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

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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 ethers³ (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-

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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).



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

⁽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.

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 compounds⁹ and reactions with various electrophiles¹⁰ have been well demonstrated and frequently employed as reliable methods for introducing difluoroacyl moiety into organic molecules.

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

(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.

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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).

The current demand in medicinal science for a variety of difluoromethylene compounds,¹² which have been less explored as compared with trifluoromethylated and mono-fluorinated 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, CuCl₂, Ag₂O, CAN (cerium ammonium nitrate)], solvents [THF, DMF, CH₂Cl₂, 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; C₆H₅ (71%), 4-ClC₆H₄ (72%), 4-MeC₆H₄ (70%), 4-MeOC₆H₄ (86%), 2-furyl (58%)] as shown in Scheme 4.



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

^{(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.



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

Table 1 12 ^a	. Oxidati	Oxidative Cross-coupling of 10 with Heteroaromatics				
	12		10			
entry	R	X	Ar	product	yield, ^b %	
1	Н	0	C ₆ H ₅	13a	88	
2	Н	0	4-Cl-C ₆ H ₄	13b	72	
3	Н	0	4-Me-C ₆ H ₄	13c	75	
4	Н	0	4-MeO-C ₆ H ₄	13d	82	
5	Н	0	2-furyl	13e	63	
6	CO ₂ Me	0	4-MeO-C ₆ H ₄	13f	61	
7	Н	N-Ts	4-MeO-C ₆ H ₄	14	67	
8	Н	S	4-MeO-C ₆ H ₄	15	84	

 a Each reaction was carried out in MeCN–H₂O (50:1 v/v) at 0 °C for 3 h. b Isolated yield.

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.

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 crosscoupled 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 promising extension of the present reaction.

As for the mechanism for the present oxidative crosscoupling, 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-

⁽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-C₆H₄) 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 Cuoxidant 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-H₂O-Cu(OTf)₂ system suggests the reactive intermediate would be the radical cation **7** rather than difluoro(benzoyl)methyl radical.