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Palladium-catalyzed P(O)R₂ directed C–H arylation to synthesize electron-rich polyaromatic monophosphorus ligands[†]

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Palladium-catalyzed arylation of (diisopropylphosphoryl)biphenyl skeleton derivatives by the $P(O)R_2$ directed C-H functionalization was reported. The related products were obtained in high regioselectivity and good functional group tolerance was observed. This reaction provided a new and efficient pathway for the synthesis of polyaromatic monophosphorus ligands.

Transition-metal-catalyzed C-H functionalization of directinggroup-containing substrates has emerged as a promising strategy in synthetic reactions.¹ By assisting chelation and subsequently promoting further C-H functionalization, directing groups provide a whole new way for the valuable structural frameworks and the improvement of the overall synthetic efficiency and regioselectivity. Because biphenyl derivatives are important structural units in numerous functional molecules relevant to medicinal chemistry and materials science,² so many directing groups such as heterocycles,³ anilides,⁴ amides,⁵ oximes,⁶ benzylamines,⁷ carboxylic acids⁸ and ketones⁹ have been successfully applied in transition metal-catalyzed direct C-H arylation of arenes to construct these skeletons. However, in spite of tremendous progress, the application of innovative directing groups with improved directing qualities, representing useful functional groups that are tunable and show increased levels of reactivity and selectivity, should be beneficial. Our ongoing interest is focused on finding new organophosphorus transformations,¹⁰ which also prompts us to examine the utilization of the phosphorus as the directing group for selective C-H functionalization reaction. Phosphorous acid and phosphate ester have already been used as directing groups to access C-H functionalization through a five- or six-membered cyclopalladium pretransition state.¹¹ Very recently, our group has also developed the process of R2(O)P directed palladium-catalyzed

C-H olefination and hydroxylation.¹² In particular, $R_2(O)P$ is not only acting as the directing group, but also the useful composition of the product in our case. Herein, we report a $R_2(O)P$ directed palladium-catalyzed C-H arylation to synthesize a series of polyaromatic monophosphorus compounds, and this directing group can be easily reduced to trivalent phosphorus by trichlorosilane, which are useful ligands for transition-metalcatalyzed cross-coupling reactions.¹³ Moreover, instead of forming a five-membered cyclopalladium pretransition state, the reaction may go through a seven-membered cyclopalladium pretransition state, and shows high regioselectivity (Scheme 1 path b).

We began our optimization with [1,1'-biphenyl]-2-yldiisopropylphosphine oxide (1a) and diphenyliodonium trifluoromethanesulphonate (2) as template substrates. After a series of screens, theoptimized reaction conditions were obtained (Table S1, entry 32;see ESI†). Subsequently, various substrates which have been usedto determine the scope and limitations of present methodologywere investigated (Table 1). Firstly, different directing groups wereexamined, when R is cyclohexyl or*t*-butyl, we could obtain thearylated product in moderate yields. With 2-diphenylphosphinooxide as the directing group, 3d and 3e could be obtained inmoderate yields. When diisopropylphenyl phosphorous oxide(non-biphenyl skeleton) was used as a substrate, the product 3fwas not detected, this suggested that the five-membered cyclopalladium transition state was unfavourable. Next, the scope ofdifferent substituted 2-(diisopropylphosphoryl)biphenyl derivatives



Scheme 1 Regioselective C-H activation by cyclopalladium.

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 Table 1
 Highly regioselective monophenylation of various biphenyl skeletons^{ab}



^{*a*} Reaction conditions: **1a-1p** (0.2 mmol), **2** (2.5 equiv.), $PdCl_2$ (10 mol%), Ag_2CO_3 (0.2 equiv.), PivOH (2.0 equiv.), DMF (4.0 mL), air atmosphere, 80 °C, 36 h. ^{*b*} Isolated yields. ^{*c*} $PdCl_2$ (20 mol%) and Ag_2CO_3 (0.4 equiv.) were used.

was evaluated. The arylation of diisopropylphosphoryl biphenyl substituted by an electron-donating group, such as methyl or methoxy, on the *ortho-*, *meta-* or *para-*position of the aromatic ring Ar¹ proceeded smoothly to give the corresponding products. Remarkably, the phenylnaphthalene skeleton was also further arylated and yielded **31** in 63% yield under standard conditions. For electron-deficient substrates, the chloride or trifluoromethyl substituent was also well tolerated, and gave **3m** and **3n** in 63% and 55% yields. When substituted by methyl or methoxy on aromatic ring Ar², the products were obtained in moderate yield.

Next, different hypervalent iodines as arylation reagents¹⁴ were evaluated in this transformation (Table 2), this kind of skeleton was also further functionalized. The *ortho*-position substituted aryl iodine reagent was ineffective in this system. The substrate which was substituted by fluoride, chlorine and bromine was successfully arylated in moderate to good



^{*a*} Reaction conditions: **1** (0.2 mmol), **2** (2.5 equiv.), $PdCl_2$ (20 mol%), Ag_2CO_3 (0.4 equiv.), PivOH (2.0 equiv.), DMF (4.0 mL), air atmosphere, 80 °C, 36 h. ^{*b*} Isolated yields of products.



Scheme 2 Reduction of phosphorous oxides to monophosphorus ligands.



Scheme 3 Plausible mechanism of Pd(II)-catalyzed C–H arylation.

yields, which also provided the possibility for further functional transformation.

The polyaromatic monophosphorus ligand may be an important ligand in transition-metal-catalyzed cross-coupling reactions, so we used the classical reduction system for our arylated product, and obtained the reduction product by flash chromatography (Scheme 2).¹⁵ Therefore, our report provided a new and efficient pathway for the synthesis of the polyaromatic monophosphorus ligand.

According to the previously reported literature¹⁶ and the preliminary mechanistic studies, we proposed the catalytic cycle as shown in Scheme 3; firstly, $PdCl_2$ combined with PivOH and Ag_2CO_3 generated the higher activity $Pd(PivO)_2$ **A** as a pre-activated state. Then P=O-directed C-H activation occurred and generated the seven-membered cyclopalladium intermediate **B**; next, subsequent oxidative addition of the Pd(n) complex to a Pd(nv) intermediate **C** by Ph₂IOTf occurred. Finally, the desired product **3a** was formed by reductive elimination and released the Pd(n), which regenerated the species **A**. Furthermore, the Pd(0) also could prompt this reaction, so we couldn't exclude the cycling of Pd(0)-Pd(n)-Pd(0).

In conclusion, we have developed a synthesis approach for preparation of the terphenyl electron-rich phosphorus compounds by palladium-catalyzed $P(O)R_2$ directed C–H arylation. It is note-worthy that the terphenyl products were obtained in high regioselectivity and good functional group tolerance was observed.

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These products can be reduced easily to monophosphorus ligands. In addition, a seven-membered cyclopalladium intermediate may be involved in this transformation. Investigation of the detailed mechanism is underway in our laboratory.

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