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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]

$$E-H \ + \ Z-H \ \xrightarrow{\text{cat. M}} \ E-Z$$
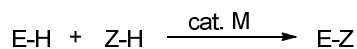
EH, ZH: a hydrocarbon and/or a heteroatom compound   (1)

20   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 $R_2P(O)Cl$ 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 terminal alkynes to selectively produce the valuable alkynylphosphorus compounds **2** in high yields under mild conditions (eq 2).

$$R^1R^2P(O)H \ + \ \equiv\!\!-R \ \xrightarrow{\text{cat Pd(OAc)}_2, \text{ Ag(I)}} \ R^1R^2P(O)\!-\!\!\equiv\!\!-R$$

1 **2**   (2)
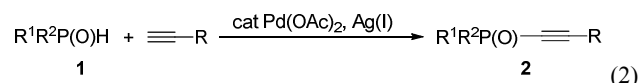
40   We accidently found this reaction during our studies on metal-catalyzed P(O)H additions to alkynes.[7] We noted that a trace amount of **2** could be occasionally detected by GC-Mass from the reaction mixture when $Pd(OAc)_2$ was used as a catalyst precursor. A careful pursuit of this phenomena 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]

Entry	5 mol% Pd	Additive	Solvent	Tem.	Yield[b]
1	$Pd(OAc)_2$	$AgBF_4$	THF	40 °C	91%
2	$Pd(OAc)_2$	$AgBF_4$	THF	60 °C	99%
3	$Pd(OAc)_2$	$Cu(OAc)_2$	THF	40 °C	7%
4	$Pd(OAc)_2$	$CuCl_2$	THF	40 °C	none
5	$Pd(OAc)_2$	$Cu(NO_3)_2$	THF	40 °C	8%
6	$Pd(OAc)_2$	AgOAc	THF	40 °C	trace
7	$Pd(OAc)_2$	Ag_2CO_3	THF	40 °C	trace
8	$Pd(OAc)_2$	AgOTf	THF	40 °C	trace
9	$Pd(OAc)_2$	$AgPF_6$	THF	40 °C	12%
10	$Pd(OAc)_2$	KBF_4	THF	60 °C	trace
11	none	$AgBF_4$	THF	40 °C	none
12	$PdCl_2$	$AgBF_4$	THF	40 °C	17%
13	$Pd_2(dba)_3$	$AgBF_4$	THF	40 °C	trace
14	$Pd(OAc)_2$	$AgBF_4$	CH_3OH	60 °C	90%
15	$Pd(OAc)_2$	$AgBF_4$	DMF	40 °C	trace
16	$Pd(OAc)_2$	$AgBF_4$	toluene	40 °C	trace
17	$Pd(OAc)_2$	$AgBF_4$	Et_2O	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).

[b]GC yield using dodecane as an internal standard.

55   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 AgBF$_4$ at 40 ^{o}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
5 was conducted at a slightly higher temperature (60 ^{o}C) (entry 2). Among the additives investigated, AgBF$_4$ 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,
15 toluene and ether (entries 15-17). Another remarkable feature of this reaction is that although the palladium catalyzed addition of Ph$_2$P(O)H to phenylacetylene forming the addition adducts could be possible,[7] no such adducts was detected under the present reaction conditions.

20 This palladium-catalyzed dehydrocoupling is a rather general 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 Ph$_2$P(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$_2$P(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 1-ethynylnaphthalene with Ph$_2$P(O)H gave 60% yield of the corresponding dehydrocoupling product **2l** (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 Ph$_2$P(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$_2$P(O)H **1a**, n-Bu$_2$P(O)H **1b** also readily reacts with phenylacetylene to produce the corresponding
55 (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
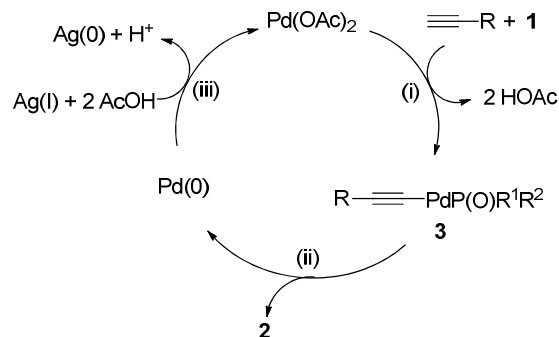65 (entries 25 and 26).

Table 2 Palladium-catalyzed dehydrocoupling of secondary phosphine oxides **1** with terminal alkynes producing alkynylphosphine oxides **2**[a]

$$R\!-\!\!\!\equiv\ +\ R^1R^2P(O)H \xrightarrow[\text{60 }^o\text{C, 1 mL THF}]{\text{cat. Pd(OAc)}_2,\ \text{AgBF}_4} R^1R^2P(O)\!-\!\!\!\equiv\!-\!R$$

Entry	Alkyne	P(O)-H	Product	Isolated Yield
1	Ph—≡	Ph$_2$P(O)H **1a**	**2a**	92%
2	o-Me-C$_6$H$_4$—≡		**2b**	86%
3	m-Me-C$_6$H$_4$—≡		**2c**	89%
4	p-Me-C$_6$H$_4$—≡		**2d**	87%
5	p-MeO-C$_6$H$_4$—≡		**2e**	trace
6	p-H$_2$N-C$_6$H$_4$—≡		**2f**	n.d.
7	p-F-C$_6$H$_4$—≡		**2g**	84%
8	p-Cl-C$_6$H$_4$—≡		**2h**	89%
9	p-Br-C$_6$H$_4$—≡		**2i**	81%
10	p-F$_3$C-C$_6$H$_4$—≡		**2j**	85%
11	p-Ac-C$_6$H$_4$—≡		**2k**	84%
12	α-naphthyl—≡		**2l**	60%
13	≡—C$_6$H$_4$—≡		**2m**	trace
14	n-C$_6$H$_{13}$—≡		**2n**	95%
15	MeO$_2$C(H$_2$C)$_8$—≡		**2o**	92%
16	HO$_2$C(H$_2$C)$_8$—≡		**2p**	70%
17	(cyclohexyl-CH$_2$)—≡		**2q**	90%
18[b]	(cyclohexyl)—≡		**2r**	74%
19[b]	t-Bu—≡		**2s**	56%
20	(cyclohexenyl)—≡		**2t**	91%
21	Ph—≡	n-Bu$_2$P(O)H **1b**	**2u**	68%
22	Ph—≡	n-BuPhP(O)H **1c**	**2v**	80%
23	n-C$_6$H$_{13}$—≡		**2w**	75%
24	Ph—≡	Cy$_2$P(O)H **1d**	**2x**	59%
25[c]	Ph—≡	Ph(EtO)P(O)H **1e**	**2y**	91%
26[c,d]	Ph—≡	(i-PrO)$_2$P(O)H **1f**	**2z**	85%

[a]Reaction conditions: 0.2 mmol **1**, 0.2 mmol alkyne, 5 mol% Pd(OAc)$_2$,
0.4 mmol AgBF$_4$, 1 mL THF, 60 ^{o}C, 3-24 h. [b]100 ^{o}C, 18 h. [c]0.4 mmol
70 Et$_3$N, 100 ^{o}C, 18 h. [d] 0.4 mmol alkyne was added.

On the basis of the above experimental results, several control experiments[10] and the previous studies,[11] we assume that this

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 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 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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10   Since Ag(I) could mediate phosphorylation of indoles with H-phosphonates via a radical pathway (H. Wang, X. Li, F. Wu, F. and B. Wan, *Synthesis*, 2012, **44**, 941), it was assumed that (Ph)$_2$P(O)Ag and silver phenylacetylide migh be generated in situ and work as the active species in the coupling reaction (table 1). However, isolated (Ph)$_2$P(O)Ag (1 equiv) with phenylacetylene (1 equiv) in the presence of AgBF$_4$ (1 equiv) only gave trace product, while no product was detected from (Ph)$_2$P(O)Ag (1 equiv) and silver phenylacetylide (1 equiv). In additon, the palladium catlyzed

coupling of phenylacetylene with Ph$_2$P(O)H also work efficeintly 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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