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Oxidative Cross-Coupling of *β*,*β*-Difluoroenol Silyl Ethers with Nucleophiles: A Dipole-Inversion Method to Difluoroketones

Kenji Uneyama,* Hiroaki Tanaka, Satoru Kobayashi, Manabu Shioyama, and Hideki Amii

Department of Applied Chemistry, Faculty of Engineering, Okayama University, 3-1-1 Tsushimanaka, Okayama 700-8530, Japan

uneyamak@cc.okayama-u.ac.jp

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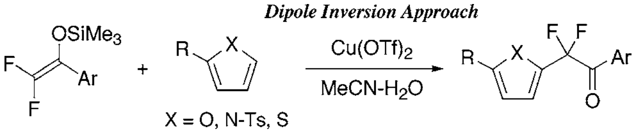
ABSTRACT

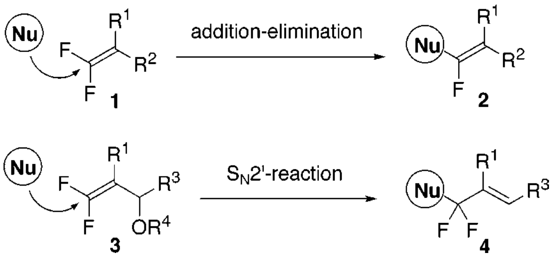


Oxidative cross-coupling of α-aryl-*β*,*β*-difluoroenol silyl ethers with heteroaromatics in the presence of $Cu(OTf)_2$ in wet acetonitrile proceeds smoothly, affording heteroaryldifluoromethyl aryl ketones in 61–88% yields. Alcohols also react as nucleophiles under the same conditions to provide alkoxydifluoromethyl aryl ketones in 73–80% yields.

Dipole inversion (umpolung) has been recognized as being highly useful in synthetic organic chemistry and has been employed as a basic concept for organic synthesis since Seebach's proposal.[1,2] The synthetic utility of a substrate could be greatly extended if a building block which, for instance, is reactive as a nucleophile, is easily converted in situ to an electrophile by a chemically induced dipole inversion. Electrochemical oxidative generation of radicals from carbanions and their subsequent reaction with vinyl ethers[3] (conversion of a nucleophile to an electrophile) and lithium−halogen exchange of acyl halides with butyllithium (conversion of an electrophile to a nucleophile)[4] are some of the typical examples.

gem-Difluoroalkenes mostly react electrophilically with nucleophiles at the difluoromethylene carbon by addition−elimination leading to α-substituted monofluoroalkenes (**1** to **2**)[5] and by S_N2'-type addition or Claisen rearrangement to deliver formal products of S_N2'-type addition (**3** to **4**)[6] in aprotic solvents due to the activation of the difluoromethylene carbon atom by the strong electron-withdrawing nature of fluorine atom[7,8] (Scheme 1).

Scheme 1



In contrast, the introduction of an alkoxy or siloxy group at the 2-carbon of 1,1-difluoro-1-alkenes alters the reactivity

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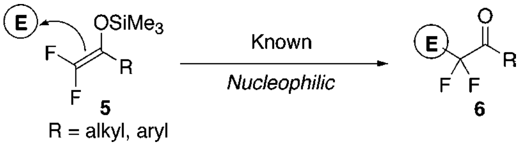
[1] Seebach, D. *Angew. Chem., Int. Ed.* **1976**, *18*, 239.
[2] (a) Hase, T. A. *Umpolung Synthons*; Wiley: Nerw York, 1987. (b) Schmittel, M. *Top. Curr. Chem.* **1994**, *169*, 183. (c) Enders, D.; Shilvock, J. P. *Chem. Soc. Rev.* **2000**, *29*, 359.
[3] (a) Schafer, H.; Alazrak, A. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 474. (b) Torii, S.; Uneyama, K.; Onishi, T.; Fujita, Y.; Ishiguro, M.; Nishida, T. *Chem. Lett.* **1980**, 1603.
[4] Braun, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 430.

10.1021/ol049055m CCC: $27.50

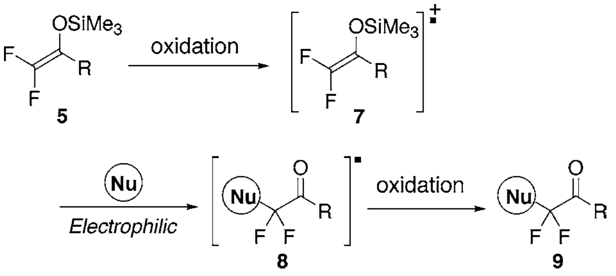
of the difluoroalkenes from electrophilic to the nucleophilic. Thus, difluoroenol ethers and silyl ethers react with electrophiles leading to α-substituted α,α-difluoroketones due to the electron-donating nature of the ethereal oxygen atom of **5** (**5** to **6**) in Scheme 2. Lewis acid-catalyzed carbon−carbon bond formations of **5** with carbonyl compounds[9] and reactions with various electrophiles[10] have been well demonstrated and frequently employed as reliable methods for introducing difluoroacyl moiety into organic molecules.

Scheme 2



An important question is whether difluoroenol silyl ethers **5**, typical nucleophiles react with other nucleophiles, affording α-substituted α,α-difluoroketones **9** or not? The transformation of **5** to **9** as shown in Scheme 3, if possible, is categorized as an addition reaction and would expand a scope of the synthetic utility of the readily available difluoroenol silyl ethers **9**,[11] but has never been reported. In this context, the dipole-inversion approach would be promising to realize the addition of a nucleophile to **5**. The above hypothesis suggests the oxidized form **7** should in principle react with nucleophiles via simultaneous Si−O bond cleavage to provide α-substituted α,α-difluoroketones **9**; otherwise, the transformation of **5** to **9** is difficult (Scheme 3).

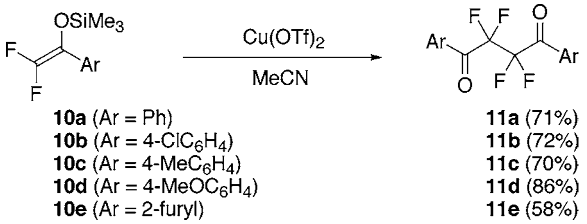
Scheme 3



The current demand in medicinal science for a variety of difluoromethylene compounds,[12] which have been less explored as compared with trifluoromethylated and monofluorinated compounds, have prompted us to develop a new synthetic method for difluoromethylene compounds. This is the first example of the oxidative cross-coupling of difluoroenol silyl ethers with nucleophiles such as heteroaromatics and alcohols.[13]

An extensive survey of oxidants [$Cu(OTf)_2$, CuO, $CuCl_2$, Ag_2O, CAN (cerium ammonium nitrate)], solvents [THF, DMF, CH_2Cl_2, HFIP (hexafluoro-2-propanol), *n*-BuCN, *i*-PrCN, *n*-PrCN, EtCN, MeCN] and reaction temperatures revealed that a combination of copper(II) triflate and wet acetonitrile at 0 °C was a choice for the optimized reaction conditions and that the use of less polar solvents induced the formation of triflate **17c**. Although difluoroenol silyl ethers are less oxidizable than nonfluorinated ones,[14] the Cu(II) reagent cleanly oxidized **10** at −30 °C to room temperature within 15 min in acetonitrile to provide the dimer 2,2,3,3-tetrafluoro-1,4-diketones **11** in good to excellent yields [**11**, Ar; C_6H_5 (71%), 4-ClC_6H_4 (72%), 4-MeC_6H_4 (70%), 4-$MeOC_6H_4$ (86%), 2-furyl (58%)] as shown in Scheme 4.

Scheme 4



Under the optimized conditions for homocoupling, cross-coupling of **10d** with furan **12** (X = O) was studied (Scheme

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(5) For intermolecular reactions, see: (a) Tellier, F.; Sauvetre, R. *J. Fluorine Chem*. **1996**, *76*, 181. (b) Shi, G.-Q.; Cao, Z.-Y. *J. Chem. Soc., Chem. Commun*. **1995**, 1969. (c) De Tollenaere, C.; Ghosez, L. *Tetrahedron* **1997**, *53*, 17127. (d) Huang, X.-H.; He, P.-Y.; Shi, G.-Q. *J. Org. Chem*. **2000**, *65*, 627. For intramolecular reactions, see: (e) Ichikawa, J.; Wada, Y.; Okauchi, T.; Minami, T. *Chem. Commun*. **1997**, 1537. (f) Wada, Y.; Ichikawa, J.; Katsume, T.; Nohiro, T.; Okauchi, T.; Minami, T. *Bull. Chem. Soc. Jpn*. **2001**, *74*, 971. (g) Ichikawa, J.; Sakoda, K.; Wada, Y. *Chem. Lett*. **2002**, 282. (h) Sato, A.; Okada, M.; Nakamura, Y.; Kitagawa, O.; Hirokawa, H.; Taguchi, T. *J. Fluorine Chem*. **2003**, *123*, 75.

(6) (a) Patel, S. T.; Percy, J. M.; Wilkes, R. D. *J. Org. Chem*. **1996**, *61*, 166. (b) Percy, J. M.; Prime, M. E.; Broadhurst, M. J. *J. Org. Chem*. **1998**, *63*, 8049. (c) Broadhurst, M. J.; Brown, S. J.; Percy, J. M.; Prime, M. E. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3217. (d) Park, H. M.; Uegaki, T.; Konno, T. Ishihara, T.; Yamanaka, H. *Tetrahedron Lett*. **1999**, *40*, 2985. (e) Yamazaki, T.; Ueki, H.; Kitazume, T. *Chem. Commun*. **2002**, 2670.

(7) As exceptional examples, 1,1-difluoroethene with *sec*-butyllithium and 1,1-difluorovinyl phenyl ether with *n*-butyllithium undergo deprotonation−lithiation rather than addition of alkyllithiums. (a) Tellier, F.; Sauvetre, R. *J. Fluorine Chem*. **1993**, *62*, 183. (b) Tellier, F.; Sauvetre, R. *J. Fluorine Chem*. **1995**, *70*, 265. (c) Purrington, S. T.; Thomas, H. N. *J. Fluorine Chem*. **1998**, *90*, 47.

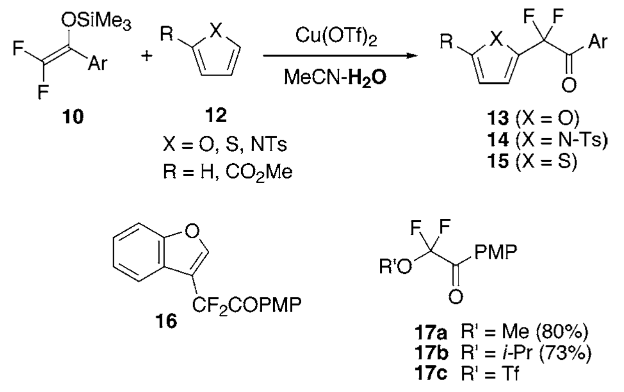
(8) Hydroalkoxylation and hydrothioalkoxylation of some 1,1-difluoroalkenes in protic solvents are known. (a) De Tollenaere, C.; Ghosez, L. *Tetrahedron* **1997**, *53*, 17127. (b) Mae, M.; Amii, H.; Uneyama, K. *Tetrahedron Lett*. **2000**, *41*, 7893.

(9) (a) Yamanaka, M.; Ishihara, T.; Ando, T. *Tetrahedron Lett*. **1983**, *24*, 507. (b) Xu, Y.-Y. *J. Chem. Soc., Perkin Trans. 1* **1993**, 795. (c) Iseki, K.; Kuroki, Y.; Asada, D.; Kobayashi, Y. *Tetrahedron Lett*. **1997**, *38*, 1447.

(10) For reaction with carbocations, see: (a) Whitten, J. P.; Barney, C. L.; Huber, E. W.; Bey, P.; McCarthy, J. R. *Tetrahedron Lett*. **1989**, *30*, 3649. (b) Tellier, F.; Baudry, M.; Sauvetre, R. *Tetrahedron Lett*. **1997**, *38*, 5989. (c) Chorki, F.; Crousse, B.; Bonnet-Delpon, D.; Bégué, J.-P.; Brigaud, T.; Portella, C. *Tetrahedron Lett*. **2001**, *42*, 1487. (d) Kodama, Y.; Okumura, M.; Yanabu, N.; Taguchi, T. *Tetrahedron Lett*. **1996**, *37*, 1061. (e) Lefebvre, O.; Brigaud, T.; Portella, C. *Tetrahedron* **1999**, *55*, 7233. (f) For the reactions with other electrophiles, see: Prakash, G. K. S.; Hu, J. B.; Olah, G. A. *J. Fluorine Chem*. **2001**, *112*, 357.

(11) (a) Amii, H.; Kobayashi, T.; Hatamoto, Y.; Uneyama, K. *Chem. Commun*. **1999**, 1323. (b) Mae, M.; Amii, H.; Uneyama, K. *Tetrahedron Lett*. **2000**, *41*, 7893. (c) Amii, H.; Kobayashi, T.; Uneyama, K. *Synthesis* **2000**, 2001. (d) Amii, H.; Kobayashi, T.; Terasawa, H.; Uneyama, K. *Org. Lett*. **2001**, *3*, 3103. (e) Amii, H.; Hatamoto, Y.; Seo, M.; Uneyama, K. *J. Org. Chem*. **2001**, *66*, 7216. (f) Kobayashi, T.; Nakagawa, T.; Amii, H.; Uneyama, K. *Org. Lett*. **2003**, *5*, 4297.

Scheme 5



5). However, the desired cross-coupled product **13d** was produced in unsatisfactory yields, while homocoupled product **11d** was mainly formed and triflate **17c** was always produced as a byproduct. The cation radical **7** reacted with furan, the silyl ether **10d**, and even triflate anion competitively. Therefore, decreasing the rate of addition of **10d** to suppress the sharp increase of the concentration of **10d** and also increasing the concentration of heteroaromatics in the reaction mixture resulted in the predominant formation of **13d** in satisfactory yields. Interestingly, water is a good additive for the selective formation of cross-coupling product **13d**.

Both electron-withdrawing and electron-donating groups attached to the phenyl ring of **10** affected the yield slightly as shown in Table 1. Particularly noteworthy is the fact that *p*-methoxyphenyl compound **10d** provided **13d** in an excellent yield, which is readily transformed to the corresponding 2-(2-furyl)-2,2-difluoroacetate by Baeyer−Villiger oxidation in hexafluoro-2-propanol.[15] These heteroaryl-substituted difluoroketones and acetates are useful synthetic building blocks but have been less available so far.[16] The present cross-coupling approach provides us a straightforward access to these important difluorinated compounds.

Table 1. Oxidative Cross-coupling of **10** with Heteroaromatics **12**[a]

	12		**10**		
entry	R	X	Ar	product	yield,[b] %
1	H	O	C_6H_5	**13a**	88
2	H	O	4-Cl-C_6H_4	**13b**	72
3	H	O	4-Me-C_6H_4	**13c**	75
4	H	O	4-MeO-C_6H_4	**13d**	82
5	H	O	2-furyl	**13e**	63
6	CO_2Me	O	4-MeO-C_6H_4	**13f**	61
7	H	N-Ts	4-MeO-C_6H_4	**14**	67
8	H	S	4-MeO-C_6H_4	**15**	84

[a] Each reaction was carried out in MeCN−H_2O (50:1 v/v) at 0 °C for 3 h. [b] Isolated yield.

In entry 6, methyl 2-furancarboxylate was less reactive, but gave **13f** in 61% yield. In contrast to the higher reactivity at the 2-position of furan, benzo[*b*]furan reacted at the 3-position, affording **16** in 50% yield. The reactions of **10** with other heteroaromatics such as *N*-tosylpyrrole and thiophene were successful, suggesting the generality of the oxidative cross-coupling of **10**. Thus, both *N*-tosylpyrrole and thiophene reacted at the 2-position to provide the desired **14** and **15** in 67% and 84% yields, respectively.

The key factor which decisively governs the feasibility for the cross-coupling is the relative oxidizability between **10** and heteroaromatics **12**. The successful cross-coupling strictly requires the heteroaromatics**12** must be less oxidizable than **10**. The more oxidizable heteroaromatics are oxidized exclusively and the ether **10** remains intact. In fact, no cross-coupled products were formed on reacting **10** with 2-methoxyfuran and pyrrole. A simple calculation of HOMO levels of **10** and heteroaromatics **12** by PM3 level geometry optimization is useful for estimation of the feasibility for the cross-coupling.[17]

As one of the applications for the cross-coupling reaction, Cu(II)-promoted alkoxylation of **10** in the presence of alcohols provided α-alkoxylated α,α-difluoroketones **17** in good yields, demonstrating the further promisimg extension of the present reaction.

As for the mechanism for the present oxidative cross-coupling, it is most plausible that the radical cations **7** initially formed by the oxidation of **10** with Cu(OTf)$_2$ would attack heteroaromatics **12** to generate radicals **8** with the simultaneous release of trimethylsilyl group.[18] Then, the radicals **8** of which radical center is located on the heteroaromatic ring-

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(12) The difluoromethylene moiety has been recognized as a mimic of ethereal oxygen in phosphates and sugars, and these difluorinated compounds often behave as enzyme inhibitors: (a) Berkowitz, D. B.; Bose, M.; Pfannenstiel, T. J.; Doukov, T. *J. Org. Chem.* **2000**, *65*, 4498. (b) Burke, T. R.; Yao, Z. J.; Liu, D. G.; Voigt, J.; Gao, Y. *Biopolymers* **2001**, *60*, 32. (c) Akahoshi, F.; Ashimori, A.; Sakashita, H. *J. Med. Chem.* **2001**, *44*, 1297. (d) Skiles, J. W. Miao, C.; Sorcek, R. *J. Med. Chem.* **1992**, *35*, 4795.

(13) Schmittel first reported oxidative alkoxylation of phenylacetone and its enolsilyl ethers: (a) Schmittel, M.; Levis, M. *Chem. Lett.* **1994**, 1935. (b) Schmittel, M.; Levis, M. *Chem. Lett.* **1994**, 1939.

(14) Oxidative homocoupling of nonfluorinated enolsilyl ethers is well-known. (a) Ito, Y.; Konoike, T.; Saegusa, T. *J. Am. Chem. Soc.* **1975**, *97*, 649. (b) Kobayashi, Y.; Taguchi, T.; Tokuno, E. *Tetrahedron Lett.* **1977**, *18*, 3741. (c) Moriarty, R. M.; Penmasta, R.; Prakash, I. *Tetrahedron Lett.* **1987**, *28*, 873. (d) Moriarty, R. M.; Prakash, O.; Duncan, M. P. *J. Chem. Soc., Chem. Commun.* **1985**, 420. (e) Inaba, S.; Ojima, I. *Tetrahedron Lett.* **1977**, *18*, 2009. (f) Baciocchi, E.; Casu, A.; Ruzziconi, R. *Tetrahedron Lett.* **1989**, *30*, 3707. (h) Schmittel, M.; Burghart, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2550 and references therein. (i) Ryter, K.; Livinghouse, T. *J. Am. Chem. Soc.* **1998**, *120*, 2658.

(15) Baeyer−Villiger oxidation of **13d**, **14**, and **15** with *m*-CPBA in dichloromethane−HFIP (1:1 v/v) at rt for 10 min provided the corresponding *p*-methoxyphenyl esters in 90%, 80%, and 87% yields, respectively. See the following reference for the detailed Baeyer−Villiger oxidation conditions: Kobayashi, S.; Tanaka, H.; Amii, H.; Uneyama, K. *Tetrahedron* **2003**, *59*, 1574.

(16) There have been no report on the syntheses of difluoro(heteroaryl)-methyl aryl ketones **13** and **14**. Difluoro(2-thienyl)methyl aryl ketone **15** (Ar = 4-F-C_6H_4) was prepared in an overall yield of 52% in two steps. For the arylation of ethyl difluoro(2-thienyl) acetate with 4-fluorophenyllithium, which was derived from the Cu-catalyzed cross-coupling of 2-bromothiophene with ethyl 2-bromo-2,2-difluoroacetate in DMSO, see: Eto, H.; Kaneko, Y.; Sakamoto, T. *Chem. Pharm. Bull.* **2000**, *48*, 982.

(17) HOMO levels of **10**, furan, *N*-tosylpyrrole, thiophene, 2-methoxyfuran, and pyrrole estimated by MacSpartan Pro package program with PM3 level geometry optimization are −9.0, −9.4, −9.1, −9.5, −8.8, −8.9 eV, respectively.

(Nu of **8** in Scheme 3) would be further oxidized with Cu-oxidant followed by deprotonation leading to the formation of **13**−**15** as final products.

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Supporting Information Available: Experimental procedures and details of compound characterization for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) The ethers **17** would be formed by the cross-coupling of radical cation **7** with alcohols. Therefore, the fact that three products **11**, **13**, and **17c** were produced at the same time under the reaction conditions in MeCN−H_2O−Cu(OTf)$_2$ system suggests the reactive intermediate would be the radical cation **7** rather than difluoro(benzoyl)methyl radical.