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10. Crystal data. $Pd_2Cl_2C_{26}H_{46}$, monoclinic C2/c, Z=4, a=21.631 (4), b=12.308 (2), c=11.375 (3) Å, β=107.55 (2)°, ρ_{calc}=1.468 g/cm^3, μ=14.27 cm^{-1}, (MoKα, λ=0.71069 Å, graphite-monochromated). The structure was solved by a heavy atom method and refined to R=0.052 and Rw=0.075 ($\omega=1/\sigma_F 2$) against 1621 observed ($I \geq 3\sigma_I$) reflections. C(10) and C(11) were disordered over two possible configurations with occupancy ratio of 0.61 (3) : 0.39.
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A Great Importance of the Acid Additives in Cyclizations *via* Neopentyl-Type Alkyl Palladium Intermediates

Chang Ho Oh*, Andre Kim, Chul Yun Rhim, Ji Hye Kang, and Bun Seang Park

Department of Chemistry, Inje University, Kimhae 621-749, Korea

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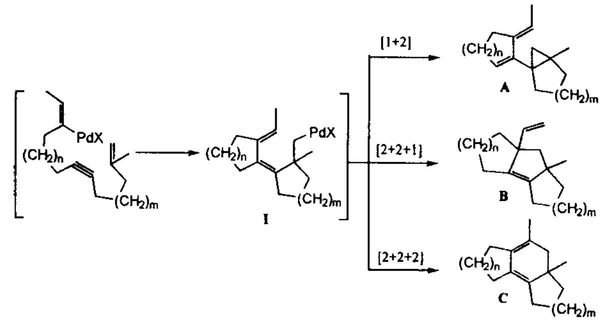
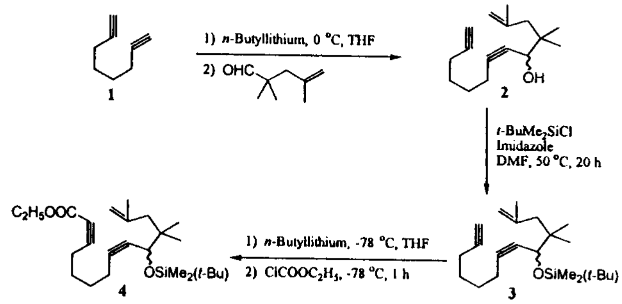
Effective construction of polycyclic compounds has been a major challenge in synthetic organic chemistry due to the large appearance of biologically active natural products possessing polycyclic rings.[1] For the past few years, palladium catalyzed cyclization has emerged as an efficient methodology which can provide various types of cyclic compounds in a very easy one step process.[2] In connection of our interest in palladium catalyzed enediyne cyclizations forming tricyclic compounds, we have envisioned the feasibility of these regio- and stereo-selective polycyclizations which require to form neopentyl-type alkylpalladium intermediates.[3]



Scheme 1.

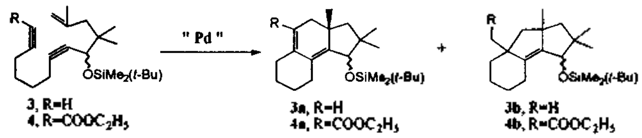


Scheme 2.

The neopentyl-type alkylpalladium intermediates (I) having a conjugated diene unit were known to undergo three different types of cyclization to form the corresponding three (A), five (B), and six membered ring (C) depending on reaction conditions and substrates (Scheme 1).[4] Due to the complexity of these reactions, little attention has been devoted to clarify which factors govern each of these cyclization pathways. In this paper we wish to report an important clue to change those reaction pathways to form chemoselectively either the five-membered ring B or the six-membered ring C. We have prepared simple substrates **3** and **4** shown in Scheme 2. 1,7-Octadiyne (**1**) was deprotonated with n-butyllithium and then condensed with 2,2,5-trimethyl-5-pentenal[5] in THF to yield the corresponding alcohol **2**. The alcohol **2** was protected with *tert*-butyldimethylsilyl chloride to give the substrate **3**. Deprotonation of the substrate **3** with n-butyllithium and treatment of ethyl chloroformate at −78 ℃ gave the substrate **4**.

Enediyne **3** and **4** serve as our substrates shown in Scheme 3. When a dimethylformamide solution of substrate **3**, 5 mol% of π-allylpalladium chloride dimer,[6] 10 mol% of triphenylphosphine, and 0-5 mol% of acetic and was stirred for 4 h at 100 ℃, the reaction was sluggish to give the corresponding cyclized product **3a** in 10-20% yield along with a dimerized product in 40-50% yidle.[7]

We have tried to cyclize the substrate **3** using other pala-



Scheme 3.

Table 1. Palladium Catalyzed Reactions of Enediynes 3 and 4 Under Various Conditions

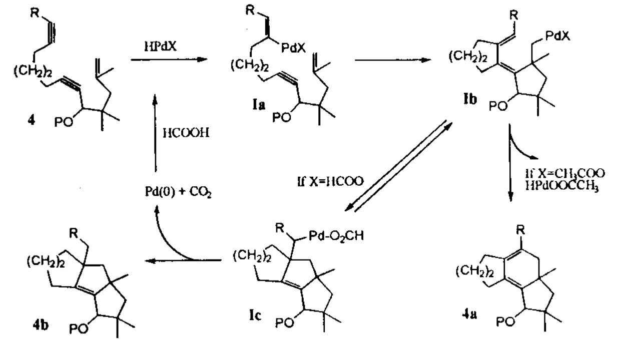
SM	Conditions	Results	Notes
3	5 mol% $(\pi\text{-}C_3H_5)_2Pd_2Cl_2$, 5 mol% AcOH, 100 ℃, 4 h	**3a**, 10-20%	~1:1 mixture[a]
	5 mol% $PdCl_2$, 5 mol% AcOH, 100 ℃, 4 h	**3a**, trace	no reaction
	5 mol% $Pd(OAc)_2$, 5 mol% AcOH, 100 ℃, 4 h	**3a**, trace	dimer (63%)
	4 mol% $P(PPh_3)_4$, 5 mol% AcOH, 100 ℃, 4 h	**3a**, trace	dimer (67%)
3	7 mol% $(\pi\text{-}C_3H_4)_2Pd_2Cl_2$, 200 mol% HCOOH, 60 ℃, 4 h	**3b**, 82%	single isomer
4	7 mol% $(\pi\text{-}C_3H_5)_2Pd_2Cl_2$, 7 mol% CH_3COOH, 90 ℃, 6 h	**4a**, 86%	1:2 mixture[a]
4	7 mol% $(\pi\text{-}C_3H_5)_2Pd_2Cl_2$, 200 mol% HCOOH, 90 ℃, 6 h	**4b**, 87%	single isomer

[a]: The isomeric ratios were determined by ^1H NMR of the crude reaction mixtures

dium catalysts such as palladium chloride, palladium acetate, and tetrakis(triphenylphosphine)palladium in DMF shown in Table 1. None of these could catalyze the enediyne **3** to the corresponding tricyclic product **3a** under the given conditions. A major isolated product was a dimeric product formed by C-C coupling between the terminal acetylene groups. However, substrate **4** under the similar condition underwent to the corresponding cyclic product **4a** in 86% yield. Note that a neopentyl type alkylpalladium species has been successfully cyclized to form 6-6-5 tricyclic compounds.[4a,8]

In contrast to these results, when a dimethylformamide solution of substrate **3**, 7 mol% of π-allylpalladium chloride dimer, 20 mol% of triphenylphosphine, and ***200 mol% of formic acid*** was stirred for 2 h at 100 ℃, the corresponding cyclic product **3b** was isolated as a clean single product. After optimizing the reaction conditions, we could isolate the cyclic product in 82% yield at 60 ℃ for 4 h. Structural determination for the cyclized product **3b** has been made by analyzing ^1H NMR, ^{13}C NMR, IR, and high resolution mass spectra.[9] Likewise, the substrate **4** at 90 ℃ for 6 h under the same condition also cleanly underwent the cyclization to form the corresponding product **4b** in 87% yield. We believe that the acyclic enediyne substrates like **3** or **4 with the palladium catalyst** exclusively form 6-5-5 tricyclic compounds for the first time.

The formation of these 6-6-5- and 6-5-5 tricyclic compounds could be understood as our proposed mechanism as shown in Scheme 4. A neopenthyl type alkylpalladium intermediate **Ib**, a generally accepted intermediate, may equilibrate with a kinetically unstable intermediate **Ic**. In the presence of only a catalytic amount of acids, the intermediate **Ib** can irreversibly cyclize to form the tricyclic product **4a**; in the presence of stoichiometric amount of formic acid, however, the kinetically unstable intermediate Ic may undergo reductive cleavage to form the stable product **4b** and palladium (0) which can reform HPdX with formic acid.



Scheme 4.

In conclusion, present cyclizations *via* the neopentyl-type alkylpalladium species offer an important clue to change the cyclization pathways; (1) use of catalytic amount of acetic acid as an initiator under these palladium reaction conditions resulted in formation of 6-5-5 tricyclic compounds exclusively; (2) use of stoichiometric amount formic acid provided the 6-5-5 tricyclic compounds by reductive cleavage of the alkylpalladium species. This methodology might be widely applicable to the n-6-5- or n-5-5-tricyclic compounds from the corresponding substrates *via* [2+2+2] or [2+2+1] cyclization, respectively.

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9. Spectral data for substrates and cyclized products are given. **3**: ^{1}H NMR (300 MHz, $CDCl_3$) δ4.83 (m, 1H), 4.66 (m, 1H), 4.00 (t, J=1.2 Hz, 1H), 2.25-2.16 (m, 4H), 2.08 (d, J=2.1 Hz, 2H), 1.91 (t, J=2.7 Hz, 1H), 1.76 (s. 3H), 1.66-1.58 (m, 4H), 0.912 (s, 6H), 0.89 (s, 9H), 0.12 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 143.62, 114.25, 85.18, 83.99, 80.87, 71.39, 68.44, 45.21, 39.67, 27.54, 27.43, 25.75, 25.40, 23.12, 23.07, 18.10, 17.80, 13.98, −4.36, −5.32; FT-IR ($CHCl_3$, cm^{-1}) 3280, 2910, 2860, 1460, 1240. **3a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ For major 5.40-5.17 (m, 1H), 3.83 (s, 1H), 2.42-2.22 (m, 1H), 2.22-2.07 (m, 1H), 2.06-1.65 (m, 3H), 1.64-1.45 (m, 2H), 1.30-1.18 (m, 4H), 1.04 (s, 3H), 0.94 (s, 3H), 0.90 (s, 9H), 0.88 (s, 3H), 0.95-0.82 (m, 2H), 0.06 (s, 3H), 0.02 (s, 3H), 0.02 (s, 3H). **3b**: ^{1}H NMR (300 MHz, $CDCl_3$), δ 3.79 (s, 1H), 2.34 (ddd, J=12.6, 6.0, 1.8 Hz, 1H), 1.93 (ddd, J=12.6, 11.8, 6.0 Hz, 1H), 1.84-1.70 (m, 1H), 1.76 (d, J=12.6 Hz, 1H), 1.62 (d, J=12.6 Hz, 1H), 1.57-1.48 (m, 1H), 1.52 (d, J=12.9 Hz, 1H), 1.32-1.62 (m, 2H), 1.30 (s, 3H), 1.26 (d, J=12.9 Hz, 1H), 1.21 (s, 3H), 1.05 (s, 3H), 0.96-0.86 (m, 2H), 0.89 (s, 9H), 0.84 (s, 3H), 0.06 (s, 3H), −0.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.01, 139.72, 76.58, 59.69, 54.34, 51.41, 49.16, 45.41, 44.34, 31.95, 29.92, 27.77, 25.81, 24.91, 24.81, 24.31, 22.45, 18.14, −4.54, −5.33; FT-IR ($CHCl_3$ cm^{-1}) 2955, 2928, 2858, 1563, 1371, 1254, 1084, 1069, 1043; HRMS calcd for $C_{22}H_{40}OSi$ (M^+) 348.2848, found 338.2838. **4**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.83 (m, 1H), 4.66 (d, J=1.5 Hz, 1H), 4.20 (q, J=7.2 Hz, 2H), 4.00 (t, J=2.0 Hz, 1H), 2.35 (t, J=6.9 Hz, 2H), 2.24 (td, J=6.9, 2.0 Hz, 2H), 2.07 (d, J=2.0 Hz, 2H), 1.77 (s, 3H), 1.73-1.56 (m, 4H), 1.29 (t, J=7.2 Hz, 3H), 0.91 (s, 6H), 0.89 (s, 9H), 0.11 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.89, 143.61, 114.22, 88.64, 84.78, 81.08, 73.42, 71.33, 61.70, 45.15, 39.62, 27.53, 26.46, 25.71, 25.37, 23.08, 23.01, 18.10, 18.05, 18.00, 13.88, −4.40, −5.34; FT-IR ($CHCl_3$ cm^{-1}) 2920, 2845, 2210, 1700, 1450, 1243, 1066, 832. **4a**: ^{1}H NMR (300 MHz $CDCl_3$) δ For major isomer 4.41 (d, J=2.0 Hz, 1H), 4.22-4.08 (m, 2H), 3.30-3.04 (m, 1H), 2.45-2.20 20 (m, 3H), 2.20-2.02 (m, 1H), 1.80-0.82 (m, 7H), 1.28 (t, J=7.2 Hz, 3H), 1.09 (s, 3H), 1.03 (s, 3H), 0.98 (s, 3H), 0.94 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.40, 150.11, 147.65, 147,49, 145.12, 127.52, 127.35, 120.93, 119.33, 82.17, 79.83, 59.74, 59.65, 51.93, 50.24, 43.71, 42.72, 40.26, 38.68, 38.76, 34.95, 28.31, 28.05, 27.80, 27.73, 27.50, 25.97, 25.78, 25.72, 24.39, 24.15, 23.65, 23.65, 22.85, 22.71, 22.03, 18.20, 18.00, 14.23, 13.96, −3.97, −4.10, −4.12, −4.68; IR (neat, cm^{-1}) 2905, 1696, 1562, 1440, 1358, 1238. **4b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.21-4.08 (m, 2H), 3.79 (s, 1H), 2.75 (d, J=13.2 Hz, 1H), 2.44-2.32 (m, 2H), 2.25 (d, J=13.2 Hz, 1H), 2.16-2.07 (m, 1H), 2.04-1.75 (m, 2H), 1.72-1.48 (m, 5H), 1.29 (s, 3H), 1.25 (t, J=7.0 Hz, 3H), 1.32-1.24 (m, 1H), 1.04 (s, 3H), 0.98-0.86 (m, 1H), 0.87 (s, 9H), 0.84 (s, 3H), 0.04 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.59, 146.67, 138.25, 76.61, 59.84, 54.87, 54.40, 51.69, 51.63, 45.30, 40.48, 39.89, 31.53, 30.01, 27.38, 25.76, 24.83, 24.71, 22.03, 18.10, 14.18, −4.47, −5.33; IR ($CHCl_3$, cm^{-1}) 2910, 2845, 1721, 1450, 1248, 1164, 1084.