

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

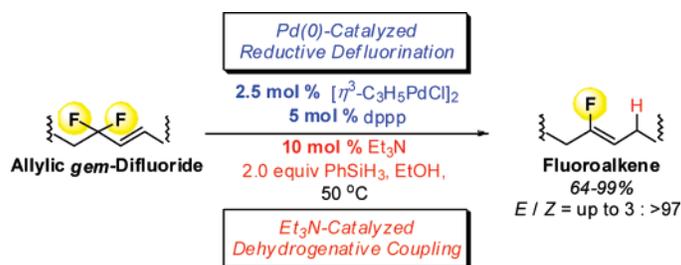
Tetsuo Narumi, Kenji Tomita, Eriko Inokuchi, Kazuya Kobayashi, Shinya Oishi, Hiroaki Ohno, and Nobutaka Fujii*

Graduate School of Pharmaceutical Sciences, Kyoto University,
Sakyo-ku, Kyoto 606-8501, Japan

nfujii@pharm.kyoto-u.ac.jp

Received July 13, 2007

ABSTRACT



Chemo- and stereoselective synthesis of fluoroalkenes was achieved in excellent yields via Pd-catalyzed C–F bond activation. In this transformation, Et₃N plays a crucial role to produce reactive hydride species such as Ph(EtO)SiH₂ 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

(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.

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

(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.

important class of molecules such as peptide isosteres,^{5a-d} enzyme inhibitors,^{5e} and liquid-crystalline materials.^{5f}

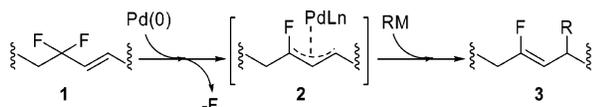
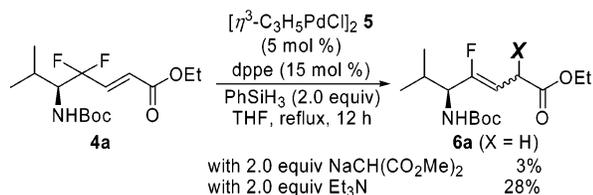


Figure 1. Synthesis of fluoroalkene via Pd catalysis.

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 alkylation⁶ of γ,γ -difluoro- α,β -enoate **4a**, which can be readily prepared from isobutyl aldehyde⁷ 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 $[\eta^3\text{-C}_3\text{H}_5\text{PdCl}]_2$ (**5**) and dppe. Although TMSiCl, Et₄Si, (EtO)₄Si, or Me₃Al did not promote the desired defluorination reaction, we found that, when using PhSiH₃, a small amount of reductive defluorinated product **6a** was obtained (3%), without forming alkylated products **6b** [X = CH(CO₂Me)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.

(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.

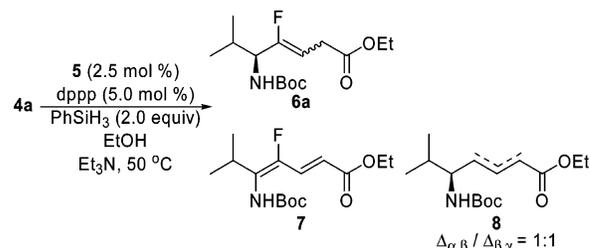
(5) (a) Dutheil, G.; Couve-Bonnaire, S.; Pannecoucke, X. *Angew. Chem., Int. Ed. Engl.* **2007**, *46*, 1290–1292. (b) Narumi, T.; Niida, A.; Tomita, K.; Oishi, S.; Otaka, A.; Ohno, H.; Fujii, N. *Chem. Commun.* **2006**, 4720–4722. (c) Nakamura, Y.; Okada, M.; Sato, A.; Horikawa, H.; Koura, M.; Saito, 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.

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**,

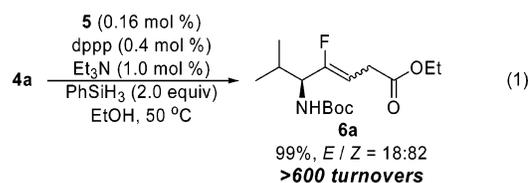
Table 1. Effect of the Amount of Et₃N^a



| entry | Et ₃ N [equiv] | yield of 6a ^b [%] | <i>E</i> : <i>Z</i> ^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), PhSiH₃ (0.25 mmol), Et₃N, $[\eta^3\text{-C}_3\text{H}_5\text{PdCl}]_2$ **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 Et₃N-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 Et₃N to obtain the desired defluorinated products in 99% yield without the formation of the β -elimination product **7** (entry 2). Unexpectedly, the reduction of Et₃N 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 Et₃N.⁹ Finally, the reaction can be conducted in quantitative conversion at catalyst loadings as low as 0.16 mol % (eq 1).



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

(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 Et₃N-Catalyzed Reductive Defluorination^a

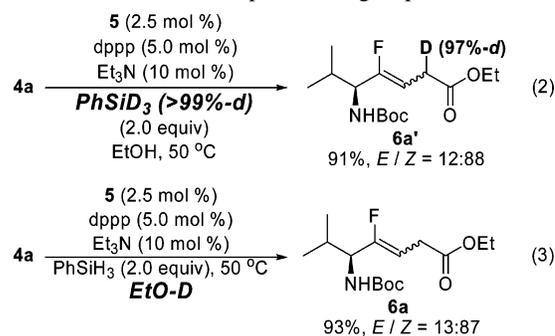
| entry | substrate | product(s) (<i>E/Z</i>) ^b | yield [%] ^c |
|-------|---|--|------------------------|
| 1 | 4a | 6a (<i>E/Z</i> = 9:91) | 99 |
| 2 | 4b | 6b (<i>E/Z</i> = 18:82) | 97 |
| 3 | 9 | 10 (<i>E/Z</i> = 3:>97) | 91 |
| 4 | 11a (X = NH ₂) | 12a (X = NH ₂) (<i>E/Z</i> = 30:70) | 64 |
| 5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

^a All reactions were carried out with allylic *gem*-difluoride (1.0 equiv), PhSiH₃ (2.0 equiv), Et₃N (10 mol %), [η³-C₃H₅PdCl]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 ¹H NMR spectroscopy. ^d A trace amount of starting material was detected by ¹H 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 silyloxy 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 PhSiD₃ 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 PhSiH₃ promoted no deuterium incorporation (eq 3), suggesting that the introduced hydrogen originates from PhSiH₃. Furthermore, to determine the hydride species, we performed the reaction with PhSiH₃, Ph(EtO)SiH₂, and Ph(EtO)₂SiH in the absence of Et₃N (Table 3). While no reaction was observed

Table 3. Investigation of the Hydride Species^a

| entry | organosilane | yield of 6a ^b [%] | <i>E/Z</i> ^c |
|-------|--------------------------|-------------------------------------|-------------------------|
| 1 | PhSiH ₃ | <i>d</i> | |
| 2 | Ph(EtO)SiH ₂ | 83 | 13:87 |
| 3 | Ph(EtO) ₂ SiH | 70 | 45:55 |

^a Reactions were carried out with **4a** (0.13 mmol), organosilane (0.25 mmol), [η³-C₃H₅PdCl]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 ¹H NMR spectroscopy. ^d No reaction was observed.

with PhSiH₃ (entry 1), the reactions with Ph(EtO)SiH₂ and Ph(EtO)₂SiH proceeded smoothly to provide the desired defluorinated products **6a** (entries 2 and 3). Therefore, these alkoxy-silanes would be considered as the actual reactive species. On the basis of these results and Buchwald's observation,¹⁰ Et₃N plays a crucial role for the generation of these active hydride sources such as Ph(EtO)SiH₂ and Ph(EtO)₂SiH by promoting catalytic dehydrogenative coupling of PhSiH₃ with EtOH.¹¹ Once those active species have

been generated, they could work both as reducing agents to generate Pd⁰ complexes and as hydride sources.

These results could explain the dependence of the chemical yield and stereoselectivity on the amount of Et₃N in Table 1. A catalytic amount of Et₃N would generate the reactive alkoxy-silanes in an appropriate rate through dehydrogenative coupling, while the excess of Et₃N 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

(10) Involvement of alkoxy-silane accounts for the titanium-catalyzed hydrosilylation of imine with PhSiH₃, see: Verdager, 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.

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 Et₃N promotes the dehydrogenative coupling of PhSiH₃ with EtOH to produce reactive species.

Acknowledgment. This research was supported in part by the 21st Century COE Program “Knowledge Information Infrastructure for Genome Science”, a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan, the Japan Society for the Promotion of Science (JSPS), and the Japan Health Science Foundation.

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