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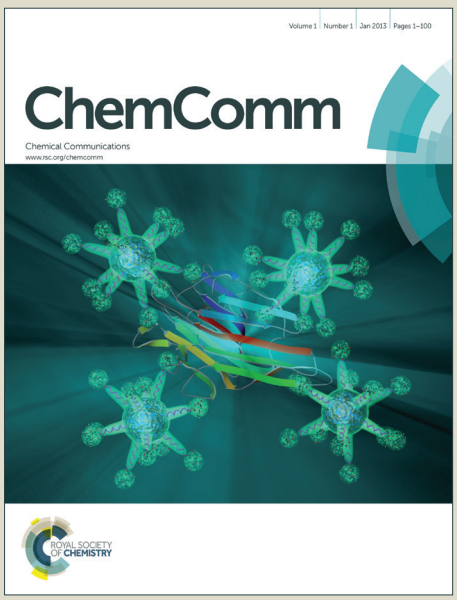

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Palladium-Catalyzed P(O)R_2 Directed C-H Arylation to Synthesize Electron-rich Polyaromatic Monophosphorus Ligands

Cite this: DOI: 10.1039/x0xx00000x

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Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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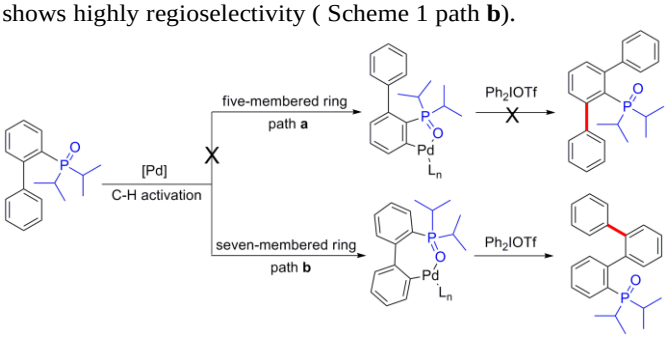
Palladium-catalyzed arylation of (diisopropylphosphoryl) biphenyl skeleton derivatives by the P(O)R_2 directed C-H functionalization was reported. The related products were obtained in high regioselectivity and well functional groups tolerance. This reaction provided a new and efficient pathway for the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

Transition-metal-catalyzed C-H functionalization of directing-group-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. Due to 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 acids[8] and ketones[9] 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. Although phosphorous acid and phosphate ester have already been used as directing group to access C-H functionalization through a five- or six-membered cyclopalladium pretransition state.[11] In very recently, our group have also developed the process of R_2(O)P directed palladium-catalyzed C-H olefination and hydroxylation.[12] In particular, the R_2(O)P is not only acting as directing group, but also the useful composition of product in our cases. Herein, we reported 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-metal-catalyzed 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 highly regioselectivity (Scheme 1 path **b**).

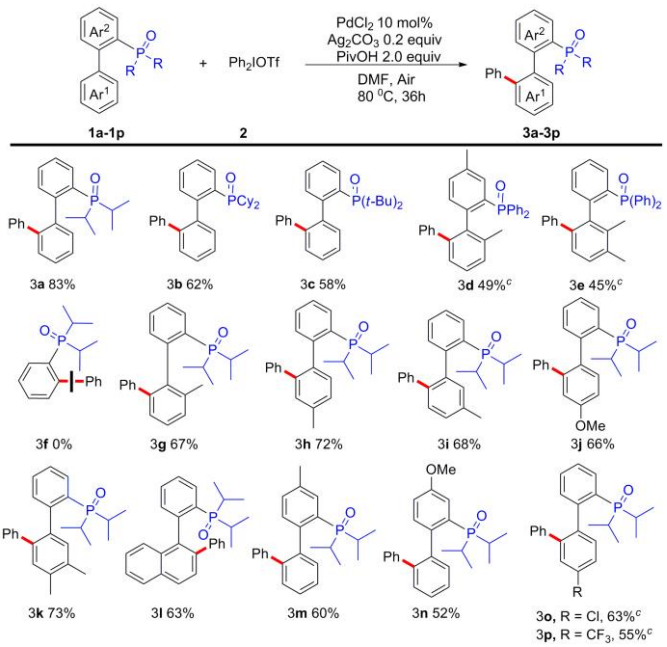


Scheme 1. Regioselective C-H Activation by Different Cyclopalladium

We began our optimization with [1,1'-biphenyl]-2-yldiisopropylphosphine oxide(**1a**) and diphenyliodonium trifluoromethanesulphonate(**2**) as template substrates. After a series of screens, the optimized reaction condition was obtained in hand (Table S1, entry 32; see Supporting Information). Subsequently, various substrates which have been used to determine the scope and limitations under present methodology were investigated (Table 1). Firstly, different directing group were examined, when R is cyclohexyl or *t*-butyl, we could obtain the arylated product in moderate yields. As 2-diphenylphosphino oxide was selected as the directing group,

3**d** and 3**e** could be obtained in moderate yields. When diisopropylphenyl phosphorous oxide (non-biphenyl skeleton) as a substrate, the product 3**f** wasn't detected, this suggested that the five-membered cyclopalladium transition state was unfavourable. Next, the scope of different substituted 2-(diisopropylphosphoryl)biphenyl derivatives have been evaluated. The arylation of diisopropylphosphoryl biphenyl substituted by electron-donating group, such as methyl or methoxy on the ortho-, meta- or para- position of aromatic ring Ar^1 proceeded smoothly to give their corresponding products. Remarkably, the phenylnaphthalene skeleton was also further arylated and yielded 3**l** in 63% on standard conditions. For electron-deficient substrates, the chloride or trifluoromethyl substituent was also well tolerated, and gave 3**m**, 3**n** in yields 63% and 55%. Substituted by methyl or methoxy on aromatic ring Ar^2, the products were obtained in moderate yield.

Table 1. Highly Regioselective Monophenylation of Various Biphenyl Skeleton[a,b]

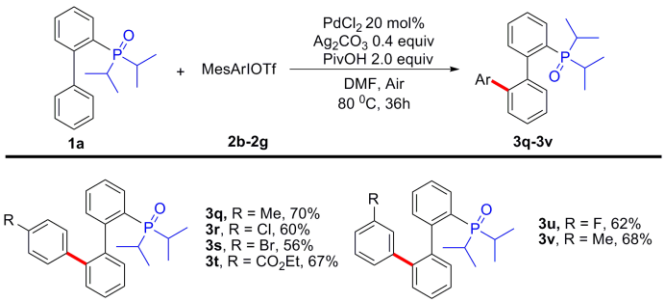


[a] Reaction conditions:**1a-1p** (0.2 mmol), **2** (2.5 equiv), $PdCl_2$ (10 mol%), Ag_2CO_3 (0.2 equiv), PivOH (2.0 equiv), DMF (4.0 mL), air atmosphere, 80℃, 36 h. [b] Isolated yields. [c] $PdCl_2$ (20 mol%), Ag_2CO_3 (0.4 equiv) was used.

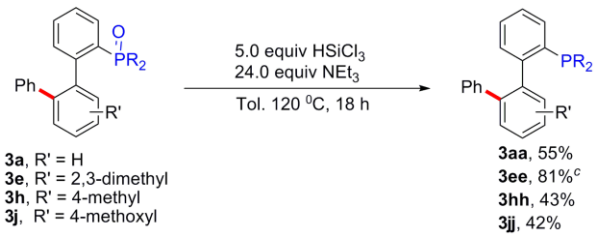
Next, different of hypervalent iodines as arylation reagent[14] were evaluated in this transformation (Table 2), this kind of skeleton was also further functionalized. Ortho-position substituted aryl iodine reagent was ineffective in this system. The substrate which was substituented by fluoride, chlorine and bromine was successfully arylated in moderate to good yields, which also provided the possibility for further functional transformation.

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

Table 2. Arylation of Biphenyl Skeleton With MesArIOTf [a,b]

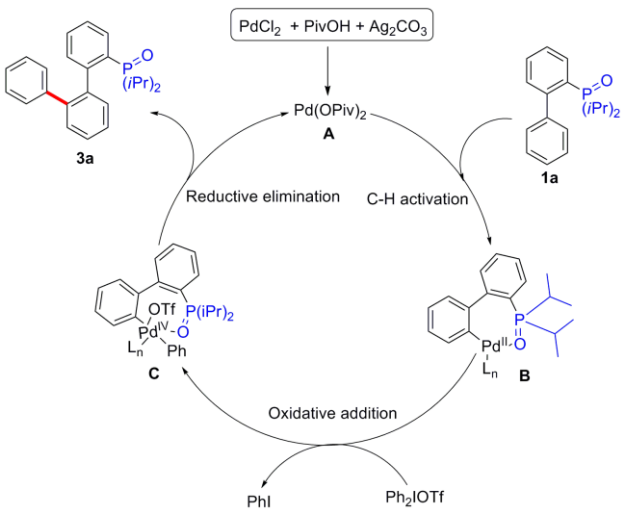


[a] Reaction conditions:**1** (0.2 mmol), **2** (2.5 equiv), $PdCl_2$ (20 mol%), Ag_2CO_3 (0.4 equiv), PivOH (2.0 equiv), DMF (4.0 mL), air atmosphere, 80°C, 36 h. [b]Isolated yields of products.



Scheme 2. Reductive of phosphorous oxides to monophosphorus ligands

According to the previously reported literatures[16] and the preliminary mechanism studies, we proposed the catalytic cycle as scheme **3**; Firstly, $PdCl_2$ combined with PivOH and Ag_2CO_3 generated the higher activity $Pd(PivO)_2$ **A** as a pre-activated step. Then P=O-directed C-H activation occurred and generated the seven-membered cyclopalladium intermediate **B**; Next, subsequent oxidative addition of the Pd(II) complex to a Pd(IV) intermediate **C** by Ph_2IOTf was occurred. Finally, the desired product 3**a** was formed by reductive elimination and released



Scheme 3. Plausible Mechanism of Pd(II)-Catalyzed C-H Arylation

the Pd(II), which was regenerated the species **A**. Furthermore, the Pd(0) also could prompt this reaction, so we couldn't exclude the cycling of Pd(0)-Pd(II)-Pd(0).

In conclusions, we have developed a synthesis approach of the terphenyl electron-rich phosphorus compounds by palladium-catalyzed $P(O)R_2$ directed C-H arylation. It's noteworthy that the terphenyl products were obtained in high regioselectivity and well functional groups tolerance. These products can be reduced easily to monophosphorus ligands. In addition, a seven-membered cyclopalladium intermediate may be contained in this transformation. The detailed mechanism is underway in our laboratory.

Acknowledgement

We are grateful for the NSFC (Nos. 21272100), Program for Changjiang Scholars and Innovative Research Team in University (PCSIRT: IRT1138) and Research Fund for the Doctoral Program of Higher Education of China (Nos. 20100211120014) financial support.

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/ c3cc

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