OL Organic Letters

pubs.acs.org/OrgLett Letter

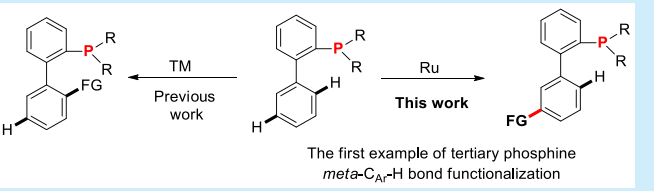
m-C_{Ar}–H Bond Alkylations and Difluoromethylation of Tertiary Phosphines Using a Ruthenium Catalyst

Gang Li,* Jiangzhen An, Chunqi Jia, Bingxu Yan, Lei Zhong, Junjie Wang, and Suling Yang

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c03377 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

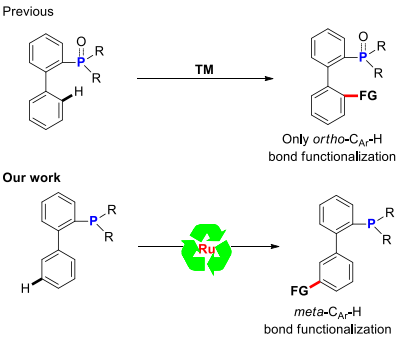
ABSTRACT: *m*-C_{Ar}–H bond functionalization of tertiary phosphines was developed using $[Ru(p\text{-cymene})Cl_2]_2$ as a catalyst. Desired product structures were confirmed by single-crystal X-ray diffraction. Mechanistic experiments indicated that *m*-C_{Ar}–H bond functionalization was a radical reaction and that a hexagonal ruthenacycle complex was a crucial intermediate in the process. Therefore, this study provides a novel method for the late-stage *meta*-position modification of biphenyl monophosphine ligands.



Tertiary phosphines (PAr_3) are important molecular skeletons widely found in agricultural chemicals, biologically active molecules, and functional materials, and as ligands in transition-metal catalysts.[1] Their characteristics, including physicochemical, steric, and electronic properties, and biological and catalytic activities, are significantly changed by different R group structures.[2] In particular, biphenyl monophosphines that are air-stable and have greater steric hindrance are often employed as highly efficient ligands in the transition-metal catalysis of diverse C–X bond construction (X = C, O, N, and others).[3] Consequently, the straightforward and efficient synthesis of biphenyl monophosphines has attracted considerable research interest. In recent years, transition-metal-catalyzed C–H bond functionalization has seen intensive development and extensive applications in organic synthesis owing to its atom and step efficiency compared with traditional functional group chemistry.[4] Initially, as the strong chelating properties of undisguised monophosphines readily poison the metal catalyst, P(V)=O was often employed as a directing group to realize transition-metal-catalyzed selective C_{Ar}–H bond functionalization,[5] with subsequent reduction providing various biphenyl monophosphine derivatives. Recently, undisguised P(III) atom-directed transition-metal-catalyzed selective C_{Ar}–H bond functionalization has been reported, providing a step-economical method for the late-stage modification of monophosphine ligands.[6] However, these modification and functionalization methods for biphenyl monophosphines are limited to the *ortho* position relative to the directing group (Scheme 1). Therefore, remote C_{Ar}–H bond functionalization of biphenyl monophosphines remains challenging.

In recent years, remote C_{Ar}–H bond functionalization has made important progress through several ingenious strategies, including using steric effects,[7] electronic effects,[8] U-shaped templates,[9] a norbornene relay,[10] traceless directing groups,[11] a copper-promoted four-ring intermediate,[12] and the *ortho*/*para*-directing effect of the Ru–C_{Ar} bond.[13] In these *m*-C_{Ar}–H bond functionalization strategies, the ruthenium-catalyzed *m*-C_{Ar}–H bond functionalization reaction type is diverse, the ruthenium catalyst is relatively inexpensive, and the reaction system is relatively simple. Furthermore, special substrate structures, large U-shaped directing groups, directing group removal, and the addition of an extra cocatalyst are not needed. However, ruthenium-catalyzed *m*-C_{Ar}–H bond functionalizations have been limited to nitrogen-containing groups as directing groups. Using other atoms, such as phosphine and oxygen, to assist ruthenium-catalyzed *m*-C_{Ar}–H bond functionalization remains challenging. Herein, we report P atom-directed *m*-C_{Ar}–H bond functionalization catalyzed by ruthenium, which provides a

Scheme 1. P=O or P-Assisted C_{Ar}–H Bond Functionalization

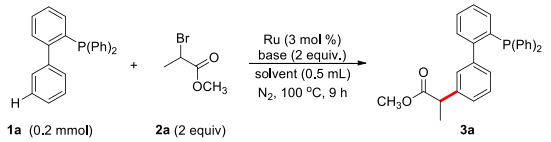


Received: October 9, 2020

new approach to the *meta*-position-modified synthesis of biphenyl monophosphine ligands.

To realize the phosphine-assisted modification and decoration of *m*-C_{Ar}–H bonds, [1,1′-biphenyl]-2-yldiphenylphosphane and methyl-2-bromopropanoate were selected as classic reactants, and $[Ru(p\text{-cymene})Cl_2]_2$ and K_2CO_3 were used as the catalyst and base, respectively, to explore and optimize the C–H bond functionalization conditions. In a thick-walled pressure Schlenk tube under a N_2 atmosphere, the reaction was carried out at 100 °C for 9 h, as shown in Table 1. Pleasingly, a small amount of the desired product was obtained in the benzene solvent (entry 1). Base screening indicated that KOAc was the most suitable base for the transformation, providing desired product **3a** in 73% isolated yield (entry 2). Other bases, such as Na_2CO_3, Cs_2CO_3, CsOAc, NaOAc, and K_3PO_4, were also effective in the process (entries 3–7, respectively), although the yields were lower than that obtained using KOAc. The target product was also obtained in other aromatic solvents, such as toluene, xylene, 1,4-dioxane, and THF (entries 8–11, respectively). The reaction did not proceed in CH_3CN and DMF as solvents (entries 12 and 13, respectively). Further investigation indicated that $Ru(PPh_3)_3Cl_2$ was also an effective catalyst for *m*-C_{Ar}–H bond alkylation, giving the target product in a moderate yield (entry 14). Other ruthenium complexes, such as $RuCl_3$ and $Ru_3(CO)_{12}$, were ineffective in the process (entries 15 and 16, respectively). The desired product was not obtained when no catalyst was added to the system (entry 17). Furthermore, additional experiments indicated that the temperature and reaction time were critical factors in the transformation. Both prolonging the reaction time and increasing the reaction temperature resulted in product decomposition and reduced yields.

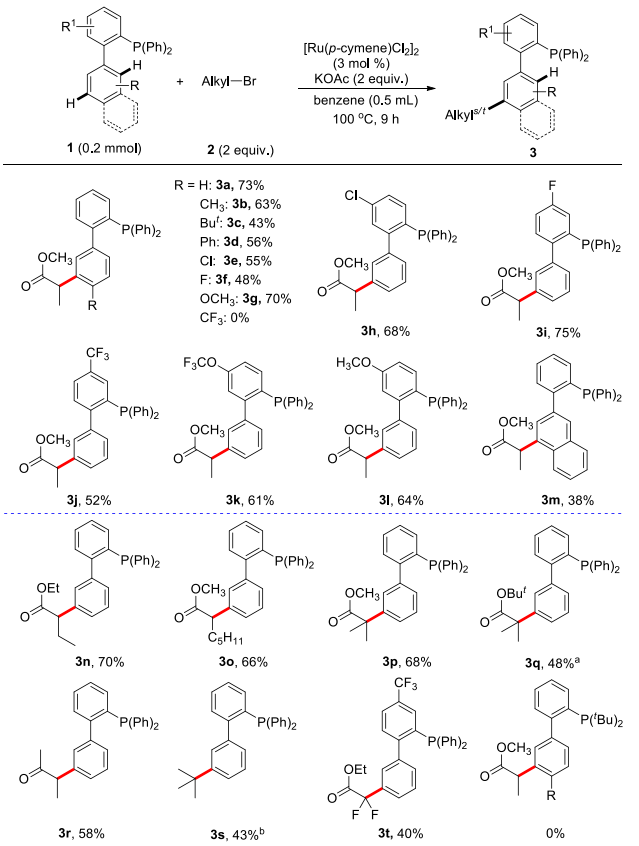
Table 1. Screening of Reaction Conditions



entry	Ru catalyst	base	solvent	yield (%)
1	$[Ru(p\text{-cymene})Cl_2]_2$	K_2CO_3	benzene	13
2	$[Ru(p\text{-cymene})Cl_2]_2$	KOAc	benzene	73
3	$[Ru(p\text{-cymene})Cl_2]$	Cs_2CO_3	benzene	18
4	$[Ru(p\text{-cymene})Cl_2]$	Na_2CO_3	benzene	25
5	$[Ru(p\text{-cymene})Cl_2]$	CsOAc	benzene	56
6	$[Ru(p\text{-cymene})Cl_2]$	NaOAc	benzene	70
7	$[Ru(p\text{-cymene})Cl_2]$	K_3PO_4	benzene	30
8	$[Ru(p\text{-cymene})Cl_2]$	KOAc	toluene	62
9	$[Ru(p\text{-cymene})Cl_2]$	KOAc	xylene	45
10	$[Ru(p\text{-cymene})Cl_2]$	KOAc	1,4-dioxane	22
11	$[Ru(p\text{-cymene})Cl_2]$	KOAc	THF	28
12	$[Ru(p\text{-cymene})Cl_2]$	KOAc	CH_3CN	0
13	$Ru(p\text{-cymene})(OAc)_2$	KOAc	DMF	0
14	$Ru(PPh_3)_3Cl_2$	KOAc	benzene	42
15	$RuCl_3$	KOAc	benzene	0
16	$Ru_3(CO)_{12}$	KOAc	benzene	0
17		KOAc	benzene	0

With optimized conditions in hand, we next investigated the scope and generality of this phosphine-assisted ruthenium-catalyzed *m*-C_{Ar}–H bond alkylation of arenes with alkyl bromides, as shown in Scheme 2. Initially, several [1,1′-biphenyl]-2-yldiarylphosphane molecules with various substituents in different positions on the phenyl ring were selected as substrates. [1,1′-Biphenyl]-2-yldiphenylphosphanes with different alkyl (**3b** and **3c**) and aryl (**3d**) groups were suitable substrates for the transformation. Although the bulky *tert*-butyl group usually has a marked steric effect in many organic reactions, the desired product was afforded in a moderate yield under the optimized conditions (**3c**). Halogen substituents survived in the *m*-C_{Ar}–H bond alkylation, offering the potential opportunity to construct complex functional molecules (**3e**, **3f**, **3h**, and **3i**). Further experiments indicated that the electronic effect of the reactive phenyl ring was obvious in the transformation. An electron-donating substituent (-OCH_3, **3g**) was favorable for transformation, while an electron-withdrawing (-CF_3) group completely impeded the reaction. The electronic effect of the directing group on the phenyl ring was not obvious in the process. Neither electron-withdrawing groups nor electron-donating groups had a significant effect on the reaction (**3h**–**3l**). Fluorine-containing groups with unique chemical, biological, and physical properties were also compatible with the *m*-C_{Ar}–H bond functionalization (**3i**–**3k**). Notably, [2-(naphthalen-2-yl)phenyl]-diphenylphosphane was also tolerated in the process, providing the product in a moderate isolated yield (**3m**). Furthermore, various alkyl bromides were employed as alkylating reagents in the transformation. The results showed that both *sec*-alkyl and

Scheme 2. Substrate Scope[c]



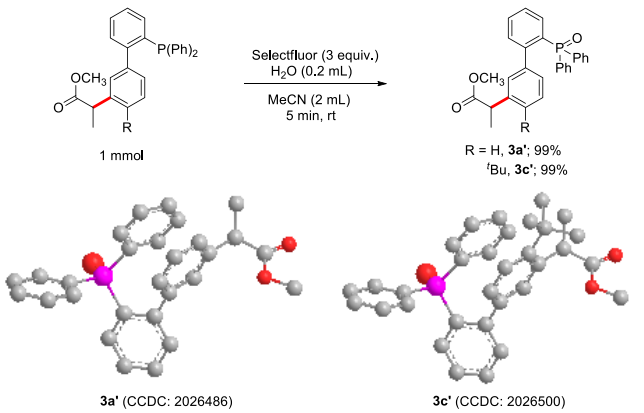
[a]For 3.5 h. [b]For 12 h. [c]Reaction conditions: **1** (0.2 mmol), **2** (2 equiv), $[Ru(p\text{-cymene})Cl_2]_2$ (3 mol %), KOAc (2 equiv), benzene (0.5 mL), N_2, 100 °C, 9 h. Isolated yield.

https://dx.doi.org/10.1021/acs.orglett.0c03377
Org. Lett. XXXX, XXX, XXX–XXX

tert-alkyl bromides were good coupling reagents in the phosphine-assisted *m*-C_{Ar}–H bond alkylation (**3b**–**3s**). However, no alkylated products were found in the system when primary alkyl bromides, such as ethyl 2-bromoacetate and ethyl 4-bromobutanoate, were employed as alkylation reagents. To our delight, the alkylation conditions were also extended to phosphine-assisted *m*-C_{Ar}–H bond difluoroalkylation (**3t**), providing a novel method for preparing *meta*-fluoroalkylated biphenyl monophosphine compounds. Unfortunately, when alkyl phosphine was used as the directing group, the desired product was not found in the system.

To further confirm the product structures obtained by phosphine-assisted *m*-C_{Ar}–H bond alkylation, the liquid desired products were oxidized to solid phosphine oxides in a H_2O/CH_3CN solvent [1:10 (v/v)] at room temperature for 5 min using Selectfluor as an oxidant (Scheme 3).[14] The

Scheme 3. Oxidation of Desired Products and Single-Crystal X-ray Structures

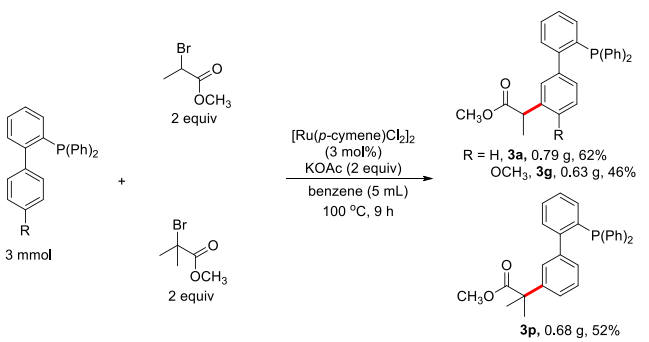


phosphine oxide single crystals were grown in a CH_2Cl_2/petroleum ether mixed solvent by slow evaporation at room temperature, and their crystal structures were determined by single-crystal X-ray diffraction.

In a gram-scale experiment, the phosphine-assisted ruthenium-catalyzed *m*-C_{Ar}–H bond alkylation of arenes with alkyl bromides also proceeded smoothly, giving the target product in a moderate yield (Scheme 4). This development provides a novel and practical strategy for the late-stage *meta*-position modification of biphenyl monophosphine ligands.

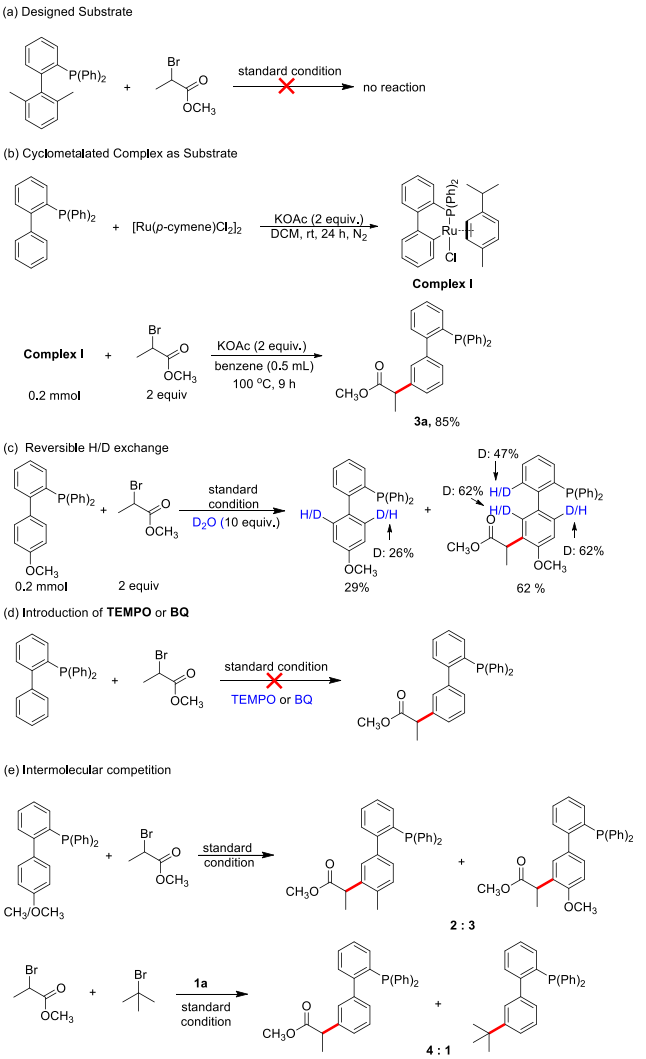
To clarify the mechanism of this ruthenium-catalyzed tertiary phosphine *m*-C_{Ar}–H bond functionalization, some experiments were designed and conducted, as shown in

Scheme 4. Gram-Scale Experiment



Scheme 5. First, when (2′,6′-dimethyl-[1,1′-biphenyl]-2-yl)-diphenylphosphane, in which the two *ortho* sites of the tertiary

Scheme 5. Designed Experiment



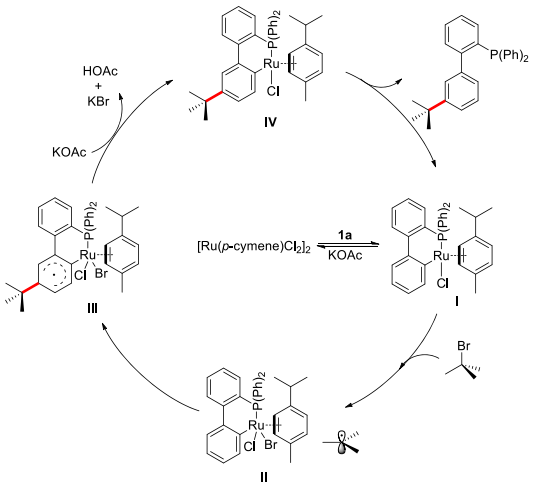
phosphine directing group were blocked by two methyl groups, was employed as the substrate, the desired product was not found in the system under the optimized conditions (Scheme 5a). The results showed that *o*-C_{Ar}–H bond ruthenation was essential for *m*-C_{Ar}–H bond functionalization. Second, hexagonal ruthenacycle complex **I** was synthesized by the reaction of [1,1′-biphenyl]-2-yldiphenylphosphane with $[Ru(p\text{-cymene})Cl_2]_2$ in CH_2Cl_2 at rt for 24 h (for details, see the Supporting Information).[6c] The desired product was obtained in excellent yield when complex **I** was used as the substrate, indicating that the hexagonal ruthenacycle was a crucial intermediate in the *m*-C_{Ar}–H bond functionalization process (Scheme 5b). Third, obvious H/D exchange was observed in the residual substrate and desired product when 10 equiv of D_2O was injected into the *m*-C_{Ar}–H bond functionalization process. This phenomenon showed not only that *o*-C–H ruthenation was a reversible process but also that water was tolerated in the reaction system (Scheme 5c). Fourth, the desired product was not observed when free radical quenchers, such as TEMPO and BQ, were added to the reaction tube (Scheme 5d), showing that *m*-C_{Ar}–H bond

https://dx.doi.org/10.1021/acs.orglett.0c03377
Org. Lett. XXXX, XXX, XXX–XXX

functionalization might be a single-electron-transfer (SET) radical process. Finally, intermolecular competition experiments of two reactant analogues were conducted to evaluate the impact of electrons and structure on the transformation (Scheme 5e). The results showed that tertiary phosphines with higher electron density showed higher reactivity, and that α-bromocarboxylates showed better reactivity than alkyl bromides.

On the basis of our experimental results and literature reports relating to ruthenium-catalyzed C_{Ar}–H bond functionalization,[13] a plausible mechanism for the *m*-C_{Ar}–H bond alkylation process was proposed, as shown in Scheme 6. First,

Scheme 6. Plausible Mechanism



reversible *o*-C_{Ar}–H bond ruthenation of substrate **1a** by $[Ru(p\text{-cymene})Cl_2]_2$ assisted by the phosphine directing group gives key hexagonal ruthenacycle(II) intermediate **I**. SET from ruthenacycle(II) intermediate **I** to the alkyl bromide generates an alkyl radical and ruthenium(III) complex **II** after bromide transfer. Then, the radical reacts with intermediate **II** at the directing group *meta* position, aided by the C_{Ar}–Ru *ortho*/*para*-directing effect, to provide active intermediate **III**. Deprotonation of intermediate **III** generates stable intermediate **IV**. Finally, ligand exchange of intermediate **IV** with **1a** gives the desired product and regenerates intermediate **I** for the next catalytic cycle.

In summary, we have developed a *m*-C_{Ar}–H bond alkylation and fluoroalkylation of tertiary phosphines with alkyl bromides using $[Ru(p\text{-cymene})Cl_2]_2$ as the catalyst. Mechanistic experiments indicated that the *m*-C_{Ar}–H bond functionalization of tertiary phosphines was a radical process, and that a hexagonal ruthenacycle complex was a crucial reaction intermediate. This study provides a novel approach to accessing *meta*-position-modified biphenyl monophosphine ligands. Further investigations to develop new *m*-C_{Ar}–H bond functionalization reactions of tertiary phosphines and apply this chemistry in synthesis are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03377.

Detailed experimental procedures and compound characterization data (PDF)

Accession Codes

CCDC 2026486 and 2026500 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Gang Li − *College of Chemistry and Chemical Engineering, Henan Province Key Laboratory of New Optoelectronic Functional Materials, Anyang Normal University, Anyang 455002, P. R. China*; orcid.org/0000-0002-1609-449X; Email: ligang@aynu.edu.cn

Authors

Jiangzhen An − *College of Chemistry and Chemical Engineering, Henan Province Key Laboratory of New Optoelectronic Functional Materials, Anyang Normal University, Anyang 455002, P. R. China*

Chunqi Jia − *Engineering Research Center of Molecular Medicine of Ministry of Education, Key Laboratory of Fujian Molecular Medicine, Key Laboratory of Xiamen Marine and Gene Drugs, School of Biomedical Sciences, Huaqiao University, Xiamen 361021, P. R. China*

Bingxu Yan − *College of Chemistry and Chemical Engineering, Henan Province Key Laboratory of New Optoelectronic Functional Materials, Anyang Normal University, Anyang 455002, P. R. China*

Lei Zhong − *College of Chemistry and Chemical Engineering, Henan Province Key Laboratory of New Optoelectronic Functional Materials, Anyang Normal University, Anyang 455002, P. R. China*

Junjie Wang − *College of Chemistry and Chemical Engineering, Henan Province Key Laboratory of New Optoelectronic Functional Materials, Anyang Normal University, Anyang 455002, P. R. China*

Suling Yang − *College of Chemistry and Chemical Engineering, Henan Province Key Laboratory of New Optoelectronic Functional Materials, Anyang Normal University, Anyang 455002, P. R. China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c03377

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors gratefully acknowledge the Program of Science and Technology Innovation Talents of Henan Province (19HASTIT035).

■ REFERENCES

(1) (a) Fernández-Pérez, H.; Etayo, P.; Panossian, A.; Vidal-Ferran, A. Phosphine-phosphinite and phosphine-phosphite ligands: preparation and applications in asymmetric catalysis. *Chem. Rev.* **2011**, *111*, 2119−2176. (b) Baumgartner, T. Insights on the design and electron-acceptor properties of conjugated organophosphorus materials. *Acc. Chem. Res.* **2014**, *47*, 1613−1622.

(2) (a) Wu, K.; Doyle, A. G. Parameterization of phosphine ligands demonstrates enhancement of nickel catalysis via remote steric effects.

Nat. Chem. **2017**, *9*, 779−784. (b) Wu, L.; Fleischer, I.; Jackstell, R.; Profir, I.; Franke, R.; Beller, M. Ruthenium-catalyzed hydroformylation/reduction of olefins to alcohols: extending the scope to internal alkenes. *J. Am. Chem. Soc.* **2013**, *135*, 14306−14312. (c) Wu, L.; Fleischer, I.; Jackstell, R.; Beller, M. Efficient and regioselective ruthenium-catalyzed hydro-aminomethylation of olefins. *J. Am. Chem. Soc.* **2013**, *135*, 3989−3996. (d) Li, H.; Dong, K.; Jiao, H.; Neumann, H.; Jackstell, R.; Beller, M. The scope and mechanism of palladium-catalysed Markovnikov alkoxycarbonylation of alkenes. *Nat. Chem.* **2016**, *8*, 1159−1166. (e) Yeung, P. Y.; So, C. M.; Lau, C. P.; Kwong, F. K. A mild and efficient palladium-catalyzed cyanation of aryl mesylates in water or ^{t}BuOH/Water. *Angew. Chem., Int. Ed.* **2010**, *49*, 8918−8922.

(3) (a) Ruiz-Castillo, P.; Buchwald, S. L. Applications of palladium-catalyzed C-N cross-coupling reactions. *Chem. Rev.* **2016**, *116*, 12564−12649. (b) Sather, A. C.; Buchwald, S. L. The evolution of Pd^{0}/Pd^{II}-catalyzed aromatic fluorination. *Acc. Chem. Res.* **2016**, *49*, 2146−2157.

(4) (a) Gandeepan, P.; Müller, T.; Zell, D.; Cera, G.; Warratz, S.; Ackermann, L. 3d Transition metals for C-H activation. *Chem. Rev.* **2019**, *119*, 2192−2452. (b) Evano, G.; Theunissen, C. Beyond friedel and crafts: directed alkylation of C-H bonds in arenes. *Angew. Chem., Int. Ed.* **2019**, *58*, 7202−7236. (c) Sambiagio, C.; Schönbauer, D.; Blieck, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Zia, M. F.; Wencel-Delord, J.; Besset, T.; Maes, B. U. W.; Schnürch, M. A comprehensive overview of directing groups applied in metal-catalysed C-H functionalisation chemistry. *Chem. Soc. Rev.* **2018**, *47*, 6603−6743. (d) Qin, Y.; Zhu, L.; Luo, S. Organocatalysis in inert C-H bond functionalization. *Chem. Rev.* **2017**, *117* (13), 9433−9520. (e) Xue, X.-S.; Ji, P.; Zhou, B.; Cheng, J.-P. The essential role of bond energetics in C-H activation/functionalization. *Chem. Rev.* **2017**, *117* (13), 8622−8648. (f) Wu, S.; Wu, X.; Wu, Z.; Zhu, C. Regioselective introduction of vinyl trifluoromethylthioether to remote unactivated C(sp3)-H bonds via radical translocation cascade. *Sci. China: Chem.* **2019**, *62*, 1507−1511. (g) Zhang, D.; Huang, Z.; Lei, A. Oxidation-induced *ortho*-selective C-H bond functionalization of 2-naphthylamine derivative. *Sci. China: Chem.* **2018**, *61*, 1274−1277.

(5) (a) Liu, Z.; Wu, J.-Q.; Yang, S.-D. Ir(III)-catalyzed direct C-H functionalization of arylphosphine oxides: a strategy for MOP-type ligands synthesis. *Org. Lett.* **2017**, *19*, 5434−5437. (b) Du, Z.-J.; Guan, J.; Wu, G.-J.; Xu, P.; Gao, L.-X.; Han, F.-S. Pd(II)-catalyzed enantioselective synthesis of P-stereogenic phosphinamides via desymmetric C-H arylation. *J. Am. Chem. Soc.* **2015**, *137*, 632−635. (c) Yang, Y.; Qiu, X.; Zhao, Y.; Mu, Y.; Shi, Z. J. Palladium-catalyzed C-H arylation of indoles at the C7 position. *J. Am. Chem. Soc.* **2016**, *138*, 495−498. (d) Unoh, Y.; Satoh, T.; Hirano, K.; Miura, M. Rhodium(III)-catalyzed direct coupling of arylphosphine derivatives with heterobicyclic alkenes: a concise route to biarylphosphines and dibenzophosphole derivatives. *ACS Catal.* **2015**, *5*, 6634−6639. (e) Kim, Y.; Li, C.-J. Perspectives on green synthesis and catalysis. *Green Synth. Catal.* **2020**, *1*, 1−11. (f) Ma, Y.-N.; Li, S.-X.; Yang, S.-D. New approaches for biaryl-based phosphine ligand synthesis via P = O directed C-H functionalizations. *Acc. Chem. Res.* **2017**, *50*, 1480−1492. (g) Zhang, H.; Yang, S. Palladium-catalyzed $R_2(O)P$-directed C(sp2)-H activation. *Sci. China: Chem.* **2015**, *58*, 1280−1285.

(6) (a) Qiu, X.; Wang, M.; Zhao, Y.; Shi, Z. Rhodium(I)-catalyzed tertiary phosphine directed C-H arylation: rapid construction of ligand libraries. *Angew. Chem., Int. Ed.* **2017**, *56*, 7233−7237. (b) Qiu, X.; Wang, P.; Wang, D.; Wang, M.; Yuan, Y.; Shi, Z. P(III)-chelation-assisted indole C7-arylation, olefination, methylation, and acylation with carboxylic acids/anhydrides by rhodium catalysis. *Angew. Chem., Int. Ed.* **2019**, *58*, 1504−1508. (c) Luo, X.; Yuan, J.; Yue, C.-D.; Zhang, Z.-Y.; Chen, J.; Yu, G.-A.; Che, C.-M. Synthesis of peri-substituted (naphthalen-1-yl)phosphine Ligands by rhodium(I)-catalyzed phosphine-directed C-H arylation. *Org. Lett.* **2018**, *20*, 1810−1814. (d) Crawford, K. M.; Ramseyer, T. R.; Daley, C. J. A.; Clark, T. B. Phosphine-directed C-H borylation reactions: facile and selective access to ambiphilic phosphine boronate esters. *Angew. Chem., Int. Ed.* **2014**, *53*, 7589−7593. (e) Wright, S. E.; Richardson-Solorzano, S.; Stewart, T. N.; Miller, C. D.; Morris, K. C.; Daley, C. J. A.; Clark, T. B. Accessing ambiphilic phosphine boronates through C-H borylation by an unforeseen cationic Iridium complex. *Angew. Chem., Int. Ed.* **2019**, *58*, 2834−2838. (f) Wen, J.; Wang, D.; Qian, J.; Wang, D.; Zhu, C.; Zhao, Y.; Shi, Z. Rhodium-catalyzed P^{III}-directed *ortho*-C-H borylation of arylphosphines. *Angew. Chem., Int. Ed.* **2019**, *58*, 2078−2082. (g) Fukuda, K.; Iwasawa, N.; Takaya, J. Ruthenium-catalyzed *ortho* C-H borylation of arylphosphines. *Angew. Chem., Int. Ed.* **2019**, *58*, 2850−2853. (h) Qiu, X.; Wang, M.; Zhao, Y.; Shi, Z. Rhodium(I)-catalyzed tertiary phosphine directed C-H arylation: rapid construction of ligand libraries. *Angew. Chem., Int. Ed.* **2017**, *56*, 7233−7237. (i) Li, J.-W.; Wang, L.-N.; Li, M.; Tang, P.-T.; Luo, X.-P.; Kurmoo, M.; Liu, Y.-J.; Zeng, M.-H. Ruthenium-catalyzed gram-scale preferential C-H arylation of tertiary phosphine. *Org. Lett.* **2019**, *21*, 2885−2889. (j) Wang, D.; Zhao, Y.; Yuan, C.; Wen, J.; Zhao, Y.; Shi, Z. Rhodium(II)-catalyzed dehydrogenative silylation of biaryl-type monophosphines with hydrosilanes. *Angew. Chem., Int. Ed.* **2019**, *58*, 12529−12533. (k) Wang, D.; Dong, B.; Wang, Y.; Qian, J.; Zhu, J.; Zhao, Y.; Shi, Z. Rhodium-catalysed direct hydroarylation of alkenes and alkynes with phosphines through phosphorous-assisted C-H activation. *Nat. Commun.* **2019**, *10*, 3539. (l) Zhang, Z.; Roisnel, T.; Dixneuf, P. H.; Soulé, J.-F. Rh^{I}-catalyzed PIII-directed C-H bond alkylation: design of multifunctional phosphines for carboxylation of aryl bromides with carbon dioxide. *Angew. Chem., Int. Ed.* **2019**, *58*, 14110−14114. (m) Li, J.-W.; Wang, L.-N.; Li, M.; Tang, P.-T.; Zhang, N.-J.; Li, T.; Luo, X.-P.; Kurmoo, M.; Liu, Y.-J.; Zeng, M.-H. Late-stage modification of tertiary phosphines via ruthenium(II)-catalyzed C-H alkylation. *Org. Lett.* **2020**, *22*, 1331−1335.

(7) (a) Cheng, C.; Hartwig, J. F. Rhodium-catalyzed intermolecular C-H silylation of arenes with high steric regiocontrol. *Science* **2014**, *343*, 853−857. (b) Bisht, R.; Hoque, E.; Chattopadhyay, B. Amide effects in C-H activation: noncovalent interactions with L-shaped ligand for *meta* borylation of aromatic amides. *Angew. Chem., Int. Ed.* **2018**, *57*, 15762−15766.

(8) Ye, M.; Gao, G.-L.; Yu, J.-Q. Ligand-promoted C-3 selective C-H olefination of pyridines with Pd catalysts. *J. Am. Chem. Soc.* **2011**, *133*, 6964−6967.

(9) (a) Tang, R.-Y.; Li, G.; Yu, J.-Q. Conformation-induced remote *meta*-C-H activation of amines. *Nature* **2014**, *507*, 215−220. (b) Xu, H.-J.; Kang, Y.-S.; Shi, H.; Zhang, P.; Chen, Y.-K.; Zhang, B.; Liu, Z.-Q.; Zhao, J.; Sun, W.-Y.; Yu, J.-Q.; Lu, Y. Rh(III)-catalyzed *meta*-C-H alkenylation with alkynes. *J. Am. Chem. Soc.* **2019**, *141*, 76−79. (c) Jayarajan, R.; Das, J.; Bag, S.; Chowdhury, R.; Maiti, D. Diverse *meta*-C-H functionalization of arenes across different linker lengths. *Angew. Chem., Int. Ed.* **2018**, *57*, 7659−7663. (d) Xu, J.-C.; Chen, J.-J.; Gao, F.; Xie, S.-G.; Xu, X.-H.; Jin, Z.; Yu, J.-Q. Sequential functionalization of *meta*-C-H and *ipso*-C-O bonds of phenols. *J. Am. Chem. Soc.* **2019**, *141*, 1903−1907. (e) Li, S.; Cai, L.; Ji, H.; Yang, L.; Li, G. Pd(II)-catalysed *meta*-C-H functionalizations of benzoic acid derivatives. *Nat. Commun.* **2016**, *7*, 10443.

(10) (a) Wang, X.-C.; Gong, W.; Fang, L.-Z.; Zhu, R.-Y.; Li, S.; Engle, K. M.; Yu, J.-Q. Ligand-enabled *meta*-C-H activation using a transient mediator. *Nature* **2015**, *519*, 334−338. (b) Dong, Z.; Wang, J.-C.; Dong, G.-B. Simple amine-directed *meta*-selective C-H arylation via Pd/norbornene catalysis. *J. Am. Chem. Soc.* **2015**, *137*, 5887−5890.

(11) (a) Kumar, N. Y. P.; Bechtoldt, A.; Raghuvanshi, K.; Ackermann, L. Ruthenium(II)-catalyzed decarboxylative C-H activation: versatile routes to *meta*-alkenylated arenes. *Angew. Chem., Int. Ed.* **2016**, *55*, 6929−6932. (b) Qin, X.; Sun, D.; You, Q.; Cheng, Y.; Lan, J.; You, J. Rh(III)-catalyzed decarboxylative *ortho*-heteroarylation of aromatic carboxylic acids by using the carboxylic acid as a traceless directing group. *Org. Lett.* **2015**, *17*, 1762−1765. (c) Yu, D.-G.; de Azambuja, F.; Glorius, F. Direct functionalization with complete and switchable positional control: free phenol as a role model. *Angew. Chem., Int. Ed.* **2014**, *53*, 7710−7712. (d) Luo, J.; Preciado, S.; Larrosa, I. Overriding *ortho-para* selectivity via a traceless directing group relay strategy: The *meta*-selective arylation of phenols. *J. Am. Chem. Soc.* **2014**, *136*, 4109−4112. (e) Zhang, Y.; Zhao, H.; Zhang,

https://dx.doi.org/10.1021/acs.orglett.0c03377
Org. Lett. XXXX, XXX, XXX−XXX

M.; Su, W.-P. Carboxylic acids as traceless directing groups for the rhodium(III)-catalyzed decarboxylative C-H arylation of thiophenes. *Angew. Chem., Int. Ed.* **2015**, *54*, 3817−3821.

(12) (a) Phipps, R. J.; Gaunt, M. J. A *meta*-selective copper-catalyzed C-H bond arylation. *Science* **2009**, *323*, 1593−1597. (b) Yang, Y.-Q.; Li, R.-R.; Zhao, Y.; Zhao, D.-B.; Shi, Z.-Z. Cu-catalyzed direct C6-arylation of indoles. *J. Am. Chem. Soc.* **2016**, *138*, 8734−8737.

(13) (a) Leitch, J. A.; Frost, C. G. Ruthenium-catalysed σ-activation for remote *meta*-selective C-H functionalization. *Chem. Soc. Rev.* **2017**, *46*, 7145−7153. (b) Ruan, Z.; Zhang, S.-K.; Zhu, C.; Ruth, P. N.; Stalke, D.; Ackermann, L. Ruthenium(II)-catalyzed *meta* C-H mono- and difluoromethylations by phosphine/carboxylate cooperation. *Angew. Chem., Int. Ed.* **2017**, *56*, 2045−2049. (c) Yu, Q.; Hu, L. A.; Wang, Y.; Zheng, S.-S.; Huang, J.-H. Directed *meta*-selective bromination of arenes with ruthenium catalysts. *Angew. Chem., Int. Ed.* **2015**, *54*, 15284−15288. (d) Fan, Z.-L.; Ni, J.-B.; Zhang, A. *meta*-Selective C_{Ar}-H nitration of arenes through a $Ru_3(CO)_{12}$-catalyzed *ortho*-metalation strategy. *J. Am. Chem. Soc.* **2016**, *138*, 8470−8475. (e) Li, B.; Li, D.-Z.; Zhang, J.-Y.; Shi, D.-Q.; Zhao, Y.-S. Ligand-enabled regioselectivity in the oxidative cross-coupling of arenes with toluenes and cycloalkanes using ruthenium catalysts: tuning the site-selectivity from the *ortho* to *meta* positions. *ACS Catal.* **2017**, *7*, 4138−4143. (f) Li, B.; Fang, S.-L.; Huang, D.-Y.; Shi, B.-F. Ru-catalyzed *meta*-C-H benzylation of arenes with toluene derivatives. *Org. Lett.* **2017**, *19*, 3950−3953. (g) Jing, K.; Li, Z.-Y.; Wang, G.-W. Direct decarboxylative *meta*-selective acylation of arenes via an *ortho*-ruthenation strategy. *ACS Catal.* **2018**, *8*, 11875−11881. (h) Li, G.; Jia, C. Q.; Cai, X. F.; Zhong, L.; Zou, L.; Cui, X. L. Ruthenium-catalyzed *meta*-C-H bond alkylation of aryl 2-pyridyl ketones. *Chem. Commun.* **2020**, *56*, 293−296. (i) Gandeepan, P.; Koeller, J.; Korvorapun, K.; Mohr, J.; Ackermann, L. Visible-light-enabled ruthenium-catalyzed *meta*-C-H alkylation at room temperature. *Angew. Chem., Int. Ed.* **2019**, *58*, 9820−9825. (j) Wang, X.-G.; Li, Y. K.; Liu, H.-C.; Zhang, B.-S.; Gou, X.-Y.; Wang, Q.; Ma, J. W.; Liang, Y.-M. Three-component ruthenium-catalyzed direct *meta*-selective C-H activation of arenes: A new approach to the alkylarylation of alkenes. *J. Am. Chem. Soc.* **2019**, *141*, 13914−14922. (k) Sagadevan, A.; Greaney, M. F. *meta*-Selective C-H activation of arenes at room temperature using visible light: dual-function ruthenium catalysis. *Angew. Chem., Int. Ed.* **2019**, *58*, 9826−9830. (l) Li, J.; Korvorapun, K.; De Sarkar, S.; Rogge, T.; Burns, D. J.; Warratz, S.; Ackermann, L. Ruthenium(II)-catalysed remote C-H alkylations as a versatile platform to *meta*-decorated arenes. *Nat. Commun.* **2017**, *8*, 15430. (m) Reddy, G. M.; Rao, N. S.; Maheswaran, H. Highly *meta*-Selective halogenation of 2-phenylpyridine with a ruthenium(I) catalyst. *Org. Chem. Front.* **2018**, *5*, 1118−1123. (n) Yuan, C. C.; Chen, X. L.; Zhang, J. Y.; Zhao, Y. S. *meta*-Selective C-H difluoromethylation of various arenes with a versatile ruthenium catalyst. *Org. Chem. Front.* **2017**, *4*, 1867−1871. (o) Khan, F. F.; Sinha, S. K.; Lahiri, G. K.; Maiti, D. Ruthenium-mediated distal C-H activation. *Chem. - Asian J.* **2018**, *13*, 2243−2256. (p) Sasmal, S.; Sinha, S. K.; Lahiri, G. K.; Maiti, D. A directing group-assisted ruthenium-catalyzed approach to access *meta*-nitrated phenols. *Chem. Commun.* **2020**, *56*, 7100−7103. (q) Hofmann, N.; Ackermann, L. *meta*-Selective C-H bond alkylation with secondary alkyl halides. *J. Am. Chem. Soc.* **2013**, *135*, 5877−5884. (r) Li, J.; Warratz, S.; Zell, D.; De Sarkar, S.; Ishikawa, E. E.; Ackermann, L. *N*-Acyl amino acid ligands for ruthenium(II)-catalyzed *meta*-C-H *tert*-alkylation with removable auxiliaries. *J. Am. Chem. Soc.* **2015**, *137*, 13894−13901. (s) Korvorapun, K.; Kaplaneris, N.; Rogge, T.; Warratz, S.; Stückl, A. C.; Ackermann, L. Sequential *meta*-/*ortho*-C-H functionalizations by one-pot ruthenium(II/III) catalysis. *ACS Catal.* **2018**, *8*, 886−892. (t) Korvorapun, K.; Kuniyil, R.; Ackermann, L. Late-stage diversification by selectivity switch in *meta*-C-H activation: evidence for singlet stabilization. *ACS Catal.* **2020**, *10*, 435−440. (u) Korvorapun, K.; Moselage, M.; Struwe, J.; Rogge, T.; Messinis, A. M.; Ackermann, L. Regiodivergent C-H and decarboxylative C-C alkylation by ruthenium catalysis: *ortho* versus *meta* position-selectivity. *Angew. Chem., Int. Ed.* **2020**, *59*, 18795−18803. (v) Fumagalli, F.; Warratz, S.; Zhang, S.-K.; Rogge, T.; Zhu, C.; Stückl, A. C.; Ackermann, L. Arene-ligand-free ruthenium(II/III) manifold for *meta*-C-H alkylation: remote purine diversification. *Chem. - Eur. J.* **2018**, *24*, 3984−3988. (w) Paterson, A. J.; St John-Campbell, S.; Mahon, M. F.; Press, N. J.; Frost, C. G. Catalytic *meta*-selective C-H functionalization to construct quaternary carbon centres. *Chem. Commun.* **2015**, *51*, 12807−12810. (x) Paterson, A. J.; Heron, C. J.; McMullin, C. L.; Mahon, M. F.; Press, N. J.; Frost, C. G. α-Halo carbonyls enable *meta* selective primary, secondary and tertiary C-H alkylations by ruthenium catalysis. *Org. Biomol. Chem.* **2017**, *15*, 5993−6000.

(14) Chen, Q.; Zeng, J.; Yan, X.; Huang, Y.; Du, Z.; Zhang, K.; Wen, C. Mild and efficient oxidation of phosphorus(III) compounds with Selectfluor. *Tetrahedron Lett.* **2016**, *57*, 3379−3381.

https://dx.doi.org/10.1021/acs.orglett.0c03377
Org. Lett. XXXX, XXX, XXX−XXX