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The first palladium-catalyzed 1,4-addition of terminal alkynes to conjugated enones

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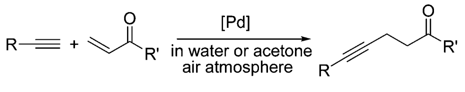
The first palladium-catalyzed 1,4-addition of terminal alkynes to conjugated enones has been developed in water and in acetone, producing the corresponding γ,δ-alkynyl ketones in high yields.

Within the past few decades, the development of palladium-catalyzed C–C bond formation reactions has dramatically advanced the "state-of-the-art" of organic synthesis.[1] The well known palladium catalyzed C–C bond formation reactions include the Heck reaction,[2] the Stille reaction,[3] the Suzuki reaction,[4] the Trost–Tsuji reaction,[5] the Sonogashira-coupling,[6] to name a few. On the other hand, an addition reaction is an atom-economical way to construct more complex molecules from simpler units.[7] Recently, increased interest has been shown in the addition of terminal alkynes to those compounds that involve sp^2 carbon, such as C=O bonds[8] or C=N bonds.[9] However, only a few examples of addition of terminal alkynes to C=C bonds have been reported.[10] Furthermore, although palladium is one of the most used metals from the periodic table in catalysis, palladium-catalyzed conjugated addition of alkynes to enones has not been reported to the best of our knowledge.[11] We hypothesized that the failure could be attributed to (1) either the facile homo- or heterodimerization of terminal alkynes (a well-known, synthetically useful process)[12] to form by-products or (2) a lower reactivity of the alkynyl palladium intermediate towards enones. Conceivably, such obstacles can be overcome by tuning the electronic properties of the ligands to coordinate with palladium. As part of a continued interest in developing organic synthesis in water,[13] herein we wish to report a simple and highly efficient Pd-catalyzed addition of a terminal alkyne to a C=C double bond such as a conjugated enone, either in water or in acetone in air (Scheme 1).

In order to increase the reactivity of the alkynyl–palladium bond, we plan to examine palladium catalysts with electron-rich ligands.[14] The initial investigation started with the reaction of phenylacetylene (R=Ph) and ethyl vinyl ketone (R′=Et) in the presence of 5 mol% of Pd(OAc)$_2$ and 10 mol% of the common ligand PPh$_3$ in water at 60 °C for 40 h. As expected, the reaction yielded only a tiny amount of the desired product (Table 1, entry 1). Then we tested a more electron-rich ligand, tris(4-methoxyphenyl)phosphine, and the yield increased significantly to 27% (Table 1, entry 2). Encouraged by this result, we tested other electron-rich ligands. PMe$_3$, both an electron-rich and a smaller size ligand, was the most effective for the coupling, providing a 77% yield of the desired product (Table 1, entry 5). Other palladium salts were also tested; the results showed that the counter ion of the palladium salt also had an effect on the reaction. With an electron-deficient trifluoroacetate as the counter ion, the reaction was less effective (Table 1, entry 8). To examine whether the phosphine ligand served as a base or a real ligand, we also tested the catalyst system in the presence of inorganic base and organic base. The Pd(OAc)$_2$/PMe$_3$ yielded less product in the presence of a base, especially in the case of the base NEt$_3$ (Table 1, entries 11 and 12) possibly because of a competing coordination between NEt$_3$ and the phosphine ligand. The Pd(OAc)$_2$/base system without a phosphine ligand also was tested, and little product was observed. As a further effort to determine the responsible catalyst, reactions were performed with either PMe$_3$ alone or Pd(OAc)$_2$ alone. Whereas Pd(OAc)$_2$ alone as the catalyst was only slightly effective, PMe$_3$ did not show any catalytic activity (although phosphines have been shown to catalyze conjugate additions with alcohols, amines, and activated methylene as nucleophiles).[15] The reason for lacking of catalytic activity for alkynes with PMe$_3$ is possibly due to the relatively weak nucleophilicity of terminal alkynes. Since PMe$_3$ is easily oxidized to trimethylphosphine oxide, we also tested the Pd(OAc)$_2$/trimethylphosphine oxide as a catalyst. Almost no catalytic activity was observed (Table 1, entry 13) and trimethylphosphine oxide alone did not show any catalytic activity. Finally, when the ratio of PMe$_3$/Pd(OAc)$_2$ was increased to 4:1, the desired product was obtained in 91% yield (Table 1, entry 17). The yield enhancement with increasing the amount of trimethylphosphine possibly because either the extra phosphine activated the vinyl ketone[16] or trimethylphosphine was lost partially due to oxidation. However too much phosphine may occupy all the coordination sites on palladium and decreases the catalytic activity[17] (Table 1, entry 18).



Scheme 1

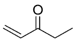
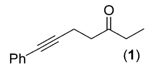
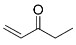
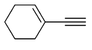
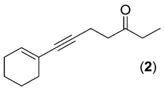
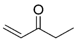
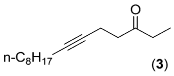
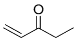
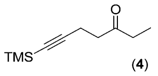
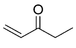
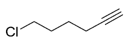
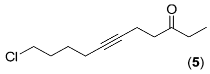
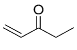
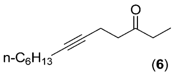
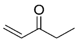
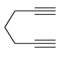
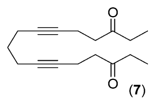
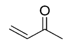
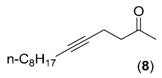
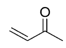
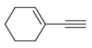
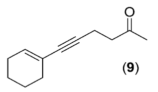
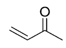
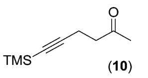
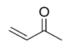
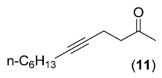
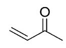
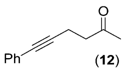
Subsequently, a broad range of substrates were examined with this new palladium-catalyzed reaction in water and in acetone (Table 2). It was shown that alkynes bearing silyl, alkenyl, aromatic, aliphatic or halide all reacted smoothly with vinyl ketone to afford good yields of the desired 1,4-addition products.

Table 1 Addition of phenylacetylene to ethylvinylketone catalyzed by various palladium catalysts in water[a]

Entry	Catalyst	L/C ratio	Yield (%)
1	Pd(OAc)$_2$/PPh$_3$	2	$<10^{b}$
2	Pd(OAc)$_2$/tris(4-methoxyphenyl)phosphine	2	27
3	Pd(OAc)$_2$/tris(2,6-dimethoxyphenyl)phosphine	2	31
4	Pd(OAc)$_2$/tris(2,4,6-trimethoxyphenyl)phosphine	2	17
5	Pd(OAc)$_2$/PMe$_3$	2	77
6	PdCl$_2$(PPh$_3$)$_2$	—	$<10^{b}$
7	PdCl$_2$(PPh$_3$)$_2$/PMe$_3$	2	$<10^{b}$
8	Pd(O$_2$CCF$_3$)$_2$/PMe$_3$	2	$<10^{b}$
9	Pd(0) (PPh$_3$)$_4$	—	N.D[c]
10	Pd(0) (PPh$_3$)$_4$/PMe$_3$	2	32
11	Pd(OAc)$_2$/PMe$_3$/Et$_3$N(1 eq)	2	$<10^{b}$
12	Pd(OAc)$_2$/PMe$_3$/NaOAc(1 eq)	2	43
13	Pd(OAc)$_2$/trimethylphosphine oxide	2	$<10^{b}$
14	PMe$_3$	—	N.D[c]
15	Pd(OAc)$_2$	0	15
16	Pd(OAc)$_2$/Et$_3$N(1 eq)	0	$<10^{b}$
17	Pd(OAc)$_2$/PMe$_3$	4	91
18	Pd(OAc)$_2$/PMe$_3$	6	86

[a] All reactions were carried out by using 1 mmol of an alkyne, 2 mmol of a vinyl ketone, 5 mol% of palladium catalyst and the given amount of ligand in water at 60 °C for 40 h. [b] Measured by ^{1}H NMR. [c] Not detected by ^{1}H NMR.

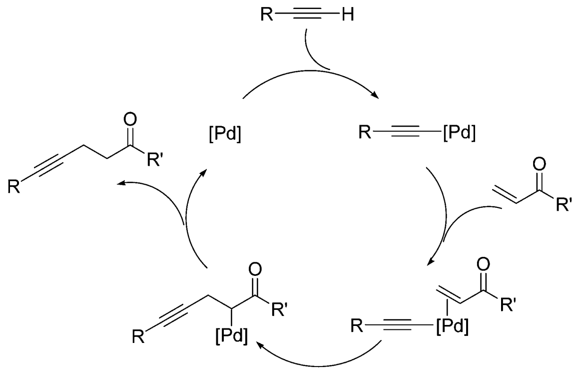
Table 2 Addition of terminal alkyne to vinyl ketone catalyzed by Pd(OAc)$_2$/PMe$_3$ in water and in acetone[a]

Entry	Vinylketone	Terminal alkyne	Conditions	Product isolated	Yield (%)
1		Ph—≡	40 h/acetone	 (1)	85
2			40 h/water		91
3			43 h/water	 (2)	74
4		n-C$_8$H$_{17}$—≡	43 h/acetone	 (3)	61
5			43 h/water		70
6		TMS—≡	42 h/acetone	 (4)	70
7			42 h/water		67
8			44 h/water	 (5)	65
9		n-C$_6$H$_{13}$—≡	44 h/acetone	 (6)	63
10			44 h/water		72
11[b]			44 h/acetone	 (7)	57
12[b]			44 h/water		62
13		n-C$_8$H$_{17}$—≡	42 h/acetone	 (8)	51
14			42 h/water		56
15			45 h/water	 (9)	58
16		TMS—≡	43 h/acetone	 (10)	49
17			43 h/water		52
18		n-C$_6$H$_{13}$—≡	45 h/water	 (11)	53
19		Ph—≡	39 h/acetone	 (12)	66
20			39 h/water		61

[a] The reactions were carried out by using 1.0 mmol of a terminal alkyne, 2 mmol of a vinylketone, 5 mol% of Pd(OAc)$_2$ and 20 mol% of PMe$_3$ at 60 °C in water or acetone. The product structures were determined by comparison with known compounds in the literature (see supplementary materials). [b] 1.0 mmol of terminal alkyne reacted with 4 mmol of vinylketone.

With diyne as a substrate, a bis-addition adduct was achieved as a major product. In addition to ethyl vinyl ketone, methyl vinyl ketone also survived in this addition reaction, albeit in a lower yield. It should be noted that both water and acetone are effective as solvents and similar results were obtained in either solvent.

When deuterated phenylacetylene-*d* was reacted with ethyl vinyl ketone in dry THF, an α-deuterated alkynyl ketone product was obtained in 76% yield with 15% *d*-incorporation; while in dry acetone which has a relatively active α-H, the deuterated product was obtained in 79% yield with less than 10% *d*-incorporation. When phenylacetylene was reacted with ethyl vinyl ketone in the presence of 10 equiv D$_2$O in acetone, the deuterated product was obtained in 68% yield with 55% *d*-incorporation; while in D$_2$O solvent, the deuterated product was obtained in 52% yield with more than 95% *d*-incorporation. No deuterium incorporation was observed at any position when 7-phenyl-6-heptyn-3-one, a γ,δ-ynone product, was reacted with D$_2$O in D$_2$O solvent.[18]



Scheme 2 Tentative mechanism for the palladium-catalyzed 1,4-addition of terminal alkynes to conjugated enones.

A tentative mechanism for the palladium-catalyzed 1,4-addition of terminal alkynes to conjugated enones is illustrated in Scheme 2. The η^2-coordination of the triple bond to the palladium center followed by direct deprotonation of the coordinated terminal alkyne to palladium catalyst[19] generated the alkynyl-palladium intermediate. Then, η^2-coordination of C=C double bond to the palladium center followed by the carbopalladation,[20] and a substitution of Pd with hydrogen (either from the solvent or terminal alkyne) to produce the γ,δ-ynone product with concomitant regeneration of the Pd catalyst (Scheme 2).

In conclusion, the first palladium-catalyzed 1,4-addition of terminal alkynes to the C=C double bond of conjugated enones was developed in water and in acetone, under an air atmosphere. The corresponding γ,δ-alkynyl ketones were obtained in high yields. The process is simple and can generate a wide range of alkynyl ketones. The scope, mechanism, and synthetic application of these novel catalytic properties of palladium are under investigation.

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18 All deuteration reactions were carried out in the presence of 5% mol $Pd(OAc)_2$, 20 mol% PMe_3 at 60 °C for 40 h. The percentage of the deuterated product was determined by ^{1}H NMR.

19 For previous examples involving direct deprotonation of terminal alkynes by palladium catalysts, please see: C. Scheffknecht and P. Peringer, *J. Organomet. Chem.*, 1997, **535**, 77–79.

20 For previous examples involving coordination of C=C double bond to transition metal, see: M. Picquet, C. Bruneau and P. H. Dixneuf, *Tetrahedron.*, 1999, **55**, 3937–3948.