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Palladium/benzoic acid-catalyzed hydroalkoxylation of alkynes

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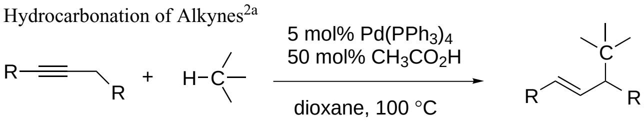
Abstract—The reaction of the internal alkyne **1** with alcohols **2** in the presence of a catalytic amount of $Pd(PPh_3)_4$ and benzoic acid in dioxane at 100°C gave the allylic ethers **3** in good to high yields. The reaction proceeds via the palladium/benzoic acid-catalyzed isomerization of the alkyne **1** to allene **6**, followed by the addition of alcohols **2** to the π-allylpalladium intermediate **7** formed by the hydropalladation of the resulting allene **6**. Furthermore, the intramolecular reaction of alkynes having a hydroxy group at the terminus of the carbon chain gave five- and six-membered cyclic ethers in good yields. © 2001 Elsevier Science Ltd. All rights reserved.

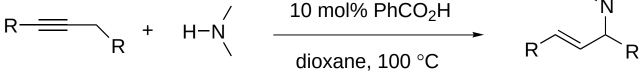
The addition of pronucleophiles to C–C multiple bonds has been considered as one of the most efficient methods for the synthesis of organic compounds, because the addition process does not produce any waste elements in contrast to nucleophilic substitution or addition reactions which inevitably afford useless by-products such as organic or inorganic salts.[1] Recently, we reported that certain alkynes react with carbon and nitrogen pronucleophiles in the presence of palladium/carboxylic acid catalyst to give the corresponding allylation products (Eqs. (1) and (2)).[2] We now report the palladium/benzoic acid-catalyzed hydroalkoxylation of alkynes (Eq. (3)).[3,4]

Hydrocarbonation of Alkynes[2a]

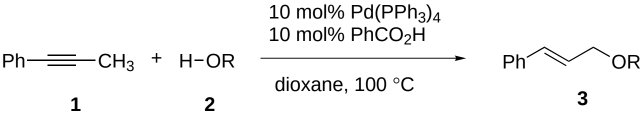


(1)

Hydroamination of Alkynes[2b]



(2)



(3)

In an initial experiment, 1-phenyl-1-propyne **1** was treated with 1.2 equiv. of benzyl alcohol **2a**, $Pd(PPh_3)_4$ (10 mol%), and benzoic acid (10 mol%) in dioxane at 100°C for 3 days. As expected, benzyl cinnamyl ether **3a** was obtained as the sole product in 96% yield (Table 1, entry 1).[5] Similarly, the reaction of **1** with the primary alcohols **2b–e** (entries 2–5) and secondary alcohols **2f–i** (entries 6–9) gave the corresponding cinnamyl ethers **3b–i**, respectively, in good to high yields. In all cases, no regio- or stereoisomers were obtained.

The mechanism of this reaction is presumably similar to those of the hydrocarbonation and hydroamination of alkynes (Scheme 1).[2] The initial step could be the hydropalladation of **1** with the hydridopalladium species **4** generated from Pd^0 and benzoic acid (catalytic cycle I).[6] The resulting vinylpalladium species **5** would produce phenyl allene **6** and the active catalyst **4** via β-elimination.[7] Hydropalladation of **6** with **4** would give the π-allylpalladium species **7** which would react with an alcohol **2** to give the product **3** along with the hydridopalladium **4** (cycle II).

The intramolecular version of the present reaction was investigated using substrates **8** and **10**, which were easily prepared from phenylacetylene (Table 2). The reaction of **8a** and **8b** gave the corresponding tetrahydrofuran derivatives **9a** and **9b** in 82 and 75% yields, respectively (entries 1 and 2). Although the

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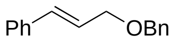
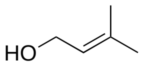
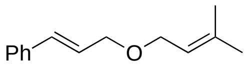
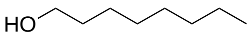
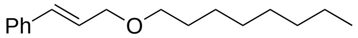
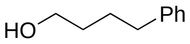
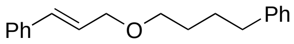
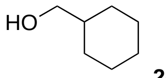
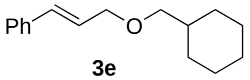
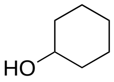
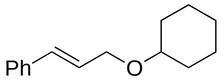
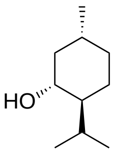
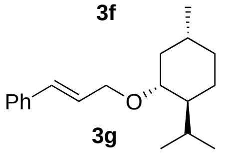
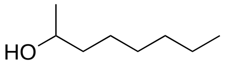
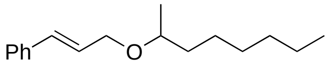
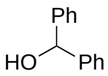
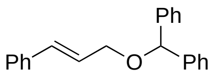
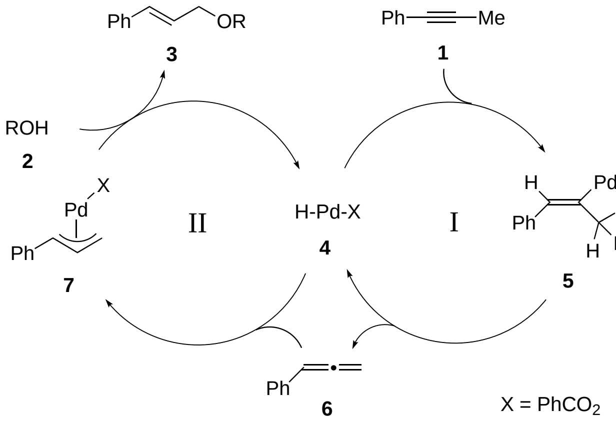
Table 1. Palladium/benzoic acid-catalyzed hydroalkoxylation of 1-phenyl-1-propyne **1**[a]

entry	alcohol	product	yield (%)[b]
1	BnOH **2a**	 **3a**	96
2	 **2b**	 **3b**	95
3	 **2c**	 **3c**	83
4	 **2d**	 **3d**	85
5	 **2e**	 **3e**	91
6	 **2f**	 **3f**	82
7	 **2g**	 **3g**	82
8	 **2h**	 **3h**	83
9	 **2i**	 **3i**	85

[a] All reactions were carried out with 0.5 mmol of **1**, 0.6 mmol of **2**, 10 mol% of $Pd(PPh_3)_4$, and 10 mol% of benzoic acid in 5 mL of dioxane at 100 °C for 3 days. [b] Isolated yield.

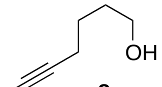
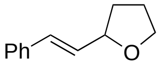
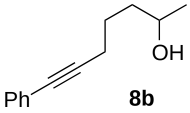
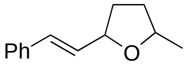
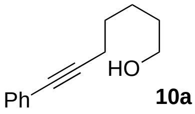
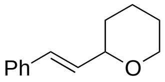
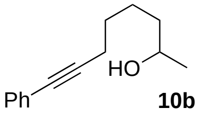
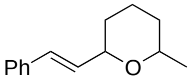


Scheme 1.

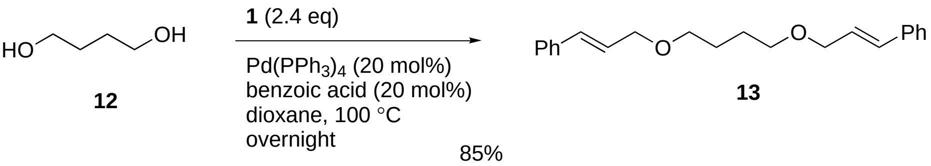
formation of the five-membered cyclic ethers proceeded in good yields, that of six-membered cyclic ethers resulted in lower yields. The reaction of **10a** and **10b** gave the corresponding tetrahydropyran derivatives **11a** and **11b** in 33 and 50% yields, respectively (entries 3 and 4). No diastereoselectivities were observed in the reactions of **8b** and **10b**; the disubstituted cyclic ethers **9b** and **11b** were obtained as a 1:1 mixture of diastereoisomers.

We next examined the reaction of polyols. Treatment of 1,4-butanediol **12** with 2.4 equiv. of **1** in the presence of 20 mol% of the catalysts gave the corresponding 2:1 adduct **13** in 85% yield (Eq. (4)). Although the reason is not clear, the reaction of triol **14** was slower than those described above and required excess amounts of the alkyne **1**. Thus, the reaction of **14** with 12 equiv. of **1** for 4 days gave the 3:1 adduct **15** in 95% yield (Eq. (5)). The reaction using 3.6 equiv. of **1** gave **15** in only 35% yield after 5 days.

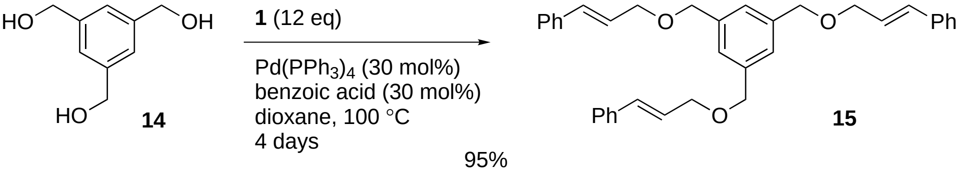
Table 2. Intramolecular hydroalkoxylation

entry	substrate	product	yield (%)[a]
1	 **8a**	 **9a**	82
2	 **8b**	 **9b**	75[b]
3	 **10a**	 **11a**	33
4	 **10b**	 **11b**	50[b]

[a]Isolated yield. [b]A 1:1 mixture of diastereoisomers.

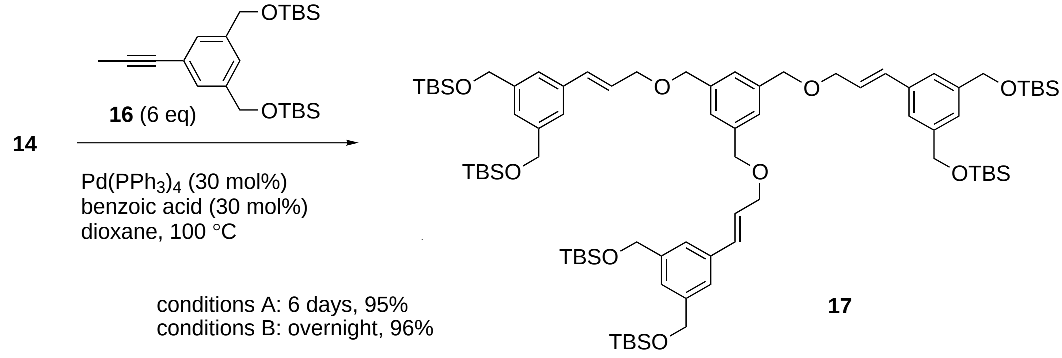


(4)



(5)

The above results prompted us to investigate the synthesis of dendritic molecules based on the present methodology. Treatment of **14** with 6 equiv. of **16**, which has two protected hydroxy groups, under the standard conditions (conditions A, see Ref. 5) used for the above reactions gave the corresponding hydroalkoxylation product **17**, a hexa-TBS ether, the first generation of a dendrimer, in 95% yield (Eq. (6)). Although the yield of **17** was quite satisfactory, a prolonged reaction time (6 days) was required for completion of the reaction. It was imagined that the synthesis of the next generation of dendrimer would need an extremely long reaction time. To solve this problem, we searched for optimum reaction conditions and finally found that premixing of the catalysts is extremely effective for acceleration of the reaction (conditions B). A solution of $Pd(PPh_3)_4$ and benzoic acid in dioxane was stirred for 30 min at 100°C. To the resulting mixture was added a solution of **14** and **16**, and the mixture was stirred overnight at 100°C to give the product **17** in 96% yield. Accordingly, the reaction time was reduced dramatically under the conditions B.



(6)

In conclusion, we have developed a simple and efficient method for the synthesis of various allylic ethers from alcohols and alkynes using a palladium/benzoic acid catalyst. The use of easily available pronucleophiles and the avoidance of the production of metal salts make this methodology an atom economical and environmentally benign process.

Acknowledgements

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3. For related hydrocarboxylation of alkynes, see: Trost, B. M.; Brieden, W.; Baringhaus, K. H. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1335–1336.
4. For palladium-catalyzed hydroalkoxylations of C–C double bonds, see: (a) Smutny, E. J. *J. Am. Chem. Soc.* **1967**, *89*, 6793–6794; (b) Yagi, H.; Tanaka, E.; Ishiwatari, H.; Hidai, M.; Uchida, Y. *Synthesis* **1977**, 334–335; (c) Inoue, Y.; Ohtsuka, Y.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3345–3346; (d) Camacho, D. H.; Nakamura, I.; Saito, S.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 3365–3367; (e) Camacho, D. H.; Nakamura, I.; Saito, S.; Yamamoto, Y. *J. Org. Chem.* **2001**, *66*, 270–275.
5. Typical procedure: To a mixture of $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) and benzoic acid (6 mg, 0.05 mmol) in dry dioxane (5 mL) were added 1-phenyl-1-propyne **1** (75 μL, 0.6 mmol) and benzyl alcohol **2a** (52 μL, 0.5 mmol), and the resulting mixture was stirred for 3 days at 100°C under Ar. The reaction mixture was then filtered through a short silica gel column using diethyl ether as an eluent. The filtrate was concentrated, and the residue was purified by silica gel column chromatography (hexane/EtOAc, 40:1) to give **3a** (108 mg, 96%).
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