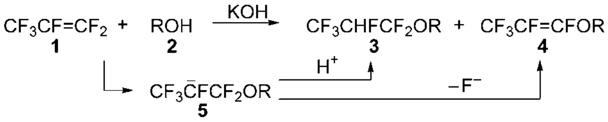
Hydrofluoroethers

Palladium(0)-Catalyzed Hydroalkoxylation of Hexafluoropropene: Synthesis of Hydrofluoroethers under Neutral Conditions**

Yasuhisa Matsukawa, Junji Mizukado, Heng-dao Quan, Masanori Tamura, and Akira Sekiya*

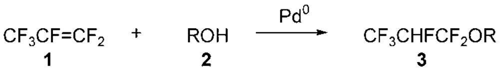
The development of alternatives to chlorofluorocarbons (CFCs) and hydrochlorofluorocarbons (HCFCs) has become an important and urgent issue. Hydrofluoroethers (HFEs) are excellent candidates as environmentally friendly replacements for refrigerants, cleaning solvents, or blowing agents characterized by low ozone-depletion and global-warming effects.[1] HFEs (R_FCHFCF_2OR) can be synthesized regioselectively by the addition of an alcohol to an industrially available fluorinated alkene such as tetrafluoroethylene (TFE) or hexafluoropropene (HFP; **1**) under strongly basic conditions.[2] However, the β-fluorinated carbanion intermediates **5**, formed by the addition of alkoxides to fluorinated alkene **1**, lead to the production of unsaturated vinyl ethers **4** by β-fluoride elimination (Scheme 1).[3]



Scheme 1. Hydroalkoxylation of HFP (**1**) under basic conditions.

In light of these environmental and safety aspects, we decided to investigate a new, alternative process to produce saturated ethers selectively under neutral conditions without the need for a basic medium. Here, we describe a novel Pd^0-catalyzed hydroalkoxylation of the fluorinated alkene HFP (**1**) (Scheme 2).

Our first attempt to hydroalkoxylate HFP with trifluoroethanol in the presence of Pd^{II} salts such as $PdCl_2$ and



Scheme 2. Pd^0-catalyzed hydroalkoxylation of HFP (**1**).

---

[*] Dr. Y. Matsukawa, Dr. J. Mizukado, Dr. H.-d. Quan, Dr. M. Tamura, Dr. A. Sekiya
Research Institute for Sustainable Chemical Innovation
National Institute of Advanced Industrial Science and Technology (AIST)
1-1-1 Higashi, Tsukuba, Ibaraki 305-8565 (Japan)
Fax: (+81) 29-861-4771
E-mail: y.matsukawa@aist.go.jp

[**] This research was supported by the New Energy and Industrial Technology Development Organization (NEDO)

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

DOI: 10.1002/ange.200462200

$Pd(OAc)_2$, the Wacker process, was unsuccessful.[4] However, we found that Pd catalysts containing phosphane ligands, such as $[PdCl_2(PPh_3)_2]$ and $[PdCl_2\{P(c\text{Hex})_3\}_2]$, gave the expected ether $CF_3CHFCF_2OCH_2CF_3$ (**3a**) in 42% and 49% yield, respectively, after 72 h at 150 °C. Interestingly, the hydroalkoxylation of **1** was efficiently catalyzed by the Pd^0 complex $[Pd(PPh_3)_4]$, even at ambient temperature, provided that HFP was bubbled continuously through the system (Table 1).[5]

Table 1: Pd^0-catalyzed hydroalkoxylation of HFP (**1**).[a]

Entry	ROH	*t* [h]	Product	Yield [%][b]
1	CF_3CH_2OH (**2a**)	18	**3a**	72
2	$CF_3CF_2CH_2OH$ (**2b**)	18	**3b**	73
3	$(CF_3)_2CHOH$ (**2c**)	18	**3c**	99
4[c]	**2c**	46	**3c**	100
5	CCl_3CH_2OH (**2d**)	18	**3d**	92
6[d]	CH_3OH (**2e**)	24	**3e**	67
7[d]	CH_3CH_2OH (**2f**)	24	**3f**	46
8[e]	$PhCH_2OH$ (**2g**)	18	**3g**	9
9	C_6H_5OH (**2h**)	18	**3h**	76
10[f]	**2h**	3	**3h**	99
11	C_6F_5OH (**2i**)	77	**3i**	41
12[f]	**2i**	18	**3i**	100

[a] Unless otherwise specified, reactions of **1** (excess) with **2** (2 mmol) in acetonitrile (5 mL) were carried out in the presence of 5 mol% of $[Pd(PPh_3)_4]$ at room temperature. [b] Yields based on alcohols **2** calculated from the ^{19}F and ^1H NMR spectra with 1,4-bis(trifluoromethyl)benzene as an internal standard. [c] The reaction was carried out in the presence of 1 mol% of $[Pd(PPh_3)_4]$. [d] Acetonitrile (15 mL) was used as the solvent. [e] Production of trace amounts of benzaldehyde (3%) was observed. [f] The reaction was conducted at 40–50 °C.

The reaction of an excess of HFP with acidic haloalcohols proceeded at room temperature to afford the corresponding ethers in good to excellent yields (Table 1, entries 1 to 5). In the case of poorly acidic alcohols, the corresponding ethers were obtained in only moderate yields (Table 1, entries 6 and 7). The reaction with benzyl alcohol (**2g**) gave ether **3g** in low yield (Table 1, entry 8).

The reaction with phenol (**2h**) also gave the ether $CF_3CHFCF_2OC_6H_5$ (**3h**) in 76% yield (Table 1, entry 9). In the case of pentafluorophenol (**2i**), the reaction required a longer time and the ether $CF_3CHFCF_2OC_6F_5$ (**3i**) was obtained in only 41% yield (Table 1, entry 11). At 40–50 °C these two phenol derivatives gave the corresponding ethers **3h** and **3i** in almost quantitative yields (Table 1, entries 10 and 12).

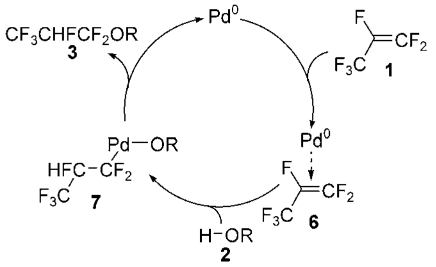
1,4-Bis(diphenylphosphanyl)butane (dppb) proved to be an effective ligand for the Pd^0-catalyzed hydroalkoxylation of HFP—the $[Pd(PPh_3)_4]$/dppb system enhanced the yields of the hydroalkoxylation with poorly acidic alcohols dramatically (Table 2).

Our results indicate the importance of the ability of the alcohols to act as a proton source and the electron donation from electron-rich Pd^0 species to HFP, which is enhanced by dppb. We propose the reaction mechanism for the Pd^0-catalyzed hydroalkoxylation of HFP shown in Scheme 3.[6] The electron-deficient alkene HFP coordinates to the electron-rich Pd^0 center to generate the η^2-complex **6**. Subsequent addition of a proton from alcohols **2** would give the intermediate **7**. Reductive elimination would then afford fluoroether **3** and regenerate the Pd^0 center. Continuous addition of **1** and dppb should enhance the formation of **6** and improve the yield. While acidic, fluorinated alcohols and phenols would stabilize intermediates **7**, the steric bulk of **2c** and **2d** might enhance the reductive elimination.

Table 2: Pd^0-catalyzed hydroalkoxylation in the presence of dppb.[a]

Entry	ROH	*t* [h]	Product	Yield [%][b]
1	CF_3CH_2OH (**2a**)	21	**3a**	84
2	$CF_3CF_2CH_2OH$ (**2b**)	21	**3b**	86
3	CH_3OH (**2e**)	24	**3e**	83
4	CH_3CH_2OH (**2f**)	24	**3f**	78
5	$PhCH_2OH$ (**2g**)	24	**3g**	82

[a] All reactions of **1** (excess) with **2** (2 mmol) in acetonitrile (15 mL) were carried out in the presence of 5 mol% of $[Pd(PPh_3)_4]$ and 10 mol% of dppb at room temperature. [b] Yields based on alcohols **2** calculated from the ^{19}F and ^1H NMR spectra with 1,4-bis(trifluoromethyl)benzene as an internal standard.



Scheme 3. Plausible mechanism for the Pd^0-catalyzed hydroalkoxylation.

In summary, we have developed a Pd^0-catalyzed hydroalkoxylation of a fluorinated alkene with various alcohols. This is the first example of the synthesis of saturated ethers by the addition of an alcohol to a C=C double bond in the presence of a palladium(0) catalyst. In this process, which is performed under neutral conditions, saturated hydrofluoroethers are selectively obtained without any formation of vinyl ethers. This procedure might be the basis for an asymmetric synthesis of hydrofluoroethers. Studies of the scope and limitations of this reaction, as well as its mechanistic details, are in progress.

Received: October 5, 2004

Keywords: alcohols · fluorinated alkenes · green chemistry · hydroalkoxylation · palladium

---

[1] A. Sekiya, S. Misaki, *J. Fluorine Chem.* **2000**, *101*, 215.
[2] a) A. L. Henne, M. A. Smook, *J. Am. Chem. Soc.* **1950**, *72*, 4378; b) J. D. Park, W. M. Sweeney, S. L. Hopwood, Jr., J. R. Lacher, *J. Am. Chem. Soc.* **1956**, *78*, 1685; c) R. E. A. Dear, E. E. Gilbert, *J. Chem. Eng. Data* **1969**, *14*, 493; d) A. V. Fokin, V. A. Komarov, A. F. Kolomiets, A. I. Rapkin, O. V. Verenikin, T. M. Potarina, *Izv. Akad. Nauk SSSR Ser. Khim.* **1977**, *9*, 2141 [*Chem. Abstr.*

1977, *88*, 22065]; e) J. Murata, M. Tamura, A. Sekiya, *Green Chem.* **2002**, *4*, 60.

[3] a) K. Okuhara, H. Baba, R. Kojima, *Bull. Chem. Soc. Jpn.* **1962**, *35*, 532; b) H. Harada, N. Ishikawa, *J. Fluorine Chem.* **1978**, *11*, 87.

[4] For a recent review on Pd^{II}-catalyzed Wacker-type hydroalkoxylation, see: M. Beller, J. Seayad, A. Tillack, H. Jiao, *Angew. Chem.* **2004**, *116*, 3448; *Angew. Chem. Int. Ed.* **2004**, *43*, 3368, and references therein.

[5] For the Pd^0-catalyzed hydroalkoxylation of dienes or allenes to afford oligomerization products via cyclic palladium intermediates, see: a) E. J. Smutny, *J. Am. Chem. Soc.* **1967**, *89*, 6793; b) H. Yagi, E. Tanaka, H. Ishiwatari, M. Hidai, Y. Uchida, *Synthesis* **1977**, 334; c) A. Krotz, F. Vollmüller, G. Stark, M. Beller, *Chem. Commun.* **2001**, 195; d) Y. Inoue, Y. Ohtsuka, H. Hashimoto, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3345; For Pd^0-catalyzed pronucleophilic addition to methylenecyclopropanes to afford allylic ethers via π-allyl palladium intermediates, see: e) D. H. Camacho, I. Nakamura, S. Saito, Y. Yamamoto, *Angew. Chem.* **1999**, *111*, 3576; *Angew. Chem. Int. Ed.* **1999**, *38*, 3365.

[6] For an "anti-Wacker"-type mechanism for the hydroalkoxylation of diynes, see: D. H. Camacho, S. Saito, Y. Yamamoto, *Tetrahedron Lett.* **2002**, *43*, 1085.