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ARTICLE TYPE

Palladium-Catalyzed Dehydrogenative Coupling of Terminal Alkynes with Secondary Phosphine Oxides

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The dehydrogenative coupling of terminal alkynes with secondary phosphine oxides is developed. In the presence of a silver additive, palladium acetate could efficiently catalyze the dehydrocoupling of secondary phosphine oxides with a 10 variety of terminal alkynes to produce the corresponding alkynylphosphine oxides in high yields. A reaction mechanism is proposed.

The transition metal-catalyzed dehydrogenative coupling reaction is a clean way for the construction of new chemical bonds (eq 15 1).^{1,2} By employing this method, two substrates can be coupled without prefunctionalization. The preparation of organophosphorus compounds via this dehydrocoupling method is recently attracting great attention.³

EH, ZH: a hydrocarbon and/or a heteroatom compound (1)

- Having a chemically reactive carbon-carbon triple bond. alkynylphosphinyl compound are versatile reagents for the preparation of highly functional phosphorus compounds through conjugate addition reactions, metallacycle formation and unique cycloadditions.^{4,5} Some of them are also biologically active.⁶ 25 Traditionally, these compounds are prepared by a few methods with the reaction using hazard chemical R₂P(O)Cl with Li or Mg acetylides being the most frequently employed, which suffers from lack of functionality's tolerance.⁵ Recently, an aerobic oxidative coupling of terminal alkynes with H-phosphonates 30 catalyzed by copper was reported.³ⁿ Very unfortunately, however, this reaction is not applicable to secondary phosphine oxides 1 to prepare the corresponding alkynylphosphine oxides 2, because of the severe oxidations of 1 and alkynes under the reaction conditions. Herein, we disclose an efficient palladium-35 mediated dehydrogenative coupling of 1 with a variety of
- ³⁵ mediated dehydrogenative coupling of **1** with a variety of terminal alkynes to selectively produce the valuable alkynylphosphorus compounds **2** in high yields under mild conditions (eq 2).

 $R^{1}R^{2}P(O)H + = R \xrightarrow{\text{cat Pd}(OAc)_{2}, Ag(I)} R^{1}R^{2}P(O) \xrightarrow{=} R$ $1 \qquad 2 \qquad (2)$

- ⁴⁰ We accidently found this reaction during our studies on metalcatalyzed P(O)H additions to alkynes.⁷ We noted that a trace amount of **2** could be occasionally detected by GC-Mass from the reaction mixture when Pd(OAc)₂ was used as a catalyst precursor. A careful pursuit of this phenomena leads to the disclosure of the
- ⁴⁵ present new reaction (eq 2). Thus, by carrying out extensive screening experiments on the reaction conditions, we realized that phenylacetylene and diphenylphosphine oxide **1a** could be coupled efficiently in the presence of a catalytic amount of palladium acetate with *a proper additive* (Table 1).

⁵⁰ **Table 1** Palladium-catalyzed dehydrocoupling of diphenylphosphine oxide **1a** with phenylacetylene^{*a*}

Ph=== +		cat. Po	l, additive	- Dh		(Ph ()
Ph ₂ P(O)H		solvent, 3 h		- Pii—	$Pn = P(O)Pn_2 \langle Ph_2(O)P \rangle$	
1a				2a		not detected
Entry	5 mol	% Pd	Additive	e Solvent	Tem.	Yield ^b
1	Pd(O	Ac) ₂	AgBF ₄	THF	40 °C	91%
2	Pd(O	Ac) ₂	$AgBF_4$	THF	60 °C	99%
3	Pd(O	Ac) ₂	Cu(OAc)	2 THF	40 °C	7%
4	Pd(O	Ac) ₂	$CuCl_2$	THF	40 °C	none
5	Pd(O	Ac) ₂	Cu(NO ₃)	2 THF	40 °C	8%
6	Pd(O	Ac) ₂	AgOAc	THF	40 °C	trace
7	Pd(O	Ac) ₂	Ag ₂ CO ₃	; THF	40 °C	trace
8	Pd(O	Ac) ₂	AgOTf	THF	40 °C	trace
9	Pd(O	Ac) ₂	$AgPF_6$	THF	40 °C	12%
10	Pd(O	Ac) ₂	KBF_4	THF	60 °C	trace
11	nor	ne	$AgBF_4$	THF	40 °C	none
12	PdC	Cl_2	$AgBF_4$	THF	40 °C	17%
13	Pd ₂ (d	ba)₃	$AgBF_4$	THF	40 °C	trace
14	Pd(O	Ac) ₂	$AgBF_4$	CH₃OH	60 °C	90%
15	Pd(O	Ac) ₂	$AgBF_4$	DMF	40 °C	trace
16	Pd(O	Ac) ₂	$AgBF_4$	toluene	40 °C	trace
17	Pd(O	Ac) ₂	$AgBF_4$	Et ₂ O	40 °C	trace

^{*a*}Reaction conditions: **1a** (0.2 mmol), phenylacetylene (0.2

mmol), 5 mol% Pd catalyst, additive (0.4 mmol), solvent (1 mL).

^bGC yield using dodecane as an internal standard.

As shown in Table 1, the catalytic dehydrocoupling reaction of diphenylphosphine oxide 1a with phenylacetylene in THF catalyzed by 5 mol% Pd(OAc)₂ took place quickly in the presence of AgBF₄ at 40 °C to give the corresponding phenylethynyldiphenylphosphine oxide **2a** in 91% yield after 3 h (entry 1). The starting materials were completely consumed and a nearly quantitative yield of **2a** was obtained when the reaction s was conducted at a slightly higher temperature (60 °C) (entry 2). Among the additives investigated, AgBF₄ gave the highest yield compared to other silver salts and copper salts (entries 3-9). A

- palladium catalyst is essential for this dehydrocoupling reaction. In the absence of the palladium catalyst, **2a** could not be detected 10 at all (entry 11). In addition to palladium acetate, palladium chloride (entry 12) also gave 17% yield of **2a**. However,
- $Pd_2(dba)_3$ hardly promoted the reaction (entry 13). In addition to THF, the dehydrocoupling could also proceed efficiently in methanol (entry 14). However, it hardly proceeded in DMF, to luene and ether (entries 15-17). Another remarkable feature of this reaction is that although the palladium catalyzed addition of $Ph_2P(O)H$ to phenylacetylene forming the addition adducts could be possible,⁷ no such adducts was detected under the present reaction conditions.

This palladium-catalyzed dehydrocoupling is a rather general 20 method for the preparation of alkynylphosphine oxides 2. Thus, as shown in Table 2, a variety of terminal alkynes, both aromatic and aliphatic, can readily react with secondary phosphine oxides 1 to produce the corresponding alkynylphosphine oxides 2 25 selectively. Worth noting is that this dehydrocoupling features a wide tolerance to a variety of functional groups. Thus fluoro (entry 7), chloro (entry 8), trifluoromethyl (entry 10), ester (entry 15), and carboxyl group (entry 16), all are compatible under the present catalytic conditions. Surprisingly, as exemplified by the 30 reaction of 4-bromophenylacetylene, even an organyl bromide that can couple with P(O)-H in the presence of a palladium catalyst,⁸ also can be used as the substrate, to give the corresponding dehydrocoupling product 2i in 81% yield (entry 9). More surprisingly, although Ph₂P(O)H can nucleophilically add $_{35}$ to a carbonyl group,⁹ the dehydrocoupling product **2k** could be obtained in a high yield from 1-(4-ethynylphenyl)ethanone (entry 11), in which no such by-product via the addition of $Ph_2P(O)H$ to the carbonyl group was detected. As shown in the table, an aryl alkyne with a methoxy or an amino group showed low reactivity 40 in this reaction (entries 5 and 6). The reaction of 1ethynylnaphthalene with Ph₂P(O)H gave 60% yield of the corresponding dehydrocoupling product 21 (entry 12). However, only trace of product was detected when 1,4-diethynylbenzene was employed under similar reaction conditions (entry 13). The 45 reaction was also applicable to aliphatic alkynes. Thus, the catalytic dehydrocoupling of Ph₂P(O)H with 1-octyne took place efficiently to afford 2n in 95% isolated yield (entry 14). Other aliphatic alkynes also served as good substrates for this reaction producing the corresponding alkynylphosphine oxides in high

50 yields (entries 14-20).

As to the secondary phosphine oxide, both aliphatic and aromatic substrates could be used in this reaction. Thus, in addition to $Ph_2P(O)H$ **1a**, *n*-Bu₂P(O)H **1b** also readily reacts with phenylacetylene to produce the corresponding (phenylethynyl)dibutylphosphine oxide **2u** in 68% yield (entry 21). Butylphenylphosphine oxide *n*-BuPhP(O)H **1c** is also as reactive as other secondary phosphine oxides. Compound **1c** efficiently reacted with phenylacetylene and 1-octyne to produce the corresponding 2v and 2w in 80% and 75% yields, ⁶⁰ respectively (entries 22 and 23). Bulky dicyclohexylphosphine oxide 1d reacted with phenylacetylene to give 2x in 59% yield (entry 24). H-Phosphinate esters 1e and H-phosphonates 1f also served good substrates in this reaction to produce the corresponding 2y and 2z in 91% and 85% yields, respectively ⁶⁵ (entries 25 and 26).

Table 2 Palladium-catalyzed dehydrocoupling of secondary phosphine

 oxides 1 with terminal alkynes producing alkynylphosphine oxides 2^a

R—=	\equiv + R ¹ R ² P(O)H -	cat. Pd(OAc) ₂ , AgBF ₄	R ¹ R ² P(0)— <u>—</u> R
	1	60 ºC, 1 mL THF		2
Entry	Alkyne	P(O)-H	Product	Isolated Yield
				0001
1	Ph	1a	2a	92%
2	о-ме-С ₆ н ₄ — <u></u>	=	2b	86%
3	<i>m</i> -Me-C ₆ H ₄ =		2c	89%
4	<i>p</i> -Me-C ₆ H ₄	=	2 d	87%
5	<i>p</i> -MeO-C ₆ H ₄ —		2e	trace
6	<i>p</i> -H ₂ N-C ₆ H ₄		2f	n.d.
7	<i>p</i> -F-C ₆ H ₄		2 g	84%
8	<i>p</i> -CI-C ₆ H ₄ —		2h	89%
9	p-Br-C ₆ H ₄		2 i	81%
10	<i>p</i> -F ₃ C-C ₆ H ₄ —	=	2j	85%
11	<i>p</i> -Ac-C ₆ H ₄ —	≣	2k	84%
12	α-naphthyl	≣	21	60%
13	<u> </u>	≣	2m	trace
14	<i>n</i> -C ₆ H ₁₃	≡	2 n	95%
15	MeO ₂ C(H ₂ C) ₈	≡	20	92%
16	HO ₂ C(H ₂ C) ₈	=	2 p	70%
	\frown			
17				000/
17		=	2 q	90%
	\frown	_	-	
18 ^b		=	2r	74%
19 ^b	t-Bu—	=	2s	56%
	~ //			
20			2t	91%
	\checkmark			
21	Ph	<i>n</i> -Bu ₂ P(O)H	2 u	68%
		1b	-	
22	Ph	<u>n-BuPhP(O)</u>	2v	80%
23	<i>n</i> -C ₆ H ₁₃ —	=	2 w	75%
24	Ph=	Cy ₂ P(O)H	2x	59%
		1d		
25 ^c	Ph-	Ph(EtO)P(O)H	2у	91%
26 ^{c,d}	Ph=	$\equiv (i-\Pr O)_2 P(O) H$	2z	85%
	· · · · -			

^aReaction conditions: 0.2 mmol 1, 0.2 mmol alkyne, 5 mol% Pd(OAc)₂,
0.4 mmol AgBF₄, 1 mL THF, 60 °C, 3-24 h. ^b100 °C, 18 h. ^c0.4 mmol
⁷⁰ Et₃N, 100 °C, 18 h. ^d 0.4 mmol alkyne was added.

On the basis of the above experimental results, several control experiments¹⁰ and the previous studies,¹¹ we assume that this

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palladium-catalyzed coupling takes place via a catalytic cycle involving (i) ligand-exchange of Pd(OAc)₂ with **1** and an alkyne to generate the alkynyl(phosphinyl)palladium intermediate **3**, which (ii) undergoes reductive elimination to give the ⁵ dehydrocoupling compound **2**. Finally, (iii) the reduced zerovalent palladium is reoxidized by Ag(I) to Pd(II) to complete the catalytic cycle (Scheme 1).



Scheme 1 A proposed mechanism for the palladium-catalyzed dehydrocoupling of 1 with terminal alkynes.

In summary, a palladium-catalyzed dehydrocoupling of terminal alkynes with secondary phosphine oxides was developed. This new reaction is applicable to a variety of secondary phosphine oxides and terminal alkynes, and is a general way for the 15 preparation of the valuable alkynylphosphine oxides. Studies on the mechanism and applications to other substrates are under way

Notes and references

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 ²⁵ information, experimental procedures, copies of ¹H, ¹³C and ³¹P NMR
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coupling of phenylacetylene with $Ph_2P(O)H$ also work efficiently in the presence of a radical scavanger (1 equiv of butylated hydroxytoluene) to give 75% yield of **2a**, that should exclude a similar radical mechanism.

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