Palladium-catalyzed carbocyclization of 1,6-enynes leading to six-membered rings or oxidized five-membered trifluoroacetates

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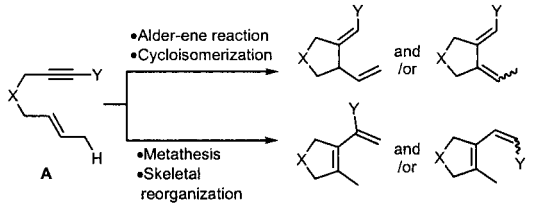
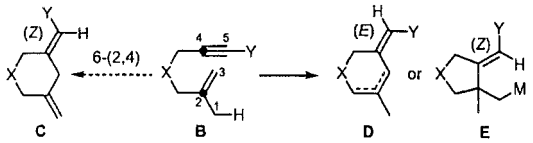
We describe palladium-catalyzed carbocyclization of 1,6-enynes leading to six-membered rings by water-originated hydride addition. Mechanistic features of this anomalous carbocyclization and isolation of a chiral five-membered C-Pd intermediate as an oxidized form of trifluoroacetate are also reported.

Transition metal-catalyzed carbocyclizations of 1,6-enynes **A** (1–4), such as cycloisomerization (5–11), metathesis (12–22), skeletal reorganization (23–26), and ene reactions (27–29), are useful synthetic methods leading to five-membered rings (Scheme 1). By contrast, we challenged six-membered cyclization of 1,6-enynes of type **B** by alkyne-metal- or carbonyl (Y = C═O)-Lewis acid complexation by 6-(2, 4) ene-type cyclization (30) (after [1,5]-hydrogen shift numbering) (Oppolzer's type II) (31) (Scheme 2). A six-membered ring was obtained, however, not as the expected (*Z*)-olefin **C**. Herein, we report that dicationic palladium-catalyzed carbocyclization of 1,6-enynes (32, 33), unlike ruthenium-, rhodium-, and platinum-catalyzed metathesis, leads to the (*E*)-six-membered rings (**D**), wherein water-derived hydride is involved to fix the (*E*)-olefin geometry. We also present the mechanistic features of this anomalous carbocyclization and isolation of a chiral five-membered C-Pd intermediate (**E**) as an oxidized trifluoroacetate.



Scheme 1. Typical transition metal-catalyzed carbocyclizations.



Scheme 2. 6-(2,4) ene-type cyclization and anomalous carbocyclization of 1,6-enynes.

Methods

General. ^{1}H, ^{13}C, and ^{31}P NMR spectra were measured on Varian Gemini 300 (300 MHz) and Varian Gemini 400 (400 MHz) spectrometers. IR spectra were measured on a FT/IR-5000 spectrometer (Jasco, Tokyo). Optical rotations were measured on a Jasco DIP-370. Liquid chromatographic analyses (HPLC) were conducted on a Jasco PU-980, LG-980–02, DG-980–50, AS-950, and CO-966 instrument equipped with model UV-975 spectrometers as an ultraviolet light. Peak areas were calculated by JASCO-BORWIN (WINDOWS NT) as an automatic integrator. Capillary GC analyses were conducted on a Shimadzu GC-14B instrument by using N_2 (75 kPa) as a carrier gas. Peak areas were calculated by a Shimadzu C-R6A as an automatic integrator; chiral columns were CP-Cyclodextrin-β-2,3,6-M-19 (i.d. 0.25 mm × 25 m; Chrompack, GL Sciences, Tokyo) and CP-Chirasil-Dex CB (i.d. 0.32 mm × 25 m; Chrompack, GL Sciences). The split ratio was 100:1. Analytical TLC was performed on glass plates (Merck Kieselgal 60 F_{254}; layer thickness, 0.25 and 0.2 mm). Visualization was accomplished by UV light (254 nm), anisaldehyde, $KMnO_4$, and phosphomolybdic acid. Column chromatography was performed on Kanto Silica Gel 60N (spherical, neutral; Kanto Kagaku, Tokyo). All experiments were carried out under an argon atmosphere unless otherwise noted.

Materials. $[(MeCN)_4Pd](BF_4)_2$ and $Pd(OCOCF_3)_2$ were purchased from Aldrich. (*S*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl [(*S*)-BINAP] and (*S*)-(4,4′-bi-1,3-benzodioxole)-5,5′-diylbis(diphenylphosphine) [(*S*)-SEGPHOS] were provided by Takasago International (Tokyo).

Typical Procedure for Pd-Catalyzed Ene-Type Cyclization. To a Pyrex test tube well degassed DMSO (2.0 ml) was injected, and argon was charged. $[(MeCN)_4Pd](BF_4)_2$ (11.1 mg, 0.025 mmol) and (*R*)-BINAP (17.1 mg, 0.050 mmol) were added under an argon atmosphere, and the suspension was stirred at room temperature for 5 min to become a clear solution. Then 4-(2-methylallyloxy)-but-2-ynoic acid methyl ester (**1a**) (84.0 mg, 0.500 mmol) was added under an argon atmosphere. The Pyrex tube was tightened with a screw cap. The mixture was stirred at 80°C and monitored by TLC. Then the crude was extracted with ether and purified by short neutral silica-gel chromatography (pentane/ether) to give the six-membered ring products.

Results and Discussion

The Pd(II)-catalyzed cyclization of enyne **1a** took place with 5 mol% of $[(MeCN)_4Pd](BF_4)_2$ or $Pd(OCOCF_3)_2$ and 5.5 mol% of diphosphine ligands such as (*R*)-BINAP in well deaerated DMSO or benzene, respectively, to afford the six-membered cyclization products **2a** and **3a** (type **D**) in good yields (Table 1). The dicationic $[(MeCN)_4Pd](BF_4)_2$ complex (34–37) in DMSO was found to be catalytically more active, affording 19% of (*E*)-**2a** and 61% of (*E*)-**3a** at lower temperatures (entry 2). The (*E*)-olefin geometries of cyclized products **2a** and **3a**

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Abbreviations: (*S*)-BINAP, (*S*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; (*S*)-SEGPHOS, (*S*)-(4,4′-bi-1,3-benzodioxole)-5,5′-diylbis(diphenylphosphine); ee, enantiomeric excess.

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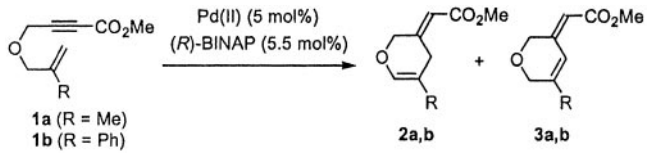
Table 1. Pd^{2+}-catalyzed six-membered ring formation of 1,6-enynes



Entry	Substrate	Pd catalyst	Temperature, °C	Time, h	Yield, % of 2	Yield, % of 3
1	**1a**	$Pd(OCOCF_3)_2/C_6D_6$	100	15	15	53
2	**1a**	$[(MeCN)_4Pd](BF_4)_2$/DMSO	80	24	19	61
3	**1b**	$[(MeCN)_4Pd](BF_4)_2$/DMSO	100	24	26	55

were unambiguously determined on the basis of the ^1H NMR, ^{13}C NMR, ^1H–^1H decoupling, hetero-COSY, and the nuclear Overhauser effect of **2a** and **3a** and their alcohol and aldehyde derivatives. In sharp contrast, ruthenium ($[Ru(CO)_3Cl_3]_2$) (38) or platinum ($PtCl_2$) (39–44) catalyzed carbocyclization led only to the five-membered cyclization products.

A possible triggering complex, palladacyclopropene (**B′**) (Scheme 3) could be isolated (see below) but did not provide the cyclization product (**D′**) under the reaction conditions (80–100°C). This result indicates that the alkyne–metal complex (**B′**) does not initiate the present cyclization leading to the six-membered ring product (**D′**) by the ionic intermediate (**F**).

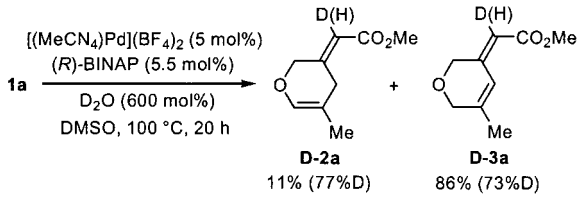
An attempted isolation of another possible intermediate, palladacyclopentene (Scheme 3, **G**) by using β-phenyl substrate **1b** without β-methyl (allylic hydrogen) and carbon monoxide or isonitriles was totally unsuccessful; it resulted simply in the formation of the six-membered products **2b** and **3b** in 26% and 55% yields, respectively (Table 1, entry 3).

No equilibrium exists between **2** and **3** under the reaction conditions. However, the generation of palladium hydride (H-Pd) (45) from adventitious water and *syn*-addition of H-Pd to the alkyne portion is highly likely to initiate the six-membered carbocyclization. We thus examined the cyclizations in the presence of an excess amount (600 mol%) of deuterated water (D_2O) (46, 47). Indeed, the products **D-2a** and **D-3a**, regiospecifically deuterated at the *exo*-olefin in α-position to the ester functionality, were obtained with ≈75% deuterium content (Scheme 4).

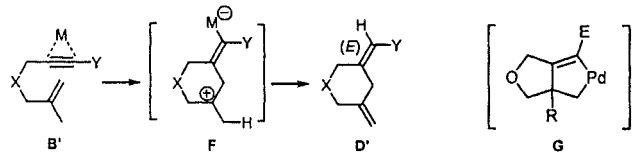
Therefore, the key intermediate should be a deuterated vinylpalladium species (**H**) generated by *syn*-addition of D-Pd species (Scheme 5). This vinylpalladium intermediate **H** is quite similar in its structure to Negishi's intermediate in the Mizoroki–Heck-type cyclization of 2-iodo-1,6-dienes to six-membered carbocycles, which proceed with olefinic geometry inversion (48–51). Thus, our plausible mechanism follows C-Pd *syn*-addition and -elimination mechanism effective in controlling olefin inversion by means of the cyclopropane intermediate (**E′** and then **I**).

Next we turned our attention to the asymmetric synthesis of six-membered ring because substrate **1** led to achiral products by β-H elimination, although the intermediates could be enantiomerically enriched. Pd^{2+}/(*S*)-BINAP system was applied to substrate **4** with trisubstituted olefin to give the cyclized product **5** with 26% enantiomeric excess (ee) and 25% yield (Table 2, entry 1). (*S*)-SEGPHOS was more effective than (*S*)-BINAP to afford **5** in 56% ee (entry 2). Moreover, the enantioselectivity dramatically increased up to 76% ee by sterically demanding (*S*)-DM-SEGPHOS (entry 3).

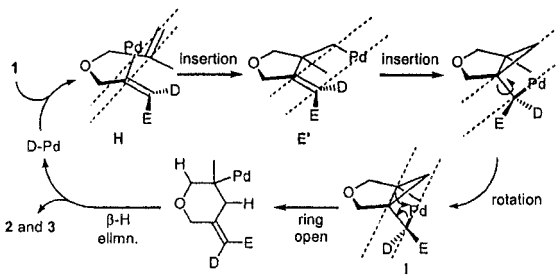
The isolation of a proposed chiral five-membered C-Pd intermediate (**E″**) is the next challenge (Scheme 6). To isolate this cyclized intermediate, we added one more equivalent of BINAP ligand. Unfortunately, we could not isolate the C-Pd species itself. However, oxidized five-membered trifluoroacetate product **6** was obtained in an enantio-enriched form (35% ee), presumably by the reductive elimination of BINAP-Pd^0 leading to palladacyclopropene **7** (see above) from [C-Pd($OCOCF_3$)](BINAP) (**E″**). In this reaction, a proper ratio (1:2) of $Pd(OCOCF_3)_2$ (37.5 mol%) and (*R*)-BINAP (75 mol%) is critical to give good isolated yield (67%) of the oxidized five-membered trifluoroacetate **6**, along with 26% of alkyne–Pd(BINAP) complex **7** (52, 53), thus implying a "catalytic" process of a tandem cyclization–oxidation reaction sequence. BINAP and enyne substrate **1a** were released immediately from alkyne–Pd(BINAP) complex **7** on addition of KCN/MeOH by ligand exchanges with CN^- at room temperature.



Scheme 4. Effect of water in Pd^{2+}-catalyzed six-membered ring formation of 1,6-enynes.

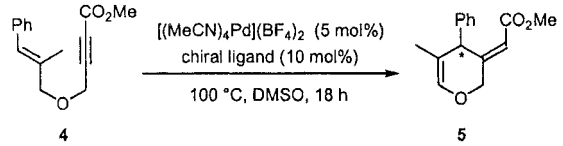


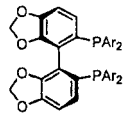
Scheme 3. Ionic intermediates of palladscyclopentene.



Scheme 5. Proposed mechanism of six-membered ring formations.

Table 2. Asymmetric catalytic six-membered ring formation by Pd[2]



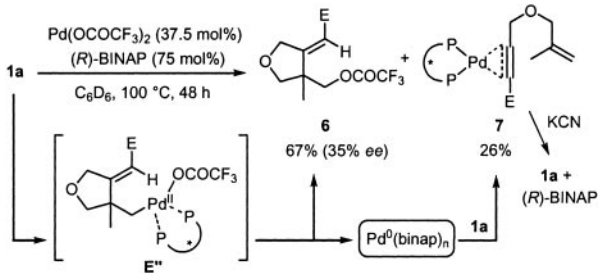


(*S*)-SEGPHOS (Ar = Ph)
(*S*)-DM-SEGPHOS (Ar = 3,5-xylyl)

Entry	Chiral ligand	Yield (ee)
1	(*S*)-BINAP	25 (26)
2	(*S*)-SEGPHOS	25 (56)
3	(*S*)-DM-SEGPHOS	22 (76)

Values given are percentages.

In summary, we have uncovered palladium-catalyzed carbocyclization of 1,6-enynes leading to six-membered rings by water-originated hydride addition and asymmetric catalytic cyclization-oxidation process leading to 5-membered trifluoroacetates. Further mechanistic studies on the generation of palladium hydride species from water and the asymmetric catalytic cyclization–oxidation process are currently under way.



Scheme 6. Oxidation and Pd complexation.

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