ORGANIC LETTERS

2000
Vol. 2, No. 4
563−564

A Novel and Highly Efficient Synthesis of *gem*-Difluorocyclopropanes

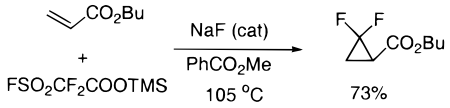
Feng Tian,[†] Virginie Kruger,[†] Olivia Bautista,[†] Jian-Xin Duan,[†] An-Rong Li,[†] William R. Dolbier, Jr.,*[,†] and Qing-Yun Chen[‡]

Department of Chemistry, University of Florida, Gainesville, Florida 32611-7200, and Shanghai Institute of Organic Chemistry, 354 Fenglin Lu, Shanghai, 200032, China

wrd@chem.ufl.edu

Received January 18, 2000

ABSTRACT

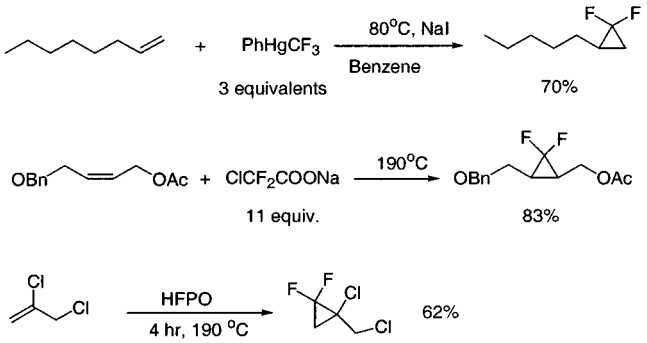


A new and highly versatile source of difluorocarbene is reported. Trimethylsilyl fluorosulfonyldifluoroacetate (TFDA) undergoes decomposition in the presence of catalytic fluoride to form difluorocarbene under conditions that allow its addition to relatively electron deficient alkenes in high yield. For example, unprecedented CF_2: addition to *n*-butyl acrylate proceeded in 73% yield.

Because of their interesting thermochemical and dynamic properties, as well as their potential commercial importance, there has been a continuing effort among organic chemists for nearly four decades to find new and more practical methods of synthesizing *gem*-difluorocyclopropanes.[1−4] Every important method for synthesis of *gem*-difluorocyclopropanes involves the addition of difluorocarbene or carbenoid reagents to alkenes. However, difluorocarbene, because of the interaction of the long pairs of its two fluorine substituents with the carbene center, is a relatively stabilized carbene, and it is therefore less reactive than other dihalocarbenes. Thus, although electron rich alkenes react readily with difluorocarbene under mild conditions, this is not the case for less nucleophilic alkenes. In practice, there are only few difluorocarbene reagents that have been found to react with even modestly electron deficient alkenes to give reasonable yields of difluorocyclopropanes, and these reagents all suffer from various limitations as far as their general synthetic applications are concerned.

The three most effective, currently available difluorocarbene reagents for additions to less reactive alkene substrates are probably Seyferth's phenyl(trifluoromethyl)mercury,[5] sodium chlorodifluoroacetate,[6,7] and hexafluoropropylene oxide (HFPO) (Scheme 1).[8,9] However, each of these procedures has serious drawbacks that diminish its practical synthetic potential. The main drawback of Seyferth's reagent is the fact that it contains mercury. Thus, it is no longer commercially available and is somewhat tedious (and

Scheme 1



[†] University of Florida.
[‡] Shanghai Institute of Organic Chemistry.

(1) Brahms, D. L. S.; Dailey, W. P. *Chem. Rev.* **1996**, *96*, 1585−1632.
(2) Smart, B. E. In *Chemistry of Organic Fluorine Compounds II*; Hudlicky, M., Pavlath, A. E., Eds.; American Chemical Society: Washington, DC, 1995.
(3) Burton, D. J.; Hahnfeld, J. L. *Fluorine Chem. Rev.* **1977**, *8*, 119.
(4) Seyferth, D. In *Carbenes*; Moss, R. A., Jones, M., Jr., Eds.; Wiley: New York, 1975; Vol. II.
(5) Seyferth, D.; Hopper, S. P. *J. Org. Chem.* **1972**, *37*, 4070−4075.
(6) Birchall, J. M.; Cross, G. E.; Haszeldine, R. N. *Proc. Chem. Soc.* **1960**, 81.
(7) Csuk, R.; Eversmann, L. *Tetrahedron* **1998**, *54*, 6445.
(8) Sargeant, P. B. *J. Org. Chem.* **1970**, *35*, 678.
(9) Dolbier, W. R., Jr.; Sellers, S. F.; Al-Sader, B. H.; Fielder, T. H., Jr.; Elsheimer, S.; Smart, B. E. *Isr. J. Chem.* **1981**, *21*, 176.

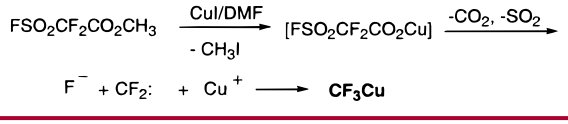
10.1021/ol0055622 CCC: $19.00
Published on Web 02/01/2000

hazardous) to synthesize. The problem with the use of sodium chlorodifluoroacetate derives from the high temperature of its use and because it must be used in large excess (11 equiv in the case given) to obtain decent conversion of most alkene substrates. The use of HFPO (a gas) requires both high temperatures and an autoclave (or sealed tube) environment.

Thus, in evaluating all difluorocarbene reagents currently available, there obviously remains a need for one that can add in decent yields to modestly electron deficient alkenes, such as allylic ethers or terminal alkenes. Addition of difluorocarbene to *highly* electron deficient alkenes, such as acrylic esters, is unprecedented.

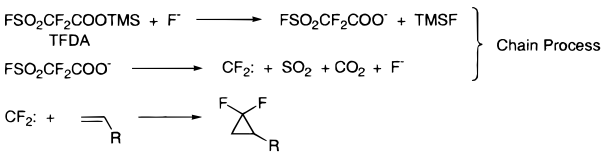
Because of our long standing interest in the reactivity of difluorocyclopropanes, we have always been alert regarding possible new methods for adding difluorocarbene to alkenes, and in the course of the development of $FSO_2CF_2COOCH_3$ as a source of trifluoromethyl copper (Scheme 2), we became

Scheme 2. Trifluoromethyl Copper Reagent



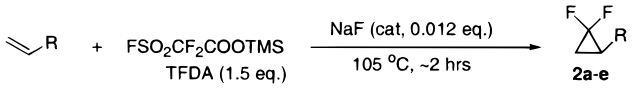
aware of the potential to modify this reaction in order to create a new difluorocarbene reagent.[10,11] The idea was to delete the copper and minimize the fluoride ion concentration by making the reaction a chain reaction, catalytic in fluoride. The ultimately designed difluorocarbene precursor was trimethylsilyl fluorosulfonyldifluoroacetate (TFDA),[12] which at moderate temperature, under N_2, was added slowly to the mixture of initiator, olefin, and solvent as shown in Schemes 3 and 4 below.[13]

Scheme 3. Difluorocarbene Formation/Reaction Process



In this preliminary study, a total of five representative olefins, known to be reluctant substrates with difluorocarbene, were examined. The reactions proceeded cleanly and

Scheme 4. Synthesis of Difluorocyclopropanes



1a, R = *n*-C_6H_{13} (74%); **b**, R = CH_2O_2CPh (78%)
c, R = $CH_2CH_2O_2CPh$ (89%); **d**. R = $(CH_2)_3O_2CPh$ (97%)
e, R = $CO_2C_4H_9$ (73%)

(Reactions of **1a** and **1e** were carried out in the presence of 0.5 and 2.0 eq. of methyl benzoate, respectively; all other reactions were carried out neat.)

with unprecedented efficiency, as shown in Scheme 4. These yields have not been optimized. For example, use of *2* equiv of TFDA led to an increase in yield to 89% for allyl benzoate **1b**.

Although at this point no single "recipe" has been found that is optimal for all potential alkene substrates, nevertheless, with a minimum of effort at optimization, we were able to find satisfactory conditions to difluorocyclopropanate in good to excellent yield virtually every alkene substrate that we examined. Although, in this preliminary study, most reactions were run on a very small (1.6 mmol) scale, the reaction with *n*-butyl acrylate **1e**, the least reactive of substrates tested, was also carried out on a 5 g (3.9 mmol) scale at 130 °C, using 25 mg of NaF as initiator, 16 g (1.6 equiv) of TFDA, and 3.6 g (1 equiv) of toluene as solvent, to obtain, after distillation, 6.1 g (89%) of *n*-butyl 2,2-difluorocyclopropanecarboxylate.

Experiments directed at optimization indicated that the choice of (a) fluoride source, (b) temperature, (c) solvent, and (d) rate of addition of the TFDA can strongly affect the yields of reactions with individual substrates. In general, NaF appears to be the best source of fluoride ion (perhaps because of its relative insolubility); a temperature of at least 90 °C is required for efficient reaction with the alkenes studied (perhaps because of the relatively high activation barrier for CF_2: addition); little or no solvent should be used (neat reactions are favored for benzoate esters of alkenols, with 1 equiv of methyl benzoate or toluene being very beneficial for other substrates);[14] the optimal addition rate appears to be ~0.8 equiv of TFDA per hour.

We have reported in this Letter a novel, highly reactive difluorocarbene reagent, which has been demonstrated to be effective in difluorocyclopropanating even the most highly electrophilic alkenes, such as acrylic esters, in excellent yields. This new methodology should open the door to the simple synthesis of a wide range of new geminal difluorocyclopropane derivatives that previously were not readily accessible.

Acknowledgment. Support of this research in part by the National Science Foundation is gratefully acknowledged.

OL0055622

(10) Chen, Q. Y.; Wu, S. W. *J. Org. Chem.* **1989**, *54*, 3023−3027.
(11) Duan, J.; Dolbier, W. R., Jr.; Chen, Q.-Y. *J. Org. Chem.* **1998**, *63*, 9486.
(12) TFDA can be readily synthesized in a yield of 78% by simply adding 3.6 equiv of trimethylsilyl chloride to fluorosulfonyldifluoroacetic acid at 0 °C, stirring overnight, and distilling the product: bp 62−63 °C at 27 mm; ^{1}H NMR, δ 0.40 ppm (s); ^{13}C NMR, δ 155.13 (t, J = 27.0 Hz), 112.22 (dt, J = 31.5, 299.0 Hz), −1.05 ppm (s); ^{19}F NMR, δ 40.58 (1F, s), −103.74 ppm (2F, s); HRMS (CI), $C_5H_{10}O_4SSiF_3$, calcd 251.0012, found 251.0015. Although neither TFDA nor fluorosulfonyldifluoroacetic acid is commonly available commercially at this time, they are in principle inexpensive, and both will certainly become available when the demand for them becomes obvious. Contact the authors regarding current sources.
(13) A critical aspect of the reaction is that the addition of TFDA be very slow, first to minimize the concentration of CF_2:, but also to control the inevitable foaming which results from evolution of CO_2 and SO_2 in the reaction. Use of a syringe pump (with a Teflon needle) for the small-scale reactions reported in this Letter proved absolutely necessary.
(14) For some reason, the presence of an aromatic ring, either in the substrate (as in benzoate esters) or in the small amount of added solvent, enhances the efficiency of CF_2: addition tremendously.