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Simple Construction of Bicyclo[4.3.0]nonane, Bicyclo[3.3.0]octane, and Related Benzo Derivatives by Palladium-Catalyzed Cycloalkenylation

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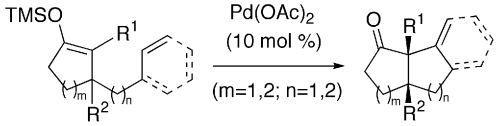
ABSTRACT



Bicyclo[4.3.0]nonanes (hydrindanes) and bicyclo[3.3.0]octanes (octahydropentalenes) are easily synthesized by palladium-catalyzed cycloalkenylations. Additionally, benzo-fused bicyclo[3.3.0]octanes are prepared for the first time through intramolecular coupling between silyl enol ethers and aromatic rings in the presence of catalytic palladium acetate.

Since the mid-1970s, transition metal promoted carbon−carbon bond-forming reactions have been widely applied in the synthesis of bioactive complex natural products.[1] Currently, it is difficult to find synthetic approaches to natural products that do not involve transition metal chemistry.[2] In our own contributions to this field, we have stereoselectively constructed several bioactive polycyclic natural products, such as methyl atis-16-en-19-oate[3] and C_{20} gibberellins,[4] employing palladium-catalyzed cycloalkenylation.[5] We sought to extend the chemistry to the intramolecular cyclization between silyl enol ethers and unactivated alkenes, allowing the simple synthesis of bicyclo[3.3.0]octanes (octahydropentalenes)[6] and bicyclo[4.3.0]nonanes (hydrindanes).[7] These ring systems are partial structures of many bioactive natural products (Scheme 1). We herein report the concise synthesis of octahydropentalenes, *cis*-hydrindanes, and benzo-fused octahydropentalenes by palladium-catalyzed cycloalkenylation.

Scheme 1

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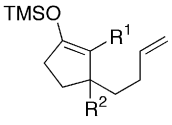
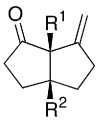
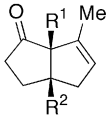
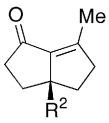
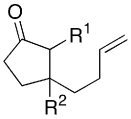
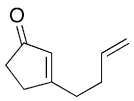
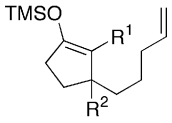
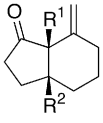
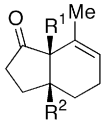
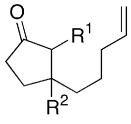
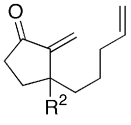
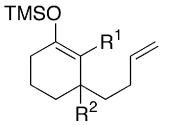
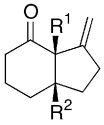
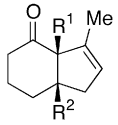
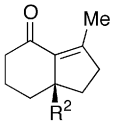
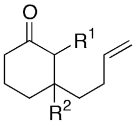
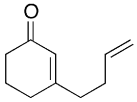
Table 1. Palladium-Catalyzed Cycloalkenylation of Silyl Enol Ethers[a]

substrate	yield (%)				
	 **4**	 **5**	 **6**	 **7**	 **8**
R^1=H, R^2=H; (**3a**)	0	11	0	29	44
R^1=H, R^2=Me; (**3b**)	30	20	15	13	0
R^1=Me, R^2=Me; (**3c**)	41	8	0	1	0
	 **10**	 **11**	 **12**	 **13**	
R^1=H, R^2=Me; (**9a**)	7	4	70	0	
R^1=Me, R^2=Me; (**9b**)	24	0	11	23	
	 **15**	 **16**	 **17**	 **18**	 **19**
R^1=H, R^2=H; (**14a**)	0	5	0	31	42
R^1=H, R^2=Me; (**14b**)	11	22	12	23	0
R^1=Me, R^2=Me; (**14c**)	37	19	0	7	0

[a] All reactions were carried out at 45 °C in DMSO in the presence of 10 mol % of palladium acetate under 1 atm of oxygen.

The requisite silyl enol ethers **1** were easily prepared from the corresponding enones by the Kuwajima protocol[8] and purified by silica gel column chromatography.[9] The palladium-catalyzed cycloalkenylations of the silyl enol ethers were investigated at 45 °C in DMSO using 10 mol % of palladium acetate under 1 atm of oxygen.[10] Results of the cyclization are summarized in Table 1. Initially, the formation of the bicyclo[3.3.0]octane ring system was examined. Although silyl enol ether **3a** provided enone **8** as the major product, the desired bicyclic compound **5a** was also isolated in 11% yield. When the reaction was performed on **3b**, the combined yield of cyclized products rose to 65%, and *exo*-olefin **4b**, *endo*-olefin **5b**, and enone **6b** were obtained in a 39:25:19 ratio. The separation of **4b**, **5b**, and **6b** was achieved by HPLC. The effect of the R^1 substituent was also evaluated. When **3c** was subjected to the catalytic reaction, *exo*-olefin **4c** (kinetic product) was produced as the major product. Thus, bicyclo[3.3.0]octanes (**4**, **5**, and **6**), potential synthons for the construction of linear and angular polyquinanes, were easily synthesized in moderate to good yield by the two-step catalytic reaction.

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(7) A review: Jankowski, P.; Marczak, S.; Wicha, J. *Tetrahedron* **1998**, *54*, 12071−12150.

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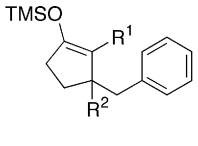
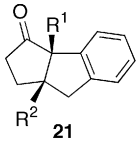
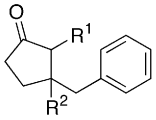
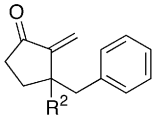
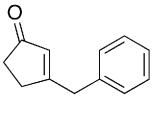
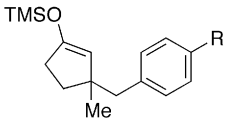
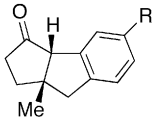
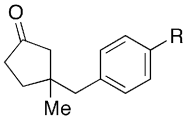
(9) Representative Procedure: To a stirred solution of homoallylmagnesium bromide[13] (5.7 mmol) in anhydrous THF (7.8 mL) were added CuBr·SMe_2 (95 mg, 0.46 mmol) and HMPA (1.3 mL, 7.5 mmol) at −78 °C. After 0.5 h of stirring at −78 °C, an anhydrous THF solution (3.1 mL) of 2,3-dimethylcyclopentenone (0.30 mL, 3.0 mmol) and TMSCl (1.1 mL, 8.7 mmol) was added dropwise at −78 °C. The mixture was stirred at −78 °C for 1 h, and then Et_3N (0.9 mL, 6.5 mmol) was added at −78 °C in one portion. The reaction mixture was warmed to room temperature over 2 h and stirred overnight. After dilution with pentane, the organic layer was washed three times with water, saturated $NaHCO_3$ solution, and brine and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel with hexane to provide silyl enol ether **3c** (672 mg, 94%) as a colorless oil. ^{1}H NMR (400 MHz) (C_6D_6) δ 5.80−5.77 (1H, m), 5.05 (1H, br d, J = 16.0 Hz), 4.97 (1H, br d, J = 12.0 Hz), 1.53 (3H, br s), 0.97 (3H, s), and 0.15 (9H, s).

(10) Procedure for Palladium-Catalyzed Cycloalkenylation: To a stirred solution of silyl enol ether **3c** (154 mg, 0.68 mmol) in DMSO (7.7 mL) was added palladium acetate (15.2 mg, 0.068 mmol) at room temperature. The mixture was stirred at 45 °C for 20 h under 1 atm of oxygen. After being cooled to room temperature, the mixture was diluted with water. The resulting mixture was extracted three times with Et_2O, and the combined ethereal layers were washed with brine, dried over $MgSO_4$, and evaporated to yield an oil, which was chromatographed. Elution with hexanes−EtOAc (9:1) afforded *exo*-olefin **4c** (46.4 mg, 41%), *endo*-olefin **5c** (7.9 mg, 8%), and ketone **7c** (0.55 mg, 1%). All the products were obtained as a colorless oil. **4c**: IR (neat) 1738 cm^{-1}. ^{1}H NMR (400 MHz) ($CDCl_3$) δ 4.96−4.95 (2H, br s), 1.02 (3H, s), and 1.01 (3H, s). **5c**: IR (neat) 1738 cm^{-1}. ^{1}H NMR (400 MHz) ($CDCl_3$) δ 5.33 (1H, br s), 1.55 (3H, br s), 1.08 (3H, s), and 0.98 (3H, s).

Table 2. Palladium-Catalyzed Cycloalkenylation of Benzyl-Substituted Silyl Enol Ethers[a]

substrate	yield (%)			
	 **21**	 **22**	 **23**	 **24**
R^1=H, R^2=H; (**20a**)	0	26	0	59
R^1=H, R^2=Me; (**20b**)	40	43	0	0
R^1=Me, R^2=Me; (**20c**)	0	0	78	0
	 **21**	 **22**		
R=H (**20b**)[b]	62	11		
R=Me (**20d**)[b]	70	16		
R=OMe (**20e**)[b]	62	33		

[a] All reactions were carried out 45 °C in DMSO in the presence of 10 mol % of palladium acetate under 1 atm of oxygen. [b] Stoichiometric amount of $Pd(OAc)_2$ was used.

Encouraged by these results, we explored the preparation of *cis*-hydrindane systems. Silyl enol ether **9a** afforded *cis*-hydrindanes (**10a** and **11a**) in only 11% yield; however, when the reaction was conducted on **9b**, *exo*-olefin **10b** was obtained in 24% yield.

An alternative approach for the formation of *cis*-hydrindane systems by cyclization of siloxycyclohexenes (**14**) was examined. Although **14a** gave only 5% of the desired product **16a**, cyclization of **14b** increased the yield of cyclized products to 45%. The additional R^1 substituent in **14c** also proved to be effective in increasing the yield, providing a mixture of hydrindanes (**15c**, **16c**) in 56% yield. Noteworthy is that the palladium-catalyzed cycloalkenylation sequence produces a doubly functionalized *cis*-hydrindane, a substitution pattern found in many bioactive natural products. These observations indicate that generation of *cis*-hydrindanes from siloxycyclohexenes is more efficient than that from siloxycyclopentenes.

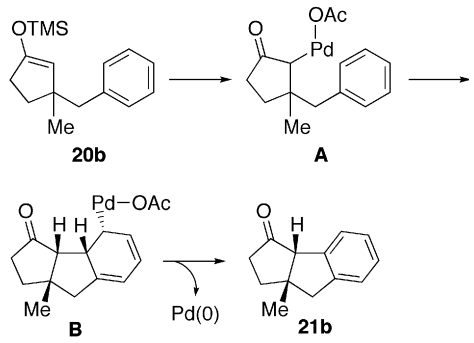
Since little is known about coupling aromatic rings and silyl enol ethers,[11] we investigated intramolecular coupling of silyl enol ethers **20**, bearing a benzyl substitution, in the presence of a catalytic amount of palladium acetate. Surprisingly, when **20b** was subjected to the palladium-catalyzed cycloalkenylation, benzo-fused bicyclo[3.3.0]octane derivative **21b**[12] was isolated in 40% yield (Table 2).

To improve the cyclization yield, the same reaction can be performed using 1 equiv of palladium acetate to give 62% of **21b**. An electron-donating group on the aromatic ring in **20d** and **20e** had little effect on the yield. To our knowledge, there is little precedent for such transition metal mediated cyclizations.

To study the substituent effects for this reaction, we designed two silyl enol ethers **20a** and **20c**. When **20a**, having no quaternary center, was treated with 10 mol % of $Pd(OAc)_2$, enone **24** was obtained as the major product. However, contiguously disubstituted **20c** gave *exo*-olefin **23c** as the single product. Although compounds **20a** and **20c** did not yield the desired cyclization products, these observations suggest possible reaction mechanisms for these reactions.

Since *exo*-olefin **23c** was obtained as single product in the case of **20c**, the reaction mechanism is speculated to occur as described in Scheme 2. Based on our previous observations[5e,f] and reports by others,[5a,b] we anticipate that the reaction takes place via an insertion pathway. Namely, initially formed alkyl palladium complex **A** inserts into the

Scheme 2. A Plausible Pathway for the Formation of Benzo-Fused Bicyclo[3.3.0]octane



(11) There is an interesting example of C−C bond formation between aromatic rings and multiple bonds utilizing strong acid and Pd(II). Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science*, **2000** *287*, 1992−1995.

double bond of the aromatic ring, giving rise to an intermediate **B**, from which Pd(0) is eliminated to yield tricyclic compound **21b**. However, the other possible reaction mechanism cannot be ruled out.[5g,h]

In conclusion, *cis*-fused bicyclo[4.3.0]nonanes, bicyclo[3.3.0]octanes, and related benzo derivatives, potential synthons for the synthesis of natural products, are easily synthesized by palladium-catalyzed cycloalkenylations. In addition, the coupling reaction between silyl enol ethers and the aromatic ring was achieved for the first time in the presence of palladium acetate. It is notable that reaction between sp^2 carbons of silyl enol ether and an aromatic ring was observed under neutral reaction conditions. Further studies to address the scope of this reaction are underway.

Acknowledgment. This work is supported by a Grant-in-Aid (No. 14571994) from the Ministry of Education, Science, Sports and Culture, Japan.

Supporting Information Available: Spectral data for **4b**, **4c**, **5a**, **5b**, **5c**, **6b**, **10a**, **10b**, **11a**, **15c**, **16a**, **16b**, **16c**, **21a**, **21b**, **21c**, and **23c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Recently, benzo-fused bicyclo[3.3.0]octane derivatives have generated interest among organic chemists because of their biological activity[14] or structural analogy to natural products.[15] We envision that palladium-catalyzed cycloalkenylation can serve as an alternative procedure for the formation of the benzo-fused bicyclo[3.3.0]ocatane ring system. The compound **21b** was also isolated as a minor product in the samarium-promoted intramolecular cyclization of 3-(1-oxo-indan-2-yl)propionitrile.[16]

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