EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Palladium-Catalyzed Direct Decarbonylative Phosphorylation of Benzoic Acids with P(O)–H Compounds

Authors: Ji-Shu Zhang, Tieqiao Chen, and Li-Biao Han

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201901865

Link to VoR: http://dx.doi.org/10.1002/ejoc.201901865

Supported by
ACES Asian Chemical Editorial Society

WILEY-VCH

10.1002/ejoc.201901865

COMMUNICATION

WILEY-VCH

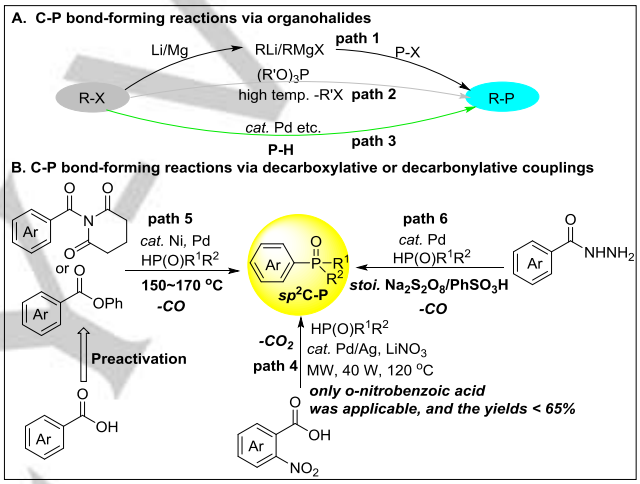
Palladium-Catalyzed Direct Decarbonylative Phosphorylation of Benzoic Acids with P(O)–H Compounds**

Ji-Shu Zhang,[a] Tieqiao Chen,*[a,b] and Li-Biao Han*[c,d]

Abstract: A direct decarbonylative phosphorylation of benzoic acids catalyzed by palladium was disclosed. Under the reaction conditions, a wide range of benzoic acids coupled readily with all the three kinds of P(O)–H compounds, i.e. secondary phosphine oxides, H-phosphinates and H-phosphonates, producing the corresponding organophosphorus compounds in good to high yields. This reaction could be conducted at a gram scale and applied in the late-stage phosphorylative modification of carboxylic acids drug molecules. These results well demonstrated the potential synthetic value of this new reaction in organic synthesis.

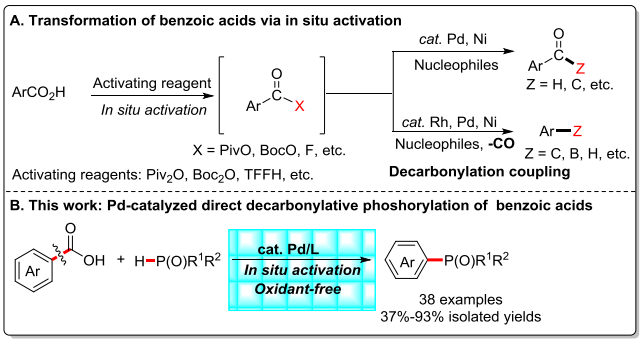
Due to the novel physical and chemical properties, organophosphorous compounds are highly valuable chemicals that are widely used in medicinal chemistry,[1] catalysis and organic synthesis,[2,3] coordination chemistry[4] and material science.[5] The development of an efficient method for the synthesis of an organophoshorus compound under mild conditions is of current concern. A lot of organophosphorus compounds have been prepared through transformation of organohalides or pseudo halides, such as the nucleophilic substitutions reactions or Michaelis-Arbusov reactions under a rather harsh condition (Scheme 1A, paths 1 and 2).[6,7] The Hirao-type's coupling is also a well-employed method for constructing C–P bonds (Scheme 1A, path 3).[8,9] An aromatic C–H/P(O)–H cross dehydrogenation coupling was accomplished by Yu and co-workers, despite requiring a N-heterocycle-directing group and (or) an over-stoichiometric oxidant.[10]

Carboxylic acids are available at low cost in great structural diversity from both natural and synthetic sources and their application in organic synthesis has attracted much attention.[11,12] Direct utilization of carboxylic acids instead of organohalides to couple with P(O)–H compounds would greatly promote the green synthesis of organophosphorus compounds. In 2014, Xiao disclosed a Pd/Ag co-catalyzed decarboxylative coupling of electron-deficient *o*-nitrobenzoic acids with H-phosphonates (Scheme 1B, path 4).[12b] This reaction was conducted under microwave conditions with the use of $LiNO_3$ as an oxidant. Despite the high reaction rate, low yields (<65%) and narrow substrate scope were suffered. Subsequently, transition metal-catalyzed decarbonylative phosphorylations of aromatic carboxylate esters and amides with P(O)–H compounds were achieved under relatively harsh conditions (>150 °C) (Scheme 1B, path 5). In the two reactions, pre-synthesis of starting carboxylic derivatives was required, stoichiometric byproducts



Scheme 1. Construction of aromatic sp^2C–P bonds.

phenol and piperidine-2,6-dione were also generated concomitantly.[13] Very recently, we reported a Pd-catalyzed oxidative decarbonylative coupling of aroylhydrazides with P(O)–H compounds under a strong acidic condition, producing the corresponding aryl phosphorus compounds (Scheme 1B, path 6).[14]



Scheme 2. Constructing chemical bonds via in situ activation of benzoic acids.

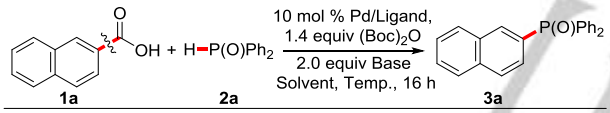
In 1990s, Prof. Yamamoto firstly introduced an in situ activation strategy of carboxylic acids with anhydrides for

[a] Dr. J.-S. Zhang, Prof. Dr. T. Chen, College of Chemistry and Chemical Engineering, Hunan University, Changsha, Hunan 410082, China.
[b] Prof. Dr. T. Chen, Key Laboratory of Ministry of Education for Advanced Materials in Tropical Island Resources, College of Chemical Engineering and Technology, Hainan University, Haikou, Hainan 570228, China.
[c] Prof. Dr. L.-B. Han, Institute of Drug Discovery Technology, Ningbo University, Ningbo, Zhejiang, 450052, China.
[d] Prof. Dr. L.-B. Han, National Institute of Advanced Industrial Science and Technology (AIST), Tsukuba, Ibaraki 305-8565, Japan.
E-mail: chentieqiao@hnu.edu.cn; libiao-han@aist.go.jp

Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

oxidative addition to Pd-catalysts, achieving the hydrogenation to aldehydes.[15a] This concept was subsequently extended to the synthesis of ketones.[15b–f] With the strategy, decarbonylative eliminations of fatty acids forming alkenes were also achieved by chemists.[15g–h] The in situ activation strategy was also employed in the decarbonylation couplings of benzoic acids with alkenes, arylboroxines, diboroxines, aromatics bearing *N*-heterocycle and hydrosilanes mediated by nickel, rhodium and palladium (Scheme 2A).[16] We envision that if the in situ activation strategy is applied in the cross coupling of carboxylic acids with P(O)–H compounds, a decarbonylation phosphorylation might be realized out through transition metal catalysis. This reaction would avoid the pre-transformation of acids into active carboxylic derivatives and the use of oxidant which usually leads to oxidation of P(O)–H compounds in the oxidative couplings, thus providing an efficient method for constructing P–C bonds. After extensive studies,[17] we achieved such a reaction through palladium catalysis. This reaction used Boc_2O as the activating reagent and was performed under a relatively mild reaction condition (115 °C). A wide substrate scope for both benzoic acids and P(O)–H compounds was demonstrated. This reaction provided a general method for sp^2C–P bonds formation (Scheme 2B). It should be noted that Szostak and co-authors reported a similar reaction with the use of Piv_2O as an activating reagent during the submission.[18] Compared with our catalytic system, the reaction was conducted at a higher temperature (160 °C) and seemed to be only applicable to H-phosphonates and Ph_2PH.

Table 1. Optimization of reaction conditions [a]



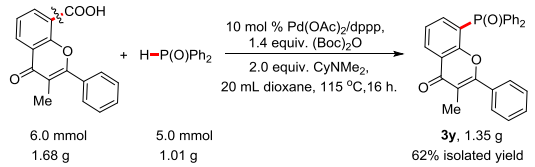
1a 2a 3a

Entry	Cat. Pd	Ligand	Base	Solvent	Temp. (°C)	Yield (%)[b]
1	$Pd(OAc)_2$	dppp	$CyNMe_2$	dioxane	115	72
2	-	dppp	$CyNMe_2$	dioxane	115	trace
3	$Pd(OAc)_2$	-	$CyNMe_2$	dioxane	115	trace
4	$Pd(OAc)_2$	dppp	$CyNMe_2$	dioxane	105	67
5	$Pd(OAc)_2$	dppp	$CyNMe_2$	dioxane	130	67
6	$Pd(OAc)_2$	dppp	Cy_2NMe	dioxane	115	47
7	$Pd(OAc)_2$	dppp	Et_3N	dioxane	115	59
8	$Pd(OAc)_2$	dppp	DBU	dioxane	115	N.D.
9	$Pd(OAc)_2$	dppp	K_2CO_3	dioxane	115	N.D.
10	$Pd(OAc)_2$	dppp	Cs_2CO_3	dioxane	115	trace
11	$Pd(OAc)_2$	dppp	$CyNMe_2$	toluene	115	68
12	$Pd(OAc)_2$	dppp	$CyNMe_2$	cyclohexane	115	40
13	$Pd(OAc)_2$	dppp	$CyNMe_2$	DMF	115	23
14	$Pd(OAc)_2$	dppp	$CyNMe_2$	DMAc	115	14
15	$Pd(OAc)_2$	dppp	$CyNMe_2$	*t*-AmylOH	115	21
16	$Pd(OAc)_2$	dcype	$CyNMe_2$	dioxane	115	trace
17	$Pd(OAc)_2$	dppm	$CyNMe_2$	dioxane	115	9
18	$Pd(OAc)_2$	dppe	$CyNMe_2$	dioxane	115	5
19	$Pd(OAc)_2$	dppb	$CyNMe_2$	dioxane	115	39
20	$Pd(OAc)_2$	dppf	$CyNMe_2$	dioxane	115	8
21	$Pd(OAc)_2$	dpph	$CyNMe_2$	dioxane	115	7
22	$Pd(OAc)_2$	Ph_3P	$CyNMe_2$	dioxane	115	trace
23[c]	$Pd(OAc)_2$	dppp	$CyNMe_2$	dioxane	115	62
24[d]	$Pd_2(dba)_3$	dppp	$CyNMe_2$	dioxane	115	60
25[e]	$Pd(OAc)_2$	dppp	$CyNMe_2$	dioxane	115	31

[a] Reaction conditions: a mixture of **1a** (0.12 mmol), $Ph_2P(O)H$ (0.1 mmol), 10 mol % Pd catalyst, phosphine ligand (Pd/P =1:2), 1.4 equiv $(Boc)_2O$, 2.0 equiv base was heated in 1 mL solvent at the indicated temperature for 18 h. [b] ^{31}P NMR yield using methyldiphenylphine oxide as an internal standard. [c] 5 mol% $Pd_2(dba)_3$. [d] 5 mol % $Pd(OAc)_2$. [e] $(PivO)_2O$ was used instead of $(Boc)_2O$.

We carried out the reaction by choosing 2-naphthoic acid with diphenylphosphine oxide as the model reaction. In the presence of 10 mol % $Pd(OAc)_2$/dppp (1,3-bis(diphenylphosphino)propane), a mixture of 2-naphthoic acid, diphenylphosphine oxide, $CyNMe_2$ and $(Boc)_2O$ was heated in dioxane[16] at 115 °C for 18 h. To our delight, 2-naphthylphosphine oxide **3a** was obtained in 72% yield (Table 1, entry 1). Both Pd catalyst and phosphine ligand were essential. Without either of them, the reaction proceeded sluggishly (Table 1, entries 2 and 3). Lowering or elevating the reaction temperature decreased the yield of **3a** (Table 1, entries 4 and 5). The choice of a suitable base was also crucial to this reaction. The yields were low with Cy_2NMe and Et_3N, while almost no reaction could be observed with DBU, K_2CO_3 and Cs_2CO_3 (Table 1, entries 6–10). The reaction also took place readily in toluene and cyclohexane, but poorly in the strongly polar DMF, DMAc and *t*-AmylOH (Table 1, entries 11–15). The phosphine ligands were subsequently screened (Table 1, entries 16–22). When dppb (1,4-bis(diphenylphosphino)butane) was used, 39% yield of **3a** was obtained. Other selected phosphine ligands, such as dcype (1,2-bis(dicyclohexylphosphino)ethane), dppm (bis(diphenylphosphino)methane), dppe (1,2-bis(diphenylphosphino)ethane), dppf (1,1'-bis(diphenylphosphino)-ferrocene), dpph (1,6-bis(diphenylphosphino)hexane) and Ph_3P, all were ineffective for the decarbonylative phosphorylation. When 5 mol% $Pd(OAc)_2$ was loaded, the yield decreased to 62% (Table 1, entry 23). Zero valent Pd catalyst like $Pd_2(dba)_3$ could also mediate the coupling reaction (Table 1, entry 24). Finally, anhydride $(PivO)_2O$ was used instead of $(Boc)_2O$, a relatively low yield was afforded (Table 1, entry 25).[16]

With the optimal conditions in hand, we then investigated the substrate scope. As shown in Table 2, this reaction was a rather general method, since various carboxylic acids including some drugs were readily decarbonylatively phosphorylated, producing the corresponding aryl phosphorus compounds in moderate to high yields. Thus, both 1-naphthoic and 2-naphthoic acids coupled with $Ph_2P(O)H$, furnishing the expected coupling products **3a**–**3c** in good yields. Polycyclic carboxylic acids served well under the reaction conditions (**3d**–**3f**). Good yields were also obtained with the heterocyclic substrates (**3g**–**3k**). By slightly tuning the reaction conditions, both electron-rich and electron-deficient benzoic acids including those bearing functional groups at the *ortho*-position underwent decarbonylative phosphorylation with $Ph_2P(O)H$, delivering the corresponding products **3l**–**3w** in moderate to good yields. Functional groups such as Me, Ph, PhO, MeO, CF_3O, acetal, ester, carbonyl, methylsulfonyl and even chloro groups all



6.0 mmol 1.68 g | 5.0 mmol 1.01 g | **3y**, 1.35 g 62% isolated yield

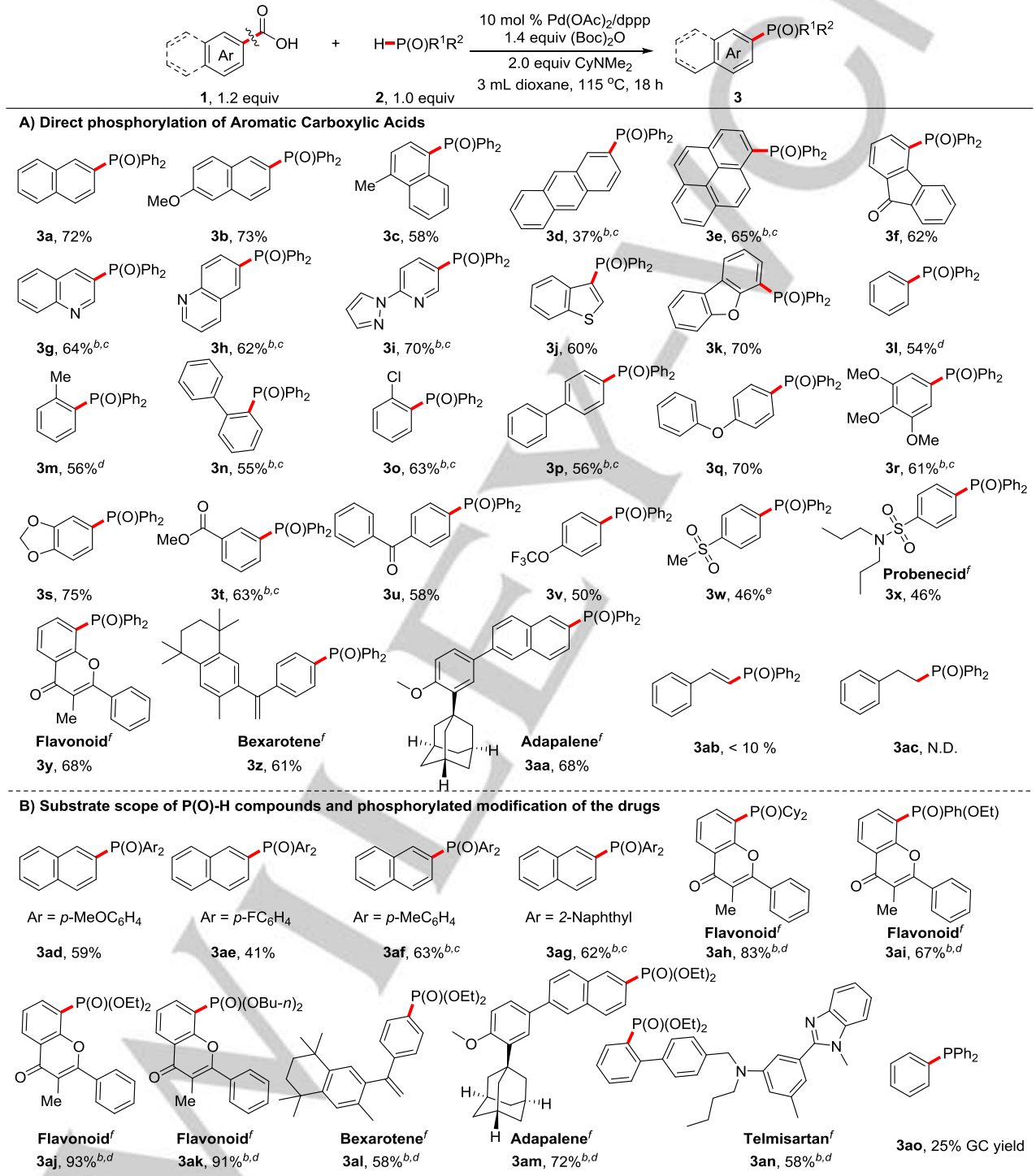
Scheme 3. Gram-scale reaction.

survived well under the current reaction conditions. The carboxylic acid drugs such as Probenecid, Flavonoid,

Bexarotene and Adpalene also proved to be good coupling partners (**3x–3aa**). However, under the reaction conditions, cinnamic acid showed poor reactivity (**3ab**), while no reaction took place with 3-phenylpropanoic acid (**3ac**).

All the three kinds of hydrogen phosphoryl compounds were applicable to this reaction (Table 2B). In addition to $Ph_2P(O)H$, other aromatic secondary phosphine oxides including the bulky di(2-naphthyl)$_2$P(O)H all produced the expected phosphine oxides in moderate to good yields under similar reaction conditions (**3ad–3ag**). Similarly, the present Pd-catalyzed decarbonylative phosphorylation also took place smoothly with

Table 2. Substrate scope [a]

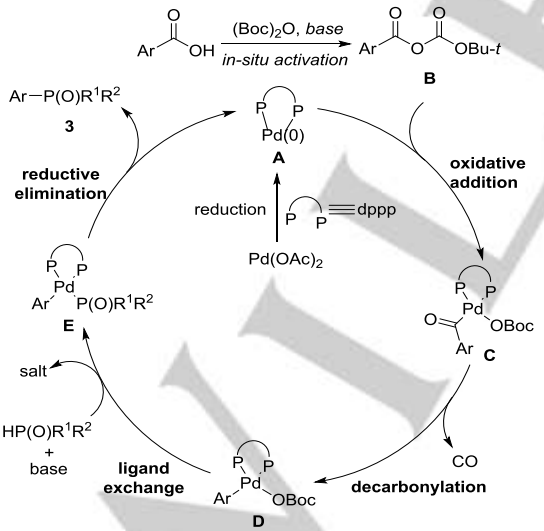


[a] Reaction conditions: a mixture of **1** (0.48 mmol), $Ph_2P(O)H$ (0.4 mmol), 10 mol % $Pd(OAc)_2$/dppp, 1.4 equiv $(Boc)_2O$, 2.0 equiv $CyNMe_2$ was heated at 115 °C in 3 mL dioxane for 18 h; isolated yield. [b] 1.5 equiv $(Boc)_2O$, 2.5 equiv $CyNMe_2$. [c] 105 °C. [d] 130 °C. [e] 1.5 equiv $(Boc)_2O$, 3 equiv $CyNMe_2$, 90 °C. [f] Names of starting carboxylic acid drugs.

aliphatic secondary phosphine oxide, hydrogen phosphinate and hydrogen phosphonates (**3ah**–**3an**). Worth noting is that the phosphorylated products from drugs with hydrogen phosphinate and hydrogen phosphonates could be easily hydrolyzed to the corresponding phosphinic acid and phosphonic acids, which might efficiently adjust the bioactivity of drugs.[19] This reaction provided an efficient method for phosphorylative modification of carboxylic acid drugs through decarbonylative C–C(O)/P(O)–H coupling. Diphenylphosphine showed a low reactivity and gave the coupling product triphenylphosphine in 25% GC yield (**3ao**).

Of note, this reaction could be conducted at a gram scale without decrease of the reaction efficiency, demonstrating its potential synthetic value in organic synthesis (Scheme 3). For instance, a mixture of Flavonoid (6.0 mmol, 1.68 g), diphenylphosphine oxide (5.0 mmol, 1.01 g), $Pd(OAc)_2$ (10 mol %, 112.0 mg), dppp (10 mol %, 206.2 mg), $(Boc)_2O$ (1.4 equiv, 1.6 mL), and $CyNMe_2$ (2.0 equiv, 1.5 mL) was heated in 20 mL dioxane at 115 °C for 18 h. After removal of the volatiles in vacuum, the residues were passed through a short silica column (eluent: petroleum ether/ethyl acetate) to give the analytically pure product **3y** in 62% isolated yield.

The reaction mechanism is not thoroughly clear at present. On the basis of previous literatures, we proposed a plausible catalytic circle as shown in Scheme 4.[16a,l–n,17,20–22] $Pd(OAc)_2$ is first reduced to generate an active Pd(0) species **A**, which oxidatively adds to a mixing anhydride **B** generated in situ from $(Boc)_2O$ and the starting carboxylic acids,[16m] yielding an complex **C**. The resulting **C** undergoes decarbonylation,[13a,14,20] followed by ligand exchange to give intermediate **E**.[17,21,22] Reductive elimination of intermediate **E** produces the phosphorylated product and regenerates the active Pd(0) catalyst,[23] thereby completing the catalytic circle.



Scheme 4. Proposed reaction mechanism.

In summarize, we disclosed a Pd-catalyzed direct decarbonylative coupling of benzoic acids with P(O)–H compounds. The reaction utilized $(Boc)_2O$ to activate carboxylic acids in situ, avoiding pre-conversion of them into the active carboxylic derivatives and the use of stoichiometric oxidant. Under the reaction conditions, a variety of aryl phosphorus compounds were produced in moderate to excellent yields. The gram-scale experiments and further applications in the phosphorylative modification of drugs like Probenecid, Flavonoid, Bexarotene, Adapalene and Telmisartan well demonstrated the potential synthetic value of this new reaction in organic synthesis.

Experimental Section

A general procedure: in a glove box, 0.48 mmol 2-naphthoic acid, 0.52 mmol $HP(O)Ph_2$, 10 mol % $Pd(OAc)_2$/dppp, 1.4 equiv $(Boc)_2O$, 2.0 equiv $CyNMe_2$, and 3 mL dioxane were charged into a 25 mL glass tube, the mixture was stirred at 115 ℃ for 18 h. After removal of the volatiles in vacuum, the residues were passed through a short silica column using petroleum ether/ethyl acetate as eluent to afford analytically pure product **3a** in 72% yield.

Acknowledgements

We gratefully acknowledge financial support from the National Natural Science Foundation of China (21573064 and 21403062) and the Fundamental Research Funds for the Central Universities (Hunan University).

Keywords: Palladium catalysis • C–P bond-forming reaction • Decarbonylative coupling • Benzoic acids • In-situ activation

[1] (a) W.-S. Huang, S. Liu, D. Zou, M. Thomas, Y. Wang, T. Zhou, J. Romero, A. Kohlmann, F. Li, J. Qi, L. Cai, T. A. Dwight, Y. Xu, R. Xu, R. Dodd, A. Toms, L. Parillon, X. Lu, R. Anjum, S. Zhang, F. Wang, J. Keats, S. D. Wardwell, Y. Ning, Q. Xu, L. E. Moran, Q. K. Mohemmad, H. G. Jang, T. Clackson, N. I. Narasimhan, V. M. Rivera, X. Zhu, D. Dalgarno, W. C. Shakespeare, *J. Med. Chem.* **2016**, *59*, 4948; (b) X. Chen, D. J. Kopecky, J. Mihalic, S. Jeffries, X. Min, J. Heath, J. Deignan, S. Lai, Z. Fu, C. Guimaraes, S. Shen, S. Li, S. Johnstone, S. Thibault, H. Xu, M. Cardozo, W. Shen, N. Walker, F. Kayser, Z. Wang, *J. Med. Chem.* **2012**, *55*, 3837; (c) Q. Dang, Y. Liu, D. K. Cashion, S. R. Kasibhatla, T. Jiang, F. Taplin, J. D. Jacintho, H. Li, Z. Sun, Y. Fan, J. DaRe, F. Tian, W. Li, T. Gibson, R. Lemus, P. D. van Poelje, S. C. Potter, M. D. Erion, *J. Med. Chem.* **2011**, *54*, 153.

[2] H. Ni, W. L. Chan, Y. Lu, *Chem. Rev.* **2018**, *118*, 9344.

[3] For selected reviews, see: (a) M. Oestreich, F. Tappe, V. Trepohl, *Synthesis* **2010**, *2010*, 3037; (b) J.-L. Montchamp, *Acc. Chem. Res.* **2014**, *47*, 77; (c) B.-G. Cai, J. Xuan, W.-J. Xiao, *Science Bulletin* **2019**, *64*, 337; (d) J.-S. Zhang, L. Liu, T. Chen, L.-B. Han, *Chem. Asian J.* **2018**, *13*, 2277; (e) T. Chen, J.-S. Zhang, L.-B. Han, *Dalton Trans.* **2016**, *45*, 1843; For selected examples, see: (f) M. Yoshida, K. Saito, H. Kato, S. Tsukamoto, T. Doi, *Angew. Chem. Int. Ed.* **2018**, *57*, 5147; *Angew. Chem.* **2018**, *130*, 5241; (g) J.-S. Zhang, J.-Q. Zhang, T. Chen, L.-B. Han, *Org. Biomol. Chem.* **2017**, *15*, 5462; (h) J. Q. Zhang, T. Chen, J. S. Zhang, L. B. Han, *Org. Lett.* **2017**, *19*, 4692; (i) J.-S. Zhang, T. Chen, Y. Zhou, S.-F. Yin, L.-B. Han, *Org. Lett.* **2018**, *20*, 6746.

[4] For reviews on phosphorus compounds as ligands and directing groups, see: (a) Y. N. Ma, S.-X. Li, S.-D. Yang, *Acc. Chem. Res.* **2017**, *50*, 1480–1492; (b) Z. Zhang, P. H. Dixneuf, J.-F. Soulé, *Chem. Commun.* **2018**, *54*, 7265; For selected recent examples, see: (c) K. Fukuda, N. Iwasawa, J. Takaya, *Angew. Chem. Int. Ed.* **2019**, *58*, 2850; *Angew. Chem.* **2019**, *131*, 2876; (d) J. Wen, D. Wang, J. Qian, D. Wang, C. Zhu, Y. Zhao, Z. Shi, *Angew. Chem. Int. Ed.* **2019**, *58*, 2078; *Angew. Chem.* **2019**, *131*, 2100.

[5] (a) For selected reviews on P-containing materials, see: (a) T. Baumgartner, R. Réau, *Chem. Rev.* **2006**, *106*, 4681; (b) C. Queffelec, M. Petit, P. Janvier, D. A. Knight, B. Bujoli, *Chem. Rev.* **2012**, *112*, 3777; (c) T. Baumgartner, *Acc. Chem. Res.* **2014**, *47*, 1613; (d) R. Szucs, P. A. Bouit, L. Nyulaszi, M. Hissler, *ChemPhysChem* **2017**, *18*, 2618; For selected examples, see: (e) C. Han, Z. Zhang, H. Xu, J. Li, G. Xie, R. Chen, Y. Zhao, W. Huang, *Angew. Chem. Int. Ed.* **2012**, *51*, 10104; *Angew. Chem.* **2012**, *124*, 10251; (f) L. Qiu, W. Hu, D. Wu, Z. Duan, F. Mathey, *Org. Lett.* **2018**, *20*, 7821.

[6] For selected examples on nucleophilic substitutions reactions, see: (a) C. P. Casey, E. L. Paulsen, E. W. Beuttenmueller, B. R. Proft, L. M. Petrovich, B. A. Matter, D. R. Powell, *J. Am. Chem. Soc.* **1997**, *119*, 11817; (b) M. V. Jiménez, J. J. Pérez- Torrente, M. I. Bartolomé, L. A. Oro, *Synthesis* **2009**, *2009*, 1916.

[7] (a) A. K. Bhattachary, G. Thyarajan, *Chem. Rev.* **1981***, 81,* 415; (b) W. P. Almeida, C. R. D. Correia, *Tetrahedron lett.* **1994**, *35*, 1367; (c) G. Yang, C. Shen, L. Zhang, W. Zhang, *Tetrahedron Lett.* **2011**, *52*, 5032; (d) R. S. Shaikh, S. J. S. Düsel, B. König, *ACS Catal.* **2016**, *6*, 8410.

[8] (a) T. Hirao, T. Masunaga, Y. Ohshiro, T. Agawa, *Tetrahedron Lett.* **1980**, *21*, 35958; (b) T. Hirao, T. Masunaga, N. Yamada, Y. Ohshiro, T. Agawa, *Bull. Chem. Soc. Jpn* **1982**, *55*, 909; For selected examples of Ar–X as coupling partners, see: (c) L. J. Dmitri Gelman, Stephen L. Buchwald, *Org. Lett.* **2003**, *5*, 2315; (d) W. C. Fu, C. M. So, F. Y. Kwong, *Org. Lett.* **2015**, *17*, 5906; (e) L. L. Liao, Y. Y. Gui, X. B. Zhang, G. Shen, H. D. Liu, W. J. Zhou,. J. Li, D. G. Yu, *Org. Lett.* **2017**, *19*, 3735.

[9] For more recently on Hirao-type coupling forming C–P bonds through C–B, C−O, C–CN, C−S, C−N, and C−Si cleavage, see: (a) G. Hu, W. Chen, T. Fu, Z. Peng, H. Qiao, Y. Gao, Y. Zhao, *Org. Lett.* **2013**, *15*, 5362; (b) Zhuang, R.; J. Xu, Z. Cai, G. Tang, M. Fang, Y. Zhao, *Org. Lett.* **2011**, *13*, 2110; (c) Y.- L. Zhao, G.- J. Wu, F.-S. Han, *Chem. Commun.* **2012**, *48*, 5868; (d) J. Yang, T. Chen, L.-B. Han, *J. Am. Chem. Soc.* **2015**, *137*, 1782; (e) J.-S. Zhang, T. Chen, J. Yang, L.- B. Han, *Chem. Commun.* **2015**, *51*, 7540; (f) J. Yang, J. Xiao, T. Chen, S.- F. Yin, L.-B. Han, *Chem. Commun.* **2016**, *52*, 12233; (g) W. Xu, G. Hu, P. Xu, Y. Gao, Y. Yin, Y. Zhao, *Adv. Synth. Catal.* **2014**, *356*, 2948; (h) B. Yang, Z. X. Wang, *J. Org. Chem.* **2019**, *84*, 1500; (i) H. Luo, H. Liu, X. Chen, K. Wang, X. Luo, K. Wang, *Chem. Commun.* **2017**, *53*, 956.

[10] For oxidative C–H/P(O)–H cross dehydrogenation coupling, see: (a) Y. H. Budnikova, O. G. Sinyashin, *Russ. Chem. Rev.* **2015**, *84*, 917; (b) C.-G. Feng, M. Ye, K. J. Xiao, S. Li, J.-Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 9322; (c) C. Li, T. Yano, N. Ishida, M. Murakami, *Angew. Chem. Int. Ed.* **2013**, *52*, 9801; *Angew. Chem.* **2013**, *125*, 9983.

[11] Carboxylic acids has been widely used for constructing chemical bonds, for selected reviews, see: (a) S. M. Bonesi, M. Fagnoni, *Chem. Eur. J.* **2010**, *16*, 13572; (b) N. Rodriguez, L. J. Goossen, *Chem. Soc. Rev.* **2011**, *40*, 5030; (c) W. I. Dzik, P. P. Lange, L. J. Gooßen, *Chem. Sci.* **2012**, *3*, 2671; (d) T. Patra, D. Maiti, *Chem. Eur.J.* **2017**, *23,* 7382; Carboxylic derivatives have also been widely applied in organic synthesis, for selected reviews, see: (e) A. Dermenci, G. Dong, *Sci. China Chem.* **2013**, *56*, 685; For recent developments, see: f) L. Guo, M. Rueping, *Acc. Chem. Res.* **2018**, *5*, 1185; (g) L. Guo, M. Rueping, *Chem. Eur.J.* **2018**, *24*, 7794.

[12] Cross coupling of carboxylic acids with P(O)–H compounds has been achieved; however, those reactions were performed under oxidative reaction conditions with CO_2 release (decarboxylation coupling) and usually suffered from oxidation of P(O)–H compounds to the corresponding acids. For a review, see: (a) A. Hosseinian, F. A. Hosseini Nasab, S. Ahmadi, Z. Rahmani, E. Vessally, *RSC Adv.* **2018**, *8*, 26383. For transformation of *o*-nitro benzoic acids, see: (b) J. Li, X. Bi, H. Wang, J. Xiao, *Asian J. Org. Chem.* **2014**, *3*, 1113. For transformations of alkyl or alkenyl carboxylic acids, see: (c) J. Hu, N. Zhao, B. Yang, G. Wang, L. N. Guo, Y. M. Liang, S.-D. Yang, *Chem.-Eur. J.* **2011**, *17*, 5516; (d) Y. Wu, L. Liu, K. Yan, P. Xu, Y. Gao, Y. Zhao, *J. Org. Chem.* **2014**, *79*, 8118; (e) L. Tang, L. Wen, T. Sun, D. Zhang, Z. Yang, C. Feng, Z. Wang, *Asian J. Org. Chem.* **2017**, *6*, 1683; (f) L. Liu, D. Zhou, J. Dong, Y. Zhou, S.-F. Yin, L.-B. Han, *J. Org. Chem.* **2018**, *83*, 4190.

[13] (a) C. Liu, M. Szostak, *Angew. Chem. Int. Ed.* **2017**, *56*, 12718; *Angew. Chem.* **2017**, *129*, 12892; (b) R. Isshiki, K. Muto, J. Yamaguchi, *Org. Lett.* **2018**, *20*, 1150.

[14] J. Dong, L. Liu, X. Ji, Q. Shang, L. Liu, L. Su, B. Chen, R. Kan, Y. Zhou, S.-F. Yin, L.-B. Han, *Org. Lett.* **2019**, *21*, 3198.

[15] For a pioneering work, see: (a) K. Nagayama, I. Shimizu, A. Yamamoto, *Chem. Lett.* **1998**, *27*, 1143; Synthesis of ketones with the strategy, see: (b) L. J. Gooßen, K. Ghosh, *Eur. J. Org. Chem.* **2002**, *2002*, 3254; (c) R. Kakino, S. Yasumi, I. Shimizu, A. Yamamoto *Bull. Chem. Soc. Jpn.* **2002**, *75*, 137; (d) R. Kakino, H. Narahashi, I. Shimizu, A. Yamamoto *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1333; (e) H. Yin, C. Zhao, H. You, K. Lin, H. Gong, *Chem. Commun.* **2012**, *48*, 7034; (f) X. Jia, X. Zhang, Q. Qian, H. Gong, *Chem. Commun.* **2015**, *51*, 10302; For decarbonylation elimination of alkyl carboxylic acids forming alkenes, see: (g) S. Maetani, T. Fukuyama, N. Suzuki, D. Ishihara, I. Ryu, *Chem. Commun.* **2012**, *48*, 2552. (h) X. Zhang, F. Jordan, M. Szostak, *Organ. Chem. Front.* **2018**, *5*, 2515.

[16] The strategy that carboxylic acids activated *in situ* coupled with nucleophiles with CO release (decarbonylation coupling) has attracted chemists' attention. For a related reviews, see: (a) J. Buchspies, M. Szostak, *Catalysts* **2019**, *9*, 53. For Rh-catalyzed examples, see: (b) L. J. Gooßen, J. Paetzold, *Adv. Synth. Catal.* **2004**, *346*, 1665; (c) F. Pan, Z. Q. Lei, H. Wang, H. Li, J. Sun, Z. J. Shi, *Angew. Chem. Int. Ed.* **2013**, *52*, 2063; *Angew. Chem.* **2013**, *125*, 2117; (d) L. Zhang, X. Xue, C. Xu, Y. Pan, G. Zhang, L. Xu, H. Li, Z. Shi, *ChemCatChem* **2014**, 6, 3069; (e) L. Zhang, R. Qiu, X. Xue, Y. Pan, C. Xu, D. Wang, X. Wang, L. Xu, H. Li, *Chem. Commun.* **2014**, *50*, 12385; (f) R. Qiu, L. Zhang, C. Xu, Y. Pan, H. Pang, L. Xu, H. Li, *Adv. Synth. Catal.* **2015**, *357*, 1229; (g) J. Xu, C. Chen, H. Zhao, C. Xu, Y. Pan, X. Xu, H. Li, L. Xu, B. Fan, *Organ. Chem. Front.* **2018**, *5*, 734; (h) X. Qiu, P. Wang, D. Wang, M. Wang, Y. Yuan, Z. Shi, *Angew. Chem. Int. Ed.* **2019**, *58*, 1504; *Angew. Chem.* **2019**, *131*, 1518; (i) H. Zhao, X. Xu, Z. Luo, L. Cao, B. Li, H. Li, L. Xu, Q. Fan, P. J. Walsh, *Chem. Sci.* **2019**, *10*, 10089; For Ni-catalyzed examples, see: (j) C. A. Malapit, J. R. Bour, S. R. Laursen, M. S. Sanford, *J. Am. Chem. Soc.* **2019**, *141*, 17322; (k) C. A. Malapit, J. R. Bour, C. E. Brigham, M. S. Sanford, *Nature* **2018**, *563*, 100; For Pd-catalyzed examples, see: (l) L. J. Gooßen, J. Paetzold L. Winkel, *Synlett* **2002**, *2002*, 1721; (m) C. Liu, C. L. Ji, X. Hong, M. Szostak, *Angew. Chem. Int. Ed.* **2018**, *57*, 16721; *Angew. Chem.* **2018**, *130*, 16963; (n) C. Liu, Z. X. Qin, C. L. Ji, X. Hong, M. Szostak, *Chem. Sci.* **2019**, *10*, 5736; (o) C. Liu, C. L. Ji, Z. X. Qin, X. Hong, M. Szostak, *iScience* **2019**, *19*, 749.

[17] Due to the strong coordination between P(O)–H compounds to transition metals, it is difficult to directly extend the established catalytic coupling system to the synthesis of organophosphorus compounds using P(O)–H compounds. For selected examples on $R^1R^2P(O)H$ as ligands, see: (a) G. Y. Li, *Angew. Chem. Int. Ed.* **2001**, *40*, 1513; *Angew. Chem.* **2001**, *113*, 1561; (b) J. Bigeault, L. Giordano, G. Buono, *Angew. Chem. Int. Ed.* **2005**, *44*, 4753; *Angew. Chem.* **2005**, *117*, 4831; (c) L. Ackermann, R. Born, J. H. Spatz, D. Meyer, *Angew. Chem. Int. Ed.* **2005**, *44*, 7216; *Angew. Chem.* **2005**, *117*, 7382; (d) I. Cano, A. M. Chapman, A. Urakawa, P. W. van Leeuwen, *J. Am. Chem. Soc.* **2014**, *136*, 2520; (e) I. Cano, M. A. Huertos, A. M. Chapman, G. Buntkowsky, T. Gutmann, P. B. Groszewicz, P. W. van Leeuwen, *J. Am. Chem. Soc.* **2015**, *137*, 7718.

[18] C. Liu, C. L. Ji, T. Zhou, X. Hong, M. Szostak, *Org. Lett.* **2019**, *21*, 9256.

[19] Phosphonic and phosphinic acids in lieu of carboxylic acids in bioisostere can hugely reform its intrinsic drug activity, see: (a) C. Ballatore, D. M. Huryn, A. B. Smith, *ChemMedChem* **2013**, *8*, 385; (b) P. Lassalas, B. Gay, C. Lasfargeas, M. J. James, V. Tran, K. G. Vijayendran, K. R. Brunden, M. C. Kozlowski, C. J. Thomas, A. B. Smith, D. M. Huryn, C. Ballatore, *J. Med. Chem.* **2016**, *59*, 3183.

[20] G. Meng, M. Szostak, *Angew. Chem. Int. Ed.* **2015**, *54*, 14518; *Angew. Chem.* **2015**, *127*,14726.

[21] T. Chen, C.-Q. Zhao, L.-B. Han, *J. Am. Chem. Soc.* **2018**, *140*, 3139.

[22] Ligand exchange takes place prior to decarbonylation could not be excluded at present. Meanwhile, it is also unknown when the possible decomposition of carbonate derivatives upon heating to generate CO_2 occurs.

[23] Stockland *et al.* have investigated the reductive elimination step using C−Pd−P(O) complexes. (a) M. C. Kohler, T. V. Grimes, X. Wang, T. R. Cundari, R. A. Stockland, *Organometallics* **2009**, *28*, 1193; (b) M. C. Kohler, R. A. Stockland, N. P. Rath, *Organometallics* **2006**, *25*, 5746; (c) A. M. Levine, R. A. Stockland, R. Clark, I. Guzei, *Organometallics* **2002**, *21*, 3278. The reaction has also been studied by calculation, see: (d) T. Wang, S. Sang, L. Liu, H. Qiao, Y. Gao, Y. Zhao, *J. Org. Chem.* **2014**, *79*, 608.

10.1002/ejoc.201901865

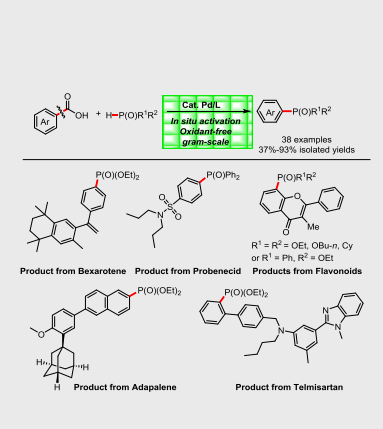
WILEY-VCH

Entry for the Table of Contents (Please choose one layout)

Layout 1:

COMMUNICATION

A direct decarbonylative phosphorylation of benzoic acids catalyzed by palladium was disclosed. Under the reaction conditions, a wide range of carboxylic acids coupled readily with all the three kinds of P(O)–H compounds, i.e. secondary phosphine oxides, H-phosphinates and H-phosphonates, producing the corresponding organophosphorus compounds in good to high yields. This reaction could be conducted at a gram scale and applied in the late-stage phosphorylative modification of carboxylic acids drug molecules. These results well demonstrated the potential synthetic value of this new reaction in organic synthesis.



Ji-Shu Zhang, Tieqiao Chen, Li-Biao Han**

Page No. – Page No.

Palladium-Catalyzed Direct Decarbonylative Phosphorylation of Carboxylic Acids with P(O)–H Compounds