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Efficient Pd-Catalyzed Dehydrogenative Coupling of P(O)H with RSH: A Precise Construction of P(O)−S Bonds

Yueyue Zhu,[†] Tieqiao Chen,*[,†] Shan Li,[†] Shigeru Shimada,[‡] and Li-Biao Han*[,‡]

[†]State Key Laboratory of Chemo/Biosensing and Chemometrics, College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, China

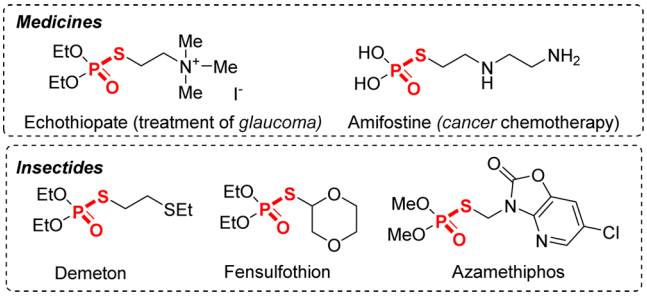
[‡]National Institute of Advanced Industrial Science and Technology (AIST), Tsukuba, Ibaraki 305-8565, Japan

Supporting Information

ABSTRACT: A Pd-catalyzed dehydrogenative phosphorylation of thiols is developed. A variety of thiols dehydrogenatively couple readily with all three kinds of P(O)−H compounds, i.e., H-phosphonates, H-phosphinates, and secondary phosphine oxides, providing a general access to the valuable phosphorothioates including the *P*-chiral compounds. A plausible mechanism is proposed.

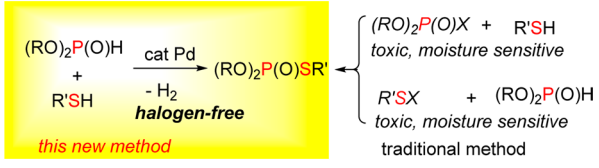
Phosphorothioates **1** are an important class of molecules in biological chemistry.[1] A number of well-known medicines and insecticides are based on these compounds (Scheme 1).[1a−e]

Scheme 1. Selected Examples of Drugs and Insecticides of Phosphorothioates



Their applications in organic synthesis are also well recognized.[1b,f−h] However, efficient and precise preparations of these compounds are rather unexplored (Scheme 2).[2−5] These

Scheme 2. Efficient Synthesis of Phosphorothioates



compounds are traditionally prepared by nucleophilic substitution of the *toxic and moisture sensitive* halides $(RO)_2P(O)Cl$ or RSX directly or indirectly.[2,3] However, in addition to safety and efficiency problems, these old methods also have severe limitations toward the copresence of functional groups in the molecules.

Herein, we report an efficient Pd-catalyzed dehydrogenative phosphorylation of the readily available P(O)H compounds with thiols **2** to produce phosphorothioates **1** in high yields (Scheme 2).[4,6−8] This reaction is general and a variety of substrates, i.e., all the three kinds of P(O)−H compounds **3** (H-phosphonates, H-phosphinates, and secondary phosphine oxides) can couple with both aromatic and aliphatic thiols. This new method also easily overcomes the limitations of the traditional methods. For example, *P*-chiral phosphorothioates and phosphorothioates **1** with OH and NH_2 groups, which could hardly be prepared by the old nucleophilic substitutions,[2,3] were readily obtained by this new method. Mechanistic studies showed that this transformation would proceed via a Pd(0)/Pd(II) process involving oxidative addition, ligand exchange releasing dihydrogen, and reductive elimination.

In the presence of 2.5 mol % $Pd_2(dba)_3$ and 5 mol % dppf (1,1′-bis(diphenylphosphino)ferrocene), diethyl phosphonate **3a** reacted with an equivalent amount of 4-(*tert*-butyl)-benzenethiol **2a** in dioxane at 100 °C for 20 h, producing the coupling product **1a** in 40% yield (Table 1, entry 1).[9] By adding 2 equiv of styrene to the reaction mixture, the yield of **1a** increased to 80% (Table 1, entry 2).[10] Further elevating the reaction temperature to 120 °C did not improve the yield of the product; whereas only 41% yield of **1a** was obtained when the reaction was conducted at 80 °C (Table 1, entries 4 and 5). The choice of a suitable phosphine ligand was the key factor for this transformation (Table 1, entries 6−14) since only a trace amount of **1a** was detected with Ph_3P, Cy_3P, 1,1-bis(diphenylphosphino)-methane (dppm), 1,2-bis(diphenylph-osphino)ethane (dppe), 1,3-bis(diphenylphosphino)propane (dppp), 1,6-bis-(diphenylphosphino)hexane (dpph), and 1,2-bis-(dicyclohexylphosphino)ethane (dcype). The yields were low with 1,4-bis(diphenylphosphino)butane (dppb) and xantphos too. The coupling reaction also proceeded in other solvents with toluene being the best choice (Table 1, entries 15−17). A very high yield (93%) of phosphorothioate **1a** was produced when 1.2 equiv of **2a** was employed (Table 1, entry 18).[10]

This Pd-catalyzed dehydrogenative phosphorylation was a rather general reaction for the synthesis of phosphorothioates. A variety of thiols readily coupled with P(O)−H compounds under the present reaction conditions to produce the corresponding phosphorothioates **1** in good to excellent yields. Thus, aromatic thiols with *tert*-butyl, methyl, methoxyl, and amide group on the

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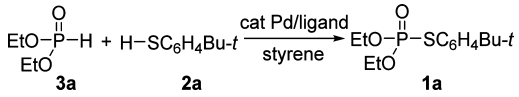
Table 1. Pd-Catalyzed Dehydrogenative Coupling of Diethyl Phosphonate with 4-(*tert*-Butyl)benzenethiol[a]



entry	ligand	solvent	yield[b]
1[c]	dppf	dioxane	40%
2	dppf	dioxane	80%
3[d]	dppf	dioxane	66%
4[e]	dppf	dioxane	80%
5[f]	dppf	dioxane	41%
6	Ph_3P	dioxane	trace
7	Cy_3P	dioxane	trace
8	dppm	dioxane	trace
9	dppe	dioxane	trace
10	dppp	dioxane	trace
11	dppb	dioxane	21%
12	dpph	dioxane	trace
13	dcype	dioxane	trace
14	xantphos	dioxane	17%
15	dppf	MeCN	34%
16	dppf	cyclohexane	62%
17	dppf	toluene	84%
18[g]	dppf	toluene	93%

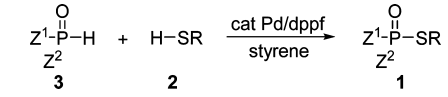
[a]Reaction conditions: 0.2 mmol **2a**, 0.2 mmol **3a**, 0.4 mmol styrene, 2.5 mol % Pd_2dba_3/phosphine ligand (Pd/P = 1:2), and 1 mL solvent were heated in a 25 mL glass tube at the indicated temperature for 20 h. [b]^{31}P NMR yield using triphenylphosphine oxide as an internal standard. [c]Without styrene. [d]1 mol % $Pd_2(dba)_3$ was loaded. [e]120 °C. [f]80 °C. [g]1.2 equiv of **2a** was used.

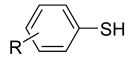
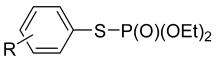
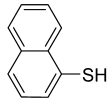
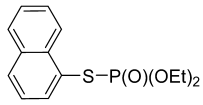
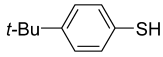
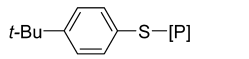
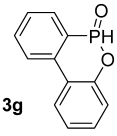
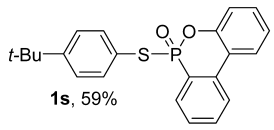
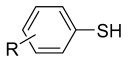
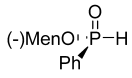
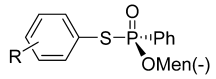
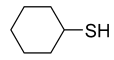
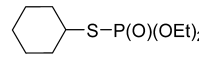
benzene ring all gave the corresponding coupling products in good yields (Table 2, entries 1–4). A substrate bearing a highly coordinative methylthio group also produced the product **1e** in 79% yield (Table 2, entry 5). Functional groups such as the free amine, hydroxyl, and even the easily hydrolyzed OCF_3 groups were tolerated well under the current reaction conditions (Table 2, entries 6–8). A halogen like fluoro and chloro groups also survived, facilitating further functionalization of the products (Table 2, entries 9 and 10). The substrates with electron-withdrawing groups like CF_3 and NO_2 coupled readily with diethyl phosphonate, generating the coupling products in moderate yields (Table 2, entries 11 and 12). Naphthalene-1-thiol was also proved to be a good substrate (Table 2, entry 13).

Interestingly, all the three kinds of hydrogen phosphoryl compounds were applicable to this reaction. Thus, in addition to diethyl phosphonate, diisopropyl phosphonate and even the easily hydrolyzed five-membered H-phosphonate **3c** also coupled readily with 4-(*tert*-butyl)benzenethiol **2a** under similar reaction conditions (Table 2, entries 14 and 15). This Pd-catalyzed dehydrogenative phosphorylation also took place efficiently with H-phosphinates and secondary phosphine oxides (Table 2, entries 16–22).

Notably, by using the present Pd-catalyzed dehydrogenative phosphorylation strategy, the *P*-chiral phosphorothioates **1** were synthesized stereoselectively in high yields with retention of configuration at phosphorus (Table 2, entries 20–22).[11] This is the first synthesis of *P*-chiral phosphorothioates via catalytic process.[12] It was noted that the classical Atherton–Todd reaction could not produce such products but gave those with inversed configuration at phosphorus.[3c,d]

Table 2. Pd-Catalyzed Dehydrogenative Phosphorylation of Thiols[a]



Entry	SH, **2**	P(O)H, **3**	Product, **1** (isolated yield)
			
1	**2a**, R = 4-*t*-Bu	**3a**, $(EtO)_2P(O)H$	**1a**, R = 4-*t*-Bu, 90%
2	**2b**, R = 4-Me		**1b**, R = 4-Me, 84%
3[b]	**2c**, R = 4-OMe		**1c**, R = 4-OMe, 85%
4[b]	**2d**, R = 4-NHAc		**1d**, R = 4-NHAc, 70%
5	**2e**, R = 4-SMe		**1e**, R = 4-SMe, 79%
6[b]	**2f**, R = 4-NH_2		**1f**, R = 4-NH_2, 76%
7[b]	**2g**, R = 4-OH		**1g**, R = 4-OH, 74%
8	**2h**, R = 4-OCF_3		**1h**, R = 4-OCF_3, 74%
9	**2i**, R = 4-F		**1i**, R = 4-F, 87%
10	**2j**, R = 4-Cl		**1j**, R = 4-Cl, 79%
11[c]	**2k**, R = 4-CF_3		**1k**, R = 4-CF_3, 54%
12[d]	**2l**, R = 4-NO_2		**1l**, R = 4-NO_2, 49%
			
13	**2m**		**1m**, 81%
			
14	**2a**	**3b**, $(i\text{-PrO})_2P(O)H$	**1n**, [P] = $(i\text{-PrO})_2P(O)$, 70%
15		**3c**, $(Me_2CO)_2P(O)H$	**1o**, [P] = $(Me_2CO)_2P(O)$, 49%
16		**3d**, Ph(EtO)P(O)H	**1p**, [P] = Ph(EtO)P(O), 73%
17		**3e**, $Ph_2P(O)H$	**1q**, [P] = $Ph_2P(O)$, 62%
18[c]		**3f**, *n*-$Bu_2P(O)H$	**1r**, [P] = *n*-$Bu_2P(O)$, 42%
19		 **3g**	 **1s**, 59%
			
20	**2a**, R = 4-*t*-Bu	***R*$_P$-3h**	***S*$_P$-1t**, R = 4-*t*-Bu, 94%
21	**2c**, R = 4-OMe		***S*$_P$-1u**, R = 4-OMe, 97%
22	**2d**, R = 4-NHAc		***S*$_P$-1v**, R = 4-NHAc, 77%
		**3a**	
23	**2n**		**1w**, 79%
	C_8H_{17}–SH		C_8H_{17}–S–P(O)$(OEt)_2$
24	**2o**		**1x**, 87%

[a]Reaction conditions: 0.24 mmol **2**, 0.2 mmol **3**, 0.4 mmol styrene, 2.5 mol % Pd_2dba_3/dppf (Pd/P = 1:2), and 1 mL toluene were heated in a 25 mL glass tube at 100 °C for 20 h. [b]Dioxane was used as solvent. [c]5 mol % $Pd_2(dba)_3$ was loaded. [d]0.4 mmol scale, 0.5 mL toluene was used.

Importantly, aliphatic thiols were also phosphorylated efficiently under the current reaction conditions (Table 2, entries 23 and 24). Thus, both cyclohexanethiol and octane-1-thiol coupled readily with diethyl phosphonate, producing the coupling product **1w** and **1x** in 79% and 87% yields, respectively. It was noted that the traditional Atherton–Todd reaction was not applicable to the synthesis of these compounds.[3d]

Mechanistic studies show that the oxidative addition of five-membered H-phosphonate **3c** to $Pd(PEt_3)_4$ produced a

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hydridopalladium complex **4a** quantitatively at room temperature. Subsequent addition of an equivalent benzenethiol **2a** to a solution of **4a** readily generated an unsymmetrical phosphoryl thiopalladium complex **5a** (Figure 1) with H_2 evolution (eq 1).

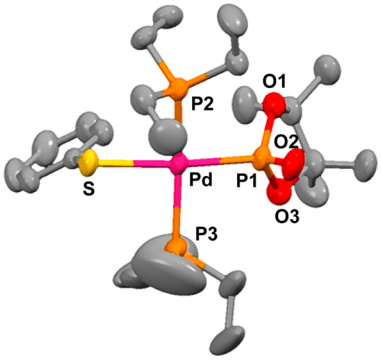
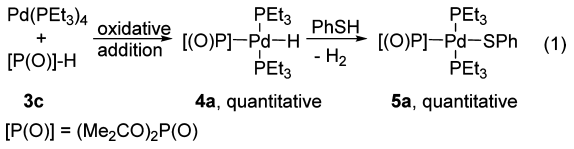


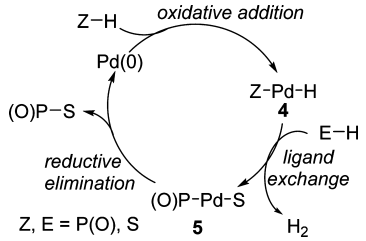
Figure 1. ORTEP drawing of complex **5a**. Hydrogen atoms are omitted for clarity. Ellipsoids are drawn at 50% probability.



This reaction can be achieved in one pot. Thus, $Pd(PEt_3)_4$ reacted with a mixture of benzenethiol and **3c** smoothly at room temperature to produce **5a** in 86% isolated yield.[13,14] The structure of complex **5a** was also determined by X-ray analysis.

Therefore, it is reasonable to propose that the current cross dehydrogenative coupling proceeds via a catalytic cycle as shown in Scheme 3. A Z—H bond first oxidatively adds to Pd(0) to

Scheme 3. Proposed Mechanism for the Pd-Catalyzed Dehydrogenative Phosphorylation of Thiols[a]



[a]The ligands were omitted for clarity.

produce a hydridometal complex **4**, which subsequently reacts with E—H, generating a species **5** and dihydrogen.[15] Reductive elimination of complex **5** affords the products and regenerates Pd(0) complex.

In summary, we have developed a Pd-catalyzed dehydrogenative phosphorylation of thiols. Both aromatic and aliphatic thiols coupled with H-phosphonates. All the three kinds of hydrogen phosphoryl compounds served well in the catalytic system. This reaction provides a general method for the synthesis of valuable phosphorothioates including the *P*-chiral phosphorus compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b03112.

General information, experimental procedures, characterization data, and copies of ^1H, ^{13}C, and ^{31}P NMR spectra for products (PDF)

Crystallographic information for **5a** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*chentieqiao@hnu.edu.cn

*libiao-han@aist.go.jp

Notes

The authors declare no competing financial interest.

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(3) Atherton—Todd-type reactions using CH_nCl_{4-n} (n = 1 or 0) as the halogenating reagent and solvent with production of stoichiometric salts, see: (a) Li, S.; Chen, T.; Saga, Y.; Han, L.-B. *RSC Adv.* **2015**, *5*, 71544. (b) Atherton, F. R.; Todd, A. R. *J. Chem. Soc.* **1947**, 674. (c) Xiong, B.; Zhou, Y.; Zhao, C.; Goto, M.; Yin, S.-F.; Han, L.-B. *Tetrahedron* **2013**, *69*, 9373. (d) Wang, G.; Shen, R.; Xu, Q.; Goto, M.; Zhao, Y.; Han, L.-B. *J. Org. Chem.* **2010**, *75*, 3890.

(4) The cross dehydrogenative coupling (CDC) between an S—H bond and an P(O)—H bond arguably represents the most straightforward and atom-economic protocol. Without exception, current strategies highly depend on the use of oxidants. This leads to the issue of oxidation of the starting material P(O)—H compounds. Thus, the development of an oxidant-free CDC procedure that does not damage P(O)—H compounds would be appreciated and still remains a great challenge. (a) Wang, J.; Huang, X.; Ni, Z.; Wang, S.; Pan, Y.; Wu, J. *Tetrahedron* **2015**, *71*, 7853. (b) Wang, J.; Huang, X.; Ni, Z.; Wang, S.; Wu, J.; Pan, Y. *Green Chem.* **2015**, *17*, 314. Special peroxides and overstoichiometric P(O)—H compounds are required in the two radical reactions (c) Kaboudin, B.; Abedi, Y.; Kato, J.-y.; Yokomatsu, T. *Synthesis* **2013**, *45*, 2323 only H-phosphonates are applicable.

(5) Other methods: (a) Ouyang, Y.-J.; Li, Y.-Y.; Li, N.-B.; Xu, X.-H. *Chin. Chem. Lett.* **2013**, *24*, 1103. (b) Panmand, D. S.; Tiwari, A. D.; Panda, S. S.; Monbaliu, J.-C. M.; Beagle, L. K.; Asiri, A. M.; Stevens, C. V.; Steel, P. J.; Hall, C. D.; Katritzky, A. R. *Tetrahedron Lett.* **2014**, *55*, 5898. (c) Kumaraswamy, G.; Raju, R. *Adv. Synth. Catal.* **2014**, *356*, 2591.

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(9) The generation of dihydrogen in the reaction could be detected by GC, see SI.

(10) Under the standard reaction conditions, 70% yield of ethylbenzene was generated (GC yield using tridecane as an internal standard).

(11) The configuration of the *P*-chiral phosphorothioates was confirmed by comparison with samples generated from Atherton−Todd reaction. For detailed information, see SI.

(12) Prof. Kumaraswamy tried to prepare *P*-chiral phosphorothioates via copper-mediated sulfenylation of *P*-chiral hydrogen phosphoryl compounds with sulfonylhydrazides, a racemic mixture was afforded, see ref 5c.

(13) To the best of our knowledge, no synthesis of phosphoryl Pd(II) complexes with such H_2 evolution was reported.

(14) Compound **5a** could also be produced by reaction of **3c** and equivalent $PhSPd(PEt_3)_2H$ with H_2 evolution, which was generated from oxidative addition of $Pd(PEt_3)_4$ to PhSH.

(15) The CDC reactions of trivalent phosphine R_2PH and RPH_2 are known, see: (a) Fermin, M. C.; Stephan, D. W. *J. Am. Chem. Soc.* **1995**, *117*, 12645. (b) Xin, S.; Woo, H.-G.; Harrod, J. F.; Samuel, E.; Lebuis, A.-M. *J. Am. Chem. Soc.* **1997**, *119*, 5307. (c) Stephan, D. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 314. (d) Bohm, V. P. W.; Brookhart, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 4694. (e) Shu, R.; Hao, L.; Harrod, J. F.; Woo, H.-G.; Samuel, E. *J. Am. Chem. Soc.* **1998**, *120*, 12988. (f) McWilliams, A. R.; Dorn, H.; Manners, I. *Top. Curr. Chem.* **2002**, *120*, 141. (g) Dorn, H.; Singh, R. A.; Massey, J. A.; Nelson, J. M.; Jaska, C. A.; Lough, A. J.; Manners, I. *J. Am. Chem. Soc.* **2000**, *122*, 6669. (h) Roering, A. J.; MacMillan, S. N.; Tanski, J. M.; Waterman, R. *Inorg. Chem.* **2007**, *46*, 6855. (i) Dorn, H.; Singh, R. A.; Massey, J. A.; Lough, A. J.; Manners, I. *Angew. Chem., Int. Ed.* **1999**, *38*, 3321. (j) Han, L.-B.; Tilley, T. D. *J. Am. Chem. Soc.* **2006**, *128*, 13698.

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