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Facile Synthesis of Fluoroalkenes by Palladium-Catalyzed Reductive Defluorination of Allylic *gem*-Difluorides

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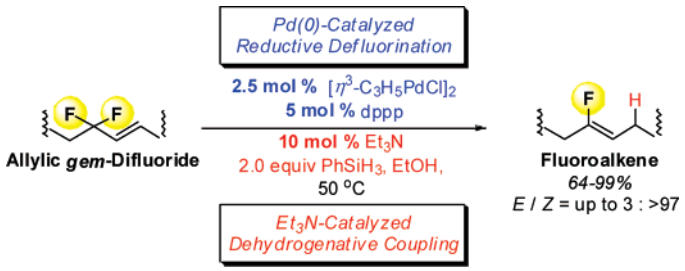
ABSTRACT



Chemo- and stereoselective synthesis of fluoroalkenes was achieved in excellent yields via Pd-catalyzed C–F bond activation. In this transformation, Et_3N plays a crucial role to produce reactive hydride species such as $Ph(EtO)SiH_2$ and $Ph(EtO)_2SiH$ by promoting dehydrogenative coupling. The reaction proceeds efficiently at 50 °C with a variety of substrates and is also useful for the synthesis of fluoroalkene peptidomimetics.

Although the development of catalytic reactions involving C−F bond activation represents a great challenge in organic chemistry,[1] only a few examples of Pd-catalyzed C−F bond activation have been reported to date.[2] Recently, several groups have disclosed cross-coupling reactions of alkyl or aryl fluorides through Pd-catalyzed C−F bond activation.[3] One example of Pd-catalyzed allylic C−F bond activation is the hydrogenolysis of allyl fluorides in the presence of Pd/C,[2a] which provides a facile method for the replacement of fluorine by hydrogen atom under mild conditions. A main drawback of this transformation exists in the chemoselectivity issue: the reaction always gives a mixture of two products, one formed by replacement of the fluorine by a hydrogen atom followed by saturation of the double bond, and the other resulting from the simple hydrogenation of the double bond. On the basis of these pioneering works, we envisioned that the reaction of allylic *gem*-difluoride **1** with a homogeneous palladium catalyst in the presence of appropriate additives having an affinity to fluorine could promote the elimination of fluorine, leading to the generation of a fluorinated π-allyl palladium intermediate **2**. By a chemoselective reaction with an appropriate nucleophile, this intermediate is expected to be transformed to (*Z*)-fluoroalkene **3**,[4] which constitutes an

(1) Recent reviews for activation and functionalization of C−F bonds, see: (a) Kiplinger, J. L.; Richmond, T. G.; Osterberg, C. E. *Chem. Rev.* **1994**, *94*, 373−431. (b) Burdeniuc, J.; Jedlicka, B.; Crabtree, R. H. *Chem. Ber./Recl.* **1997**, *130*, 145−154. (c) Murai, S. *Activation of Unreactive Bonds and Organic Synthesis*; Springer: New York, 1999; pp 243−269. (d) Hiyama, T. *Organofluorine Compounds Chemistry and Applications*; Springer: New York, 2000.

(2) Pd-catalyzed C−F bond activation: (a) Hudlicky, M. *J. Fluorine Chem.* **1989**, *44*, 345−359. (b) Hintermann, L.; Läng, F.; Maire, P.; Togni, A. *Eur. J. Inorg. Chem.* **2006**, 1397−1412. (c) Torrens, H. *Coord. Chem. Rev.* **2005**, *249*, 1957−1985. (d) Ichikawa, J.; Nadano, R.; Ito, N. *Chem. Commun.* **2005**, 4425−4427.

(3) Pd-catalyzed cross coupling via C−F bond activation: (a) Widdowson, D. A.; Wilhelm, R. *Chem. Commun.* **1999**, 2211−2212. (b) Wilhelm, R.; Widdowson, D. A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3808−3813. (c) Widdowson, D. A.; Wilhelm, R. *Chem. Commun.* **2003**, 578−579. (d) Mi, Kim, Y.; Yu, S. *J. Am. Chem. Soc.* **2003**, *125*, 1696−1697. (e) Terao, J.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2003**, *125*, 5646−5647.

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important class of molecules such as peptide isosteres,[5a−d] enzyme inhibitors,[5e] and liquid-crystalline materials.[5f]

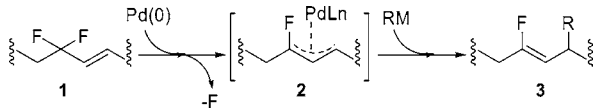
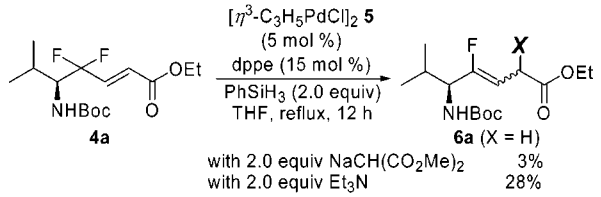


Figure 1. Synthesis of fluoroalkene via Pd catalysis.

Herein, we present a general catalytic system for the facile synthesis of fluoroalkene skeleta from readily available allylic difluorides by Pd-catalyzed reductive defluorination with phenylsilane. Some insight into the mechanistic aspect of this transformation is also described.

In an initial study, we investigated the Pd-catalyzed allylic alkylation[6] of γ,γ-difluoro-α,β-enoate **4a**, which can be readily prepared from isobutyl aldehyde[7] by modifying Honda's protocol.[8] Various additives were screened for the reaction of enoate **4a** with dimethyl sodiomalonate in the presence of a catalytic amount of $[\eta^3\text{-}C_3H_5PdCl]_2$ (**5**) and dppe. Although TMSCl, Et_4Si, $(EtO)_4Si$, or Me_3Al did not promote the desired defluorination reaction, we found that, when using $PhSiH_3$, a small amount of reductive defluorinated product **6a** was obtained (3%), without forming alkylated products **6b** [X = $CH(CO_2Me)_2$] (Scheme 1). Since

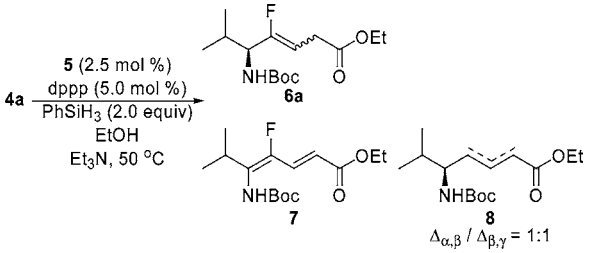
Scheme 1. Pd-Catalyzed Allylic Alkylation



the reduced product **6a** was not detected without using dimethyl sodiomalonate, we postulated that basicity of sodium malonate plays an important role in this reaction. Therefore, we tested the reaction in the presence of triethylamine instead of sodium dimethyl malonate to obtain **6a** in increased yields (28%).

After screening of the reaction conditions, we were pleased to find that the combination of dppp and EtOH at 50 °C afforded the expected products **6a** in up to 96% yield (Table 1, entry 1). However, a small amount of undesired diene **7**,

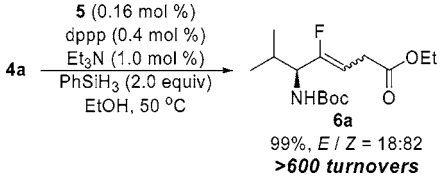
Table 1. Effect of the Amount of Et_3N[a]



entry	Et_3N [equiv]	yield of **6a**[b] [%]	*E*:*Z*[c]
1	2.0	<96	20:80
2	1.0	99	17:83
3	0.5	99	15:85
4	0.1	99	9:91
5	0.01	87	6:94

[a] Reactions were carried out with **4a** (0.13 mmol), $PhSiH_3$ (0.25 mmol), Et_3N, $[\eta^3\text{-}C_3H_5PdCl]_2$ **5** (2.5 mol %), and dppp (5.0 mol %) in EtOH (2.5 mL) at 50 °C for 2 h. [b] Yields of isolated products. [c] The ratio of *E*/*Z* isomer was determined by ^1H NMR spectroscopy.

presumably produced by Et_3N-assisted β-hydride elimination of a plausible intermediate of the type **2**, was observed in an irreproducible fashion (<10%). Therefore, we performed the reaction with 1.0 equiv of Et_3N to obtain the desired defluorinated products in 99% yield without the formation of the β-elimination product **7** (entry 2). Unexpectedly, the reduction of Et_3N to a catalytic amount improves the *E*/*Z* selectivity (entries 3−5). Of particular interest is the formation of a small amount of the bis-defluorinated product **8**, which was obtained in 8% yield when using 1 mol % of Et_3N.[9] Finally, the reaction can be conducted in quantitative conversion at catalyst loadings as low as 0.16 mol % (eq 1).



(1)

With these results in hand, we examined the scope of this reaction with readily available and synthetically useful

(4) For a recent example of the fluoroalkene synthesis: (a) Yoshida, M.; Komata, A.; Hara, S. *Tetrahedron* **2006**, *62*, 8636−8645 and references cited therein.

(5) (a) Dutheuil, G.; Couve-Bonnaire, S.; Pannecoucke, X. *Angew. Chem., Int. Ed. Engl.* **2007**, *46*, 1290−1292. (b) Narumi, T.; Niida, A.; Tomita, K.; Oishi, S.; Otaka, A.; Ohno, H.; Fujii, N. *Chem. Commun.* **2006**, 4720−4722. (c) Nakamura, Y.; Okada, M.; Sato, A.; Horikawa, H.; Koura, M.; Saito, A.; Taguchi, T. *Tetrahedron* **2005**, *61*, 5741−5753. (d) Allmendinger, T.; Felder, E.; Hungerbühler, E. *Tetrahedron Lett.* **1990**, *31*, 7301−7304. (e) Bey, P.; McCarthy, J. R.; McDonald, I. A. *ACS Symp. Ser.* **1991**, *456*, 105−133 and references cited therein. (f) Yokokoji, O.; Shimizu, T.; Kumai, S. JP 08040952, 1996 [*Chem. Abstr.* **1996**, *124*, 316586].

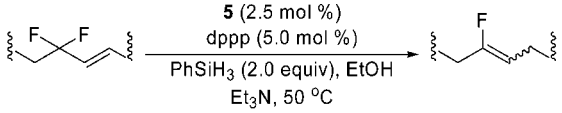
(6) For review, see: (a) Tsuji, J. *Palladium Reagents and Catalysis, Innovations in Organic Synthesis*; Wiley: New York, 1995. (b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395−422. (c) Johannsen, M.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689−1708. (d) Paquin, J.-F.; Lautens M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, Germany, 2004: Vol. 2, pp 73−95 and references cited therein. (e) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921−2943.

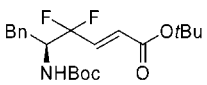
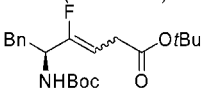
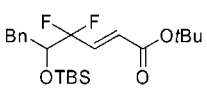
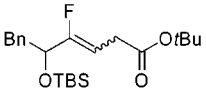
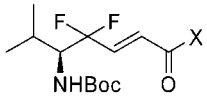
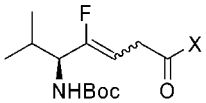
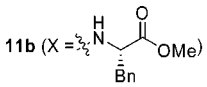
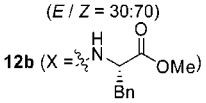
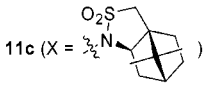
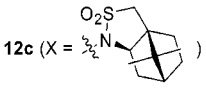
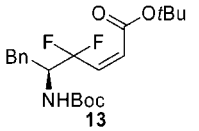
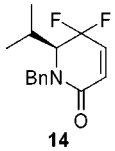
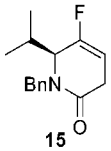
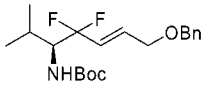
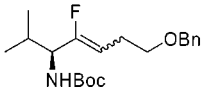
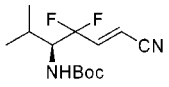
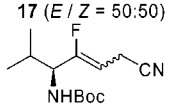
(7) (a) Otaka, A.; Watanabe, J.; Yukimasa, A.; Sasaki, Y.; Watanabe, H.; Kinoshita, T.; Oishi, S.; Tamamura, H.; Fujii, N. *J. Org. Chem.* **2004**, *69*, 1634−1645 and references cited therein.

(8) Honda, T.; Wakabayashi, H.; Kanai, K. *Chem. Pharm. Bull.* **2002**, *50*, 307−308.

(9) Formation of defluorinated product **8** could be rationalized by reaction of π-allyl Pd intermediate by hydride at the fluorinated carbon to give allyl fluoride followed by re-reductive defluorination.

Table 2. Pd- and Et_3N-Catalyzed Reductive Defluorination[a]



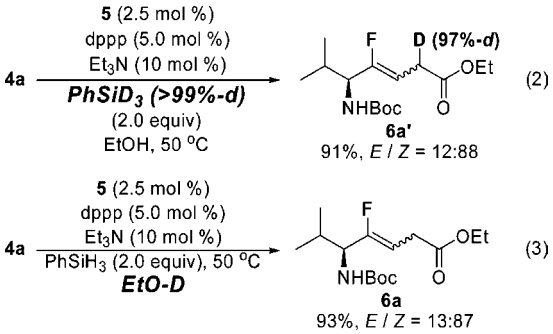
entry	substrate	product(s) (E:Z)[b]	yield [%][c]
1	**4a**	**6a** (E / Z = 9:91)	99
2	 **4b**	 **6b** (E / Z = 18:82)	97
3	 **9**	 **10** (E / Z = 3:>97)	91
			
4	**11a** (X = NH_2)	**12a** (X = NH_2) (E / Z = 30:70)	64
5	 **11b** (X =)	 **12b** (X =) (E / Z = 21:79)	97
6	 **11c** (X =)	 **12c** (X =) (E / Z = 3:>97)	76[d]
7	 **13**	**6c** (E / Z = 26:74)	99
8	 **14**	 **15**	99
9	 **16**	 **17** (E / Z = 50:50)	77
10	 **18**	 **19** (E / Z = 14:86)	73

[a] All reactions were carried out with allylic *gem*-difluoride (1.0 equiv), $PhSiH_3$ (2.0 equiv), Et_3N (10 mol %), $[\eta^3$-$C_3H_5PdCl]_2$ **5** (2.5 mol %), and dppp (5.0 mol %) in EtOH at 50 °C for 2 h. [b] Yields of isolated products. [c] The ratio of E/Z isomer was determined by ^{1}H NMR spectroscopy. [d] A trace amount of starting material was detected by ^{1}H NMR spectroscopy.

substrates possessing various functional groups (Table 2). In all cases, the reaction was completely chemoselective, and good to excellent yields of fluoroalkenes were obtained with modest to high selectivity. *N*-Boc amide, esters, and substituents such as alkyl and siloxy groups introduced at the δ-carbon did not affect the reaction (entries 1−3). Furthermore, amides, including a peptide, **11a**−**c** (entries 4−6), (*Z*)-enoate **13** (entry 7), and lactam **14** (entry 8), can be employed to give the desired fluoroalkenes **12a**−**c**, **6c**, and **15**. The applicability of this reaction to the substrates without a conjugated carbonyl moiety such as benzyl ether **16** and nitrile **18** (entries 9 and 10) clearly demonstrates an advantage of this reaction over the known related reduction using a single-electron donor,[7a] which is limited to α,β-unsaturated carbonyl compounds.

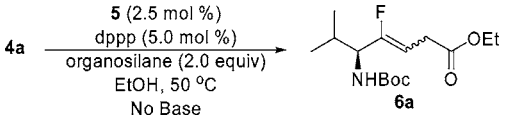
To gain some insight into the mechanism of this transformation, we examined isotopic labeling experiments (Scheme 2). The reaction with $PhSiD_3$ in EtOH induced deuterium

Scheme 2. Isotopic Labeling Experiments



incorporation at the α-position (97% -*d*) (eq 2). On the other hand, the reaction performed in EtO−D with $PhSiH_3$ promoted no deuterium incorporation (eq 3), suggesting that the introduced hydrogen originates from $PhSiH_3$. Furthermore, to determine the hydride species, we performed the reaction with $PhSiH_3$, $Ph(EtO)SiH_2$, and $Ph(EtO)_2SiH$ in the absence of Et_3N (Table 3). While no reaction was observed

Table 3. Investigation of the Hydride Species[a]



entry	organosilane	yield of **6a**[b] [%]	E:Z[c]
1	$PhSiH_3$	*d*	
2	$Ph(EtO)SiH_2$	83	13:87
3	$Ph(EtO)_2SiH$	70	45:55

[a] Reactions were carried out with **4a** (0.13 mmol), organosilane (0.25 mmol), $[\eta^3$-$C_3H_5PdCl]_2$ **5** (2.5 mol %), and dppp (5.0 mol %) in EtOH (2.5 mL) at 50 °C for 2 h. [b] Yields of isolated products. [c] The ratio of E/Z isomers was determined by ^{1}H NMR spectroscopy. [d] No reaction was observed.

with $PhSiH_3$ (entry 1), the reactions with $Ph(EtO)SiH_2$ and $Ph(EtO)_2SiH$ proceeded smoothly to provide the desired defluorinated products **6a** (entries 2 and 3). Therefore, these alkoxysilanes would be considered as the actual reactive species. On the basis of these results and Buchwald's observation,[10] Et_3N plays a crucial role for the generation of these active hydride sources such as $Ph(EtO)SiH_2$ and $Ph(EtO)_2SiH$ by promoting catalytic dehydrogenative coupling of $PhSiH_3$ with EtOH.[11] Once those active species have

been generated, they could work both as reducing agents to generate Pd^0 complexes and as hydride sources.

These results could explain the dependence of the chemical yield and stereoselectivity on the amount of Et_3N in Table 1. A catalytic amount of Et_3N would generate the reactive alkoxysilanes in an appropriate rate through dehydrogenative coupling, while the excess of Et_3N considerably accelerates this process, which would consume reactive species to cause undesired side reactions.

In summary, we have developed a novel general method for the synthesis of fluoroalkenes under mild conditions utilizing Pd-catalyzed reductive defluorination. This is an unparalleled example of a highly effective catalytic synthesis of a fluoroalkene skeleton, including peptidomimetics. Mechanistic study has proven that Et_3N promotes the dehydrogenative coupling of $PhSiH_3$ with EtOH to produce reactive species.

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Supporting Information Available: Representative procedures and spectral and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL701627V

(10) Involvement of alkoxysilane accounts for the titanium-catalyzed hydrosilylation of imine with $PhSiH_3$, see: Verdaguer, X.; Lange, U. E. W.; Reding, M. T.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 6784−6785.

(11) For examples of base-catalyzed dehydrogenative coupling of silanes with alcohols, see: (a) Lukevics, E.; Dzintara, M. *J. Organomet. Chem.* **1984**, *271*, 307−317. (b) Gilman, H.; Dunn, G. H.; Hartzfeld, H.; Smith, A. G. *J. Am. Chem. Soc.* **1955**, *77*, 1287−1288. (c) Bazant, V.; Chvalovsky, V.; Rathousky J. In *Organosilicon Compounds*; Publishing House of the Czechoslovak Academy of Science: Prague, Czechoslovakia, 1965: pp 54−56.