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Zheda-Phos for General α-Monoarylation of Acetone with Aryl Chlorides

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Abstract: A new, readily available, and air-stable monophosphine ligand, i.e., **Zheda-Phos**, has been developed for the general and highly effective palladium-catalyzed monoarylation of acetone with aryl chlorides. The reaction rate is of first-order dependence with the aryl chloride.

Keywords: acetone; C–Cl bond activation; monoarylation; phosphines

Inventing new ligands is an important topic in transition metal-catalyzed reactions since a ligand may nicely tune the reactivities and selectivities in catalytic reactions. In early 2010, we reported **LB-Phos**, **Gorlos-Phos**, etc., for the effective C–C or C–N bond formation between aryl chlorides and boronates or amines, in which an effective more rigid 5-membered coordination sphere with Pd has been proposed (Figure 1).[1–3]

Transition metal-catalyzed α-arylation reactions of ketones with aryl halides (iodides and bromides) have been of high current interest[4] and, in some cases, relatively cheaper but inert aryl chlorides were applied with new types of phosphine and NHC ligands.[5] Now the challenge is the direct monoarylation of acetone since the deprotonation could happen on both sides of the carbonyl group with the bases applied and the benzylic protons in the monoarylation product **2** are even more acidic, thus, leading to a mixture of mono- and polyarylation products.[6] In order to avoid such a complication, pre-prepared tin[7a,b] or silyl[7c,d] enolates of acetone have been used as the coupling partners. Recently, the highly selective direct monoarylation reactions of acetone with aryl chlorides, bromides, aryl iodides, or aryl triflates using **Mor-DalPhos** as the ligand or aryl imidazolylsulfonates using **XantPhos** as the ligand have been pioneeringly reported.[8,9] However, it was mentioned by the authors that the reaction with electron-deficient aryl chlorides is very slow, and thus, much less effective. Even with *p*-cyanophenyl **bromide**, the yield is low (35%).[9a] Therefore, it is desirable to develop a new and effective catalyst system which could achieve the general monoarylation reactions of acetone even with electron-deficient aryl chlorides. We reasoned that the oxidative addition of the electron-deficient aryl chlorides should be faster, thus, the slow monoarylation reaction must be caused by the slow reductive elimination. Based on our experience with the development of ligands shown in Figure 1, we predicted that such Type-I and Type-II ligands shown in Scheme 1 may address these concerns: the alkoxy and/or amine group may be responsible for the electron-rich nature of the ligand to effectively activate the C–Cl bond as well as facilitating the fast reductive elimination even for the electron-deficient aryl chloride by weakening the related C–M bonds *via* strong back-donation or increasing steric bulkiness. In this paper, in addition to **Gorlos-Phos**, we wish to introduce a highly effective air-stable new phosphine ligand, i.e., 2-methoxy-6-(*N*-methyl-*N*-phenylamino)phenyl(dicyclohexyl)-phosphine (**Zheda-Phos**) for such a purpose, especial-

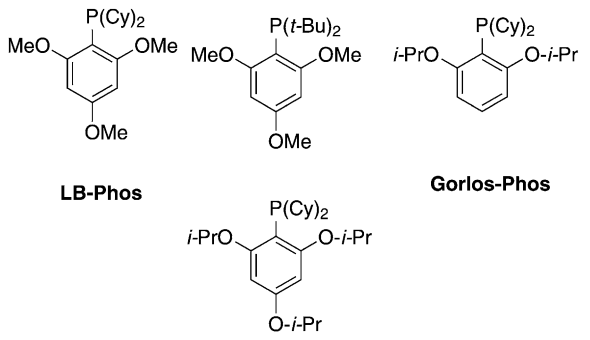
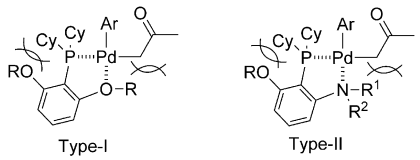


Figure 1. Ligands developed in this group for C–C or C–N bond formation with aryl chlorides.



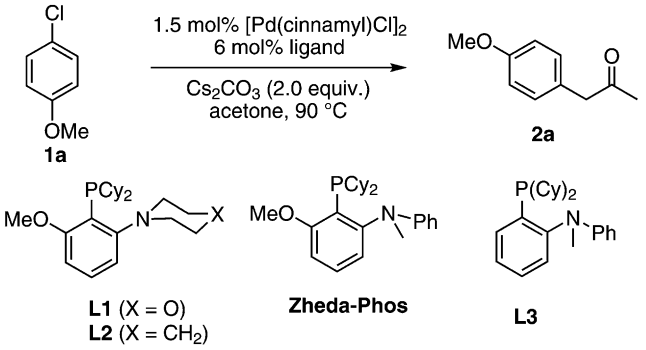
possible roles of the OR and NR^1R^2 groups:
(1) making the ligand more electron-rich for C–Cl activation;
(2) keeping the steric congestion to promote reductive elimination
(3) weakening the Ar–Pd and CH_2–Pd bonds *via* strong back donation to promote reductive elimination

Scheme 1. Working models for effective ligands.

ly with a very broad generality even for electron-deficient aryl chlorides.

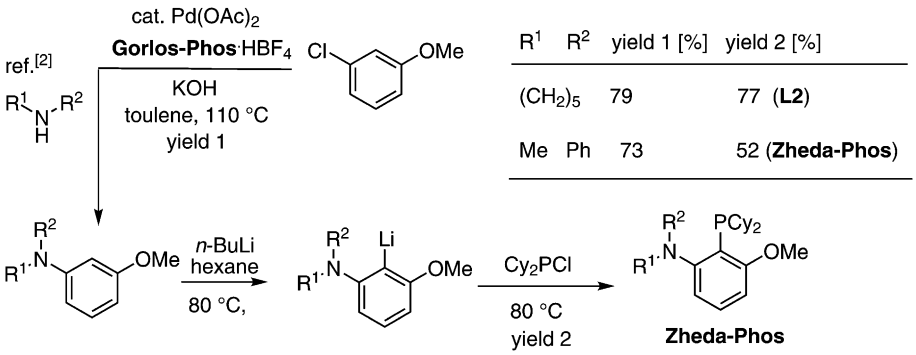
We first attempted the arylation reactions between 4-chloroanisole (**1a**) and acetone using the type of ligands listed in Figure 1 (Table 1). It is interesting to note that [Pd(cinnamyl)Cl]$_2$/**LB-Phos** did catalyze the monoarylation reaction between **1a** and acetone using Cs_2CO_3 (2.0 equiv.) as the base with 65% yield of **2a** and 35% recovery of **1a** (entry 1, Table 1). The yield was further increased to 94% using relatively more sterically bulky **Gorlos-Phos** as the ligand (entry 2, Table 1)! Based on these promising results, we further attempted to introduce an amine functionality to replace one of the two alkoxy groups in **LB-Phos** or **Gorlos-Phos**. Although we failed to prepare the **morpholine**-based **L1** (X = O), the preparation of cyclohexylamine analogue **L2** (X = CH_2) was successful (Scheme 2). To our disappointment, the result with **L2** is poor (entry 3). After some unsuccessfully attempts, to our delight, with 2-methoxy-6-(*N*-methyl-*N*-phenylamino)phenyl(dicyclohexyl)phosphine[9] (**Zheda-Phos**; Figure 2), the monoarylated product **2a** was afforded exclusively with 100% NMR yield (entry 5)! $Pd(OAc)_2$ is much less effective (entry 6, Table 1). Further reducing the loading of [Pd(cinnamyl)Cl]$_2$ or the base led to lower yields (entries 7 and 8). Using KOH, K_2CO_3 instead of Cs_2CO_3 all caused lower yields (entries 9 and 10). K_3PO_4 afforded the product in 88% yield (entry 11). Ligand **L3** without this OMe group was prepared to confirm our

Table 1. Monoarylation reactions of **1a** with acetone under different conditions.



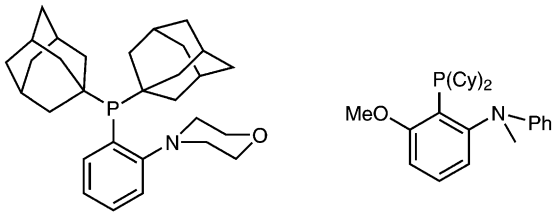
Entry	Ligand	Time [h]	Yield [%][a]	Recovery [%][a]
1	**LB-Phos·HBF$_4$**	24	65	35
2	**Gorlos-Phos·HBF$_4$**	**24**	**94**	**–**
3	**L2**	24	68	32
4	**L3**	24	27	73
5	**Zheda-Phos**	**24**	**100**	**–**
6[b]	**Zheda-Phos**	24	6	84
7[c]	**Zheda-Phos**	34	90	–
8[d]	**Zheda-Phos**	23	66	27
9[e]	**Zheda-Phos**	24	15	85
10[f]	**Zheda-Phos**	24	15	85
11[g]	**Zheda-Phos**	48	88	–

[a] Determined by ^{1}H NMR. *Reaction conditions:* **1a** (0.5 mmol), [Pd(cinnamyl)Cl]$_2$ (0.0075 mmol), ligand (0.03 mmol), Cs_2CO_3 (1.0 mmol) in acetone (2 mL) at 90 °C. All the reactions were carried out in oven-dried Schlenk vessels with screw caps.
[b] $Pd(OAc)_2$ (3 mol%) was used.
[c] [Pd(cinnamyl)Cl]$_2$ (1 mol%) and **Zheda-Phos** (4 mol%) were used.
[d] Cs_2CO_3 (1.5 equiv.) was used.
[e] KOH (2.0 equiv.) was used.
[f] K_2CO_3 (2.0 equiv.) was used.
[g] K_3PO_4 (2.0 equiv.) was used.



R^1	R^2	yield 1 [%]	yield 2 [%]
$(CH_2)_5$		79	77 (**L2**)
Me	Ph	73	52 (**Zheda-Phos**)

Scheme 2. Synthesis of **Zheda-Phos**.



Mor-DalPhos Zheda-Phos

Figure 2. Mor-DalPhos and **Zheda-Phos**.

hypothesis shown in Scheme 1. As expected, it is much less effective, affording **2a** in only 27% yield with 73% of **1a** being recovered (entry 4).

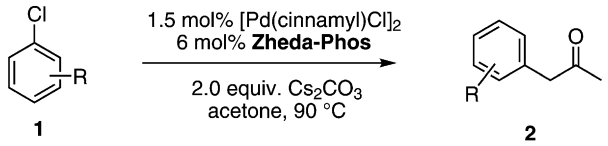
With the optimized reaction conditions in hand, phenyl and differently substituted electron-rich aryl chlorides were coupled with acetone with moderate to excellent yields (Table 2). For the sterically bulky phenyl chlorides, although the reaction time was relatively longer, the products were formed with high yields (entries 3, 8, and 9, Table 2). We also applied the Pd/**Zheda-Phos** catalyst system in one 25-mmol scale reaction of **1e** affording the monoarylation product **2e** with 94% isolated yield in 52.5 h using only 0.5 mol% of $[Pd(cinnamyl)Cl]_2$ as the catalyst (Table 2, entry 6), which indicates that the lower isolated yield compared to the NMR yield for a small-scale reaction was caused by the loss of product during the chromatographic separation process probably due to the enolizable nature of the products.

Finally, we are pleased to note that the Pd/**Zheda-Phos**-catalyzed system may indeed be smoothly applied to the monoarylation with a variety of different electron-deficient phenyl, naphthyl, 2-methylquinolinyl,[10] and pyridyl chlorides[11] in good yields (Scheme 3).

The reaction of 4-chloroanisole (1 mmol) with acetone (2 mL) was conducted in the presence of $[Pd(cinnamyl)Cl]_2$ (1.5 mol%), **Zheda-Phos** (6 mol%) and Cs_2CO_3 (4.0 equiv.) at 90 °C. It was monitored by GC analysis with biphenyl being the internal standard. A good linear relationship between $\ln(1/[\mathbf{1a}])$ and reaction time (S) was observed (Figure 3), indicating a first-order dependence of the reaction rate with **1a** ($\ln[1/\mathbf{1a}] = k^1t + \ln[1/\mathbf{1a}]^0$, see the Supporting Information).

Oxidative addition of **Zheda-Phos**/Pd(0) with aryl chloride would afford **3**.[4] Subsequent nucleophilic attack of the enolate of acetone would generate intermediate **4**, which may also be further stabilized by its tautomer **5**. The monoarylation product would be afforded *via* reductive elimination exclusively because of the large steric bulkiness in **4** while regenerating the catalytically active catalyst **Zheda-Phos**/Pd(0). It is well believed that the oxidative addition of the electron-deficient aryl chlorides should be faster as

Table 2. Monoarylation reactions of acetone with various aryl chlorides **1**.[a]



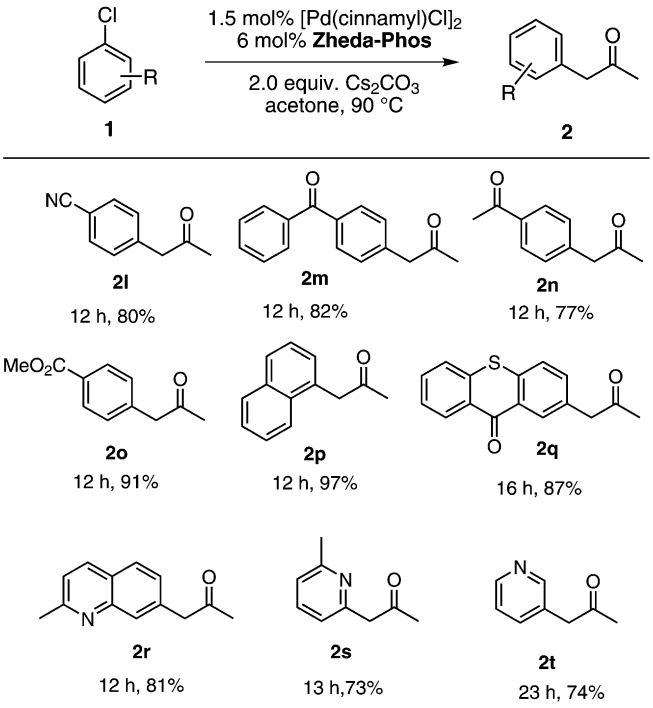
Entry	R	Time [h]	Yield [%][b]
1	4-OMe (**1a**)	24	84 (100) (**2a**)
2	3-OMe (**1b**)	12.5	87 (98) (**2b**)
3	2-OMe (**1c**)	40	89 (100) (**2c**)
4	3,5-$(OMe)_2$ (**1d**)	12	90 (99) (**2d**)
5	4-Me (**1e**)[c]	12	70(91) (**2e**)
6	4-Me (**1e**)	52.5	94 (**2e**)[d]
7	3-Me (**1f**)	12.5	71 (98) (**2f**)
8	2-Me (**1g**)	35	79 (98) (**2g**)
9	2,6-$(Me)_2$ (**1h**)	22.3	84 (98) (**2h**)
10	4-*t*-Bu (**1i**)[c]	12	86 (98) (**2i**)
11	3-NMe_2 (**1j**)	11.5	69 (78) (**2j**)
12	H (**1k**)	12	73 (100) (**2k**)

[a] The reaction was conducted with aryl chloride (1 mmol), $[Pd(cinnamyl)Cl]_2$ (0.015 mmol), **Zheda-Phos** (0.06 mmol), Cs_2CO_3 (2.0 mmol) in acetone (4 mL) at 90 °C for 11.5–40 h.

[b] Isolated yields. NMR yields are reported in parentheses.

[c] Distilled chlorides were used.

[d] This is a 25-mmol scale reaction using 0.5 mol% $[Pd(cinnamyl)Cl]_2$ and 2 mol% **Zheda-Phos** as catalyst.



Scheme 3. Monoarylation of actone with electron-deficient aryl and heteroaryl chlorides.

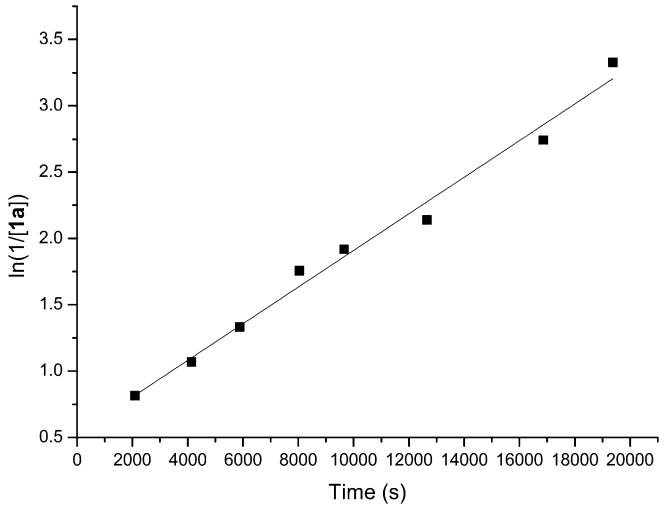


Figure 3. First order dependence with **1a**.

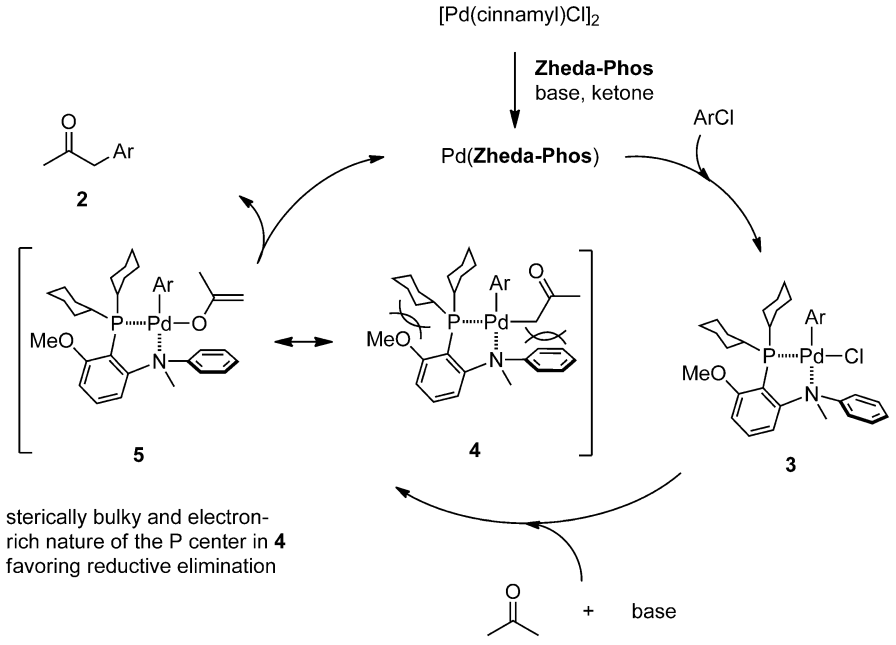
compared to the electron-rich aryl ones, thus, we concluded that the electron-rich nature of the phosphorus center in **Zheda-Phos** caused by the MeO group must also be prompting the reductive elimination by pumping electrons to the related anti-bonding orbitals in intermediate **4** by strong back-donation or increasing the steric bulkiness, thus weakening the Ar–Pd and CH_2–Pd bonds in **4**.

In conclusion, we have developed a new readily and available phosphine ligand (Scheme 4), i.e., 2-methoxy-6-(*N*-methyl-*N*-phenylamino)phenyl(dicyclohexyl)phosphine (**Zheda-Phos**),[12] for the general Pd-catalyzed effective monoarylation of acetone with a series of different functionalized aryl chlorides. The reactions could be carried out easily in a larger scale with only 0.5 mol% Pd as the catalyst. Further studies in this area including the application of **Gorlos-Phos** and other ligands are being pursued in this laboratory.

Experimental Section

Typical Procedure for the Monoarylation of Acetone

To a flame-dried and nitrogen-filled Schlenk vessel were added $[Pd(cinnamyl)Cl]_2$ (7.9 mg, 0.015 mmol), Zheda-Phos (24.5 mg, 0.060 mmol), Cs_2CO_3 (651.0 mg, 2.0 mmol), **1a** (143.2 mg, 1.0 mmol) and acetone (4 mL) sequentially. Then the vessel was sealed with a screw-cap and heated at 90 °C in a preheated oil bath. After 24 h, the reaction was complete as monitored by GC. The reaction mixture was then cooled and quenched with 10 mL of Et_2O. After transferring the mixture into separatory funnel, the reactor was further washed with 10 mL of Et_2O and 10 mL of HCl aqueous solution (5%). The combined mixture was extracted with Et_2O (10 mL × 2), washed with 20 mL of saturated $NaHCO_3$ aqueous solution, and dried over anhydrous Na_2SO_4. Filtration, evaporation, and purification by chromatography (eluent: petroleum ether/ethyl acetate = 20/1) on silica gel afforded **2a** as a liquid; yield: 137.9 mg (84%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.11$ (d, $J = 8.4$ Hz, 2H, ArH), 6.87 (d, $J = 8.4$ Hz, 2H, ArH), 3.79 (s, 3H, OCH_3), 3.63 (s, 2H, CH_2), 2.13 (s, 3H, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 206.8$, 158.5, 130.3, 126.1, 114.0, 55.1, 50.0, 29.0; IR (neat): $\nu = 3002$, 2957, 2935, 2911, 2837, 1713, 1612, 1584, 1514, 1464, 1442, 1423, 1356, 1301, 1249, 1179, 1158, 1109, 1034 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 165 ($M^+ + 1$, 2.58), 164 (M^+, 23.60), 121 (100).



Scheme 4. Rationale for the reactivity and generality.

Acknowledgements

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