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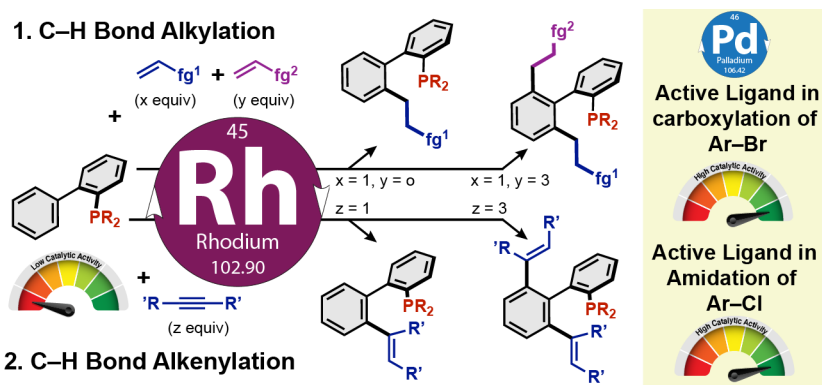
# How Rh(I)-Catalyzed P(III)-Directed C–H Bond Functionalizations Could Improve the Phosphines Catalytic Activities

Zhuan Zhang,<sup>a,b</sup> Natacha Durand<sup>a</sup> Jean-François Soulé\*<sup>a</sup>

<sup>a</sup> Univ Rennes, CNRS, UMR6226, F-3500 Rennes, France.

<sup>b</sup> Present address: Guangxi Key Laboratory of Electrochemical Energy Materials, School of Chemistry and Chemical Engineering, Guangxi University, Nanning, Guangxi 530004, P. R. China

[jean-francois.soule@univ-rennes1.fr](mailto:jean-francois.soule@univ-rennes1.fr)



**Abstract** Trivalent-phosphorus-containing molecules are widely used in fields ranging from catalysis to materials science. Efficient catalytic methods for their modifications giving straightforward access to

novel hybrid structures boosting their catalytic activities are highly desired to facilitate reaction improvement or discovery. We recently developed new methods for synthesizing multifunctional phosphines with C–C cross-couplings through Rh-catalyzed C–H activation reactions. These methods use native P(III)-atom as a directing group and can be used in regioselective late-stage functionalization of phosphine ligands. Interestingly, some modified phosphines have outperformed their parent ones in Pd-catalyzed cross-coupling reactions.

## 1. Introduction

2. Early Examples of Transition-Metal-Catalyzed P(III)-Directed C–H Bond Activation/Functionalizations

3. Synthesis of Multifunctional Biarylphosphines by late-stage Alkylation: Application in Carboxylation Reaction

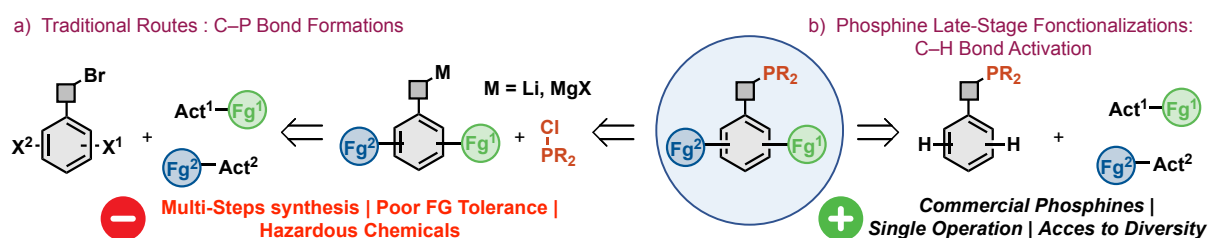
4. Synthesis of Multifunctional Biarylphosphines by late-stage Alkenylation: Application in Amidation Reaction

## 5 Conclusion

Keywords Phosphines, C–H bond Activation, Late-stage Functionalizations, Palladium Catalysis, CO<sub>2</sub>-fixation, Amidation, Ligand design

## 1. Introduction

The history of transition metal catalysis is intertwined with ligand design.<sup>(1)</sup> The intimate relationship between metal and ligand can profoundly affect the outcome of a reaction, often impacting selectivity, physical properties, and the lifetime of a catalyst. Importantly, this metal–ligand relationship can provide near limitless opportunities for reaction discovery. Although many phosphorus-based ligands have been developed over the last decades,<sup>(2)</sup> their rational design to afford highly active catalyst systems applicable for new transformations that can be easily prepared and modified continues to be an essential topic. Up to date, the traditional way to prepare novel phosphines involves the formation of C–P bonds using hazardous phosphorus derivatives (Figure 1a). Moreover, this synthetic route makes access to bifunctional ligands difficult because it involves multi-step synthesis with polar reagents (*i.e.*, Grignard or organolithium reagents), which prevent the introduction of sensitive functional groups. Besides these non-convergent methods are time-consuming and far from atom-economy due to the preparation of a wide range of starting materials.

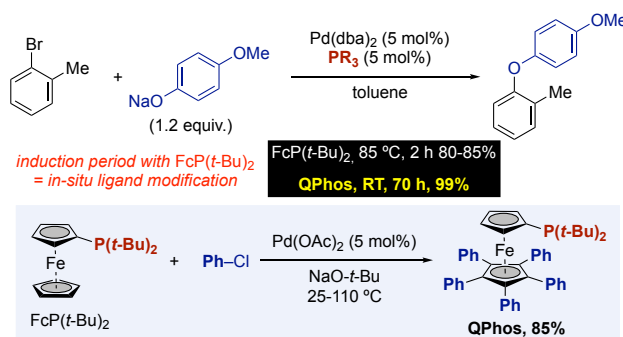


**Figure 1** Synthesis of Phosphines a) conventional approaches; b) C–H bond functionalizations

Late-stage functionalization, *via* a regioselective C–H bond activation, has accelerated efforts to develop synthetic tools to diversify natural products and materials sciences.<sup>(3)</sup> Recently, several reports have demonstrated that phosphorus-containing molecules could undergo regioselective C–H bond functionalizations using pentavalent phosphorus,<sup>(4)</sup> or trivalent phosphorus such as phosphinites,<sup>(5)</sup> phosphites,<sup>(6)</sup> or phosphinamidites<sup>(7)</sup> as directing groups. These assets pave the way for new perspectives in phosphine C–H bond functionalization with the aim to design better ligands (Figure 1b). This direct approach presents several advantages over C–P bond formation: 1) Speed up the preparation of novel multifunctional phosphines (only 1 step diversification); 2) Easy access to phosphine diversity from commercially available phosphines; 3) Sensitive chemical groups able to participate in the chemical activation can be introduced in the very last steps of the synthesis. This synthetic phosphine scheme makeover will significantly impact optimizations and reaction discovery due to access to unprecedented multifunctional phosphines in great diversities. Despite the desirability of this approach, late-stage functionalization of phosphines is not trivial because their trivalent phosphorus atom is easily oxidized, and they often display a high affinity with active metal (catalyst), which could prevent the turnover.<sup>(8)</sup> Therefore, it is necessary to discover new conditions without oxidant or phosphine-compatible ones; and consider improving the ligand-metal exchange rate.

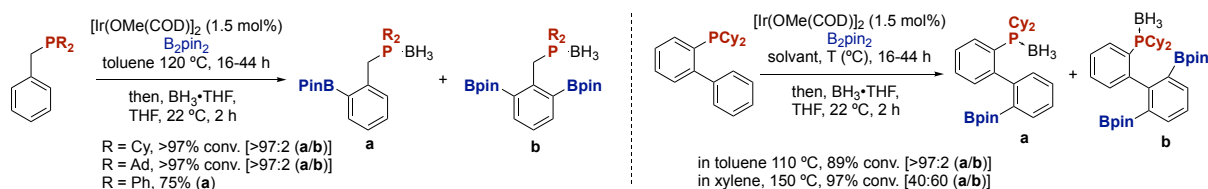
## 2. Early Examples of Transition-Metal-Catalyzed P(III)-Directed C–H Bond Activation/Functionalizations

In 2000, during their investigation on C–O bond coupling from aryl bromides and sodium phenolate using Pd(dba)<sub>2</sub> associated with FcP(*t*-Bu)<sub>2</sub> ligand, Hartwig and co-workers observed the modification of the ferrocenyl phosphine ligand throughout the reaction, inducing a rate enhancement (Scheme 1).<sup>(9)</sup> They come up with this conclusion by observing an induction period on the formation of diarylether while the aryl bromide is quickly consumed. This transformation involves the C–H bond penta-arylation of the Cp ring, opposite to the one holding the P atom. When FcP(*t*-Bu)<sub>2</sub> ligand is separately treated by 5 mol% Pd(OAc)<sub>2</sub> in the presence of chlorobenzene and base (NaO*t*-Bu), Qphos ligand is obtained in 85% yield. Palladium complex surrounded by QPhos ligand is much more catalytically active than the parent phosphine, as the C–O bond formation can be run at room temperature.



**Scheme 1** Pd-Catalyzed C–H Bond Arylation of Ferrocenyl Phosphine Ligand: Discovery of QPhos

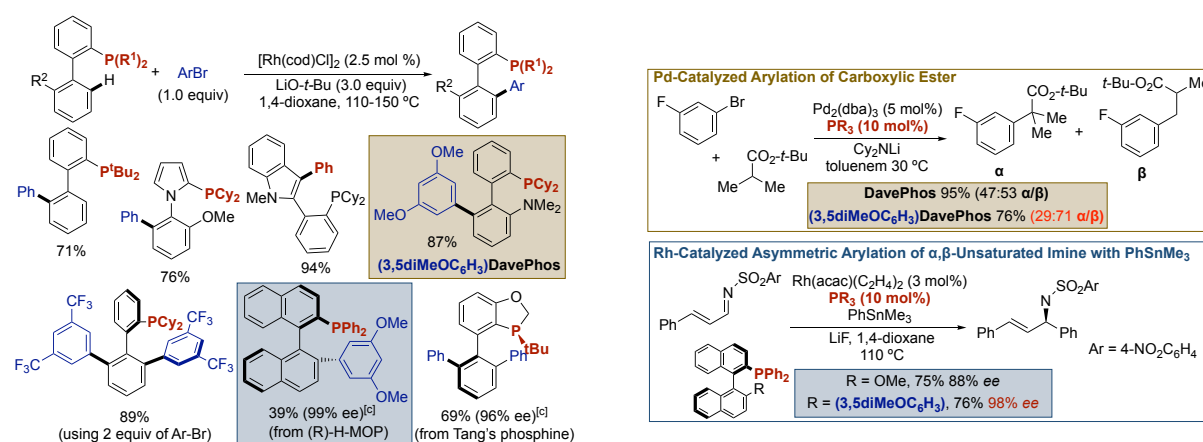
In 2014, Clark and co-workers reported Ir-catalyzed C–H borylation of benzylphosphines and biarylphosphine, in which the trivalent phosphorus atom is used as a directing group to provide selective formation of arylboronate esters with unique scaffolds of amphiphilic compounds (Scheme 2).<sup>(10)</sup> However, the influence of the C–H bond borylation on the catalytic performances of the resulting amphiphilic phosphines was not studied.



**Scheme 2.** Ir-Catalyzed C–H Borylation of Phosphines

In 2017, Shi's group reported the catalytic biphenyl C–H bond arylation of biarylphosphines using 2.5 mol% of [RhCl(COD)]<sub>2</sub> with ArBr or ArCl in the presence of 3 equivalents of LiO-*t*-Bu in 1,4-dioxane (Scheme 3, top).<sup>(11)</sup> Many commercially available biarylphosphines such as JPhos, MePhos, Davephos, cataCXium®P, cataCXium®Pin are arylated in high yields. The

*ortho*'-diarylation of commercial biarylphosphines is achieved using 2.4 equivalents of aryl bromides but at 140°C for 36 h in excellent yields, except for the phosphine holding a P(*t*Bu)<sub>2</sub> group. A few examples of successive *ortho*'-arylations have been performed, allowing the formation of mixed diarylated biphenyl phosphines. The direct transformation, *via* this arylation reaction, of chiral phosphines without racemization is also achieved. For instance, the C–H bond arylation of (*R*)-H-MOP and of the Tang's P-stereogenic phosphine were achieved in 39% and 69% yield, respectively without epimerization. To determine the impact of these modifications on the catalytic activity, the authors tested these newly constructed ligand libraries in two important catalytic transformations (Scheme 3, bottom). In Pd-catalyzed arylation of *tert*-butyl isobutyrate with *meta*-fluorobromobenzene, a mixture of  $\alpha$ - and  $\beta$ -arylated products (47:53) was observed with DavePhos. This ratio was improved (29:71) using the DavePhos which was arylated with 1-bromo-3,5-dimethoxybenzene. Subsequently, they investigated the activity of the arylated chiral phosphine in Rh-catalyzed asymmetric  $\alpha$ ,  $\beta$ -unsaturated imine. Reaction performed with commercial phosphine (*R*)-MeO-MOP afforded the product with 88% *ee*, while the reaction run with (*R*)-MOP, which is arylated at *ortho*'-position with 1-bromo-3,5-dimethoxybenzene, afforded the product with 98% *ee*. This work showed that the introduction of bulky substituent at *ortho*'-position(s) of biarylphosphines through C–H bond activation is an important strategy to improve their catalytic performances. Therefore, we decided to investigate other type of C–H bond functionalization of phosphines.

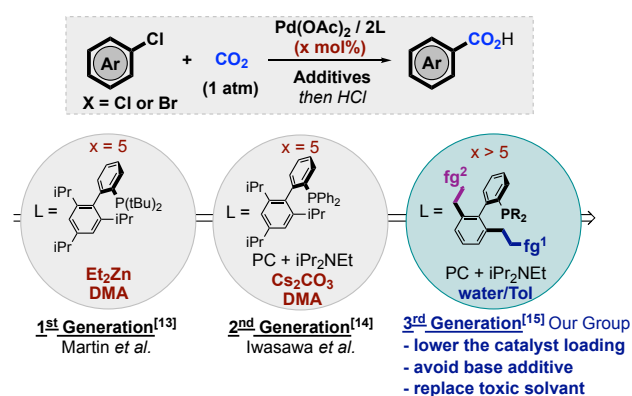


**Scheme 3.** Rh(I)-Catalyzed Arylation of Biarylphosphines

### 3. Synthesis of Multifunctional Biarylphosphines by late-stage Alkylation: Application in Carboxylation Reaction

Transition metal-catalyzed carboxylation of aryl (pseudo)halides with CO<sub>2</sub> gas has emerged as a sustainable alternative route to prepare carboxylic acid because it avoids the prefunctionalization and the generation of a stoichiometric amount of metallic waste (Figure 2).<sup>(12)</sup> In 2009, Martin *et al.* showed that XPhos phosphine associated with Pd(0) precursors in DMA (dimethylacetamide) efficiently

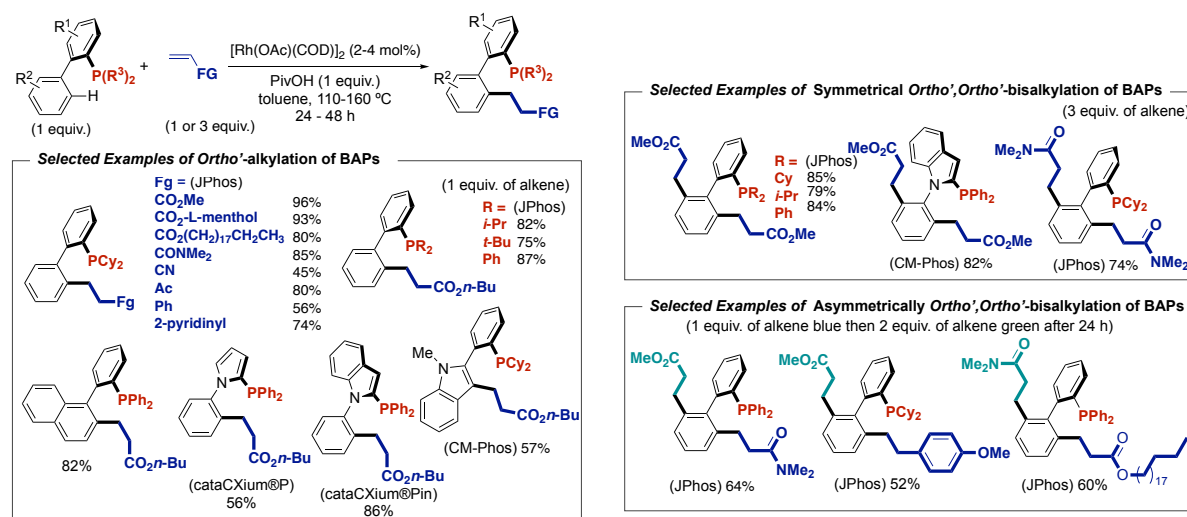
promotes the carboxylation of aryl halides, but the use of 2 equivalents of metallic reducing agents is required.<sup>(13)</sup> The reducing agents are typically employed in these both endeavors as a source of electrons in order to access Pd(0)/L<sub>n</sub>/ Pd(I)/L<sub>n</sub> species within the catalytic cycle to trigger the CO<sub>2</sub> insertion into the C–M bonds and the transmetalation releasing of ArCO<sub>2</sub><sup>-</sup> and the active catalyst. In 2017, Iwasawa *et al.* rejiggled the conditions by merging Pd and photoredox catalysis.<sup>(14)</sup> The replacement of a stoichiometric amount of metal(0) by an organic amine as an electron provider in the presence of photoredox catalysis represents a significant achievement toward sustainable processes. However, a large amount of Cs<sub>2</sub>CO<sub>3</sub> has to be employed to squeeze the formation of reductive products. Again, XPhos phosphine was employed as a ligand. In order to avoid the use of a stoichiometric amount of an external base, we questioned the possibility of incorporating a basic unit (fg) into the biarylphosphine scaffold. Such multifunctional phosphines are pretty challenging to prepare using the traditional synthetic routes and require us to develop a new strategy.



**Figure 2** Phosphine Design for Pd-Catalyzed Carboxylation Reaction of Aryl Halides with CO<sub>2</sub> Gas.

To quickly prepare a library of multifunctional phosphines containing a basic unit, we have designed Rh(I)-catalyzed C–H bond alkylation of biarylphosphines through P(III)-directed C–H bond activation using functionalized alkenes (Scheme 4).<sup>(15)</sup> We discovered that the C–H bond alkylation of biarylphosphines nicely proceeded using a mere catalytic system composed by [Rh(OAc)(COD)]<sub>2</sub> catalyst in the presence of PivOH in toluene. When one equivalent of alkene (per biarylphosphine) was employed, the reaction offered the mono-alkylated biarylphosphines at the *ortho*'-position (Scheme 4, top). Under the optimal conditions, various activated alkenes such as acrylates, acrylamides, acrylonitrile, and vinyl ketone reacted efficiently with JPhos to furnish the desired functionalized biarylphosphines in high yields with excellent regioselectivities. Less reactive styrene derivatives can also be employed as alkylation reagents. Notably, 2-vinyl pyridine is well tolerated in the reaction affording new pyridine-phosphine hybrid ligand, an essential ligand class for Pd-catalyzed carbonylation reactions<sup>(16)</sup> owing to the pyridine can act as a proton shuttle co-catalyst.<sup>(17)</sup> Rh(I)-catalyzed P(III)-directed C–H bond alkylation is not limited to biarylphosphines, as *N*-phenylpyrrole (cataCXium®P) and *N*-phenylindole (cataCXium®Pin)-based phosphines –developed by Beller's

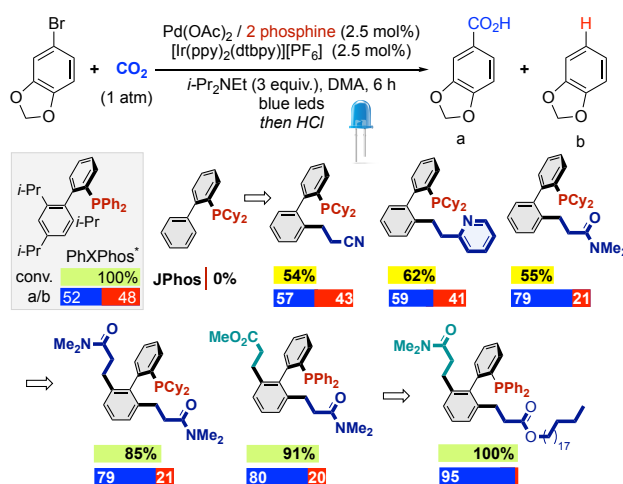
group for cross-coupling reactions with less reactive aryl chlorides<sup>(18)</sup> are alkylated on the phenyl ring to provide the corresponding phosphine-esters in 56% and 86% yield, respectively. CM-Phos developed by Kwong for cross-coupling reactions with aryl mesylates<sup>(19)</sup> is also alkylated at C3-position to afford the CM-Phos congener with pendant ester base in 57% yield. It is also possible to alkylate both *ortho*'-positions of biarylphosphines, using 4 mol% of [Rh(OAc)(COD)]<sub>2</sub>, and 3 equivalents of alkenes (Scheme 4, middle). These *ortho*',*ortho*'-dialkylated phosphines are similar to XPhos ligand, albeit the *i*-Pr groups can now be replaced by basic units such as ester or amide groups. We also shown that iterative one-pot reactions with two different alkenes can be carried out proved that the second alkene is introduced after 24 h (Scheme 4, bottom). This strategy has prepared unprecedented phosphines containing multiple basic groups (ester, amide, aryl group). We have also prepared in a single operation a unique phosphine containing a fatty ester group at the *ortho*'-position along with an amide group at the other *ortho*'-position using eicosyl acrylate and acrylamide as both alkene sources.



**Scheme 4** Rh(I)-Catalyzed C–H Bond Alkylation of Biarylphosphines using Functionalized Alkenes

We next investigated the impact of catalytic C–H bond alkylation of JPhos in Pd-catalyzed carboxylation of aryl bromides using CO<sub>2</sub> as a C1 source using slightly modified Iwasawa's conditions (Scheme 5).<sup>(14)</sup> Indeed, as our phosphine contains a basic unit, we decided to conduct the reaction without the stoichiometric amount of Cs<sub>2</sub>CO<sub>3</sub>. As observed by Iwasawa and co-workers,<sup>(14)</sup> when the carboxylation of 5-bromo-1,3-benzodioxole was conducted using 2.5 mol% of Pd(OAc)<sub>2</sub> associated with 5 mol% XPhos in the presence of 2.5 mol% [Ir(ppy)<sub>2</sub>(dtbpy)][PF<sub>6</sub>] and *i*-Pr<sub>2</sub>NEt as sacrificial electron-donor a complete conversion was obtained with the formation of a near equimolar mixture of desired carboxylic acid (**a**) and hydrogenated product (**b**). As a control experiment, we shown that JPhos is utterly inefficient for this transformation. Interestingly, the use of biarylphosphine ligands holding a cyano (**a/b** = 57:43), pyridine (**a/b** = 59:41), or amide (**a/b** = 79:21) group give better selectivity in favor of the formation of the carboxylated product **a**, and the better selectivity is obtained

with phosphine-amide ligands. However, in all cases, we observed a moderate conversion, which can be attributed to the formation of the Pd-cyclometalated phosphine complex. The formation of this inactive complex can be avoided when both *ortho*'-positions are substituted.<sup>(20)</sup> We, therefore, decided to evolve our phosphine design by incorporating an amide group at each *ortho*'-positions. The use of phosphine–diamide gives good conversion and selectivity (85%, 79:21). Interestingly, the hybrid ligand containing an ester and an amide group affords a slightly better conversion with similar selectivity (91%, 80:20). This result inspired us to design a surfactant phosphine by incorporating a fatty ester instead of methyl ester. This feature should allow to perform the reaction in water media under low catalyst loading.<sup>(21)</sup> This multifunctional phosphine, which bears an amide and fatty ester groups at the *ortho*'-positions of JPhos, enabled to run the carboxylation in water-media using as little as 0.5 mol% of Pd(OAc)<sub>2</sub>/2Phosphine. These conditions gave the best result 95:5 selectivity in favor of carboxylic acid **a** with a total conversion.



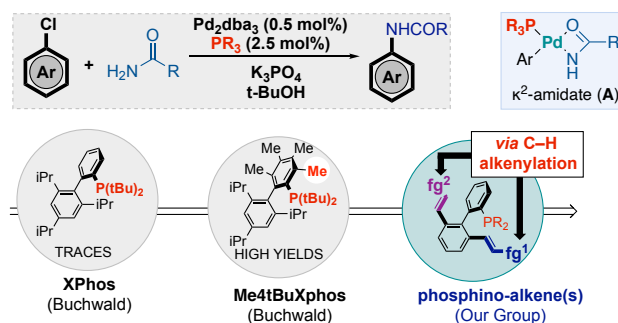
**Scheme 5** Application of Multifunctional Phosphines in Pd-Catalyzed Carboxylation of Aryl Bromides

We have shown that Rh(I)-catalyzed C–H bond alkylation directed by P(III) atom with functional alkenes has several advantages: *i*) to allow the one-step diversifications of commercially available phosphines, *ii*) to exhibit high functional group tolerance, *iii*) to modulate the catalytic activity of phosphines by incorporating functional group, *iv*) to modify the physical properties (i.e., solubility, hydrophilicity) of the ligands. Shi's group employed a similar strategy to enhance the enantioselectivity of Rh-catalyzed asymmetric addition of aryl boronic acids to isatins using alkylated (R)-H-MOP ligands.<sup>(22)</sup> It is also possible to employ Ru(II) catalysis to alkylate biarylphosphines at *ortho*'-positions, albeit only PPh<sub>2</sub> acts as a directing group.<sup>(23)</sup>



#### 4. Synthesis of Multifunctional Biarylphosphines by late-stage Alkenylation: Application in Amidation Reaction

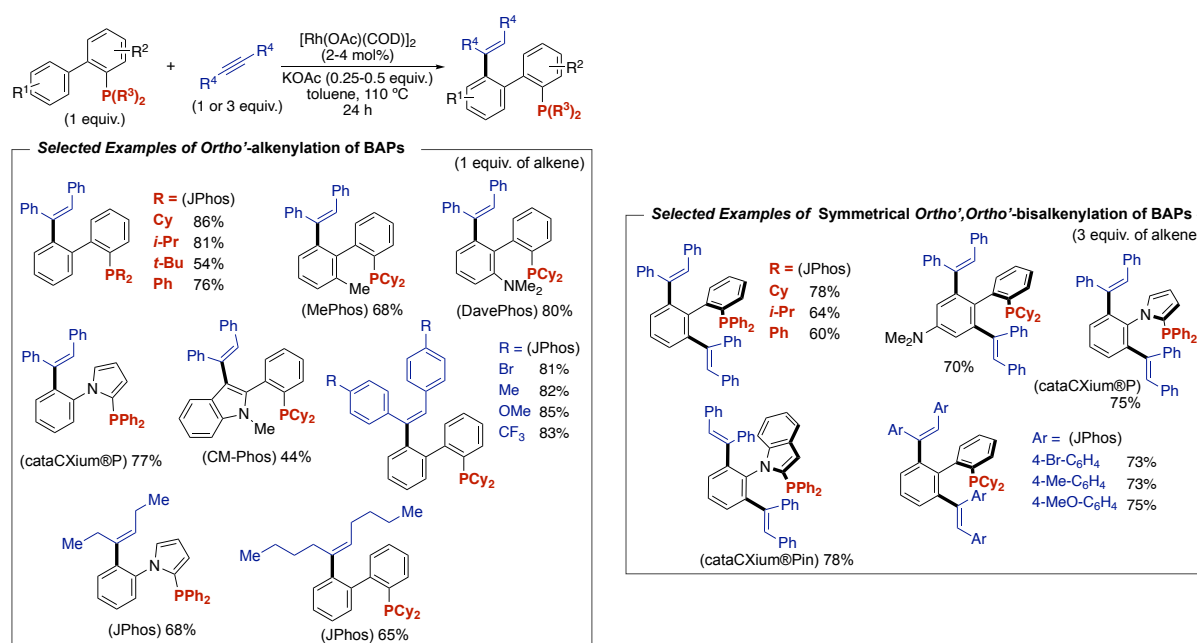
Pd-catalyzed C–N bond formation from aryl(pseudo) halides and *NH*-compounds has become a mainstream transformation to access *N*-containing molecules, but many common functional groups were still incompatible or decreased the reactivity.<sup>(24)</sup> For instance, the cross-coupling between aryl chlorides, especially *ortho*-substituted ones, with amides is often sluggish, requiring the development of specific phosphines to overcome both matters: *i*) the low rate of oxidative addition of aryl chlorides into Pd(0); *ii*) the formation of  $\kappa^2$ -amidate palladium intermediate complex (**A**), where the amidate is bound to the palladium center at both the oxygen and nitrogen atoms, which inhibits reductive elimination and therefore catalytic turnover (Figure 3).<sup>(25)</sup> Buchwald and co-workers showed that bulky biaryl monophosphine ligands such as XPhos, which is a relatively general and efficient ligand for cross-coupling reaction of aryl halides, was inactive for the intermolecular amidation of aryl chlorides. They next decided to increase the bulk of the phosphine by adding four methyl groups on the upper ring of XPhos. This design modification affords Me4tBuXPhos. When it is associated with Pd(0) salts it exhibited high catalytic performance for amidation of aryl chlorides. They proposed that the addition of a single methyl group to the upper phenyl ring of the phosphine is the source of the enhanced stability of the catalytic system due to a specific conformation preventing the formation of  $\kappa^2$ -amidate palladium intermediate complex (**A**).



**Figure 3** Phosphine Design for Pd-Catalyzed Amidations of Aryl Chlorides

We decided to design specific very bulky biarylphosphine ligands by replacing the *i*-Pr group at both *ortho*'-position of XPhos by vinyl substituents through Rh(I)-catalyzed C–H bond alkenylation directed by P(III) atom.<sup>(26)</sup> This approached allows the preparation of a library of diversely substituted phosphino-alkene ligands in only one step. The reaction conditions were similar to those employed for the C–H bond alkylation, albeit KOAc (0.25 equivalent) replaced PivOH (Scheme 6). From an equimolar ratio between phosphine and alkyne, only mono-functionalized biarylphosphines were obtained, while the use of 3 equivalents alkynes with a double amount of catalyst and base offered the difunctionalization of biarylphosphines at both *ortho*'-positions. The reactions of biphenyl bearing (dicyclohexylphosphino), (di-*iso*-propylphosphino), (di-*tert*-butylphosphino) or diphenylphosphino

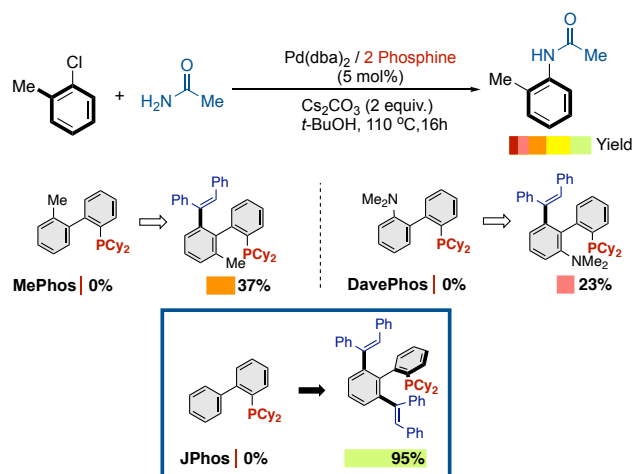
have afforded the corresponding phosphine-alkene ligands in good to excellent yields. *Ortho*'-substituted biarylphosphines such as MePhos and DavePhos could also be alkenylated in high yields. Heterocyclic biarylphosphines such as cataCXium®P or CM-Phos afforded the corresponding hybrid ligand in good yield. Diversely substituted 1,2-diarylalkynes [e.g., 4-Br (81%), 4-Me (82%), 4-OMe (85%), or 4-CF<sub>3</sub> (83%)] could also be employed as alkyne partners in cross-coupling with JPhos allowing the formation of functionalized phosphino-alkene ligands. Even the less reactive hex-3-yne and dec-5-yne were have been successfully coupled with biarylphosphines. We also surveyed the difunctionalization of biarylphosphine *ortho*' C–H bonds using three equivalent of internal alkynes in the presence of 4 mol% of [Rh(OAc)(COD)]<sub>2</sub> associated with 50 mol% KOAc in toluene at 110 °C (Scheme 2). Cy-, *i*-Pr- and Ph-JPhos were efficient bis-*ortho*'-alkenylated affording phosphino-dialkene hybrid ligand in good yields. The introduction of a strong electron-donating group, such as NMe<sub>2</sub>, did not affect the reactivity. The two-fold C–H bond activation/functionalization of cataCXium®P and cataCXium®Pin occurred in 75% and 78% yield, respectively. Symmetrical *para*-substituted diarylacetylene (*i.e.*, R = Br (73%), Me (73%), OMe (75%)] have been also coupled with Cy-JPhos.



**Scheme 6** Rh(I)-Catalyzed C–H Bond Alkenylation of Biarylphosphines using Functionalized Alkynes

We next demonstrate the positive effect of the introduction of alkenyl group on biarylphosphines by comparing the catalytic performance of a couple of these novels (bis)-alkenylated (dialkyl)biarylphosphines with their parent phosphine often used in Pd-catalyzed amidation of 2-chlorotoluene with acetamide (Scheme 7). We selected 2.5 mol% Pd(dbda)<sub>2</sub>/2phosphine and 2 equivalents of Cs<sub>2</sub>CO<sub>3</sub> in *t*-BuOH at 110 °C as reaction conditions. When commercially available MePhos was employed as phosphine ligand, no reaction occurred. However, alkenylated MePhos

allowed obtaining *N*-(*o*-tolyl)acetamide in a 37% yield. A similar trend was also observed with DavePhos and its alkenylated version. The most spectacular improvement was obtained from Cy-JPhos, which is a completely inactive ligand, while after two-fold C–H bond alkenylation with diphenylacetylene, the resulting dialkenylated phosphine exhibits high catalytic activity affording the desired *N*-(*o*-tolyl)acetamide in 95% yield. This positive rise of activity may arise from the presence of the very bulky alkenyl group at both *ortho*'-positions, which stabilize Pd intermediates by noncovalent interactions<sup>(27)</sup> or/and may avoid the formation of  $\kappa^2$ -amidate palladium intermediate complexes (A).



**Scheme 7** Application of Phosphino-Alkene(s) in Pd-Catalyzed Amidation of *ortho*-Substituted Aryl Chlorides

We have demonstrated by X-ray analysis that the introduction of 1,2-diphenylvinyl group as very bulky substituents onto JPhos scaffold at both *ortho*'-position induces a conformational switch of palladium complex from closed to open form. This conformational change as well as the noncovalent interactions between alkene group and palladium species could be responsible for the enhancement of the catalytic performance of the monophosphines paving the way for further design improvement.

## 5. Conclusion

In summary, phosphines modification by transition-metal catalyzed C–H activation, especially using rhodium catalysts, has emerged as an efficient strategy to speed up the preparation of libraries phosphine (hybrid) ligand with modulable electronic and steric properties. Facilitated by trivalent phosphorus atoms, phosphine late-stage modification can be achieved in a site-selective fashion. It is noteworthy that the C–H functionalization methods display extraordinary potency in generating highly functionalized phosphines that are usually inaccessible by other methods. Very interestingly, the structural change resulting from the C–H bond functionalization of phosphines often transforms phosphine-ligated palladium complexes displaying low catalytic activity into another system exhibiting

high performances. Representative examples are that development by our group of Rh(I)-catalyzed C–H bond alkylation or alkenylation of biarylphosphines that have morphed inactive JPhos into multifunctional phosphines enabling Pd-catalyzed carboxylation of aryl bromides or amidation of bulky aryl chlorides. In the light of this capacity to upgrade phosphine activity wrought by their C–H bond functionalizations, it would be exciting to delve deeper into many mainstream catalytic systems that employed phosphine to analyze if phosphines are modified along with the reaction and to identify the structure real catalytic active ligands.

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### Conflict of Interest

The authors declare no conflict of interest.

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### Biosketches



Zhuan Zhang (left) graduated from Jinan University (Guangzhou) with a M.Sc. in organic chemistry (2017) and received his Ph.D. at the University of Rennes 1 (France) in 2020 under the guidance of Professor P. H. Dixneuf and Dr

Jean-François Soulé, where he investigated the C–H bond functionalization of phosphine ligands. During his Ph.D. studies he had a short research stay at the Leibniz Institute for Catalysis (Germany). In 2021, he began his independent career at the Guangxi University. His current research interests include transition metal catalysis for C–H bond functionalization transformations.

Natacha Durand (middle) graduated at Le Mans University (Bachelor in Chemistry) and Rennes 1 University (Master in Molecular chemistry). During her master internship she has worked under the supervision of Dr. Jean-François Soulé on the improvement of catalytic performance of phosphines through their C–H bond functionalization.

Jean-François Soulé (right) received his Ph.D. from Paris-Saclay University under the supervision of Jean-Marie Beau. From 2010 to 2013 he worked as a postdoctoral researcher in the group of Shū Kobayashi at the University of Tokyo (Japan). He was appointed as CNRS Researcher in 2013 at the Institut des Sciences Chimiques de Rennes (ISCR) in the team led by Henri Doucet. He obtained his « Habilitation à Diriger les Recherches » HDR in 2017. His work focuses on catalysis for regioselective C–H bond functionalizations. In 2020, he was awarded by Thieme Chemistry Journal and he won the Jean-Pierre Sauvage Prize from French Chemical Society-DCO.