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Cooperative Ligand-Promoted $P^{(III)}$-Directed Ruthenium-Catalyzed Remote *Meta*-C−H Alkylation of Tertiary Phosphines

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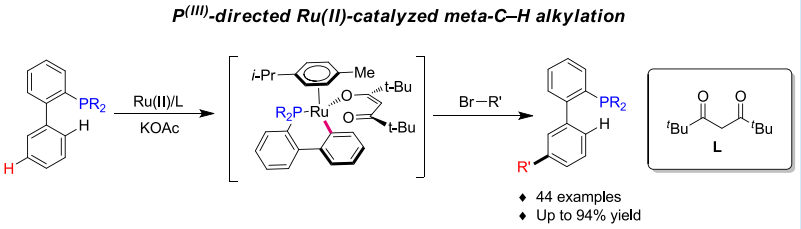
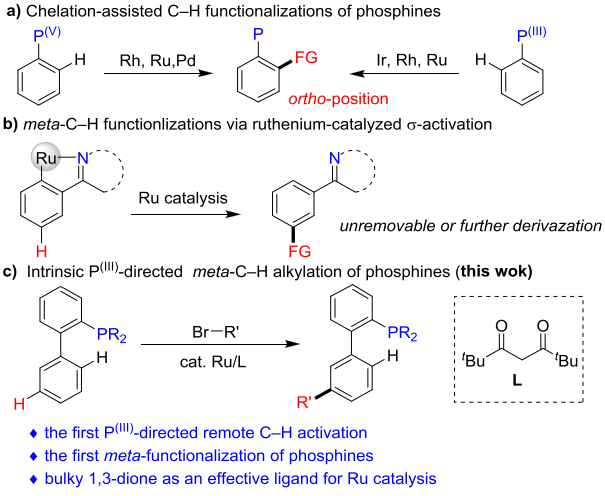


ABSTRACT: Herein, we disclose a ruthenium-catalyzed *meta*-selective C−H activation of phosphines by using intrinsic $P^{(III)}$ as a directing group. 2,2,6,6-Tetramethylheptane-3,5-dione acts as the ligand and exhibits an excellent performance in boosting the *meta*-alkylation. The protocol allows an efficient and straightforward synthesis of *meta*-alkylated tertiary phosphines. Several *meta*-alkylated phosphines were evaluated for Pd-catalyzed Suzuki coupling and found to be superior to commercially available *ortho*-substituted phosphines. The practicability of this methodology is further demonstrated by the synthesis of difunctionalized phosphines.

Organic phosphines constitute an important class of molecules, which finds widespread applications in the field of medicine, materials, organocatalysis, and particularly metal catalysis as effective ligands.[1] The importance of phosphines provides a continuous driving force for the development of more efficient synthetic methods. In recent years, transition metal-catalyzed C(sp^2)−H bond activation[2] provides an efficient approach to functionalize phosphines.[3] For instance, selective C−H functionalizations of phosphines via *O*- or *S* directed C(sp^2)−H activation were independently developed by Miura, Glorius, and other groups.[4] Recently, $P^{(III)}$-assisted *ortho*-C(sp^2)−H functionalizations of phosphines were accomplished by Clark, Shi, Soule, Takaya, and our group, respectively (Scheme 1a).[5] Compared with these advances gained in *ortho*-C−H functionalization, selective *meta*-C(sp^2)−H functionalization of phosphines remains unsolved and seems rather challenging, especially for tertiary phosphines in virtue of its strong coordination ability.[6] Herein, we report a ruthenium-catalyzed *meta*-C(sp^2)−H alkylation of tertiary phosphines by using intrinsic P^{III} as a directing group (Scheme 1c), which provides an efficient and rapid access to a variety of synthetically useful phosphines from commercially available precursors.

In recent years, *meta*-C(sp^2)−H functionalization witnessed rapid progress.[7,8] In this area, several examples of *meta*-C−H functionalization via ruthenium-catalyzed *σ*- activation were independently reported by Ackermann, Frost, Greaney, et al.[9] In those transformations, strongly *N*-based coordinating groups including heteroaromatic pyridyl, pyrazolyl, imidazolyl, and pyrimidyl are required as the directing groups. However, the difficulty in removal or derivatization of these directing groups poses a fatal threat to its synthetic practicability. Notably, Ackermann et al. designed a removable *N*-(pyrimidine-2-yl) group for directing ruthenium-catalyzed

Scheme 1. C−H Functionalizations of Phosphines



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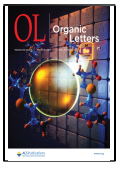

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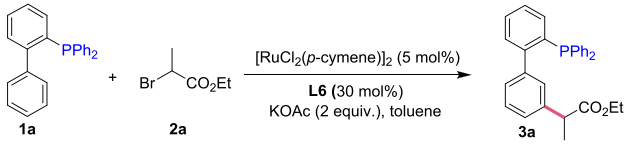
meta-C−H alkylation of anilines.[9b] Recently, we reported the ruthenium-catalyzed *ortho*-C−H functionalizations of phosphines[5k,l] in which a key six-membered ruthenacycle was successfully isolated. Based on these results, we envisioned that selective *meta*-C−H functionlization of tertiary phosphines could be achieved with the strategy of ruthenium-catalyzed σ-activation. We hypothesized that a six-membered ruthenacycle could be formed and might electronically enhance the activation of *para* position and, hence, enable *para*-functionalization to the ruthenium center. The success of this strategy lies in the identification of an efficient catalytic system, especially a suitable ligand to enhance the ruthenium center electronically as well as promote the step of reductive elimination.

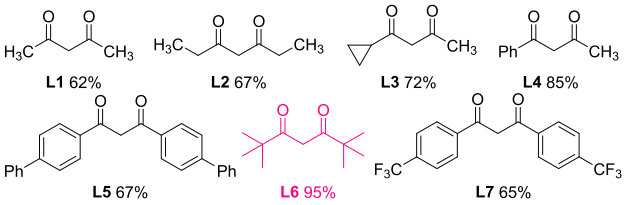
To test our hypothesis, we chose the [1,1′-biphenyl]-2-yldiphenylphosphane **1a** with **2a** as the model reactants (Table 1). After extensive investigations of various reaction parameters, the desired *meta*-C(sp^2)−H-alkylated product **3a** was obtained in 93% yield with excellent regioselectivity under the conditions of $[RuCl_2(p\text{-cymene})]_2$ as the catalyst, highly sterically hindered bidentate 2,2,6,6-tetramethylheptane-3,5-dione **L6** as the ligand and KOAc as the base, in toluene under argon (see the Supporting Information for details). Further investigations showed that organic acids, such as 1-AdCO$_2$H, MesCO$_2$H, and monoprotected amino acids, were not beneficial for the transformation, probably due to their lower steric hindrance (Table 1, entries 2−5). Other bases such as K_2CO_3 and NaOAc were also tested but did not give better results (entries 6 and 7). Control experiments indicated that ruthenium catalyst is essential to this reaction, and **L6** is rather crucial to achieve a high catalytic efficiency (entries 8 and 9). The high efficiency of 1,3-dione ligands may result from the strong coordination of the dioxygen atom to the ruthenium center.[10] Other 1,3-dione compounds were also investigated. In comparison to **L6**, less steric symmetric or unsymmetric dialkyl-substituted 1,3-diones such as **L1**−**L4** as well as less electron-withdrawing and less sterically hindered diaryl 1,3-diones such as **L5** and **L7**, unfortunately, did not afford a higher yield.

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

entry	Variation of standard conditions	yield (%)[b]
1	none	95 (93)[c]
2	1-AdCOOH instead of **L6**	17
3	MesCO$_2$H instead of **L6**	48
4	*N*-Boc-Phe-OH instead of **L6**	40
5	*N*-Ac-β-Ala-OH instead of **L6**	50
6	K_2CO_3 instead of KOAc	20
7	NaOAc instead of KOAc	62
8	Without **L6**	36
9	Without $[RuCl_2(p\text{-cymene})]_2$	0

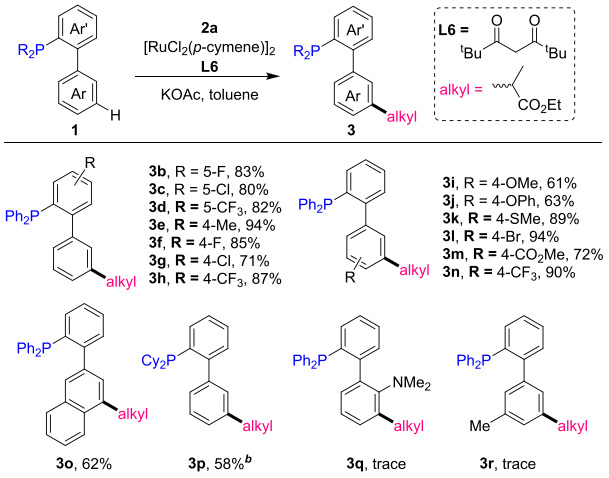


[a]Reaction conditions: **1a** (0.20 mmol), **2a** (0.60 mmol), 5 mol % $[RuCl_2(p\text{-cymene})]_2$, 30 mol % **L6**, KOAc (2 equiv), 1 mL of toluene, at 140 °C, 24 h, under argon. [b]Yields determined by ^{1}H NMR using CH_2Br_2 as the internal standard. [c]Isolated yield.

With the optimized conditions in hand, we first investigated the scope of phosphines (Scheme 2). A broad range of Buchwald-type biaryl monophosphines bearing electron-rich and electron-deficient substituents at both phenyl rings coupling with **2a** could afford the corresponding *meta*-alkylated products in moderate to high yields (**3b**−**3o**, 61−94%). Most common and widely used functional groups, such as OMe (**3i**), SMe (**3k**), F (**3b** and **3f**), Cl (**3c** and **3g**), and CO$_2$Me (**3m**), were all tolerant. Substrates with a strongly electron-withdrawing CF$_3$ substituent (**1d**, **1h** and **1n**) could undergo an organometallic C−H activation by base assistance, generating the corresponding product in high yields. Notably, the active Br group could also survive, delivering the desired product **3k** in 89% yield, which can be used for further diversification. Phosphine-containing naphthyl group (**1o**) was also compatible, affording the *meta*-alkylated product **3o** in 62% yield with high regioselectivity. Besides Ph$_2$P-based monophosphines, dialkylphosphine such as CyJohnPhos with PCy$_2$ substituent **1p** could also afford the desired product **3p** in moderate yield by using a less sterically hindered 1-cyclopropylbutane-1,3-dione ligand **L3**. Unfortunately, phosphines with substituents at *ortho*- and *meta*-positions had low activities probably due to challenges in *ortho*-C−H bond metalation.

Next, we performed the *meta*-alkylation of **1a** with various alkyl bromides **2** (Scheme 3). Diverse secondary alkyl bromides such esters, amides, and ketone could be used as *meta*-alkylating reagents. Ester substrates with primary alkyl and tertiaryl alkyl group deriving from alcohols could react

Scheme 2. Scope of Phosphines[a]



[a]All of the reactions were performed on a 0.3 mmol scale in 2 mL of toluene at 140 °C under argon, 24 h, isolated yields. [b]**L3** used as ligand at 160 °C.

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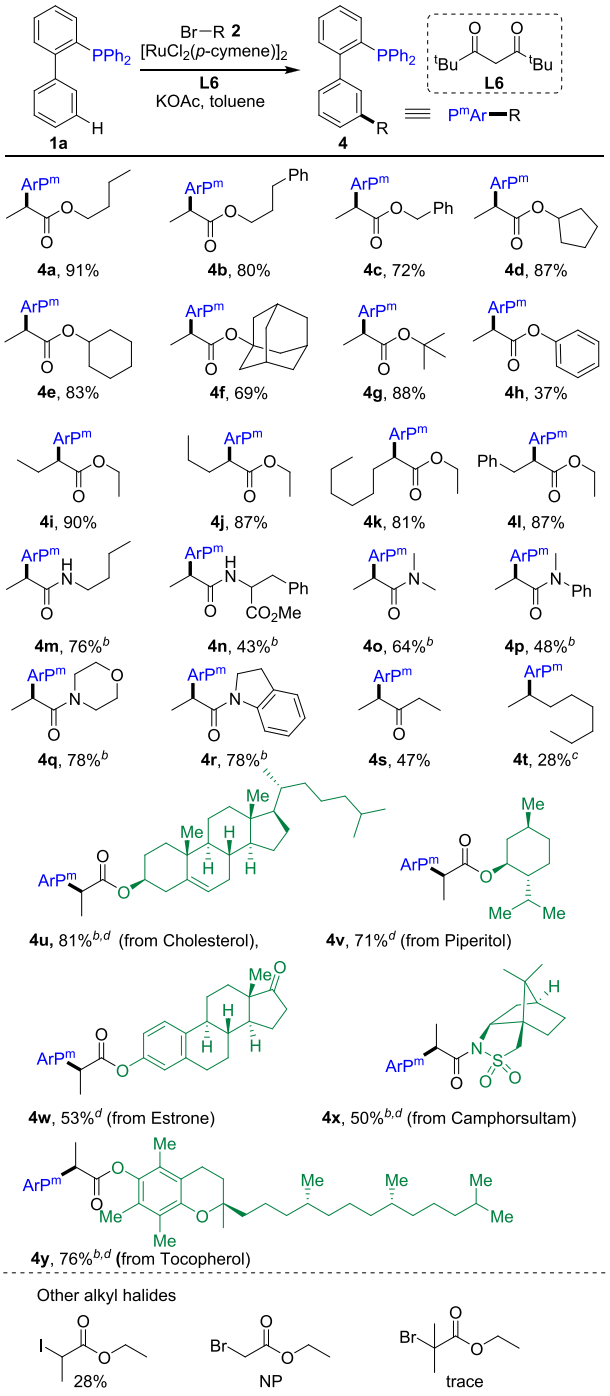
Scheme 3. Scope of the Alkyl Bromides[a]

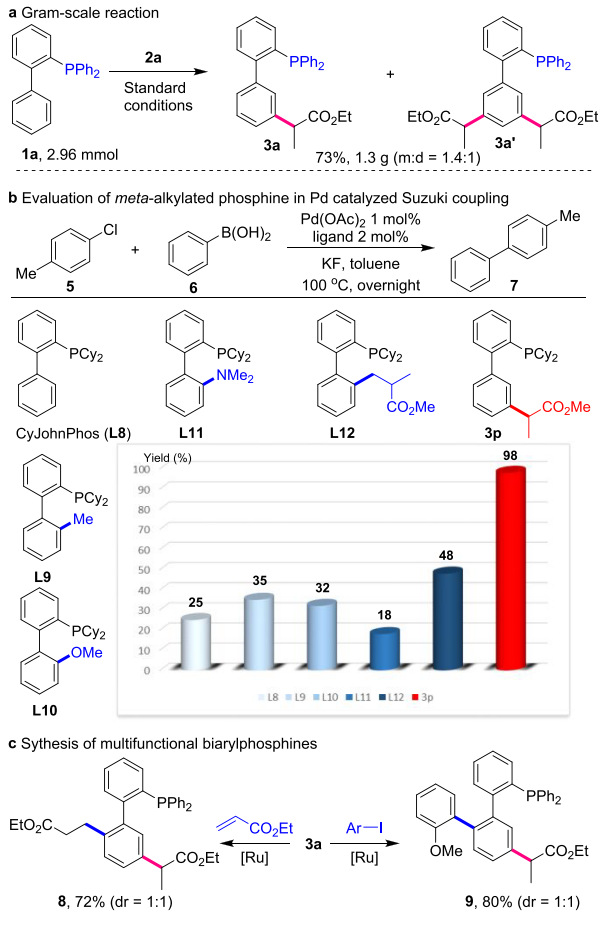


[a]Reactions were performed on a 0.3 mmol scale in 2 mL of toluene at 140 °C under argon, 24 h, isolated yields. [b]oxidized by H_2O_2. [c]at 160 °C. [d]reactions were performed on a 0.20 mmol scale. NP = no product.

with **1a**, affording the corresponding products in 69−91% yields (**4a**−**4g**). Cyclic substrates from cyclopentanol, cyclohexanol, and adamantyl alcohol could be installed at the *meta*-position of arenes in good yields (**4d**−**4f**). Besides alkyl esters, phenyl ester from phenol (**2h**) could be tolerated as well. Notably, other α-substituted substrates with Et, ^{n}Pr, ^{n}Hex, and Bn groups were suitable for this *meta*-functionalization, giving the desired products in 81−90% yields (**4i**−**4l**). Apart from esters, secondary and tertiary amides were also found to be viable for *meta*-alkylation, generating the corresponding *meta*-alkylated phosphines in moderate to high yields (**4m**−**4r**). In addition, ketone substrate (**2s**) was suitable for this *meta*-alkylation reaction, giving the alkylated phosphine (**4s**) in a lower yield, maybe due to the strong electron-withdrawing property of carbonyl group. Notably, unactivated alkylating reagent such as 2-bromooctane also worked, affording the desired *meta*-alkylation product (**4t**) in an acceptable yield at a higher temperature, in which a large proportion of the phosphine (**1a**) were retained due to the low reactivity of **2t**. Other alkyl halides such as alkyl iodide, primary alkyl bromide, and tertiary alkyl bromide were also investigated. Alkyl iodide could react with phosphine, giving the desired product in a low yield. Primary and tertiary alkyl bromides were not suitable for this reaction. Pleasingly, substrates derived from natural products and drug molecules, such as cholesterol (**2u**), piperitol (**2v**), estrone (**2w**), camphorsultam (**2x**), and tocopherol (**2y**) also tolerated the reaction, affording the corresponding products in 50−81% yields.

To demonstrate the practicability of this protocol, a gram-scale reaction of **1a** and **2a** was conducted, giving the mono- and di-*meta*-alkylation products **3a** and **3a′** (1.3 g) in 73% yield (Scheme 4a). Next, the catalytic activity of *meta*-alkylated phosphines was evaluated in the palladium-catalyzed Suzuki coupling reaction (Scheme 4b). Aryl chlorides act as promising arylating reagents in Suzuki coupling reactions owing to its low cost and easily available property. However, due to high dissociation energy of C−Cl bond, they show low activities.

Scheme 4. Synthetic Applications



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Buchwald et al. explored that bulky monobiarylphosphine can effectively improve the reaction activity of aryl chlorides. We believed that the introduction of alkyl groups into the *meta* position of biarylphosphines can increase their electron density and steric hindrance, thus promoting the oxidative addition and reduction elimination steps of palladium catalyst. Therefore, we evaluated the potential of CyJohnPhos congeners in the cross-coupling of 4-methyl-phenyl chloride **5** and phenylboronic acid **6**. A series of commercially available CyJohnPhos ligands (**L8**) bearing *othro*-substituents, such as Me (**L9**), OMe (**L10**), and NMe_2 (**L11**) groups, associated with $PdOAc_2$ gave the biaryl product **7** in low yields (18−35%). The *ortho*-alkylated CyJohnPhos (**L12**) prepared via hydroarylation of alkene and CyJohnPhos proved a higher activity, giving the product in 48% yield. To our delight, up to 98% yield was obtained when the *meta*-alkylated CyJohnPhos (**3p**) was used, probably owing to its unique *meta*-effect in electronic and steric properties. These results demonstrated the potential synthetic utilizations of *meta*-alkylated phosphines in metal catalysis. Interestingly, the product **3a** could be further transformed into *ortho*- and *meta*-difunctionalized phosphines (**8**, 72%) and (**9**, 80%) in high yields with our previous *ortho*-alkylation and arylation of biaryphosphines (Scheme 4c).

To gain insight into this transformation, radical-trapping experiments were performed. No desired product **3a** was obtained in the presence of TEMPO or 1,1-diphenylethylene, indicating the reaction may undergo a radical process (Table S4). To further explore the mechanism, control experiments were conducted (Schemes S6−S10). The possible cycloruthenated intermediate **Int A** was prepared (Scheme S6). With the **Int A** as catalyst, 80% yield of **3a** was obtained (Scheme S7). When the **Int A** was used as the substrate, product **3a** was also isolated in 20% yield (Scheme S8), suggesting that the cycloruthenated intermediate **Int A** may be an intermediate in this catalytic cycle. Next, the H/D exchange experiment was conducted under the standard conditions in the presence of methanol-d_4 (Scheme S9), 86% and 52% deuterium substitutions were observed at both *ortho* and *ortho*′-C−H bonds. However, no H/D exchange happened at the *meta*-C−H bond which implied that activations of *ortho*- and *ortho*′-C−H bonds are reversible while the cleavage of *meta*-C−H bond is irreversible. At last, the KIE value of *ortho*-C−H activation in *meta*-alkylation of **1a** and **D5−1a** with phosphine **2a** was 4.6:1 (Scheme S10), revealing that the *meta*-C−H cleavage is the rate-determining step.[11] On the basis of these experimental results and previous literatures,[9,11] a plausible catalytic cycle is proposed (Scheme S11).

In summary, we developed a novel *meta*-C−H functionalization of phosphines by using the intrinsic $P^{(III)}$ as the directing group via ruthenium-catalyzed σ-activation, which provides a straightforward and efficient access to *meta*-alkylated phosphines. This protocol features a broad scope of alkyl bromide such as esters, amides, ketone, and alkane, including complicated natural product derivatives. The choice of a bulky bidentate 1,3-dione ligand is crucial for the improvement of catalytic efficiency. Mechanistic investigations suggest the reaction may undergo a radical pathway involving the formation of six-membered cycloruthenium intermediate. This work paves a new way to the synthesis of remote-substituted phosphines. Further applications of phosphines and more detailed mechanistic investigations are ongoing in our lab.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00237.

Detailed experimental procedures and compound characterization data (PDF)

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Notes

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