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complexes: efficient head-to-tail dimerization of alkynes†

A Brønsted acid-catalyzed generation of palladium

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A Brønsted acid $Ph_2P(O)OH$ can efficiently catalyze the reaction of a Pd(0) complex with an alkyne to produce a novel alkenyl(alkynyl)palladium complex *via* selective hydropalladation and ligand exchange processes. On the basis of this finding, an efficient Pd(0)/Ph_2P(O)OH mediated head-to-tail dimerization of alkynes was disclosed.

Palladium complexes can efficiently catalyze a variety of chemical transformations and are the most popular catalysts used in modern organic synthesis.¹ Herein we disclose an unprecedented Brønsted acid catalyzed synthesis of alkenyl(alkynyl)palladium complexes **1**, important intermediates for the formation of sp^2C -spC bonds (eqn (1)).¹⁻⁴ There are thousands of palladium complex-catalyzed reactions. However, to our knowledge, such a catalytic preparation of palladium complexes seems unknown. This finding also leads to the disclosure of a highly selective head-to-tail dimerization of alkynes affording **3** catalyzed by a combination of Pd(0)/Ph₂P(O)OH (Scheme 1).

$$R \longrightarrow + Pd(PEt_3)_4 \qquad \xrightarrow{\text{cat. Ph}_2P(O)OH} \qquad \xrightarrow{PEt_3}_{Pd} \xrightarrow{Pd}_{R} \qquad (1)$$

Transition metal catalyzed dimerization of alkynes, as exemplified by Scheme 1, is a straightforward and atom-economic approach to conjugated enynes 3 which are not only useful building blocks in organic synthesis but also themselves found as the key units in various natural products such as histrionicotoxin and elatenyne.^{5,6} This reaction is currently extensively exploited with a variety of metal catalysts in order to find more efficient and selective ways for the dimerization of alkynes.^{2,3} However, despite its high importance,



Scheme 1 Metal-catalyzed head-to-tail dimerizations of alkynes

mechanistic aspects related to the catalysis are rather ambiguous and controversial (Scheme 1).^{2*a,d,3a,b,6e*} For example, it was suggested that a hydridometal species **4** formed *via* the activation of the spC–H bond of acetylene was the intermediate, which can subsequently add to acetylene to give either **1** by hydrometallation or **5** by carbometallation.^{2*a,d,3a,b,9*} However, no clear evidence supporting the presence of such intermediates **1**, **4** and **5** in the reactions was obtained.^{2*d,3b*}

Careful mechanistic studies of the current Pd/Brønsted acid mediated selective head-to-tail dimerization unambiguously revealed the reaction paths which are different from those proposed before *i.e.* firstly, a selective hydropalladation of alkynes takes place to form an alkenylpalladium **2** which then affords **1** via a ligand exchange process. Subsequent reductive elimination of **1** gives the head-to-tail conjugated dimer **3**.

An equimolar mixture of phenylacetylene, $Ph_2P(O)OH$ and $Pd(PEt_3)_4$ was dissolved in C_6D_6 at room temperature (0.05 mmol in 0.5 mL C_6D_6). The colour of the solution gradually changed from brown to light blue. Two characteristic vinyl protons were observed at 5.09 (s, 1H) and 6.02 (t, 1H, $J_{P-H} = 3.6$ Hz) by ¹H NMR spectroscopy while at the same time two new signals were also observed by ³¹P NMR spectroscopy at 19.22 and 10.72, indicative of the formation of a vinylpalladium complex **2a** *via* selective hydropalladation of phenylacetylene.⁷ Removal of the volatiles *in vacuo* afforded complex **2a** as a white solid. Good crystals suitable for X-ray analysis were obtained by recrystallization from a toluene–hexane mixed solvent at -30 °C and the structure of **2a** was unambiguously confirmed (Fig. 1). It is worth noting that an internal alkyne with an electron withdrawing phosphoryl group was also hydropalladated regio and stereoselectively generating

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Fig. 1 ORTEP drawings of complexes 2a and 1f. Thermal ellipsoids are drawn at 50% probability. H atoms are omitted for clarity.

the corresponding **2b** with palladium attached to the more electronegative carbon (eqn (2)).



Interestingly, it was found that ligand exchange between **2a** and phenylacetylene could take place easily at room temperature to generate a novel alkenyl(alkynyl)palladium complex **1a** (eqn (3)).⁸ Thus, an equimolar mixture of **2a** and phenylacetylene (0.05 mmol) was dissolved in 0.5 mL of toluene- d_8 at room temperature. After a few minutes, two new vinyl protons at 5.33 and 6.59 were observed by ¹H NMR spectroscopy while a new singlet at 13.95 was also observed by ³¹P NMR spectroscopy. As described later, these new signals are due to the formation of a new palladium complex **1a**. As estimated from ¹H NMR spectroscopy, **1a** was generated in *ca*. 45% yield after 2 h, showing that the ligand exchange between **2a** and phenylacetylene took place smoothly. Similarly, complex **2b** could react with phenylacetylene to produce **1b** in *ca*. 75% yield after 1 h (eqn (3)).

Remarkably, a trace amount of Ph₂P(O)OH could efficiently catalyze the formation of complex 1a via the combination of hydropalladation and ligand exchange reactions as described above. Thus, in the presence of 1 mol% Ph₂P(O)OH (based on Pd), 1 mmol phenylacetylene and 0.5 mmol Pd(PEt₃)₄ smoothly reacted at 25 °C and selectively generated the corresponding vinyl(alkynyl)palladium 1a quantitatively within 20 h. 1a is a pale yellow oil which precipitates out when cooling down the solution at -78 °C (83%) isolated yield). There is no need to mention that such a complex as 1a could not be formed at all from phenylacetylene and $Pd(PEt_3)_4$ in the absence of Ph2P(O)OH. In order to clearly determine the structure by X-ray analysis, the preparation of a solid 1 was thoroughly investigated. Unfortunately, although other alkynes such as p-tolylacetylene, p-t-butylphenylacetylene, and p-phenylphenylacetylene all gave the corresponding products in high yields, all the complexes were oils. Finally, when p-anisylacetylene was used as the substrate, the corresponding complex 1f was obtained as a yellow solid in 70% isolated yield. Recrystallization of the solid from hexane-toluene at -30 °C gave good crystals suitable for X-ray analysis, which, as depicted in Fig. 1, unambiguously confirmed the structure showing an alkenyl and an alkynyl group attached to Pd in



a *trans* manner. It was noted that alkenyl(alkynyl)palladium complexes **1** represents the first palladium complexes bearing sp²C–Pd and spC–Pd bonds generated *via* direct hydropalladation of alkynes. Although this kind of complexes have long been proposed as intermediates in the dimerization of alkynes^{2,3} and other reactions,⁴ they have never been obtained directly (Scheme 2).⁹

These stoichiometric reactions indicate the possibility of a highly selective head-to-tail dimerization of alkynes catalyzed by the combination of Pd(0)/Ph2P(O)OH. This indeed was the case. As shown in Table 1, in the presence of 0.25 mol% Pd₂(dba)₃, 0.5 mol% dppe and 1 mol% Ph2P(O)OH, 1-octyne could be selectively converted to the corresponding head-to-tail dimerization product 3a in 90% yield in toluene at 80 °C (entry 1).¹⁰ Under the present catalytic conditions, a variety of aliphatic alkynes could be employed as the substrates to give the corresponding conjugated enynes in good yields (entries 1-7). Valuable functional groups such as carboxylic ester (entry 2), chloro (entry 6) and nitrile (entry 7) were all compatible with the present system. In the presence of the amino group, the dimerization of dibutylpropargylamine progresses slowly and more catalysts were used (entry 5). The expected product 3c was also obtained in high yield from the bulky t-butylacetylene (entry 3). Compared to alkyl alkynes, selective dimerization of aromatic alkynes was complicated due to side reactions such as trimerization and the polymerization of the product enynes.^{2a,11} By carrying out the catalytic reaction at room temperature,11 aromatic terminal alkynes could also be readily dimerized to give the corresponding enynes in good yields. Thus, the combination of 0.5 mol% Pd₂(dba)₃, 1 mol% dppe and 2 mol% Ph₂P(O)OH could efficiently catalyze the head-to-tail dimerization of phenylacetylene in toluene at 25 °C to generate the corresponding conjugated enyne 3h in 81% yield (entry 8). Other aromatic alkynes bearing electron-donating groups could also be dimerized to the corresponding envnes selectively in good yields (entries 9-13). p-Fluorophenylacetylene was also a good substrate for this dimerization (entry 14). However, an aromatic alkyne bearing an electron-withdrawing group only produced the envne in a low yield because of severe side reactions (entry 15).

On the other hand, a cross dimerization between a terminal alkyne and an internal alkyne could also be achieved by using this $Pd(0)/Ph_2P(O)OH$ catalyst. For example, phenylacetylene reacted smoothly with 4-phenylbut-3-yn-2-one and diethyl 2-phenylethynylphosphonate at 25 °C to generate the corresponding dimerization products **3p** and **3q** in high yields with high selectivity (Scheme 3).

On the basis of the results of stoichiometric reactions (eqn (1)–(3)), this $Pd(0)/Ph_2P(O)OH$ mediated head-to-tail dimerization of terminal alkynes could be clearly rationalized to take place *via* a catalytic cycle involving the hydropalladation of alkynes with $Ph_2P(O)OH$ to generate an alkenylpalladium complex 2, followed by ligand exchange of 2 with another molecule of alkyne to produce the vinyl(alkynyl)palladium intermediate 1, which underwent reductive elimination to give the corresponding products enyne 3 (Scheme 4).¹²

Table 1Palladium(0)/Brønsted acid $Ph_2P(O)OH$ mediated head-to-tail dimer-
ization of terminal alkynes^a

R-	Pd ₂ (dba) ₃ , dppe, Ph ₂ P(O)OH		<u> В</u>	
	toluen	toluene		
Run	Alkynes	Product	Isolated yield (%)	
1	<i>n</i> -C ₆ H ₁₃ ==	3a	90	
2	t-BuO(O)C	3b	75	
3	<i>t</i> -Bu───	3c	93	
4^b	Ph	3d	85	
5 ^c	(<i>n</i> -Bu) ₂ N	3e	77	
6	CI	3f	73	
7	NC	3g	61	
8	Ph	3h	81	
9	<i>p</i> -MeC ₆ H ₄	3i	92	
10	<i>p-t</i> -BuC ₆ H ₄	3ј	91	
11	<i>p</i> -MeOC ₆ H ₄	3k	94	
12	<i>p</i> -PhC ₆ H ₄	31	91	
13	<i>p</i> -PhOC ₆ H ₄ ===	3m	69	
14	<i>p</i> -FC ₆ H ₄	3n	81	
15	<i>p</i> -F ₃ CC ₆ H ₄ ==	30	40^d	

^{*a*} Conditions: a mixture of 0.25 mol% $Pd_2(dba)_3$ (for aromatic alkynes, 0.5 mol%), phosphine ligand (Pd/P = 1 : 2), and Ph₂P(O)OH (Pd/acid = 1 : 2) in toluene was stirred at 25 °C for 10 minutes and 1 mmol alkyne was added. The mixture was heated at 80 °C (for aromatic alkynes, 25 °C) overnight. ^{*b*} 24 h. ^{*c*} 0.5 mol% Pd₂(dba)₃. ^{*d*} NMR yield.

Ph	1 mol% Pd ₂ (dba) ₃ , 2 n 4 mol% Ph ₂ P(O)OH toluene, room tempera	nol% TDMPP ature, overnight [►]	Ph=	= Ph
TDMPP =	[(2,6-(MeO) ₂ C ₆ H ₃] ₃ P	3p : R = Ac 3q : R = P(O)(OEt) ₂	85% yield 88% yield

Scheme 3 Pd(0)/Ph₂P(O)OH catalyzed cross dimerization of alkynes.



 $\mbox{Scheme 4}$ Proposed mechanism for the $\mbox{Pd}(0)/\mbox{Ph}_2\mbox{P}(0)\mbox{OH}$ mediated head-to-tail dimerization of alkynes.

In summary, by successful isolation and characterization of relevant intermediates, we reported, for the first time, a novel Brønsted acid catalyzed formation of alkenyl(alkynyl)palladiums from the reaction of a Pd(0) complex with alkynes, *via* efficient hydropalladation and subsequent ligand exchange reactions. On the basis of this finding, selective head-to-tail dimerization of alkynes efficiently affording enynes catalyzed by the combination of Pd(0)/Brønsted acid was developed. This work was partially supported by Fundamental Research Funds for the Central Universities (Hunan university) and the Canon Foundation.

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- 10 For more information, see ESI⁺-E.
- 11 The dimerization products from aromatic terminal alkynes easily polymerize at high temperatures. For example, at 80 $^{\circ}$ C, all the enynes polymerized and no 3h could be obtained.
- 12 Trost has reported that Pd(OAc)₂/phosphine was an effective catalytic system for the head-to-tail dimerization of alkynes.^{3*a,b*} However, mechanistic aspects were not clear. We guess the current mechanism is applicable to Trost's system since Pd(0)/acetic acid was also effective for the dimerization of terminal alkynes (see ESI[†]-E).