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Pd-catalyzed addition–carbocyclization of α,ω-diynes with H–P(O)R_2 compounds

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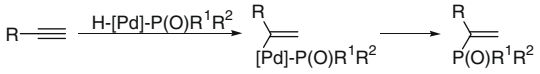
ABSTRACT

Chelating phosphines are much higher performing than mono-dentate phosphines in palladium-catalyzed reaction of α,ω-diynes with HP(O)R^1R^2 (R^1,R^2 = Ph, alkoxy) to afford (*E*)-3-(phosphorylmethylene)-2-methylcyclopentenes.

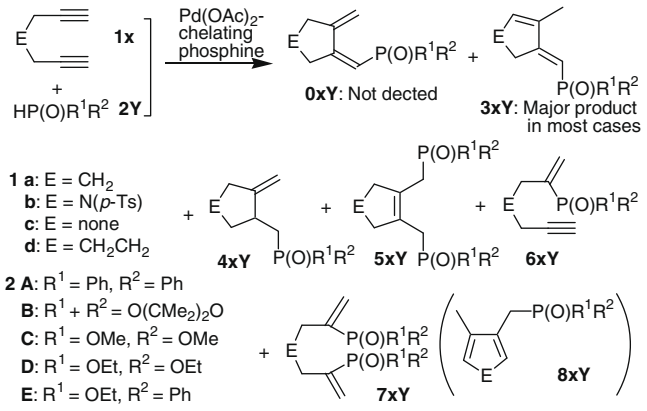
The transition-metal-complex-catalyzed cyclizations of unsaturated organic compounds have received increasing attention as powerful tools for ring construction.[1] The addition–carbocyclization reactions of α,ω-diynes with inter-element bonds (E–E′ bonds: E = heteroatom, E′ = H, metal, heteroatom or functional group)[2] are particularly useful, because the resulting cyclic compounds allow numerous synthetic applications, depending on the element introduced. Since 1996, we have been working on the addition reactions of H–P(O) bonds with various unsaturated compounds.[3] A great feature of these reactions lies in the high regioselectivity, which can be readily controlled by the selection of the central metal of the catalyst, nature of the ligands, and addition of acidic additives. Recently we have reported that dppe is a powerful branch-directing ligand in the addition reaction to alkynes, irrespective of the substituent in the starting H–P(O) compound.[4] The regioselectivity for the branched products is likely to have come from participation of (1-alken-2-yl)palladium species (Scheme 1).

Preliminary experiments with the (1-alken-2-yl)palladium species in mind have led us to find addition–cyclization reaction of α,ω-diynes with H–P(O) bonds (Scheme 2), which will be reported in this letter. Pioneering work by Parsons and later that by Jang have disclosed radical addition–cyclization reactions of α,ω-dienes with H–P(O) bonds.[5] However, addition–cyclization reaction of α,ω-diynes has never been documented.

In a representative experiment (Table 1, the first entry), a mixture of 1,6-heptadiyne **1a** (2.10 mmol) and diphenylphosphine oxide **2A** (2.00 mmol) in chlorobenzene (5 mL) was heated at



Scheme 1.



Scheme 2.

70 °C for 14 h in the presence of $Pd(OAc)_2$ (5 mol %) and 1,2-bis(diphenylphosphino)benzene (abbreviated as dppben, 1.5 equiv relative to Pd; phosphorus/Pd = 3). ^{1}H NMR analysis, after evaporation of the resulting mixture and addition of *p*-dimethoxybenzene (internal standard) and $CDCl_3$, revealed that (*E*)-3-(diphenylphosphinylmethylene)-2-methylcyclopentene (**3aA**) was formed in

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Table 1
Reaction of α,ω-diynes **1x** with H–P(O) compounds **2Y**[a]

1x	2Y	L	Solvent, temp (°C), time[b] (h)	Product[c], yield[d] (%)
1a	**2A**	dppben	C, 70, 14	 **3aA** 74 (68)
1a	**2B**	dppben	T, 100, 12	 **3aB** 66 (64)
1a	**2C**	dppben	E, 130, 3	 **3aC** 76 (69)
1a	**2D**	dppe	E, 130, 3	 **3aD** 51 (47)
1a	**2E**	dppben	E, 130, 3	 **3aE** 62 (59)
1b	**2A**	dppe	D, 100, 3	 **8bA** 33 (27)  **3bA** 24
1b	**2D**	dppben	E, 130, 3	 **8bD** 57 (41)
1b	**2E**	dppben	E, 130, 3	 **8bE** 50 (39)
1c	**2A**	dppe	T, 100, 2	 **3cA** 0  **4cA** 2
1d	**2A**	dppe	T, 100, 2	 **3dA** 26

[a] Reaction conditions: **1x** (2.1 mmol), **2Y** (2.0 mmol), Pd(OAc)2 (5.0 mol %), L (7.5 mol %; P/Pd = 3).
[b] T = toluene, C = chlorobenzene, E = ethylbenzene, D = dioxane.
[c] *N* = N(*p*-Ts).
[d] Determined by ^{1}H NMR spectroscopy. The figures in parentheses are isolated yields.

74% yield, together with 2,6-bis(diphenylphosphinyl)-1,6-heptadiene (**7aA**; 10%) and traces of other byproducts shown in Scheme 2. Evaporation of the mixture followed by column chromatography (silica gel, hexane/acetone = 1/1) led to isolation of **3aA** as colorless powder in 68% yield.

Another reaction using dppe as the ligand and toluene as the solvent also made the cyclization mainly, but was somewhat less selective to afford **3aA** (43%), 2-(diphenylphosphinylmethyl) -1-methylenecyclopentane (**4aA**; 6%), 1,2-bis(diphenylphosphinylmethyl)cyclopentene (**5aA**; <1%), 2-diphenylphosphinyl-1 -hepten-6-yne (**6aA**; 6%), and 2,6-bis(diphenylphosphinyl)-1,6-heptadiene (**7aA**; 12%). The products inclusive of the byproducts were carefully identified by spectroscopic measurements, elemental analysis, X-ray diffraction study (**3aB**, **8bA**), and/or comparison with an authentic sample synthesized by a separate procedure.

The foregoing two reactions clearly indicate that chelating phosphines direct the reaction to cyclization. On the other hand, the use of PPh_3 (3 equiv relative to Pd) resulted in low-yielding nonselective formation of **3aA**, **4aA**, **5aA**, **6aA**, and **7aA** in 5%, 10%, <1%, 5%, and 5% yields, respectively (Scheme 3). Thus, the use of a chelating phosphine is a prerequisite for efficient cyclization.[6]

After these trial experiments, we ran a series of reactions of α,ω-diynes with various H–P(O) bonds. Table 1 discloses that the procedure using either dppe or dppben ligand works fairly well with hydrogen phosphonates **2B**–**D** and hydrogen phosphinate **2E**.

1a + **2A** → (chlorobenzene, 100 °C, 1 h) **3aA** + **4aA** + **5aA** + **6aA** + **7aA**

	3aA	4aA	5aA	6aA	7aA
$Pd(OAc)_2$ + 1.5dppe	70	3	< 1	5	11
$Pd(OAc)_2$ + $3PPh_3$	5	10	< 1	5	5

Scheme 3.

N,*N*-Dipropargyl-*p*-tosylamide (**1b**) also reacted similarly, but the major products were pyrroles **8bA, 8bD,** and **8bE**. Type **5** and **6** products appeared to be formed in small quantities as judged by NMR spectroscopy. However, type **3** compound was formed only in the reaction with **2A**, which furnished **3bA** in 24% (indicating that the total cyclization yield inclusive of **8bA** was 57%). Byproduct **3bA** was found to readily isomerize to **8bA**.[7]

On the other hand, shorter- or longer-chained α,ω-diynes did not cyclize smoothly. The reaction of 1,5-hexadiyne **1c** with **2A** (80 °C, 2 h, toluene) afforded only **6cA** (64%) and **7cA** (30%); no cyclized product **3cA** was formed. The same reaction run at 100 °C for 2 h did not give **3cA** either, although a minute quantity (2%) of partially hydrogenated product **4cA** was formed. Likewise, 1,7-octadiyne **1d** gave **6dA** (40%) and **7dA** (33%) along with a trace of **3dA** (80 °C, 2 h, toluene). However, another reaction run at 100 °C formed **3dA** in 26% yield together with **6dA** (23%) and **7dA** (32%), indicating that **1d** was somewhat less reluctant than **1c** to undergo the cyclization.

The formation of the cyclized products and other byproducts is rationalized as depicted in Scheme 4.

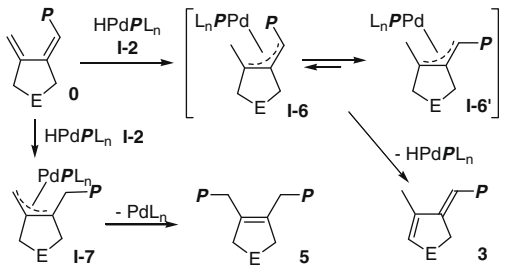
The route involving intermediates **I-2** and **I-3**, leading to **6** (and further to **7**), is conceivable in view of precedent publications.[3a,4] Oxidative addition of H–P(O) compounds with Pd(0) and insertion of alkyne into the H–Pd bond have been reported by one of us.[8] The process similar to that from **I-3** to **6** has been established with simple terminal alkynes and alkenes.[8b,8c] Intermediate **0** is also reasonable since such compounds are obtained as final products in related addition–cyclization reactions.[1,2]

One of the remaining issues to be addressed is the mechanism of the ring-forming process (**I-4** vs **I-5**). We propose that the route through **I-5** appears more reasonable. If we presume **I-4** being responsible for the cyclization, the cyclization of **1c** through a five-membered intermediate should have been easier than that of **1d** through a seven-membered intermediate, in view of the strain of the cyclic intermediates. In addition, literature survey has shown a plethora of reactions involving insertion into a carbon–Pd bond like the **I-3′**–**I-5** conversion, rather than that into a Pd–P(O) bond.[9]

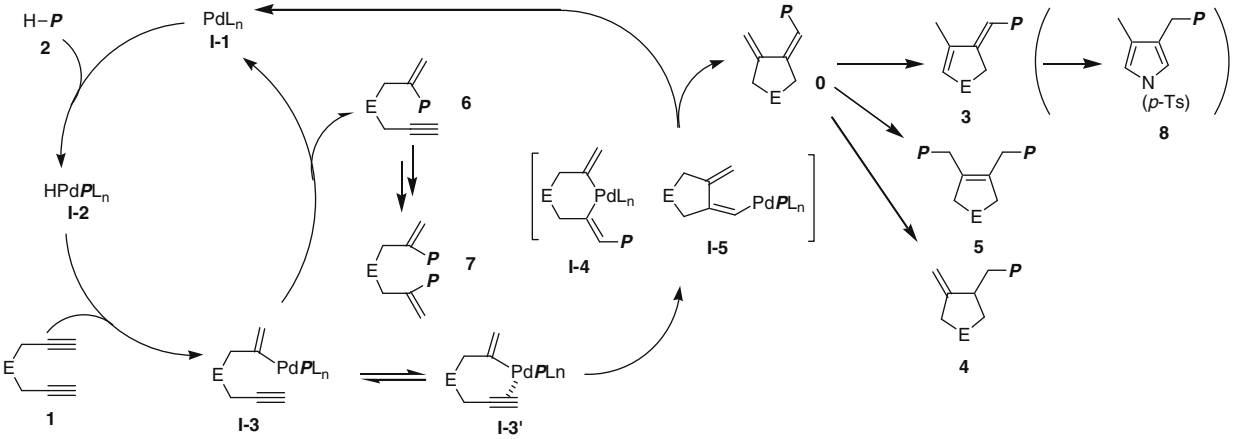
Another issue to be addressed is the favorable role of chelating phosphine. The key intermediate at the dichotomous branching point is **I-3**. As one of us has reported, the final product forming reductive elimination appears to be rate-determining in the addition reaction of **2A** with alkynes[8b] and also in the addition reaction of **2B** with alkenes.[8c] The dichotomous reactivity of **I-3** is presumably dependent on the ease of its reductive elimination. Given the reductive elimination proceeding via three coordinate species, despite some controversies,[10,11] the P–C reductive elimination from **I-3** ligated by monodentate phosphine(s) is presumed to be more facile than that ligated by a chelating phosphine,[10a,b] leading to the formation of **6**. In chelating phosphine-Pd-catalyzed reactions, on the other hand, the lack or difficulty of generation of three coordinate species eventually allows the coordination of the other triple bond to generate **I-3′**, which is ready for the ring closure.

As for the events after the formation of **0**, there are three options. One is further reaction with the H–P(O) compound affording **5**. Palladium-catalyzed 1,4-addition of an H–P(O) bond with conjugated dienes has been reported by one of us.[12] The formation of **5** presumably takes place via η^3-allylic species (vide infra).

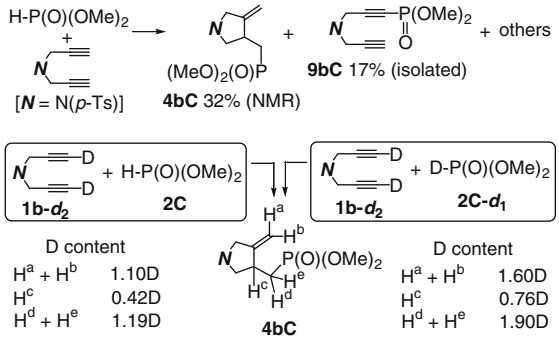
Another option is the isomerization to **3**. Hydropalladation of **0** with **I-2** is envisioned to generate η^3-allylic species **I-6**, **I-6′**, and **I-7** (Scheme 5). Species **I-6′** results in the isomerization to **3** via β-hydride elimination, but if **I-7** is generated, formation of **5** via P–C reductive elimination takes place. The stereochemistry of **3** is presumably predetermined at η^3-allylic intermediate **I-6′**. Since the *syn*-η^3-allylic complex is normally more stable than the *anti*-isomer, associated with the steric demand of the substituent,[13] one can predict that **I-6′**, which is more stable than **I-6**, proceeds to β-hydride elimination, affording **3**, as was indeed observed.



Scheme 5.



Scheme 4. ***P*** = $P(O)R^1R^2$.



Scheme 6.

A third option is the formation of **4**, which must have come from partial hydrogenation of **0**. The following observation appears relevant to the provenance of the hydrogen required for the partial hydrogenation. While we were searching for other byproducts under different conditions, we came across the formation of alkynylphosphonate **9bC** (Scheme 6) and **4bC** in 17% NMR and 32% isolated yields, respectively, along with traces of other unidentified products [$Pd(PPh_3)_4$ 3 mol %, THF, 68 °C, 48 h]. Given that the real yield of the alkynylphosphonate (by NMR) is much higher than the isolated yield, for example, ~30%, it is reasonable to assume that the hydrogen has come, at least partly, from the alkynylphosphonate formation process. Deuterium-labeling experiments to look into the possibility under identical conditions (Scheme 6) appear to support the assumption. Thus, the reaction of **1b-d_2** with **2C** and also the reaction of **1b-d_2** with **2C-d_1** furnished partially deuterated **4bC**. The D content at relevant positions in **4bC** (by ^{1}H NMR spectroscopy) agrees fairly well with the calculated value, if we allow possible H–D scrambling with a potential H source (solvent, moisture) present in the reaction system.[14] The failure of detection of alkynylphosphorus compounds in the catalytic reactions using chelating phosphines is presumably because the formation of such compounds, if any, should be very small in light of **4** being a minor product in these reactions. Isolation or detection of such compounds in these reactions is not an easy task due to the complexity of the mixture of minor products having the same phosphorus functionality.

In summary, we have developed hydrophosphorylative carbocyclization of 1,6-heptadiyne derivatives. Cyclic compounds having phosphorus substituents have been studied actively, aiming at diverse applications.[15] The new procedure disclosed in this letter may find utility in the relevant area of applications.

Acknowledgments

We thank Dr. Makoto Tanabe for his assistance in X-ray crystallography. This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas (No. 18065008, 'Chemistry of Concerto Catalysis') from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supplementary data

Experimental details, spectral data of new compounds and crystallographic data for **3aB** and **8bA** in CIF format are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.094.

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