Palladium-Catalyzed Carbonylative Cyclization of *o*-Allylbenzyl Halides To Produce Benzo-Annulated Enol Lactones and/or Bicyclo[3.3.0]hept-3-en-6-ones. An Efficient Route to U-68,215

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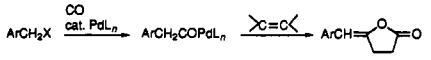
Summary: Treatment of *o*-allylbenzyl halides with CO in the presence of 1.5–2.0 equiv of a base, such as NEt_3, and a catalytic amount of a palladium complex, such as $Cl_2Pd(PPh_3)_2$, provides a 2,3,3a,4-tetrahydro-2-oxonaphthyl[2,3-*b*]furans and/or cyclobutanone derivatives tentatively identified as 2,2a,7,7a-tetrahydro-1*H*-cyclobut[*a*]inden-2-ones.

We have recently reported that palladium-catalyzed carbonylation of certain dienyl iodides can produce enol lactones.[1] The results suggested that (arylacetyl)palladium derivatives, which should be accessible via carbonylation of benzyl electrophiles, would readily undergo base-induced enol lactone formation, as in eq 1.

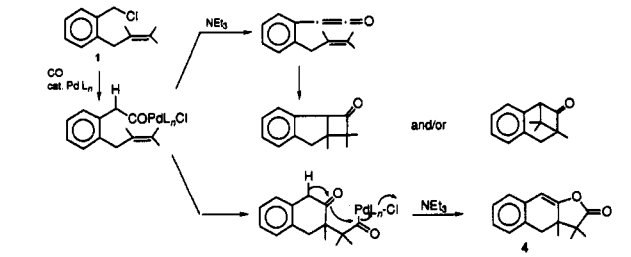


We now report that the intramolecular version of the reaction shown in eq 1 can indeed proceed smoothly to give γ-alkylidenebutyrolactones. We also report that the use of sterically hindered alkenes can lead to competitive or nearly exclusive formation of cyclobutanone derivatives. The results are consistent with the mechanisms shown in Scheme I.

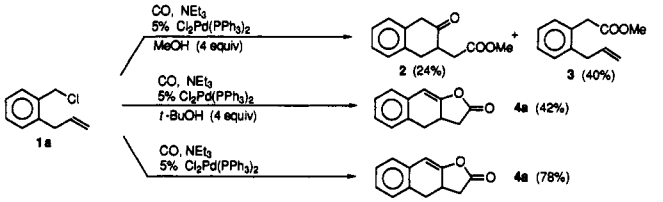
As part of our ongoing investigation of acylmetalation involving late transition metals,[2] *o*-allylbenzyl chloride[3] (**1a**) was treated with CO (600 psi) in the presence of 5 mol % of $Cl_2Pd(PPh_3)_2$ and NEt_3 (2 equiv) and MeOH (4 equiv) in a 1:1 mixture of MeCN and benzene at 100 °C for 18 h.[2b] The reaction produced the expected product **2**[4] in only 24% yield along with the straight esterification product **3**[4] (40% yield). The use of K_2CO_3 in place of NEt_3 gave **2** in only 15% yield along with **3** (79%). To alleviate the competitive methanolysis of a presumed acylpalladium intermediate before cyclization, methanol was replaced with *t*-BuOH. In this case, however, a totally different product **4a**[4] was obtained in 42% yield. Since *t*-BuOH was not incorporated in the product, we ran the same reaction in the absence of *t*-BuOH and obtained **4a** in 78% yield by GLC (67% isolated). The extent of the formation of any byproduct detectable by GLC was insignificant (Scheme II).

The use of 1,1-disubstituted alkenes **1b** and **1c** also gave the corresponding enol lactones **4b**[4] and **4c**[4] in 68 and 47% yields, respectively. In these cases, however, the formation of cyclobutanones took place to a significant extent. Thus, **5b**[4] and **5c**[4] were obtained in 15 and 26% yields, respectively.[5] In the reaction of **1d** under the same conditions a trace, if any, of **4d** was formed, the only significant monomeric product being **5d**[4] obtained in 48% yield. These data suggest that sterically hindered alkenes disfavor enol lactone formation and favor cyclobutanone formation. Although the currently available data do not permit us to rule out with certainty the bridging cyclobutanone structure for **5**, the ^{13}C NMR methine carbon signals for **5** at δ 76 ± 1 ppm are consistent with a related cyclobutanone **6**[6] than with **7**,[6] the methine carbon signals

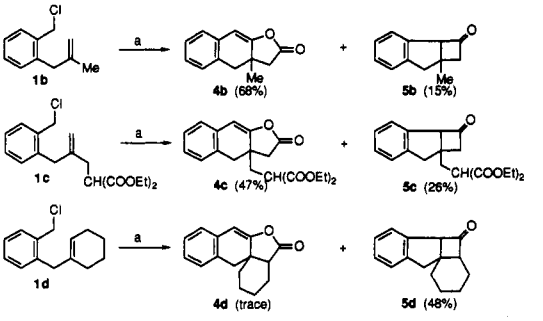
Scheme I



Scheme II



Scheme III[a]



[a] Key: a = CO (600 psi), 5 mol % $Cl_2Pd(PPh_3)_2$, NEt_3 (2 equiv), MeCN, 100 °C.

of which appear at δ 67.44 and 30.07. We tentatively choose the fused cyclobutanone structure for **5b–d**.

The enol lactone synthesis described above provides an efficient route to a key intermediate **4e** for the synthesis of a promising anti-ulcer agent U-68,215[7] (**8**), as detailed

† On leave from NKK Corporation, Japan.

(1) Shimoyama, I.; Zhang, Y.; Wu, G.; Negishi, E. *Tetrahedron Lett.* **1990**, *31*, 2841.

(2) For our previous work in this area, see: (a) Negishi, E.; Miller, J. A. *J. Am. Chem. Soc.* **1983**, *105*, 6761. (b) Tour, J. M.; Negishi, E. *J. Am. Chem. Soc.* **1985**, *107*, 8289. (c) Negishi, E.; Tour, J. M. *Tetrahedron Lett.* **1988**, *27*, 4869. (d) Negishi, E.; Wu, G.; Tour, J. M. *Tetrahedron Lett.* **1988**, *29*, 6745. (e) Negishi, E.; Zhang, Y.; Shimoyama, I.; Wu, G. *J. Am. Chem. Soc.* **1989**, *111*, 8018. (f) Tour, J. M. Ph.D. Dissertation, Purdue University, 1986.

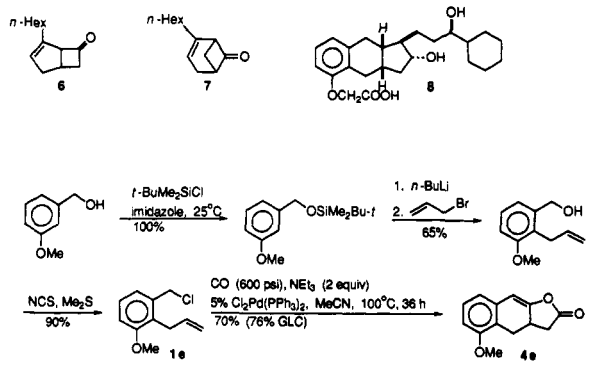
(3) Wu, G.; Lamaty, F.; Negishi, E. *J. Org. Chem.* **1989**, *54*, 2507.

(4) All new isolated products yielded satisfactory ^1H and ^{13}C NMR and IR spectra as well as HRMS data.

(5) For related ketene cyclization reactions which do not involve transition metals, see: (a) Marko, I.; Ronsmans, B.; Hesbain-Frisque, A. M.; Dumas, S.; Ghosez, L.; Ernst, B.; Greuter, H. *J. Am. Chem. Soc.* **1985**, *107*, 2192. (b) Snider, B. B.; Hui, R. A. H. F.; Kulkarni, Y. S. *J. Am. Chem. Soc.* **1985**, *107*, 2194. (c) Kulkarni, Y. S.; Snider, B. B. *J. Org. Chem.* **1985**, *50*, 2809. (d) Kulkarni, Y. S.; Burbaum, B. W.; Snider, B. B. *Tetrahedron Lett.* **1985**, *26*, 5619. (e) Kulkarni, Y. S.; Niwa, M.; Ron, E.; Snider, B. B. *J. Org. Chem.* **1987**, *52*, 1568. (f) Snider, B. B.; Ron, E.; Burbaum, B. W. *J. Org. Chem.* **1987**, *52*, 5413.

0022-3263/91/1956-6506$02.50/0

Scheme IV

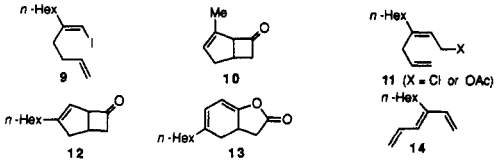


in Scheme IV and the representative procedure presented below. The overall yield of **4e** based on the commercially available monocyclic starting material, *m*-methoxybenzyl alcohol, is 41% over four steps, whereas its previously reported synthesis[7] starting with 1,6-dihydoxynaphthalene required eight steps. Conversion of **1e** to **4e** was performed as follows. To 0.36 g (1.83 mmol) of 2-allyl-3-chloromethylanisole in 4 mL of MeCN placed in a 45-mL stainless steel autoclave (Parr Instrument Co.) were added 0.38 mL (2.75 mmol) of NEt_3 and 64 mg (5 mol %) of $Cl_2Pd(PPh_3)_2$. After the autoclave was sealed and filled with CO (600 psi), it was heated to 100 °C for 36 h and then was cooled to room temperature. The residual CO was ventilated, and the mixture was poured into ice–brine, extracted with Et_2O (2 × 5 mL), washed with water, and dried over $MgSO_4$. Rotary evaporation of solvents followed by flash column chromatography (hexanes/Et_2O = 80/20) afforded 0.276 g (70%, 76% by GLC) of **4e**: mp 138–140 °C (lit.[7] mp 139–141 °C). This compound has previously been converted to U-68,215 in several steps.[7]

Acknowledgment. We thank the National Institutes of Health (GM 36792) and NKK Corporation for support of this work.

Supplementary Material Available: Experimental procedures and data and ^1H and ^{13}C NMR spectra for compounds **4a–d**, **6**, and **13** (20 pages). Ordering information is given on any current masthead page.

(6) We earlier reported the formation of a mixture of cyclobutanones **6** and **7** in 55% yield by the reaction of **9**[2b] with CO (600 psi) in the presence of 5–10 mol % of a Pd catalyst, e.g., $Cl_2Pd(PPh_3)_2$, and NEt_3 (3 equiv) in MeCN at 100 °C.[2b,2f] A mechanism involving cyclic acylpalladation was tentatively proposed. Reexamination of this case indicates that the major isomer (70–90%) is **6** rather than **7**. This conclusion is primarily based on comparison of the NMR spectra of **6** with those of **10**.[5f] The ^1H and ^{13}C NMR spectral data for the bicyclic skeleton of **6** are as follows. **6**: ^1H NMR ($CDCl_3$, Me_4Si) δ 2.3–2.5 (m, 1 H), 2.7–2.9 (m, 3 H), 3.1–3.3 (m, 1 H), 4.1 (br, 1 H), 5.45 (br, 1 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 26.46, 40.27, 53.54, 75.35, 125.69, 140.21, 208.38. The minor isomer (10–30%) must now be identified as **7**. The formation of **6** cannot be readily explained in terms of acylpalladation. On the other hand, a mechanism involving a [2 + 2] cycloaddition of a ketene intermediate readily explains the formation of both isomers. In the reaction of **11** under the same reaction conditions, **12** was produced in 30% yield along with two byproducts **13** and **14** formed in up to 20% yield each.



(7) Aristoff, P. A.; Johnson, P. D.; Harrison, A. W. *J. Am. Chem. Soc.* 1985, *107*, 7967.