

# Preparation of monodentate phosphinite ligands: their applications in palladium catalyzed Suzuki reactions

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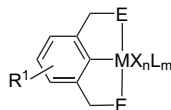
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**Abstract**—Two phosphinites 2,6-OMe, 4-Me, 1-OPR<sub>2</sub>C<sub>6</sub>H<sub>2</sub> (**5a**: R=Ph; **5b**: R=<sup>t</sup>Bu) were prepared in good yields. Two methoxy groups are placed on the 2,6 positions of the phosphinites deliberately thereby to avoid a plausible orthometallation process while coordinating toward palladium metal. Further reaction of **5a** with PdCl<sub>2</sub> in the ratio of 2:1 and 1:1 gave **5a** ligated palladium complexes {(**5a**)PdCl(μ-Cl)}<sub>2</sub> **7a** and {(**5a**)<sub>2</sub>PdCl<sub>2</sub>} **8a**, respectively. As revealed from their crystal structures, the former is a dimeric complex with anticipated molecular arrangement; nevertheless, the latter is a monomeric complex with unexpected, energetically unfavorable cis form. By contrast, only dimeric form was observed from the reaction of **5b** with PdCl<sub>2</sub>. It is believed that the bulky substituents, <sup>t</sup>Bu, on **5b** prevent the formation of a monomeric complex in cis form. Fair to good efficiencies were observed for the Suzuki–Miyaura cross-coupling reactions employed in situ-prepared **5**/Pd(OAc)<sub>2</sub> as the catalytic precursor.

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## 1. Introduction

Ligand-assisted palladium complexes catalyzed cross-coupling reactions are probably the most studied means of making the C–C bond in modern synthetic chemistry.<sup>1</sup> Among all the ligands, trialkyl- or triarylphosphines and their derivatives are almost certainly the most employed ligands in the Suzuki–Miyaura reaction.<sup>2</sup> As known, a phosphine with both the characters of bulkiness and electron-richness not only accelerates the rate of oxidative addition of arylhalide to Pd(0)L<sub>n</sub> (L: phosphine; n=1–2), but also speeds up the process of the reductive elimination of diaryl from Pd(II) center.<sup>3,4</sup> Numerous synthetic methods have been explored in search of more versatile and efficient organic phosphines for the phosphine/palladium catalyzed Suzuki–Miyaura cross-coupling reactions.<sup>4a</sup> Basically, five categories of ligands are the most commonly used: (a) bis(diphenylphosphino)alkyl; (b) trialkylphosphine; (c) aryl-dialkylphosphine; (d) palladacycle; and (e) *N*-heterocyclic carbene.<sup>5</sup> Recently, an extended version of palladacycles, the so called pincers (with a η<sup>3</sup>-E,C,E-coordination mode), had attracted much attention because of their diversities in bonding with metals.<sup>6</sup> In addition, the Pd–C (*ipso*, arene) bonding is considered stronger in pincer chelated palladium complex than in the conventional palladacycle.



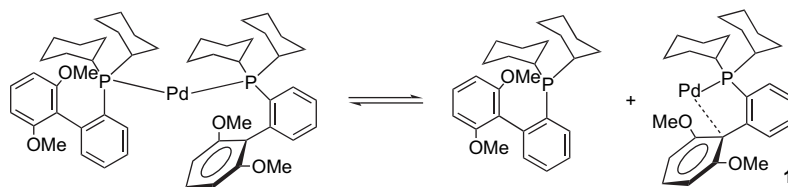
**Keywords:** Phosphinite; Palladium complex; Suzuki cross-coupling reaction; Orthometallation; Dimeric; Monomeric.

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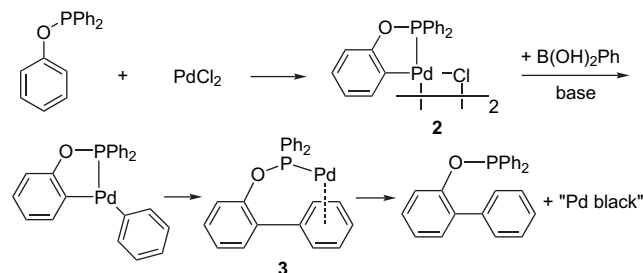
In spite of extensive studies on the reaction mechanism of the palladium/phosphine catalyzed Suzuki–Miyaura cross-coupling reactions,<sup>7</sup> there are several unambiguous points remains to be answered. For instance, the composition of the active species is normally difficult to identify by experimental means. It is speculated that the active species must be a rather unsaturated palladium complex with few coordinated ligand(s). Buchwald proposed a weak interaction between palladium and its aryl-dialkylphosphine ligand, Pd–C (*ipso*, arene), in **1** (Scheme 1).<sup>5c</sup> Compound **1** is a low-coordinated palladium(0) complex and is proposed to be responsible for the catalytic performance.

Bedford also reported a low-coordinated palladium(0) in a phosphinite assisted palladium catalyzed Suzuki reaction (Scheme 2)<sup>8</sup> in which, an orthometallation process took place and resulted in the formation of **2** when the phosphinite, C<sub>6</sub>H<sub>5</sub>OPPh<sub>2</sub>, complexed to PdCl<sub>2</sub>. It might be further reduced to Pd(0) complex **3** by the attack of organoboronic acid, PhB(OH)<sub>3</sub>, in Suzuki reaction in basic medium.<sup>8a</sup> This low-coordinated complex **3** is regarded as the catalytically active species.<sup>5f,9</sup>

The orthometallation process took place along with the formation of a relatively strong Pd(II)–C(sp<sup>2</sup>) bond in **2**. The resulted strong Pd–C bond might retard the reduction process in the formation of **3** and eventually levels down the catalytic performance. However, this unwanted orthometallation process could be prevented by placing inert substituents on both the 2 and 6-positions of the phosphinite. By doing that, there will be a good chance for forming low-coordinated Pd(0) species. At the same time, it would



Scheme 1.



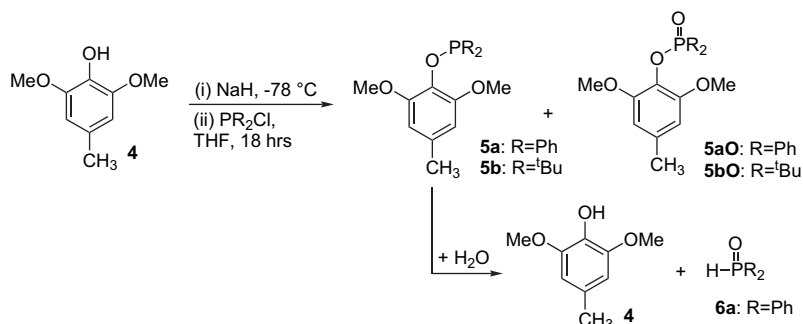
Scheme 2.

be likely to have more space for palladium active center to accommodate the upcoming reactants. Thereby, the activation energy of the oxidative addition process, the first step of Suzuki reaction, and frequently the rate determine step, might be reduced and eventually leads to the enhancement of the reaction rate. In this study, the preparation of substituted phosphinites and their applications in a phosphinite modified palladium catalyzed Suzuki cross-coupling reactions are presented.

## 2. Results and discussion

### 2.1. Preparation of phosphinite ligands **5a** and **5b**

Two phosphinites 2,6-OMe, 4-Me, 1-OPR<sub>2</sub>C<sub>6</sub>H<sub>2</sub> (**5a**: R=Ph; **5b**: R=<sup>t</sup>Bu) were prepared in good yields, accompanied with small quantities of their oxidized products 2,6-OMe, 4-Me, 1-OP(=O)R<sub>2</sub>C<sub>6</sub>H<sub>2</sub> (**5aO**: R=Ph; **5bO**: R=<sup>t</sup>Bu) according to procedures modified from the literature (Scheme 3).<sup>8a</sup> In the presence of moisture, **5a** will undergo hydrolysis rapidly and convert to **4** plus a secondary phosphine oxide HP(=O)Ph<sub>2</sub>, **6a**. By contrast, **5b** is relatively inert toward moisture. Interestingly, Trzeciak reported a quite different observation from hydrolysis based on the crystal structures of the products.<sup>10</sup>



Scheme 3.

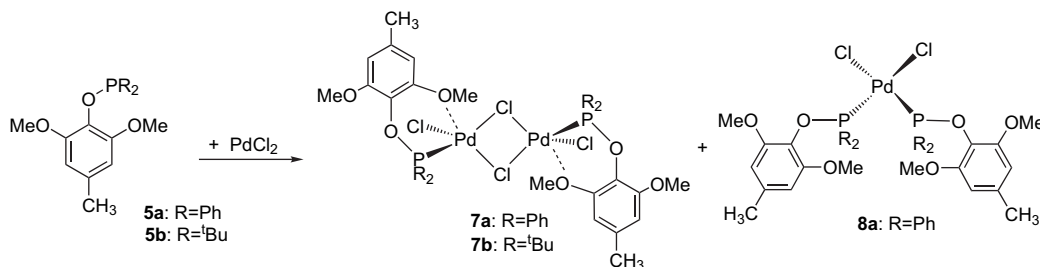
### 2.2. Complexation of **5** with PdCl<sub>2</sub>

New palladium dimeric complexes {(L)PdCl(μ-Cl)}<sub>2</sub> (**7a**: L=**5a**; **7b**: L=**5b**) were obtained from the treatment of **5** with 1 M equiv of PdCl<sub>2</sub>(COD) in CH<sub>2</sub>Cl<sub>2</sub> at 25 °C for 2 h (Scheme 4). A palladium monomeric compound, {(5a)<sub>2</sub>PdCl<sub>2</sub>} **8a**, was obtained from the reaction of **5a** with PdCl<sub>2</sub>(COD) in 2:1 ratio. Compounds **7a**, **7b**, and **8a** were characterized by spectroscopic means such as <sup>1</sup>H and <sup>31</sup>P NMR. Their crystal structures were determined by X-ray diffraction methods (Table 1).

The ORTEP diagrams for **7a**, **7b**, and **8a** are depicted in Figures 1–3, respectively. As shown, the frameworks of **7a** and **7b** are not much different. It is a doubly chloride-bridged palladium dimer. The core atoms of the molecule, Pd<sub>2</sub>Cl<sub>2</sub>, are arranged in a diamond shape and almost coplanar. Interestingly, the terminal chloride atoms are slightly off the plane. In addition, weak interactions between the palladium metal centers and the oxygen atoms of the methoxy groups were observed for **7a** and **7b**. The distance is 3.159 Å in **7a**. It is even shorter, 2.958 Å, in **7b**. The desired weak interaction between Pd and C (*ipso*, arene) did not take place.<sup>5c</sup> The distance, 3.387 Å, is even longer in **7a**. Interestingly, the crystal structure of **8a** reveals that it is a monomeric complex with unexpected, energetically unfavorable *cis* form. There are one CH<sub>2</sub>Cl<sub>2</sub> and one H<sub>2</sub>O molecule in each of the unit cell. There was no **8a** matching **8b** being observed in the reaction. It is probably due to the bulky substituents on **5b**, which prevent the formation of a monomeric complex in *cis* form.

### 2.3. Application of **5** in palladium catalyzed Suzuki reactions

As known, the performance of a palladium catalyzed carbon–carbon cross-coupling reaction is governed by a number of factors such as: palladium source, ligand, base, solvent, temperature, etc.<sup>11</sup> Furthermore, the ratio of ligand to



Scheme 4.

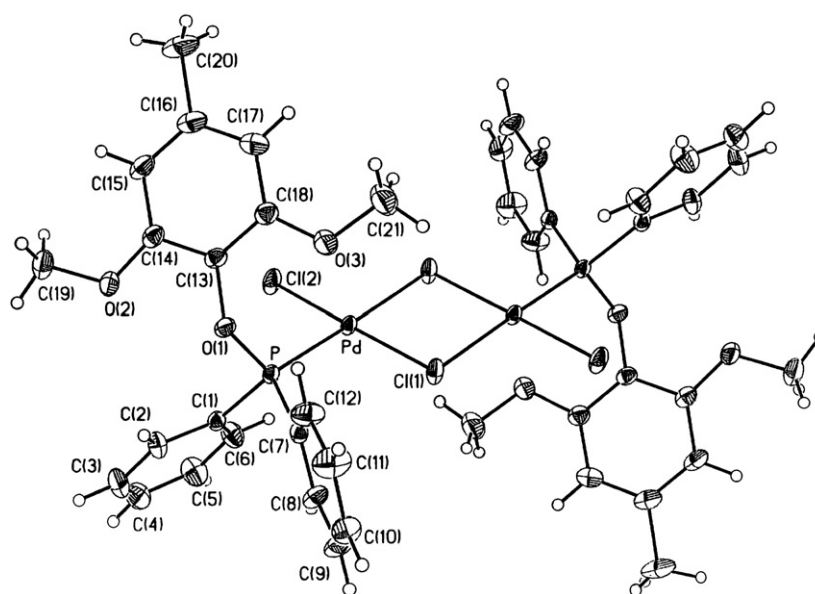
Table 1. Crystal data of **7a**, **7b**, and **8a**

Compound	<b>7a</b>	<b>7b</b>	<b>8a</b>
Formula	$\text{C}_{42}\text{H}_{42}\text{Cl}_4\text{O}_6\text{P}_2\text{Pd}_2 \cdot 2\text{CH}_2\text{Cl}_2$	$\text{C}_{34}\text{H}_{58}\text{Cl}_4\text{O}_6\text{P}_2\text{Pd}_2$	$\text{C}_{42}\text{H}_{42}\text{Cl}_2\text{O}_6\text{P}_2\text{Pd}$
Formula weight	1059.38	979.42	880.05
Crystal system	Triclinic	Monoclinic	Triclinic
Space group	<i>P</i> -1	<i>P</i> 2(1) <i>n</i>	<i>P</i> -1
<i>a</i> (Å)	9.5228(11)	13.4762(12)	11.4033(7)
<i>b</i> (Å)	10.2909(12)	8.7370(8)	14.7079(8)
<i>c</i> (Å)	13.9013(16)	17.7437(16)	16.0201(9)
$\alpha$ (°)	73.342(2)	—	65.4400(10)
$\beta$ (°)	82.599(2)	90.729(2)	74.4980(10)
$\gamma$ (°)	87.824(2)	—	71.4150(10)
<i>V</i> (Å <sup>3</sup> )	1294.3(3)	2089.0(3)	2287.8(2)
<i>Z</i>	1	4	2
<i>D<sub>c</sub></i> (Mg/m <sup>3</sup> )	1.577	1.557	1.387
$\lambda$ (Mo K $\alpha$ ), Å	0.71073	0.71073	0.71073
$\mu$ (mm <sup>-1</sup> )	1.213	1.233	0.730
$\theta$ range, °	2.07–26.03	1.89–26.00	1.91–26.02
Observed reflections ( <i>F</i> >4 $\sigma$ ( <i>F</i> ))	4983	4092	8891
No. of refined parameters	298	217	532
<i>R</i> <sub>1</sub> for significant reflections <sup>a</sup>	0.0445	0.0262	0.0377
<i>wR</i> <sub>2</sub> for significant reflections <sup>b</sup>	0.1231	0.0919	0.1014
<i>GoF</i> <sup>c</sup>	1.108	1.088	0.961

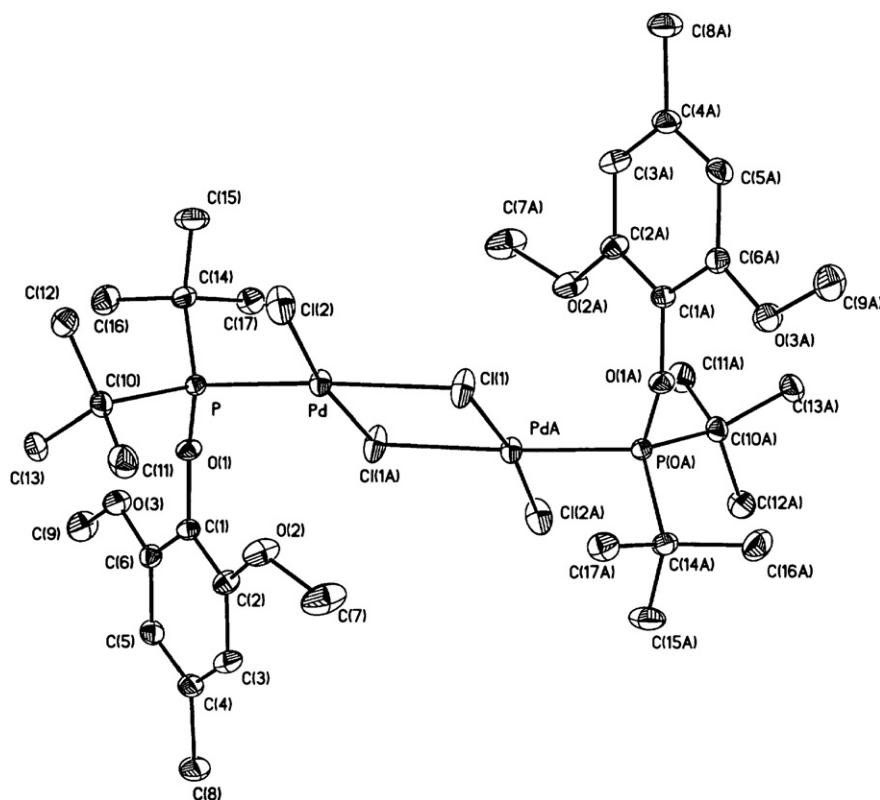
<sup>a</sup>  $R_1 = \frac{\sum (|F_o| - |F_c|)}{\sum F_o}$ .

<sup>b</sup>  $wR_2 = \left\{ \frac{\sum [w(F_o^2 - F_c^2)^2]}{\sum [w(F_o^2)^2]} \right\}^{1/2}$ ; *w*=0.0900, 0.0750, and 0.0750 for **7a**, **7b**, and **8a**, respectively.

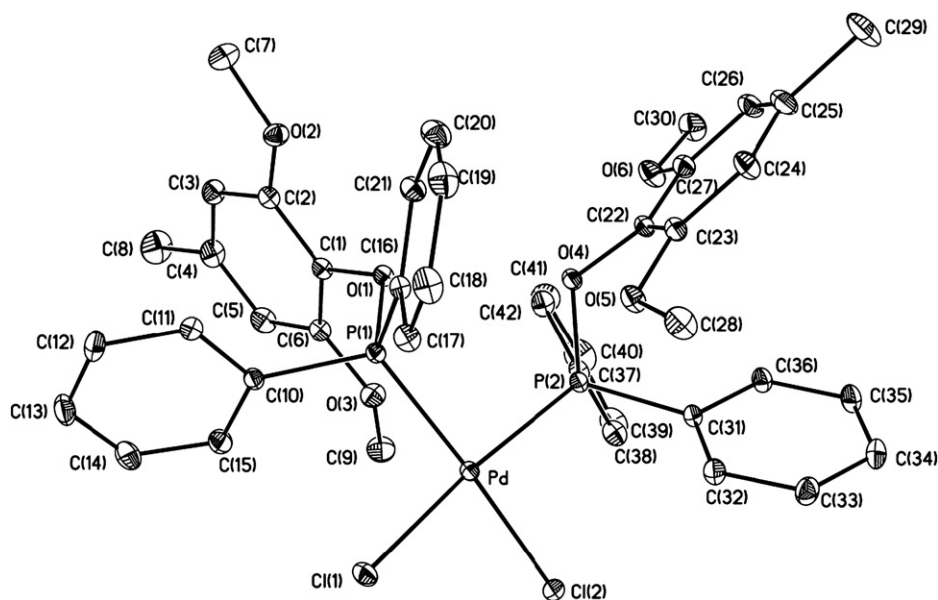
<sup>c</sup>  $GoF = \left[ \frac{\sum w(F_o^2 - F_c^2)^2}{N_{\text{reflms}} - N_{\text{params}}} \right]^{1/2}$ .



**Figure 1.** ORTEP drawing of **7a**. Selected bond lengths (Å) and angles (°): Pd–P 2.2066(8); Pd–Cl(2) 2.2696(9); Pd–Cl(1) 2.3311(9); P–O(1) 1.606(2); P–C(1) 1.803(3); P–C(7) 1.807(3); O(1)–C(13) 1.400(4); O(2)–C(14) 1.349(5); O(2)–C(19) 1.433(5); O(3)–C(18) 1.370(5); O(3)–C(21) 1.426(6); C(16)–C(20) 1.532(6); P–Pd–Cl(2) 87.63(3); P–Pd–Cl(1) 95.07(3); Cl(2)–Pd–Cl(1) 177.02(3); O(1)–P–C(1) 106.03(15); O(1)–P–C(7) 99.19(15); C(1)–P–C(7) 104.33(15); O(1)–P–Pd 115.87(9); C(1)–P–Pd 114.93(11); C(7)–P–Pd 114.70(11); C(13)–O(1)–P 128.1(2); C(14)–O(2)–C(19) 118.1(3); C(18)–O(3)–C(21) 117.8(4).

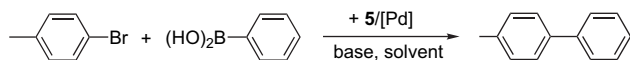


**Figure 2.** ORTEP drawing of **7b**. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (°): C(1)–O(1)–P 136.68(14); C(10)–P–Pd 119.05(8); C(14)–P–C(10) 112.90(10); C(14)–P–Pd 108.57(8); Cl(1A)–Pd–Cl(1) 84.40(2); Cl(2)–Pd–Cl(1) 89.37(2); Cl(2)–Pd–Cl(1A) 171.25(3); O(1)–C(1) 1.387(2); O(1)–P–C(10) 104.95(9); O(1)–P–C(14) 97.33(9); O(1)–P–Pd 111.86(6); P–C(10) 1.886(2); P–C(14) 1.868(2); Pd(A)–Cl(1)–Pd 95.60(2); Pd–Cl(1) 2.4293(6); Pd–Cl(1A) 2.3470(6); Pd–Cl(2) 2.2756(6); Pd–P 2.2270(5); P–O(1) 1.6115(14); P–Pd–Cl(1) 176.96(2); P–Pd–Cl(1A) 93.858(19); P–Pd–Cl(2) 92.63(2).



**Figure 3.** ORTEP drawing of **8a**. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (°): Pd–P(2) 2.2422(8); Pd–P(1) 2.2433(8); Pd–Cl(1) 2.3516(8); Pd–Cl(2) 2.3585(9); P(1)–O(1) 1.635(2); P(1)–C(16) 1.798(3); P(1)–C(10) 1.817(3); P(2)–O(4) 1.630(2); P(2)–C(31) 1.812(3); O(1)–C(1) 1.399(3); O(2)–C(2) 1.366(4); O(2)–C(7) 1.423(5); O(3)–C(6) 1.353(4); O(3)–C(9) 1.433(4); O(4)–C(22) 1.389(3); O(5)–C(23) 1.361(4); O(5)–C(28) 1.442(4); O(6)–C(27) 1.371(4); O(6)–C(30) 1.411(4); P(2)–Pd–P(1) 93.54(3); P(2)–Pd–Cl(1) 169.29(3); P(1)–Pd–Cl(1) 89.75(3); P(2)–Pd–Cl(2) 86.74(3); P(1)–Pd–Cl(2) 171.17(3); Cl(1)–Pd–Cl(2) 91.57(3); O(1)–P(1)–C(16) 102.11(13); O(1)–P(1)–C(10) 103.33(13); C(16)–P(1)–C(10) 105.86(14); O(1)–P(1)–Pd 113.81(8); C(16)–P(1)–Pd 113.86(10); C(10)–P(1)–Pd 116.35(11); O(4)–P(2)–C(37) 104.58(14); O(4)–P(2)–C(31) 103.48(13); C(37)–P(2)–C(31) 105.60(15); O(4)–P(2)–Pd 112.07(8); C(37)–P(2)–Pd 115.09(11); C(31)–P(2)–Pd 114.84(11); C(1)–O(1)–P(1) 122.08(19).

palladium is also crucial since various bonding modes are possible from different types of ligands. Here, Suzuki coupling reactions were carried out in situ by employing the newly made phosphinite ligands **5a** and **5b** modified palladium complexes (Scheme 5). The general procedures for the catalytic reactions under investigation are described as follows. A suitable Schlenk tube was charged with 1.0 mmol of bromotoluene, 1.5 mmol of phenylboronic acid, 3.0 ml solvent, 3.0 M equiv of base, and various ratios of **5**/[Pd] ([Pd]: palladium source). The reaction mixture was stirred at 60 °C for 30 min to 2 h then followed by a work-up.



Scheme 5.

Suzuki–Miyaura reactions of 4-bromotoluene and phenylboronic acid employing **5a** with various Pd sources in  $K_3PO_4/1,4$ -dioxane system were carried out at 60 °C for 0.5 h (Table 2). As shown, the best yield was obtained while **5a**/Pd(OAc)<sub>2</sub>=2:1 (entry 2). The catalytic performance is always better for systems fixed in this ratio even with different palladium sources (entry 2 vs 1; 4 vs 3). It indicates that **8a**, rather than **7a**, is the active catalytic precursor. Interestingly, almost no reaction was observed for using Pd(acac)<sub>2</sub> as the palladium source (entry 5). The inertness of Pd(acac)<sub>2</sub> toward coupling reaction might be caused by its strong chelating ligands, acac<sup>-</sup>.

As known, a well-chosen base is essential for the success of the coupling reaction.<sup>12</sup> Subsequently, the impact of the base used on the reaction was examined (Table 3). Among all the bases used,  $K_3PO_4$  was found to be the most effective while the reaction was run in toluene (entry 3). The other bases such as CsF, Cs<sub>2</sub>CO<sub>3</sub>, KOH, and NaOH are less effective (entries 4, 5, 7, and 8). The bases, KF, K<sub>2</sub>CO<sub>3</sub>, CsOH, and NaO<sup>t</sup>Bu, were failed to promote the reaction and gave very low conversions (entries 1, 2, 6, and 9).

The effects of solvents used in the coupling reaction were evaluated as well (Table 4). The best yield was observed using 1,4-dioxane as the solvent (entry 2). Although their polarities are close, 9.8 for 1,4-dioxane and 9.1 for THF, the catalytic performances are quite different (entry 1 vs 2). Water is not an adequate solvent here probably caused by its poor solubility and the hydrolysis problem of the

**Table 2.** Suzuki coupling reactions in various palladium source and ratio of **5a**/[Pd]<sup>a</sup>

Entry	Palladium source	<b>5a</b> /[Pd]	NMR conv. <sup>b</sup> (%)
1	Pd(OAc) <sub>2</sub>	1:1	53.0
2	Pd(OAc) <sub>2</sub>	2:1	94.1
3	Pd <sub>2</sub> (dba) <sub>3</sub>	1:1	57.2
4	Pd <sub>2</sub> (dba) <sub>3</sub>	2:1	90.2
5	Pd(acac) <sub>2</sub>	2:1	N.R.
6	PdCl <sub>2</sub> (CH <sub>3</sub> CN) <sub>2</sub>	2:1	87.6
7	PdCl <sub>2</sub> (η <sup>3</sup> -C <sub>3</sub> H <sub>5</sub> )	1:1	21.5
8	PdCl <sub>2</sub> (η <sup>3</sup> -C <sub>3</sub> H <sub>5</sub> )	2:1	22.2
9	PdCl <sub>2</sub> (cod)	2:1	86.7

<sup>a</sup> Reaction conditions: 1.0 mmol 4-bromotoluene, 1.5 mmol phenylboronic acid, 3.0 mmol  $K_3PO_4$ , 3 ml 1,4-dioxane, 60 °C, 0.5 h, 2 mol % **5a**, 1 mol % [Pd].

<sup>b</sup> Average of two runs. Isolated yield.

**Table 3.** Suzuki coupling reactions employing **5a**/Pd(OAc)<sub>2</sub> in various bases<sup>a</sup>

Entry	Base	NMR conv. <sup>b</sup> (%)
1	KF	32.6
2	K <sub>2</sub> CO <sub>3</sub>	33.7
3	$K_3PO_4$	94.1
4	CsF	85.5
5	Cs <sub>2</sub> CO <sub>3</sub>	70.1
6	CsOH	7.7
7	NaOH	66.9
8	KOH	72.1
9	NaO <sup>t</sup> Bu	20.6

<sup>a</sup> Reaction conditions are the same as in the footnote of Table 2 except the sources of bases.

<sup>b</sup> Average of two runs. Isolated yield.

**Table 4.** Suzuki coupling reactions employing **5a**/Pd(OAc)<sub>2</sub> in various solvent and reaction conditions<sup>a</sup>

Entry	Solvent	Time	Temp (°C)	NMR conv. <sup>b</sup> (%)
1	THF	0.5	60	61.2
2	1,4-Dioxane	0.5	60	94.1
3	CH <sub>3</sub> CN	0.5	60	31.6
4	MeOH	0.5	60	86.9
5	H <sub>2</sub> O	0.5	60	34.8
6	1,4-Dioxane	12.0	25	42.9

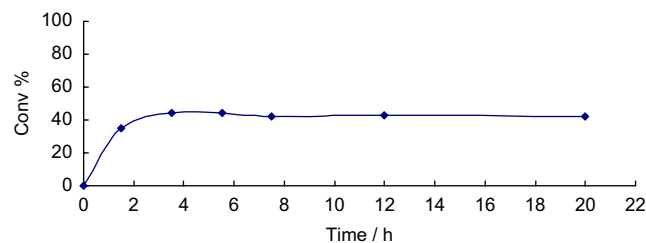
<sup>a</sup> Reaction conditions: 1.0 mmol 4-bromotoluene, 1.5 mmol phenylboronic acid, 3.0 mmol  $K_3PO_4$ , 3 ml solvent, 2 mol % **5a**, 1 mol % Pd(OAc)<sub>2</sub>.

<sup>b</sup> Average of two runs. Isolated yield.

ligand (entry 5). Low temperature has a devastating effect on the catalytic performance even though long reaction was used (entry 6). A time-dependent conversion of Suzuki reaction in 1,4-dioxane under low temperature was monitored (Fig. 4). As shown, the conversion reaches its peak at around 2.5 h. Then, it remains almost the same for the rest of reaction.

For comparison, similar Suzuki–Miyaura reactions of 4-bromotoluene and phenylboronic acid employing **5b** with various Pd sources were carried out in  $K_3PO_4$ /THF system at 60 °C for 0.5 h (Table 5). Contrast to the previous cases using **5a**, better result was observed for the case where **5b**/Pd(OAc)<sub>2</sub> equals 1:1 rather than 2:1 (entry 1 vs 2). It implies that **7b** is the active catalytic precursor. This is consistent with the observation that **8a**, counterpart of **8b**, is absent in the preparation. The overall catalytic activities shown in Table 5 are less efficient than those in Table 2. The low efficiencies are probably due to the choice of inappropriate solvent.

The following table lists the results from the **5b**/Pd(OAc)<sub>2</sub> catalyzed Suzuki reactions using various bases. Again,  $K_3PO_4$  was found to be the most effective base used (Table



**Figure 4.** The ratio of conversion of starting material versus reaction time in Suzuki reaction. Reaction condition is shown in Table 4.



**Table 5.** Suzuki coupling reactions in various palladium sources and ratio of **5b**/[Pd]<sup>a</sup>

Entry	Palladium sources	<b>5b</b> /[Pd]	NMR conv. <sup>b</sup> (%)
1	Pd(OAc) <sub>2</sub>	1:1	79.5
2	Pd(OAc) <sub>2</sub>	2:1	42.6
3	Pd <sub>2</sub> (dba) <sub>3</sub>	1:1	27.4
4	Pd <sub>2</sub> (dba) <sub>3</sub>	2:1	26.9
5	Pd(acac) <sub>2</sub>	1:1	26.3
6	PdCl <sub>2</sub> (CH <sub>3</sub> CN) <sub>2</sub>	1:1	34.7
7	[PdCl <sub>2</sub> (η <sup>3</sup> -C <sub>3</sub> H <sub>5</sub> ) <sub>2</sub> ]	2:1	11.7
8	[PdCl <sub>2</sub> (η <sup>3</sup> -C <sub>3</sub> H <sub>5</sub> ) <sub>2</sub> ]	1:1	12.2
9	PdCl <sub>2</sub> (cod)	1:1	39.0

<sup>a</sup> Reaction conditions are the same as in the footnote of Table 2 except the sources of palladium complexes and the **5b**/[Pd] ratio.

<sup>b</sup> Average of two runs. Isolated yield.

6, entry 1). The conversion reaches 90% within 40 min using K<sub>3</sub>PO<sub>4</sub> as base (entries 10–12). KOH also showed excellent efficiency (entry 6).

Table 7 lists the results from the Suzuki reactions using various solvents. Similar to the **5a** cases, the best yield was observed using 1,4-dioxane as the solvent (entry 2). The catalytic performance is better for the case using 1,4-dioxane than THF (entry 1 vs 2). Although water is still not an appropriate solvent here, it shows better result than that in **5a** case (entry 5). The fact that **5b** is less subjected to hydrolysis than **5a** is attributed to its two hydrophobic substituents, <sup>t</sup>Bu. Low temperature hinders the catalytic performance, nevertheless, a long reaction hours can compensate it (entries 6–7).

By comparing the catalytic efficiencies of both ligands, **5a** and **5b**, it is quite obvious that the latter one performs better.

**Table 6.** Suzuki coupling reactions employing **5b**/Pd(OAc)<sub>2</sub> in various bases<sup>a</sup>

Entry	Base	Time (h)	NMR conv. (%)
1	K <sub>3</sub> PO <sub>4</sub>	2	>99
2	CsF	2	26.4
3	Cs <sub>2</sub> CO <sub>3</sub>	2	15.6
4	CsOH	2	35.4
5	NaOH	2	32.9
6	KOH	2	96.1
7	NaO <sup>t</sup> Bu	2	30.0
8	KO <sup>t</sup> Bu	2	36.1
9	K <sub>3</sub> PO <sub>4</sub>	0.25	60.7
10	K <sub>3</sub> PO <sub>4</sub>	0.5	79.5
11	K <sub>3</sub> PO <sub>4</sub>	0.75	90.1
12	K <sub>3</sub> PO <sub>4</sub>	1	>99

<sup>a</sup> Reaction conditions: 1.0 mmol 4-bromotoluene, 1.5 mmol phenylboronic acid, 3.0 mmol base, 3 ml THF, 1 mol % **5b**, 1 mol % Pd(OAc)<sub>2</sub>, 60 °C.

**Table 7.** Suzuki coupling reactions employing **5b**/Pd(OAc)<sub>2</sub> in various solvents and reaction conditions<sup>a</sup>

Entry	Solvent	Time (h)	Temp (°C)	NMR conv. <sup>b</sup> (%)
1	THF	0.5	60	79.5
2	1,4-Dioxane	0.5	60	91.4
3	CH <sub>3</sub> CN	0.5	60	21.3
4	MeOH	0.5	60	60.5
5	H <sub>2</sub> O	0.5	60	43.9
6	1,4-Dioxane	1.0	rt	9.8
7	1,4-Dioxane	12.0	rt	93.4

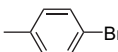

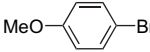
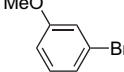

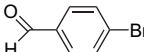
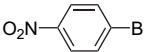
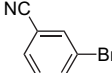


<sup>a</sup> Reaction conditions: 1.0 mmol 4-bromotoluene, 1.5 mmol phenylboronic acid, 3 mmol K<sub>3</sub>PO<sub>4</sub>, 3 ml THF, 1 mol % **5b**, 1 mol % Pd(OAc)<sub>2</sub>.

<sup>b</sup> Average of two runs. Isolated yield.

The following table shows the results from the **5b**-assisted Suzuki cross-coupling reactions with substituted arylbromides (Table 8). The catalytic performance was good for the substrate with electron-withdrawing group (entries 6, 7, and 8). Nevertheless, the efficiencies were only slightly lower for the substrates with electron-donating groups (entries 3, 4, and 5). As expected, catalytic efficiency was lower for case where the substrate bearing substituent with severe steric hindrance (entry 2). It was excellent for thiophene derivative (entry 9). Probably because of its potential coordinating capacity of the nitrogen site, catalytic efficiency is rather low for 2-bromopyridine (entry 10). It is consistent with the general observation for the palladium catalyzed Suzuki reaction.

The catalytic performance is greatly enhanced by increasing the reaction temperature and the amount of **5b**, from 1.0 to 2.5 mol %, involved (Table 9). These integrated conditions were put to use in the reaction of less active arylhalides such as arylchlorides (Table 10). Almost quantitative conversion was observed for *p*-chlorotoluene (entry 1). Good conversion was observed for *o*-chlorotoluene, even though a severe steric hindrance is anticipated (entry 2). In contrast to the case of 2-bromothiophene in Table 8, unexpected low conversion was observed for 2-chlorothiophene (entry 4). As the reaction time was prolonged, some dark spots of ‘palladium black’ was found on the wall of round flask.

**Table 8.** Reactions of various arylbromides employing **5b**/Pd(OAc)<sub>2</sub><sup>a</sup>

Entry	Substrate	Yield <sup>b</sup> (%)
1		98
2		94
3		95
4		96
5		96
6		>99
7		>99
8		99
9		>99
10		49

<sup>a</sup> Reaction conditions are the same as in the footnote of Table 5 except the sources of substrates and the reaction time, 50 min.

<sup>b</sup> Isolated yield based upon an average of two runs.

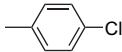
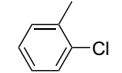
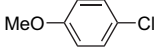

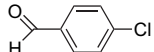
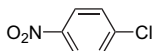
**Table 9.** Suzuki coupling reactions employing **5b**/Pd(OAc)<sub>2</sub> in various reaction conditions<sup>a</sup>

Entry	mol %	Temp (°C)	Time (h)	NMR conv. <sup>b</sup> (%)
1	2.5	60	15	63.1
2	1.0	80	16	44.8
3	2.5	80	17	97.5

<sup>a</sup> Reaction conditions: 1.0 mmol 4-chlorotoluene, 1.5 mmol phenylboronic acid, 3.0 mmol K<sub>3</sub>PO<sub>4</sub>, 3 ml 1,4-dioxane.

<sup>b</sup> Isolated yield based upon an average of two runs.

**Table 10.** Reactions of various aryl chloride employing **5b**/Pd(OAc)<sub>2</sub><sup>a</sup>

Entry	Substrate	Time (h)	Yield <sup>b</sup> (%)
1		17	98
2		17	91
3		17	66
4		17	16
5		6	91
6		6	85

<sup>a</sup> Reaction conditions: 1.0 mmol aryl chloride, 1.5 mmol phenylboronic acid, 3.0 mmol K<sub>3</sub>PO<sub>4</sub>, 3 ml 1,4-dioxane, 2.5 mol % **5b**, 2.5 mol % Pd(OAc)<sub>2</sub>, 80 °C.

<sup>b</sup> Isolated yield based upon an average of two runs.

### 3. Summary

We have demonstrated that two phosphinites 2,6-OMe, 4-Me, 1-OPR<sub>2</sub>C<sub>6</sub>H<sub>2</sub> (**5a**: R=Ph; **5b**: R=<sup>t</sup>Bu) might be prepared in good yields and be employed as effective ligands in Suzuki–Miyaura cross-coupling reactions. The best results come with the ratio of **5a**/Pd(OAc)<sub>2</sub> equals 2:1; it is 1:1 for **5b**/Pd(OAc)<sub>2</sub>. Both monomeric and dimeric forms of **5a** ligated palladium complexes {(**5a**)PdCl(μ-Cl)}<sub>2</sub> **7a** and {(**5a**)<sub>2</sub>PdCl<sub>2</sub>} **8a** were obtained from the reaction. In contrast, only dimeric form of {(**5b**)PdCl(μ-Cl)}<sub>2</sub> **7b** was observed. It is believed that the steric effect caused by the bulky <sup>t</sup>Bu group plays a critical role here in preventing the formation of a monomeric complex in cis form.

## 4. Experimental

### 4.1. General information

All manipulations were carried out under a dry nitrogen atmosphere. Solvents including deuterated solvents were purified before use. Most of the separations were performed by Centrifugal Thin Layer Chromatography (CTLC, Chromatotron, Harrison model 8924). The <sup>1</sup>H and <sup>31</sup>P NMR spectra were recorded on a Varian-400 spectrometer at 400.44 and 162.10 MHz, respectively; <sup>13</sup>C NMR spectra were recorded on a Varian VXR-300S spectrometer at 75.43 MHz. Chemical shifts are reported in parts per million relative to the residual proton signals of deuterated CHCl<sub>3</sub> or CH<sub>2</sub>Cl<sub>2</sub>. Mass

spectra were recorded on a JOEL JMS-SX/SX 102A GC/MS/MS spectrometer. Elemental analyses were obtained on a Heraeus CHN-O-S-Rapid instrument.

### 4.2. Synthesis of **5a**

A 125 cm<sup>3</sup> round-bottomed flask was charged with 2,6-dimethoxy-4-methyl-phenol (5.00 mmol, 0.841 g) and 5 ml toluene. It was stirred for a few minutes before adding 1.0 ml of NEt<sub>3</sub>. Another flask was charged with PPh<sub>2</sub>Cl (5.00 mmol, 1.103 g) and 5 ml toluene. The resulted solution was then transferred slowly to the former flask. The mixed solution was stirred at 90 °C for 18 h. Subsequently, the salt out HNET<sub>3</sub>Cl was filtered and the resulted solution was dried under reduced pressure. An oily, pale yellow solid was obtained and was identified as the title compound, 2,6-OMe, 4-Me, 1-OPPh<sub>2</sub>C<sub>6</sub>H<sub>2</sub> **5a**. The yield of **5a** is 92% (4.6 mmol, 1.621 g).

Compound **5a**: <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ/ppm): 2.28 (s, 3H), 3.63 (s, 6H), 6.37 (s, 2H), 7.35–7.37 (m, 6H), 7.63 (m, 4H); <sup>31</sup>P NMR (CDCl<sub>3</sub>, δ/ppm): 124.7 ppm; <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>, δ/ppm): 21.6 (s, C, CH<sub>3</sub>), 56.4 (s, 2C, OCH<sub>3</sub>), 106.4 (s, 2C, CH), 130.9 (s, C, COP), 128.1–129.2 (m, 12C, arene), 133.5 (s, C, CCH<sub>3</sub>), 152.3 (s, 2C, COCH<sub>3</sub>). Elemental analysis for C<sub>21</sub>H<sub>21</sub>O<sub>3</sub>P: Anal. Calcd: C, 71.58; H, 6.01. Found: C, 70.84; H, 6.51.

### 4.3. Synthesis of **5b**

A 125 cm<sup>3</sup> round-bottomed flask was charged with 2,6-dimethoxy-4-methyl-phenol (5.00 mmol, 0.841 g) and NaH (5.00 mmol, 0.120 g) in 5 ml THF. The mixture was allowed to stir at 0 °C for 1 h. Another flask contained a solution of P(<sup>t</sup>Bu)<sub>2</sub>Cl (5.00 mmol, 0.903 g) dissolved in 5 ml THF. It was then transferred slowly to the former flask. The mixed solution was stirred at 60 °C for 30 h. Subsequently, the salt out HNET<sub>3</sub>Cl was filtered and the resulted solution was dried under vacuo. A pale yellow solid was obtained and was identified as the title compound, 2,6-OMe, 4-Me, 1-OP(<sup>t</sup>Bu)<sub>2</sub>C<sub>6</sub>H<sub>2</sub> **5b**. The yield of **5b** is 95% (4.75 mmol, 1.483 g).

Compound **5b**: <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ/ppm): 1.18 (d, 18H, J<sub>P-H</sub>=11.2 Hz), 2.25 (s, 3H), 3.76 (s, 6H), 6.33 (s, 2H); <sup>31</sup>P NMR (CDCl<sub>3</sub>, δ/ppm): 171.8 ppm; <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>, δ/ppm): 21.5 (s, C, CH<sub>3</sub>), 27.6 (d, 6C, CH<sub>3</sub>, J<sub>P-C</sub>=15.6 Hz), 36.15 (d, 2C, CCH<sub>3</sub>, J<sub>P-C</sub>=30.2 Hz), 55.9 (s, 2C, OCH<sub>3</sub>), 107.0 (s, 2C, CH), 131.9 (s, C, CCH<sub>3</sub>), 151.7 (s, 2C, COCH<sub>3</sub>). Elemental analysis for C<sub>17</sub>H<sub>29</sub>O<sub>3</sub>P: Anal. Calcd: C, 65.36; H, 9.36; O, 15.37. Found: C, 64.95; H, 9.83; O, 15.37.

### 4.4. Synthesis of **7a** and **7b**

The two reactants, Pd(COD)Cl<sub>2</sub> (0.40 mmol, 0.114 g) and 0.40 mmol of **5** (**5a**: 0.141 g; **5b**: 0.125 g) with 10 ml CH<sub>2</sub>Cl<sub>2</sub> were placed in a 100 ml round-bottomed flask charged with magnetic stirrer. The solution was stirred at 25 °C for 2 h before the solvent was removed in reduced pressure. The residue was washed with 10 ml hexanes first and dried again. An orange colored solid was obtained and identified as **7a**; meanwhile, **7a** is a red colored solid. The

yields of **7a** and **7b** are 95% (0.201 g, 0.19 mmol) and 53.5% (0.104 g, 0.11 mmol), respectively. Both crystals of **7a** and **7b** were grown from a hexanes/CH<sub>2</sub>Cl<sub>2</sub>=1:1 mixed solvent in 4 °C environment.

Compound **7a**: <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ/ppm): 2.29 (s, 3H), 3.79 (s, 6H), 6.37 (s, 2H), 7.40–7.49 (m, 6H), 7.84–7.89 (m, 4H); <sup>31</sup>P NMR (CDCl<sub>3</sub>, δ/ppm): 107.2 ppm; MS (FAB): *m/z*=1021 [M<sup>+</sup>–Cl].

Compound **7b**: <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ/ppm): 1.52 (d, 18H, *J*<sub>P–H</sub>=16.0 Hz), 2.27 (s, 3H), 3.98 (s, 6H), 6.35 (s, 2H); <sup>31</sup>P NMR (CDCl<sub>3</sub>, δ/ppm): 167.1 ppm; MS (FAB): *m/z*=942 [M<sup>+</sup>–Cl].

#### 4.5. Synthesis of **8a**

The two reactants, **5a** (0.40 mmol, 0.114 g) and Pd(COD)Cl<sub>2</sub> (0.20 mmol, 0.057 g) with 10 ml CH<sub>2</sub>Cl<sub>2</sub> were placed in a 100 ml round-bottomed flask charged with magnetic stirrer. The solution was stirred at 40 °C for 8 h before the solvent was removed in reduced pressure. The residue was washed with 10 ml hexanes first and dried again. A yellow colored solid was obtained and was identified as **8a**. The yield of **8a** is 94% (0.166 g, 0.188 mmol). Suitable crystals of **8a** for X-ray determination were obtained from a hexanes/CH<sub>2</sub>Cl<sub>2</sub>=1:1 mixed solvent in 4 °C environment.

Compound **8a**: <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ/ppm): 2.07 (s, 3H), 3.26 (s, 6H), 5.89 (s, 2H), 7.16–7.30 (m, 6H), 7.89–7.91 (m, 4H); <sup>31</sup>P NMR (CDCl<sub>3</sub>, δ/ppm): 118.9 ppm; MS (FAB): *m/z*=846 [M<sup>+</sup>–Cl].

#### 4.6. X-ray crystallographic studies

Suitable crystals of **7a**, **7b**, and **8a** were sealed in thin-walled glass capillaries under nitrogen atmosphere and mounted on a Bruker AXS SMART 1000 diffractometer. Intensity data were collected in 1350 frames with increasing ω (width of 0.3° per frame). The absorption correction was based on the symmetry equivalent reflections using SADABS program. The space group determination was based on a check of the Laue symmetry and systematic absences, and was confirmed using the structure solution. The structure was solved by direct methods using a SHELXTL package.<sup>13</sup> All non-H atoms were located from successive Fourier maps and hydrogen atoms were refined using a riding model. Anisotropic thermal parameters were used for all non-H atoms, and fixed isotropic parameters were used for H atoms.<sup>14</sup> Crystallographic data for compounds **7a**, **7b**, and **8a** are summarized in Table 1.

#### Acknowledgements

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#### Supplementary data

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Center,

CCDC no. 653963, 653964, and 653965 for compounds **7a**, **7b**, and **8a**, respectively. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or www: <http://www.ccdc.cam.ac.uk>). Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.09.070.

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14. The hydrogen atoms were ride on carbons or oxygens in their idealized positions and held fixed with the C–H distances of 0.96 Å.