined as moles of product per mole of catalyst per hour. [e]3-bromopyridine was used as the substrate.

Table 5
Suzuki couplings of aryl bromides with arylboronic acids at 50 °C catalyzed by the NC(sp^3)O pincer Pd(II) complex **3b**[a].



Entry	R^1	R^2	Time (h)	Yield[b] (%)	TON[c]	TOF[d] (h^{-1})
1	2-CH_3	H	1	94	9400	9400
2	4–OCH_3	H	1	93	9300	9300
3	3–OCH_3	H	1	98	9800	9800
4	2–OCH_3	H	4	95	9500	2375
5	4-CH_3	H	1	99	9900	9900
6	4-CHO	H	1	99	9900	9900
7	4-CN	H	1	99	9900	9900
8[e]	3-Br	H	7	94	9400	1343
9	2-CH_3	4–OCH_3	5	96	9600	1920
10	4-CH_3	4–OCH_3	3	96	9600	3200
11	4-CH_3	2–OCH_3	2	98	9800	4900
12	4–OCH_3	3-Cl	4	98	9800	2450

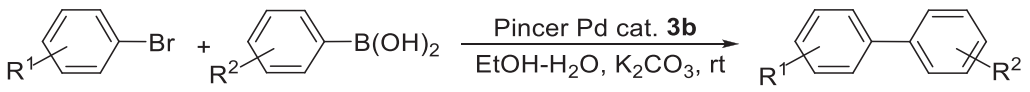
[a] Reaction conditions: ArBr (0.5 mmol), $ArB(OH)_2$ (0.6 mmol), pincer Pd cat. **3b** (0.01 mol%), K_2CO_3 (1.0 mmol), EtOH–H_2O (v/v = 1:1, 3.0 mL), 50 °C, under air. [b]Isolated yield. [c]Defined as moles of product per mole of catalyst. [d]Defined as moles of product per mole of catalyst per hour. [e]1,3-dibromobenzene (0.5 mmol), $PhB(OH)_2$ (1.2 mmol), K_2CO_3 (2.0 mmol).

ing biaryl products in 93–99% yields within several hours. In most cases, excellent yields were achieved after only 1–2 h. Particularly, the reactions of electronically deactivated and/or sterically hindered 2-bromoanisole and 2-bromotoluene also proceeded quite well in a short reaction time (entries 1,4 and 9). Furthermore, for the reactions of 2-bromotoluene and 4-bromoanisole with phenylboronic acid, decreasing the temperature from 70 °C to 50 °C did not result in any appreciable loss of the activity of complex **3b** (Table 4, entries 1 and 2 vs Table 5, entries 1 and 2).

Considering the high activity of complex **3b** at 50 °C, we next explored its performance at room temperature (Table 6). The reaction of 4-bromoanisole with phenylboronic acid was first tested (entries 1 and 2). In the presence of 0.01 mol% complex **3b** as the catalyst, a promising yield of 39% was obtained after 1 h even though the yield was much lower than that at 50 °C (39% vs 93%). By extending the reaction time to 12 h, a good yield of 79% was achieved (entry 2). Under these conditions, reactions of the more reactive 4-bromotoluene and 4-bromobenzaldehyde with phenylboronic acid provided the coupled products in excellent yields as expected (95%, entries 3 and 4). When the catalyst loading was increased to 0.1 mol%, good to excellent yields (86–98%) could be achieved within several hours for the reactions of some representative aryl bromides with arylboronic acids (entries 5–11). Of particular significance is that electronically deactivated and/or sterically hindered 2-bromoanisole and 2-bromotoluene reacted very well with arylboronic acids at room temperature, furnishing the corresponding biaryls in excellent yields (entries 8–11). Overall, complex **3b** was a quite effective catalyst for the Suzuki reaction of aryl bromides with arylboronic acids. Especially, the complex maintained high activity in the room temperature reactions. But unfortunately, employment of complex **3b** as catalyst for the Suzuki reaction of 4-chlorotoluene with phenylboronic acid proved to be unsuccessful. The desired coupled product was obtained in rather low yields (5–17%) with a catalyst loading of 0.1–1.0 mol% (for details see Table S1 in the Supporting Information).

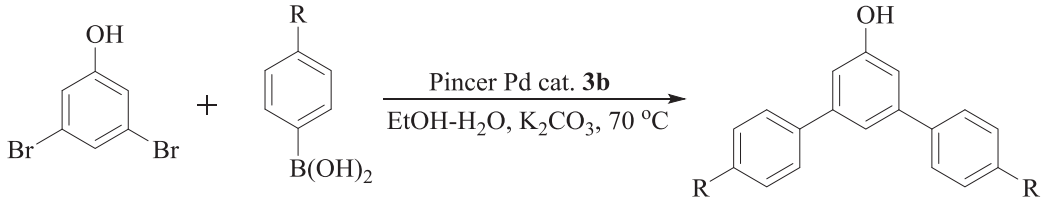
To further explore the practical potential of complex **3b**-catalyzed Suzuki reaction, we conducted the reactions of 3,5-dibromophenol with arylboronic acids catalyzed by **3b** for the synthesis of 3,5-diarylphenols **4a-b**, which are the key precursors to the inhibitors of the luteinizing hormone (LH) receptor [50]. With a catalyst loading of 0.01 mol% the reaction on a 0.5 mmol scale proceeded well, delivering the desired product **4a** in a 92% yield (Scheme 3). However, the yield dropped dramatically to 76% when the same reaction was scaled up to 5 mmol level. Gratifyingly, upon increasing the catalyst loading to 0.05 mol%, the gram-scale syntheses of **4a** and **4b** were successfully accomplished with 98% and 95% yields, respectively (Scheme 3).

Table 6
Suzuki couplings of aryl bromides with arylboronic acids at room temperature catalyzed by the NC(sp^3)O pincer Pd(II) complex **3b**[a].



Entry	Cat. (mol%)	R^1	R^2	Time (h)	Yield[b] (%)	TON[c]	TOF[d] (h^{-1})
1	0.01	4–OCH_3	H	1	39	3900	3900
2	0.01	4–OCH_3	H	12	79	7900	658
3	0.01	4-CH_3	H	12	95	9500	792
4	0.01	4-CHO	H	12	95	9500	792
5	0.1	4–OCH_3	H	3	94	940	313
6	0.1	4-CH_3	H	2.5	96	960	384
7	0.1	4-NO_2	H	6	86	860	143
8	0.1	2-CH_3	H	3	97	970	323
9	0.1	2–OCH_3	H	8	97	970	121
10	0.1	2-CH_3	4–OCH_3	6	90	900	150
11	0.1	2-CH_3	3-Cl	3	98	980	327

[a] Reaction conditions: ArBr (0.5 mmol), $ArB(OH)_2$ (0.6 mmol), pincer Pd cat. **3b**, K_2CO_3 (1.0 mmol), EtOH–H_2O (v/v = 1:1, 3.0 mL), room temperature, under air. [b]Isolated yield. [c]Defined as moles of product per mole of catalyst. [d]Defined as moles of product per mole of catalyst per hour.



4a R = H; **4b** R = OCH_3

Entry	**3b** (mol%)	R	Isolated yield (weight)
1[a]	0.01	H	92% (0.113 g)
2[b]	0.01	H	76% (0.936 g)
3[b]	0.05	H	98% (1.207 g)
4[b]	0.05	OCH_3	95% (1.455 g)

Reaction conditions: [a]3,5-Dibromophenol (0.5 mmol), $PhB(OH)_2$ (1.2 mmol), pincer Pd cat. **3b** (0.01 mol%), K_2CO_3 (2.0 mmol), EtOH-H_2O (v/v = 1:1, 3.0 mL), 70 °C, 12 h, under air. [b]3,5-Dibromophenol (5 mmol), $PhB(OH)_2$ or 4-methoxyphenylboronic acid (12 mmol), pincer Pd cat. **3b**, K_2CO_3 (20 mmol), EtOH-H_2O (v/v = 1:1, 30 mL), 70 °C, 12 h, under air.

Scheme 3. Application of complex **3b** in the synthesis of 3,5-diarylphenols.

In order to gain some insights into the mechanism of the complex **3b**-catalyzed Suzuki reaction, the mercury drop experiments were performed. Specifically, the coupling reaction of 4-bromobenzaldehyde with phenylboronic acid catalyzed by 0.0005 mol% of **3b** was carried out in EtOH–H_2O (1:1) at 70 °C and with addition of one drop of elemental mercury. It turned out that the reaction was almost completely inhibited by the presence of mercury and the desired coupled product was obtained in only 3% yield after 24 h (3% vs 92% in entry 10, Table 4). The result suggested that at 70 °C palladium nanoparticles were probably the catalytically active form of complex **3b** and the reactions likely proceeded via a classical Pd(0)/Pd(II) catalytic cycle consisting of oxidative addition, transmetalation and reductive elimination steps. For the pincer Pd(II)-catalyzed Suzuki reaction, it was reported that in many cases pincer Pd(II) complexes acted as precursors for the release of palladium nanoparticles as the active catalytic species [19,21,29]. On the other hand, the addition of one drop of mercury to the room temperature reaction of 4-bromoanisole with phenylboronic acid catalyzed by 0.1 mol% of **3b** led to some decrease in the yield but did not inhibit the reaction (81% vs 94% in entry 5, Table 6). The result indicated that the room temperature reactions likely occurred through a mechanism different from that of the reactions at 70 °C.

2.3. Conclusions

In summary, we have synthesized two NC(sp^3)O pincer palladium(II) complexes in a facile, convenient and high-yielding fashion. Complex **3b** was found to be a highly efficient catalyst for the Suzuki reaction of aryl bromides with arylboronic acids in aqueous ethanol under air. In particular, this complex still exhibited high activity even at room temperature, which is rare for the Pd pincer catalysts suggested for this reaction. Mercury drop experiments indicate that palladium nanoparticles may be the actual catalytic species for reactions at 70 °C while for reactions at room temperature other catalytically active form of complex **3b** is responsible for the high activity.

3. Experimental

3.1. General

Solvents were dried with standard methods and freshly distilled prior to usage if needed. 2-alkenoylpyridines **1a**-**1b** [51] and Pd pincer catalyst **A** (X = Cl) [18] were prepared according to the literature methods. All other chemicals were used as purchased. Melting points were measured on a WC-1 microscopic apparatus and were uncorrected. ^{1}H NMR, ^{13}C{^{1}H} NMR and ^{31}P{^{1}H} NMR spectra were recorded on a Bruker DPX-400 spectrometer in $CDCl_3$ with TMS as an internal standard for ^{1}H, ^{13}C{^{1}H} NMR and 85% H_3PO_4 as the external standard for ^{31}P{^{1}H} NMR.

3.2. Synthesis of the NC(sp^3)O pincer Pd complexes *3a-3b*

In a 10 mL Schlenk tube a mixture of PCP pincer Pd catalyst **A** (12.4 mg, 5 mol%) and KOAc (3.9 mg, 10 mol%) in toluene (4 mL) was stirred at room temperature for 0.5 h under Ar atmosphere. Upon addition of diphenylphosphine (74.5 mg, 0.4 mmol), the mixture was stirred for additional 0.5 h. Subsequently, 2-alkenoylpyridine **1** (0.6 mmol) was added and the resulting mixture was stirred at room temperature for 12 h. Then, H_2O_2 aqueous solution (30%, 120 μL) was added to oxidize the catalysis product. Once being stirred at room temperature for 2 h, the reaction mixture was purified directly by chromatography on silica gel plates with CH_2Cl_2/acetone (5/1 or 10/1) as eluent to afford the pyridine-functionalized phosphine oxides **2**.

To a stirred solution of **2** (0.5 mmol) in CH_2Cl_2 (4 mL) was added Et_3N (84 μL, 0.6 mmol) and $PdCl_2$ (106.4 mg, 0.6 mmol, 1.2 equiv) under Ar atmosphere. After being stirred at 50 °C for 12 h, the reaction mixture was filtered through Celite. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel with CH_2Cl_2/acetone (5/1) as eluent to give the NC(sp^3)O pincer Pd(II) complexes **3**.

Complex **3a**: pale yellow solids, M.p. 208–209 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.08 (d, J_{HH} = 5.3 Hz, 1H), 7.96–7.83 (m, 3H), 7.64–7.52 (m, 7H), 7.46–7.40 (m, 3H), 7.21–7.15 (m, 3H), 6.99–6.97 (m, 2H), 5.20 (dd, J_{HH} = 9.6 Hz, J_{HP} = 4.1 Hz, 1H, PCHC*H*), 4.92 (dd, J_{HH} = 9.6 Hz, J_{HP} = 16.4 Hz, 1H, PC*H*CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.8 (d, J_{CP} = 13.2 Hz), 157.4, 151.5, 139.4, 133.70, 133.65 (d, J_{CP} = 2.5 Hz), 133.2 (d, J_{CP} = 2.6 Hz), 132.9 (d, J_{CP} = 8.9 Hz), 131.8 (d, J_{CP} = 10.0 Hz), 129.0 (d, J_{CP} = 12.0 Hz), 128.9 (d, J_{CP} = 98.0 Hz), 128.7 (d, J_{CP} = 5.3 Hz), 128.6 (d, J_{CP} = 2.3 Hz), 128.4 (d, J_{CP} = 11.8 Hz), 127.8 (d, J_{CP} = 3.1 Hz), 127.2, 125.0 (d, J_{CP} = 94.1 Hz), 122.6, 56.0, 48.6 (d, J_{CP} = 72.0 Hz). ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 73.5. Anal. Calcd for $C_{26}H_{21}ClNO_2PPd{\cdot}H_2O$: C, 54.76; H, 4.07; N, 2.46. Found: C, 54.29; H, 4.43; N, 2.15.

Complex **3b** [46]: pale yellow solids, M.p. 173–174 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.09 (d, J_{HH} = 5.4 Hz, 1H), 7.95–7.91 (m, 1H), 7.85–7.80 (m, 2H), 7.64–7.58 (m, 5H), 7.55–7.50 (m, 2H), 7.46–7.43 (m, 3H), 6.87 (dd, J = 8.6 and 1.9 Hz, 2H), 6.70 (d, J_{HH} = 8.6 Hz, 2H), 5.14 (dd, J_{HH} = 10.0 Hz, J_{HP} = 4.0 Hz, 1H, PCHC*H*), 4.87 (dd, J_{HH} = 10.0 Hz, J_{HP} = 16.8 Hz, 1H, PC*H*CH), 3.75 (s, 3H).

3.3. General procedure for Suzuki-Miyaura cross-coupling reactions

A 10 mL Schlenk tube was charged with complex **3b**, ArBr (0.5 mmol), $ArB(OH)_2$ (0.6 mmol), K_2CO_3 (138.2 mg, 1.0 mmol), and solvent (3 mL). The mixture was stirred at specified temperature under air for a certain time (monitored by TLC). Upon completion of the reaction, the mixture was let to cool down (for the reaction being conducted at room temperature this cooling step was unnecessary) and quenched with saturated brine, and then extracted with ethyl acetate (EtOAc) and dried over Na_2SO_4. After filtration and evaporation of the solvent, the resulting residue was purified by column chromatography on silica gel with EtOAc-petroleum ether as the eluent to give the biaryl products. All the products are known compounds and identified by ^{1}H NMR spectroscopy.

3.4. X-ray diffraction studies

Crystals of **3a** (CCDC 1999573) were obtained by recrystallization from acetone/*n*-hexane at ambient temperature. The data were collected on an Oxford diffraction Gemini E diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). The structure was solved by direct methods using the SHELXS-97 program, and all non-hydrogen atoms were refined anisotropically on F^2 by the full-matrix least-squares technique, using the SHELXL-97 crystallographic software package [52]. The hydrogen atoms were included but not refined.

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.2020.121645.

References

[1] M. Albrecht, G. van Koten, Angew. Chem. Int. Ed. 40 (2001) 3750–3781.
[2] M.E. van der Boom, D. Milstein, Chem. Rev. 103 (2003) 1759–1792.
[3] J.T. Singleton, Tetrahedron 59 (2003) 1837–1857.
[4] R.B. Bedford, Chem. Commun. (2003) 1787–1796.
[5] E. Peris, R.H. Crabtree, Coord. Chem. Rev. 248 (2004) 2239–2246.
[6] D. Pugh, A.A. Danopoulos, Coord. Chem. Rev. 251 (2007) 610–641.
[7] D. Morales-Morales, Mini-Rev. Org. Chem. 5 (2008) 141–152.
[8] J.M. Serrano-Becerra, D. Morales-Morales, Curr. Org. Synth 6 (2009) 169–192.
[9] I. Moreno, R. SanMartin, B. Inés, M.T. Herrero, E. Domínguez, Curr. Org. Chem 13 (2009) 878–895.
[10] N. Selander, K.J. Szabó, Dalton Trans. (2009) 6267–6279.
[11] N. Selander, K.J. Szabó, Chem. Rev. 111 (2011) 2048–2076.
[12] H. Valdés, M.A. García-Eleno, D. Canseco-Gonzalez, D. Morales-Morales, ChemCatChem 10 (2018) 3136–3172.
[13] L. González-Sebastián, D. Morales-Morales, J. Organomet. Chem. 893 (2019) 39–51.
[14] C.J. Moulton, B.L. Shaw, J. Chem. Soc., Dalton Trans. (1976) 1020–1024.
[15] G. van Koten, K. Timmer, J.G. Noltes, A.L. Spek, J. Chem. Soc., Chem. Comun. (1978) 250–252.
[16] R.B. Bedford, S.M. Draper, P.N. Scully, S.L. Welch, New J. Chem 24 (2000) 745–747.
[17] T. Kimura, Y. Uozumi, Organometallics 25 (2006) 4883–4887.
[18] J.-F. Gong, Y.-H. Zhang, M.-P. Song, C. Xu, Organometallics 26 (2007) 6487–6492.
[19] M.C. Lipke, R.A. Woloszynek, L. Ma, J.D. Protasiewicz, Organometallics 28 (2009) 188–196.
[20] J.L. Bolliger, O. Blacque, C.M. Frech, Angew. Chem. Int. Ed. 46 (2007) 6514–6517.
[21] J.L. Bolliger, C.M. Frech, Adv. Synth. Catal 352 (2010) 1075–1080.
[22] D. Benito-Garagorri, V. Bocokić, K. Mereiter, K. Kirchner, Organometallics 25 (2006) 3817–3823.
[23] F. Churruca, R. SanMartin, I. Tellitu, E. Domínguez, Synlett (2005) 3116–3120.
[24] T. Takemoto, S. Iwasa, H. Hamada, K. Shibatomi, M. Kameyama, Y. Motoyama, H. Nishiyama, Tetrahedron Lett. 48 (2007) 3397–3401.
[25] Q.-L. Luo, J.-P. Tan, Z.-F. Li, W.-H. Nan, D.-R. Xiao, J. Org. Chem. 77 (2012) 8332–8337.
[26] X.-Q. Hao, Y.-N. Wang, J.-R. Liu, K.-L. Wang, J.-F. Gong, M.-P. Song, J. Organomet. Chem. 695 (2010) 82–89.
[27] B.-S. Zhang, C. Wang, J.-F. Gong, M.-P. Song, J. Organomet. Chem. 694 (2009) 2555–2561.

[28] B. Inés, R. SanMartin, F. Churruca, E. Domínguez, M.K. Urtiaga, M.I. Arriortua, Organometallics 27 (2008) 2833–2839.
[29] V.A. Kozlov, D.V. Aleksanyan, Y.V. Nelyubina, K.A. Lyssenko, A.A. Vasil'ev, P.V. Petrovskii, I.L. Odinets, Organometallics 29 (2010) 2054–2062.
[30] D. Gelman, R. Romm, Top. Organomet. Chem. 40 (2013) 289–318.
[31] K.J. Jonasson, O.F. Wendt, Chapter 8, 213-227, in: K.J. Szabó, O.F. Wendt (Eds.), Pincer and Pincer-Type Complexes: Applications in Organic Synthesis and Catalysis, Wiley-VCH, Weinheim, 2014.
[32] G.C. Dickmu, I.P. Smoliakova, Coord. Chem. Rev. 409 (2020) 213203.
[33] D. Olsson, O.F. Wendt, J. Organomet. Chem. 694 (2009) 3112–3115.
[34] R. Gerber, O. Blacque, C.M. Frech, ChemCatChem 1 (2009) 393–400.
[35] B.-S. Zhang, W. Wang, D.-D. Shao, X.-Q. Hao, J.-F. Gong, M.-P. Song, Organometallics 29 (2010) 2579–2587.
[36] J.-L. Niu, Q.-T. Chen, X.-Q. Hao, Q.-X. Zhao, J.-F. Gong, M.-P. Song, Organometallics 29 (2010) 2148–2156.
[37] A.-T. Hou, Y.-J. Liu, X.-Q. Hao, J.-F. Gong, M.-P. Song, J. Organomet. Chem. 696 (2011) 2857–2862.
[38] T. Wang, X.-Q. Hao, X.-X. Zhang, J.-F. Gong, M.-P. Song, Dalton Trans. 40 (2011) 8964–8976.
[39] M.-J. Yang, Y.-J. Liu, J.-F. Gong, M.-P. Song, Organometallics 30 (2011) 3793–3803.
[40] T. Wang, X.-Q. Hao, J.-J. Huang, K. Wang, J.-F. Gong, M.-P. Song, Organometallics 33 (2014) 194–205.
[41] X.-Q. Hao, Y.-W. Zhao, J.-J. Yang, J.-L. Niu, J.-F. Gong, M.-P. Song, Organometallics 33 (2014) 1801–1811.
[42] C. Wang, Y. Li, B. Lu, X.-Q. Hao, J.-F. Gong, M.-P. Song, Polyhedron 143 (2018) 184–192.
[43] J.-L. Niu, X.-Q. Hao, J.-F. Gong, M.-P. Song, Dalton Trans. 40 (2011) 5135–5150.
[44] X.-Q. Hao, J.-L. Niu, X.-M. Zhao, J.-F. Gong, M.-P. Song, Chin. J. Org. Chem. 33 (2013) 663–674.
[45] J.-K. Liu, J.-F. Gong, M.-P. Song, Org. Biomol. Chem. 17 (2019) 6069–6098.
[46] X.-Q. Hao, J.-J. Huang, T. Wang, J. Lv, J.-F. Gong, M.-P. Song, J. Org. Chem. 79 (2014) 9512–9530.
[47] X.-Y. Yang, W.S. Tay, Y. Li, S.A. Pullarkat, P.-H. Leung, Chem. Commun. 52 (2016) 4211–4214.
[48] W.S. Tay, X.-Y. Yang, Y. Li, S.A. Pullarkat, P.-H. Leung, RSC Adv 6 (2016) 75951–75959.
[49] L.B. Balázs, W.S. Tay, Y. Li, S.A. Pullarkat, P.-H. Leung, Organometallics 37 (2018) 2272–2285.
[50] L.H. Heitman, R. Narlawar, H. de Vries, M.N. Willemsen, D. Wolfram, J. Brussee, A.P. IJzerman, J. Med. Chem. 52 (2009) 2036–2042.
[51] P.K. Singh, V.K. Singh, Org. Lett. 10 (2008) 4121–4124.
[52] (a) G.M. Sheldrick, SHELXS-97, Program for Crystal Structure Solution, University of Göttingen, Göttingen, Germany, 1997; (b) G.M. Sheldrick, SHELXL-97, Program for Crystal Structure Refinement, University of Göttingen, Göttingen, Germany, 1997.