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Synthesis of Cyclic Ethers via the Palladium Catalyzed Intramolecular Hydrocarbonation of Alkoxyallenes

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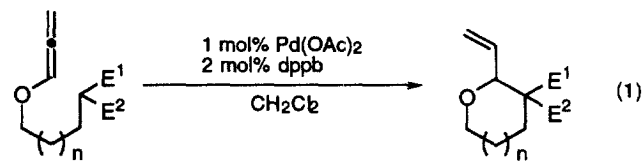
Abstract: The intramolecular hydrocarbonation of certain alkoxyallenes (**1**, **3** and **5**), bearing active methine groups at the terminus of the carbon chain, proceeded smoothly in the presence of catalytic amounts of a palladium complex [$Pd(OAc)_2$-dppb] to give 5- to 7-membered cyclic ethers (**2**, **4** and **6**, respectively) in good to high yields.

Keywords: Cyclization; Oxygen heterocycles; Allenes; Palladium catalysts

Great attention has been paid to the synthesis of polycyclic ethers since these structural frameworks are often found in marine natural products which exhibit unique biological activities.[1] Although many useful methodologies have been developed to construct cyclic ethers,[2] a new flexible procedure which tolerates the introduction of a wide variety of functional groups is still needed. We previously found that certain activated methylene and methine compounds (carbon pronucleophiles, H-Nu) add to the double-bond of allenes ($RCH=C=CH_2$) in the presence of palladium catalysts to give the corresponding addition products ($RCH=CHCH_2Nu$) in good to high yields.[3] This direct addition reaction of carbon pronucleophiles, the so called hydrocarbonation reaction, is one of the ideal C-C bond forming procedures for a concise synthesis of molecules having multi-functional groups. Trost's[3g,3h] and our group[3f] succeeded in constructing carbocycles by utilizing the intramolecular hydrocarbonation of allenes. We now report that the cyclization of alkoxyallenes **1**, **3** and **5** proceeds smoothly in the presence of catalytic amounts of $Pd(OAc)_2$-dppb complex, affording the corresponding 5- to 7-membered cyclic ethers **2**, **4** and **6**, respectively, in good to high yields (eq 1).



(1)

1 n = 0 **2** n = 0
3 n = 1 **4** n = 1
5 n = 2 **6** n = 2

The results are summarized in Table 1. The starting materials **1**, **3** and **5** were synthesized by standard procedures.[4] The cyclization of **1** proceeded very smoothly in the

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presence of catalytic amounts of $Pd(OAc)_2$ and dppb in CH_2Cl_2 at room temperature affording the corresponding 5-membered cyclic ether **2** in 79% yield (entry 1). We next investigated the cyclization of the allenes **3**, having a three carbon tether between the methine carbon and the oxygen atom. The reaction of **3a** in the presence of 1.0 mol% $Pd(OAc)_2$ and 2.0 mol% dppb in CH_2Cl_2 at room temperature proceeded very well to give the corresponding 6-membered cyclic ether **4a** in 86% yield (entry 2). We examined other palladium catalysts and bidentate phosphine ligands such as $Pd_2(dba)_3 \cdot CHCl_3$-dppb, $[(\eta^3\text{-}C_3H_5)PdCl]_2$-dppf, $Pd(PPh_3)_4$, $Pd(OAc)_2$-COD, $PdCl_2(CH_3CN)_2$-dppf and so on, but the above combination gave the best results with respect to both chemical yield and reaction time. No cyclized product was obtained in the absence of the palladium catalyst. Additives such as acetic acid[5], *t*-BuOK[3g], 4-DMAP and 4-DMAP/acetic acid[3h] did not improve the yield at all. Furthermore, we found that a lesser amount of the palladium catalyst, 0.1 mol% $Pd(OAc)_2$ and 0.2 mol% dppb, was enough to carry out the cyclization of **3a**, giving **4a** in 82% yield though it took a longer reaction time (entry 3). The reaction of (phenylsulfonyl)acetonitrile derivative **3b**, bisphenylsulfonyl derivative **3c** and cyanoacetate derivative **3d** gave the corresponding cyclic ethers **4b**, **4c** and **4d**, respectively, in good to high yields (entries 4-6). The cyclization of (phenylsulfonyl)acetate derivative **3e** was completed in 2 hours at 50 °C to give **4e** in 70% yield (entry 7). The reaction of dimethyl malonate derivative **3f** did not proceed at all even at 50 °C for 6 hours and a significant amount of the starting material was recovered (entry 8). The cyclization of malononitrile derivative **5** gave the corresponding 7-membered cyclic ether **6** in 88% yield (entry 9).

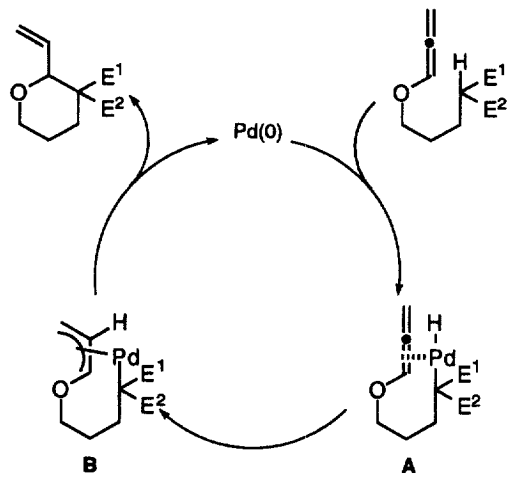
Table 1. Palladium catalyzed intramolecular hydrocarbonation of alkoxyallenes[a]

Entry	Alkoxyallene n	E^1	E^2		Reaction time, h	Product	Yield[b], % (Diastereomeric ratio)
1	0	CN	CN	**1**	0.5	**2**	79
2	1	CN	CN	**3a**	0.25	**4a**	86
3[c]	1	CN	CN	**3a**	0.5	**4a**	82
4	1	CN	SO_2Ph	**3b**	3.5	**4b**	88 (94:6)
5	1	SO_2Ph	SO_2Ph	**3c**	1.5	**4c**	92
6	1	CN	CO_2Me	**3d**	1	**4d**	77 (80:20)
7[d]	1	SO_2Ph	CO_2Me	**3e**	2	**4e**	70 (81:19)
8[d]	1	CO_2Me	CO_2Me	**3f**	6	**4f**	0[e]
9[f]	2	CN	CN	**5**	1	**6**	88

[a] The reaction was conducted in the presence of 1 mol% $Pd(OAc)_2$ / 2 mol% dppb in CH_2Cl_2 (1.0 M) at room temperature unless otherwise indicated. [b] Isolated yield. The ratio of the stereoisomers was determined by ^1H-NMR. [c] 0.1 mol% $Pd(OAc)_2$ / 0.2 mol% dppb was used as a catalyst system. [d] The reaction was conducted at 50 °C. [e] A significant amount of the allene was recovered. [f] The reaction was conducted in 0.1 M CH_2Cl_2 solution.

There are several characteristic points on the present intramolecular hydrocarbonation of alkoxyallenes. Firstly, the reactivity of the alkoxyallene **3a** was so high that the cyclization

proceeded smoothly in the presence of 0.1 mol% $Pd(OAc)_2$ and 0.2 mol% dppb catalyst system at room temperature. The turnover number was 820. Secondly, neutral conditions gave the best results in the cyclization reaction and no other additives gave better results. Thirdly, the reaction gave only *exo*-cyclized products and no *endo*-cyclized products were observed. Finally, the palladium catalyzed reaction affords not only 5- and 6-membered cyclic ethers but also a 7-membered cyclic ether.



Scheme 1. Proposed mechanism for the intramolecular hydrocarbonation of alkoxyallenes

A proposed mechanism for the palladium catalyzed cyclization is shown in Scheme 1. Pd(0) catalytic species would be generated *in situ* and would add oxidatively to the C-H bond of the pronuleophiles to form a hydridopalladium(II) intermediate **A**. Both hydropalladation and carbopalladation could account for the formation of the cyclic ether, however, our previous study on the construction of carbocycles suggests that the cyclization reaction proceeds through hydropalladation to the coordinated allene to form π-allylpalladium intermediate **B**.[3f] Reductive elimination would afford a desired cyclic ether and Pd(0) catalytic species. Although further investigation is needed to settle the precise mechanism, the present cyclization reaction provides a new procedure for constructing 5- to 7-membered cyclic ethers under extremely mild and neutral conditions.

The cyclization of the malononitrile derivative **3a** is representative. To a CH_2Cl_2 (0.4 ml) solution of $Pd(OAc)_2$ (2.0 mg, 0.0090 mmol) and dppb (7.7 mg, 0.018 mmol) in a reaction vial was added a solution of **3a** (146.0 mg, 0.9 mmol) in CH_2Cl_2 (0.5 ml) under Ar atmosphere. The reaction mixture was stirred at room temperature. The consumption of the allene was monitored by TLC. When it was consumed completely (0.25 h), the reaction mixture was filtered through a short florisil column using *n*-hexane/ethyl acetate (1/1) as an eluent. The solvent was evaporated and the product was purified by a silica gel column chromatography using *n*-hexane/ethyl acetate (5/1) as an eluent. 2-Vinyl-3,3-dicyanotetrahydropyran **4a** was obtained in 86% yield (126.1 mg).

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4. The synthesis of 1,1-dicyano-5-oxa-6,7-octadiene **3a** is representative. 1-*t*-Butyldimethyl siloxy-4-oxa-6-heptyne (9.0 g, ~40 mmol) was treated with *t*-BuOK (4.49 g, 40 mmol) in *t*-BuOH for 4 h at reflux. The crude 1-*t*-butyldimethylsiloxy-4-oxa-5,6-heptadiene was obtained almost quantatively and was used without further purification. To a THF solution of the alkoxyallenyl ether (8.8 g, ~38 mmol) was added TBAF (60 ml, 1.0 M in THF, 60 mmol) and stirred for 2 h at room temperature. The crude 4-oxa-5,6-heptadien-1-ol was obtained with silyl residue, which was immediately used for the next reaction without futher purification because of its instability. To a mixture of the alcohol and triethylamine (6.7 ml, 50 mmol) in CH_2Cl_2 was added methanesulfonyl chloride (3.0 ml, 40 mmol) and stirred for 30 min at 0 °C. The crude product was obtained after extraction with ether and was purified by silica gel column chromatography to give 1-methanesulfonyl-4-oxa-5,6-heptadiene in 57 % yield (for 2 steps). To a suspension of NaH (0.34 g, 60 % in mineral oil, 8 mmol) in THF was added malononitrile (1.6 g, 24 mmol) at 0 °C and stirred for 10 min at room temperature, then, DMF was added and stirred for extra 20 min. A solution of the mesylate (1.54 g, 8 mmol) in THF and a catalytic amounts of potassium iodide was introduced to the reaction mixture and stirred for 2 h at 80 °C. The crude product was purified by silica gel column chromatography using *n*-hexane/ethyl acetate (5/1) to give **3a** in 54 % yield.
5. Unpublished result. Addition of acetic acid dramatically enhances the cyclization of allenes to afford carbocycles.