

# SYNLETT Spotlight 205

## A Fluorinating Hypervalent Iodine(III) Reagent: 4-Iodotoluene Difluoride

Compiled by Samir Augusto Pino Quintiliano



This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Samir Augusto Pino Quintiliano was born in 1982 in São Caetano do Sul, Brazil. He received his BSc in chemistry in 2004 from the University of São Paulo, and started his PhD studies under the supervision of Prof. Luiz F. Silva, Jr. with a FAPESP scholarship in March 2005. His thesis is mainly focused on a comparative study of the reactivity of thallium(III) and iodine(III).

Instituto de Química, Universidade de São Paulo, CP 26077, CEP 05513-970, São Paulo SP, Brazil  
E-mail: samirpq@gmail.com

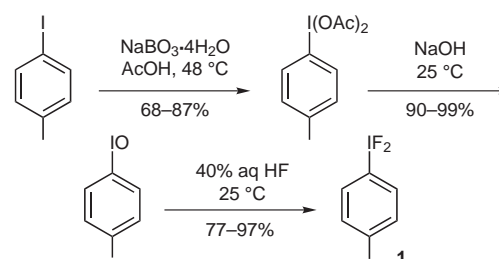
### Introduction

There is a great interest of organic chemists in hypervalent iodine reagents because a wide range of reactions can be performed selectively under mild conditions and, in some cases, catalytically.<sup>1</sup> Fluorinated molecules are highly valuable due to the unique characteristics displayed by the fluorine atom.<sup>2</sup>

4-Iodotoluene difluoride (*p*-TolIF<sub>2</sub>, **1**) is a hypervalent iodine reagent that promotes chemoselective fluorinations avoiding the use of fluorine gas, as well as the expensive xenon difluoride. Several N-fluoro compounds have been developed as stable and effective fluorinating reagents; their preparation, however, generally demands the use of fluorine gas. Compound **1** is usually preferred over its iodobenzene difluoride analogue because of easier preparation, purification, and handling.

### Preparation

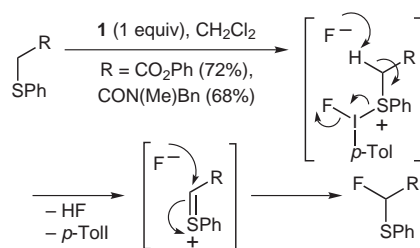
Compound **1** is commercially available. However, it can be prepared in different ways from 4-iodotoluene.<sup>3</sup> In one of them, the use of harmful gases or mercury salts is avoided (Scheme 1).<sup>4</sup>



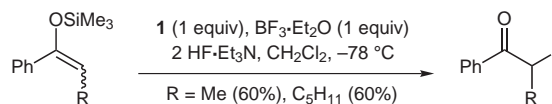
Scheme 1

### Abstracts

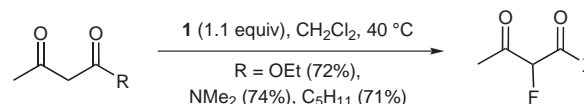
(A) Reacting  $\alpha$ -phenylsulfanylated esters<sup>5</sup> and amides<sup>6</sup> with 1 equiv of **1** led to  $\alpha$ -monofluoro sulfides via a fluoro-Pummerer reaction.  $\alpha$ -Selenocarboxylic acid derivatives could be easily  $\alpha$ -monofluorinated via a similar Pummerer reaction.<sup>4</sup>



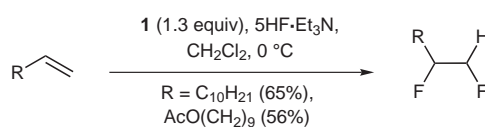
(B) Hara and co-workers achieved  $\alpha$ -fluorinated monoketones using the corresponding silyl enol ethers as substrates.<sup>7</sup>



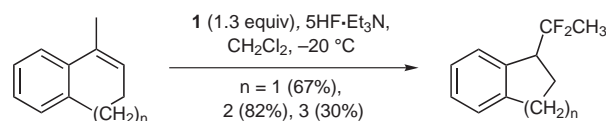
(C) The  $\alpha$ -monofluorination of  $\beta$ -keto esters, amides, and ketones was easily accomplished using **1**, overcoming the problematic use of amine-HF complexes.<sup>8</sup> However, the fluorination under these conditions is slower than that using an acid medium.<sup>9</sup>



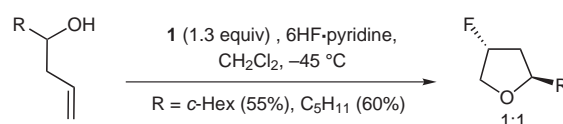
(D) The preparation of vicinal difluoroalkanes was achieved reacting aliphatic alkenes with **1**.



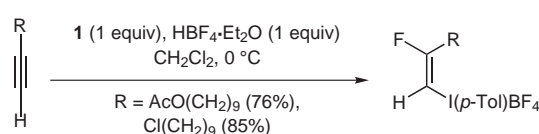
(E) The behavior of cyclic alkenes towards **1** can be different from the acyclic variant because a fluorinative and diastereoselective ring-contraction reaction may take place.<sup>10</sup>



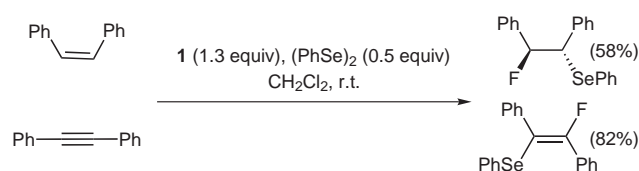
(F) Unsaturated alcohols and acids are fluorocyclized when treated with **1** in the presence of amine-HF complexes and afford cyclic ethers and lactones with poor or no stereoselectivity, respectively.<sup>11</sup>



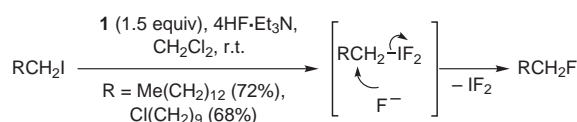
(G) (*E*)-β-Fluoroalkenyliodonium salts were prepared regio- and stereoselectively by Hara and co-workers from the corresponding terminal alkynes and **1** without using 5HF·Et<sub>3</sub>N.<sup>12</sup> These compounds could be subsequently used in Pd-catalyzed cross-coupling reactions<sup>12,13</sup> or Pd-catalyzed carbomethoxylation.<sup>14</sup>



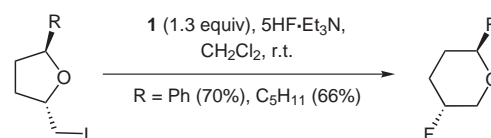
(H) Alkynes and alkenes undergo phenylselenofluorination in the presence of **1** and PhSeSePh in high stereo- and regioselectivity.<sup>15</sup> Analogously, when iodine instead of PhSeSePh is employed, iodo-fluorination of alkenes and alkynes affords fluoroiodoalkanes and fluoroiodoalkenes.<sup>16</sup>



(I) Iodoalkanes give the corresponding alkyl fluoride when treated with **1** in the presence of amine-HF complexes, via an iodonium intermediate.<sup>17</sup>



(J) Stereoselective ring expansion of iodine-containing 4-, 5-, and 6-membered cyclic ethers took place using **1**, affording 5-, 6-, and 7-membered cyclic fluoro ethers.<sup>18</sup>



## References

- (a) Stang, P. J. *J. Org. Chem.* **2003**, *68*, 2997. (b) Wirth, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 3656. (c) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893. (d) Silva, L. F. Jr. *Molecules* **2006**, *11*, 421. (e) Richardson, R. D.; Wirth, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 4402.
- Dolbier, W. R. Jr. *J. Fluorine Chem.* **2005**, *126*, 157.
- (a) Carpenter, W. J. *J. Org. Chem.* **1966**, *31*, 2688. (b) Fuchigami, T.; Fujita, T. *J. Org. Chem.* **1994**, *59*, 7190. (c) Sawaguchi, M.; Ayuba, S.; Hara, S. *Synthesis* **2002**, 1802. (d) Ye, C.; Twamley, B.; Shreeve, J. M. *Org. Lett.* **2005**, *7*, 3961.
- Arrica, M. A.; Wirth, T. *Eur. J. Org. Chem.* **2005**, 395.
- Greaney, M. F.; Motherwell, W. B. *Tetrahedron Lett.* **2000**, *41*, 4463.
- Greaney, M. F.; Motherwell, W. B. *Tetrahedron Lett.* **2000**, *41*, 4467.
- Sato, S.; Yoshida, M.; Hara, S. *Synthesis* **2005**, 2602.
- Yoshida, M.; Fujikawa, K.; Sato, S.; Hara, S. *ARKIVOC* **2003**, (vi), 36.
- Hara, S.; Sekiguchi, M.; Ohmori, A.; Fukuhara, T.; Yoneda, N. *Chem. Commun.* **1996**, 1899.
- Hara, S.; Nakahigashi, J.; Ishi-i, K.; Fukuhara, T.; Yoneda, N. *Tetrahedron Lett.* **1998**, *39*, 2589.
- Sawaguchi, M.; Hara, S.; Fukuhara, T.; Yoneda, N. *J. Fluorine Chem.* **2000**, *104*, 277.
- Yoshida, M.; Kawakami, K.; Hara, S. *Synthesis* **2004**, 2821.
- (a) Yoshida, M.; Nagahara, D.; Fukuhara, T.; Yoneda, N.; Hara, S. *J. Chem. Soc., Perkin Trans. 1* **2001**, *1*, 2283. (b) Yoshida, M.; Yoshikawa, S.; Fukuhara, T.; Yoneda, N.; Hara, S. *Tetrahedron* **2001**, *57*, 7143.
- Yoshida, M.; Komata, A.; Hara, S. *J. Fluorine Chem.* **2004**, *125*, 527.
- Panunzi, B.; Picardi, A.; Tingoli, M. *Synlett* **2004**, 2339.
- (a) Conte, P.; Panunzi, B.; Tingoli, M. *Tetrahedron Lett.* **2006**, *47*, 273. (b) Conte, P.; Panunzi, B.; Tingoli, M. *Tetrahedron Lett.* **2006**, *47*, 3325.
- Sawaguchi, M.; Hara, S.; Nakamura, Y.; Ayuba, S.; Fukuhara, T.; Yoneda, N. *Tetrahedron* **2001**, *57*, 3315.
- Inagaki, T.; Nakamura, Y.; Sawaguchi, M.; Yoneda, N.; Ayuba, S.; Hara, S. *Tetrahedron Lett.* **2003**, *44*, 4117.