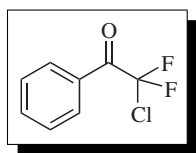


## 2-Chloro-2,2-difluoroacetophenone



[384-67-8]  $C_8H_5ClF_2O$  (MW 190.56)

InChI = 1/C8H5ClF2O/c9-8(10,11)7(12)6-4-2-1-3-5-6/h1-5H

InChIKey = MNOONJNILVDSW-UHFFFAOYAN

(precursor for the preparation of 2,2-difluoro enol silyl ethers or 2,2-difluoro enol silyl phosphates;<sup>9–12</sup> difluorocarbene precursor;<sup>6</sup> precursor for the synthesis of *gem*-difluoromethene-containing compounds<sup>13–22</sup>)

**Physical Data:** colorless liquid; bp 84–85 °C/25 mmHg.<sup>1</sup>

**Solubility:** sol alcohols, ethers,  $CH_2Cl_2$ ,  $CHCl_3$ , benzene, toluene, acetonitrile, DMF, and DMSO.

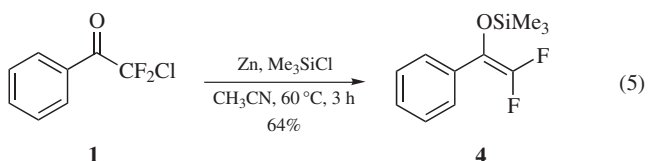
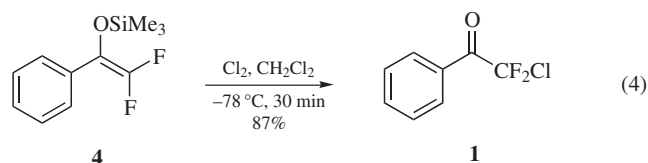
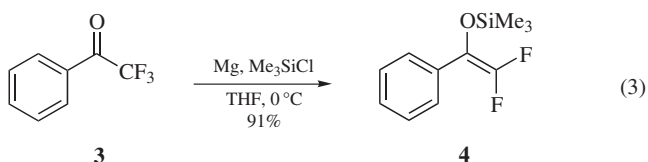
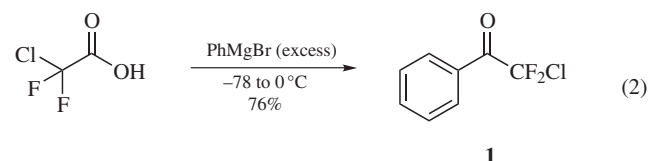
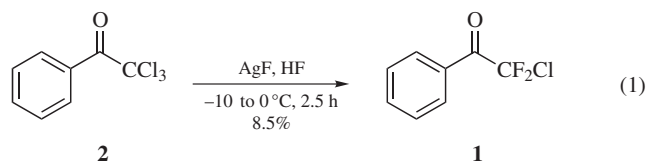
**Form Supplied in:** colorless liquid; often prepared by the reaction between chlorodifluoroacetic acid and  $PhMgBr$ ,<sup>2–5</sup> or prepared by chlorination of [2,2-difluoro-1-[(trimethylsilyl)oxy]ethenyl] benzene.<sup>6</sup>

**Handling, Storage, and Precautions:** 2-chloro-2,2-difluoroacetophenone ( $PhCOCF_2Cl$ ) has high reactivity with bases, nucleophiles, reducing agents, and single-electron transferring agent; store under anhydrous, neutral conditions; use in a fume hood.

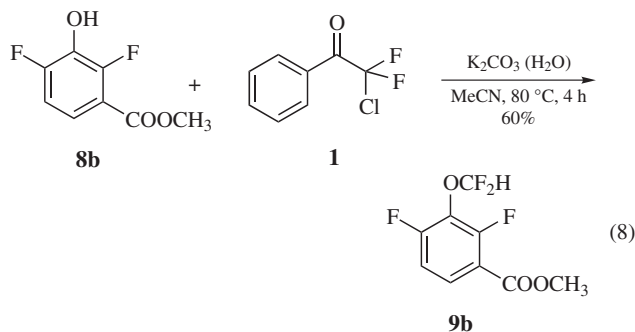
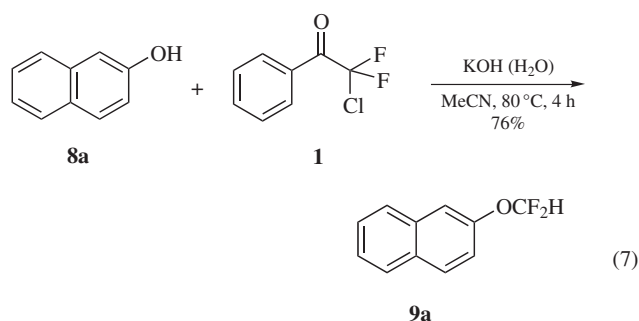
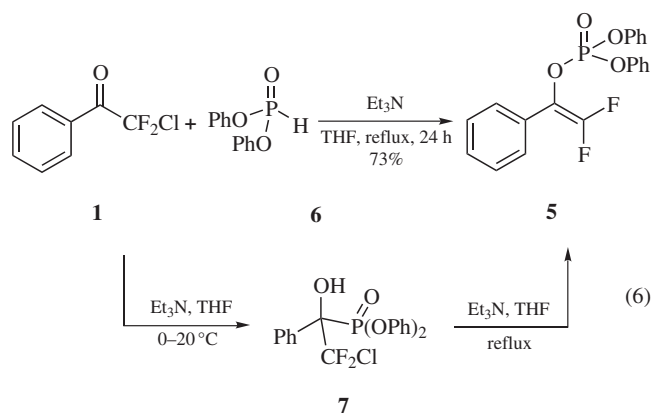
**Preparation of 2-Chloro-2,2-Difluoroacetophenone (1).** 2-Chloro-2,2-difluoroacetophenone (**1**) was initially prepared by the halogen-exchange reaction (Swarts reaction) of 2,2,2-trichloroacetophenone (**2**) in only 8.5% yield (eq 1), using silver fluoride and anhydrous hydrogen fluoride as the fluorinating agent.<sup>7</sup> Compound **1** is more commonly prepared from the reaction of chlorodifluoroacetic acid with the Grignard reagent  $PhMgBr$ .<sup>2–5</sup> By use of an excess amount of  $PhMgBr$  ( $ClCF_2COOH:PhMgBr = 1:2.5–3.5$ ) and careful control of the reaction temperature ( $< 5\text{ }^\circ\text{C}$ ), 2-chloro-2,2-difluoroacetophenone (**1**) can be obtained in good yield (eq 2).<sup>2–5</sup> Moreover, a novel and non-ODS-based (ODS = ozone-depleting substance) preparation of compound **1** was also achieved in high yield by using 2,2,2-trifluoroacetophenone (**3**) as the starting material.<sup>6</sup> Magnesium metal-mediated reductive defluorination of **3** gives 2,2-difluoro enol silyl ether (**4**) (eq 3),<sup>8</sup> which can be readily chlorinated by  $Cl_2$  to afford compound **1** in 87% yield (eq 4).<sup>6</sup>

**Conversion to 2,2-Difluoro Enol Silyl Ether (4) and 2,2-Difluoro Enol Silyl Phosphates (5).** 2-Chloro-2,2-difluoroacetophenone (**1**) can be converted to 2,2-difluoro enol silyl ether (**4**) in 64% yield by treatment of Zn dust and  $Me_3SiCl$  in dry  $CH_3CN$  at 60 °C (eq 5).<sup>9,10</sup> Like normal enol silyl ethers, compound **4** is a highly useful compound in the synthesis of various difluoromethylene-containing compounds. 2-Chloro-2,2-difluoroacetophenone (**1**) can also react readily with dialkyl or diaryl phosphite (**6**) in the presence of triethylamine at the reflux temperature of tetrahydrofuran to give the corresponding dialkyl or diaryl 1-substituted-2,2-difluoroethenyl phosphate **5** in good yields, whereas the similar reaction conducted at lower temper-

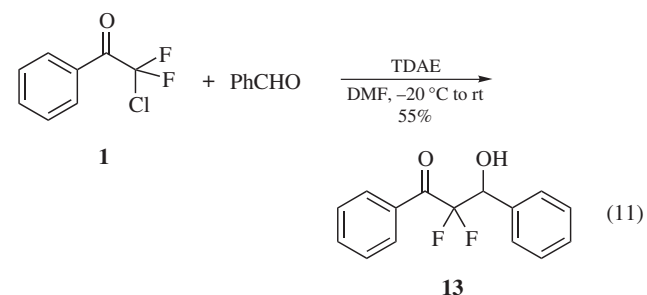
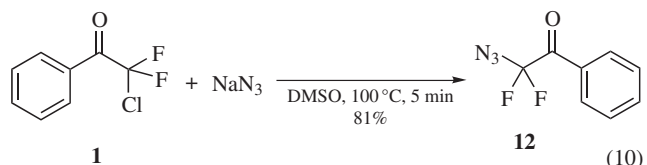
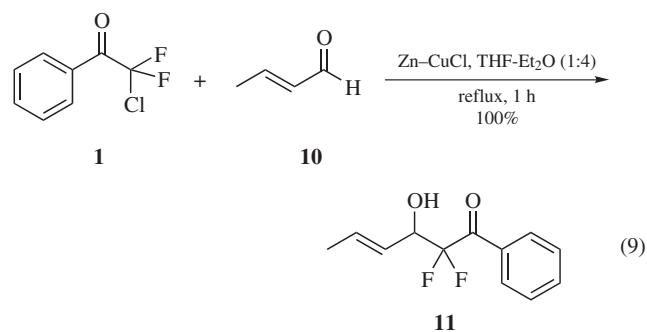
ature (0–20 °C) affords 1-(chlorodifluoromethyl)-1-hydroxyalkanephosphonate (**7**) almost exclusively. The latter compound can be converted to the former enol phosphate **5** by treatment with triethylamine or sodium methoxide in refluxing tetrahydrofuran (eq 6).<sup>11,12</sup> Compound **5** can react with  $Bu_2CuLi$  and successively with allyl halides to give allylated *gem*-difluoro olefins in 30–90% yield.<sup>11</sup>



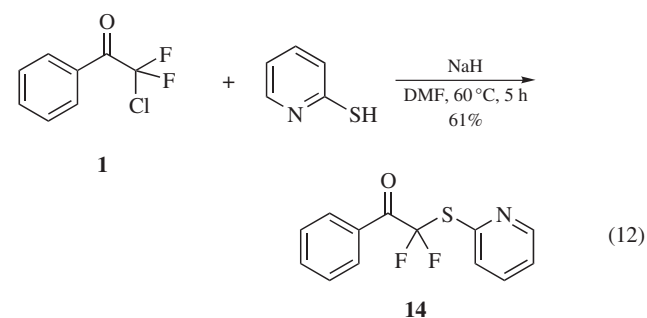
**Use as a Difluorocarbene Reagent.** 2-Chloro-2,2-difluoroacetophenone (**1**) can act as a good difluorocarbene reagent, which readily reacts with a variety of structurally diverse phenol derivatives **8** in the presence of potassium hydroxide or potassium carbonate to produce aryl difluoromethyl ethers (**9**) in good yields (eqs 7 and 8).<sup>6</sup> This easy-to-handle synthetic methodology offers an environmental-friendly alternative to other Freon- or Halon-based difluoromethylating approaches.

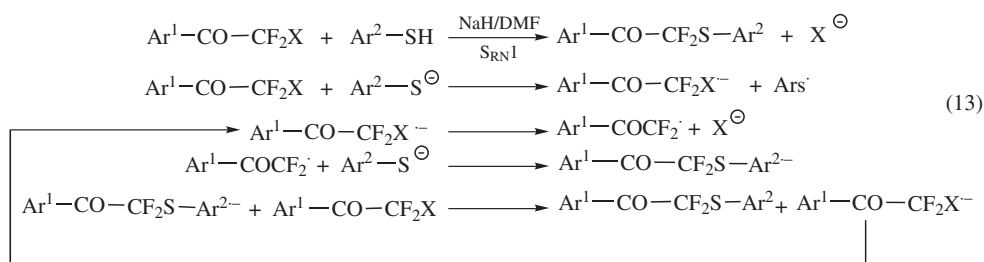


**Use in the Reformatsky-type Reactions.** 2-Chloro-2,2-difluoroacetophenone (**1**) can undergo Reformatsky-type aldol reactions with a wide variety of aldehydes and ketones in the presence of zinc, a catalytic amount of CuCl or AgOAc, and molecular sieves to give the corresponding  $\alpha,\alpha$ -difluoro- $\beta$ -hydroxy ketones in good to excellent yields.<sup>13</sup> Specific activation of zinc metal with the metal salt is essential to achieve high efficiency of the reaction, depending upon the structures of the carbonyl compounds employed (eq 9). In situ formed intermediates in these reactions were successfully detected by <sup>19</sup>F NMR spectroscopy, which suggests that their structure is not an  $\alpha$ -metallo ketone but an oxygen-metallated species possessing zinc(II) as the counterion.<sup>14</sup> Similar reaction can also be accomplished with zinc dust in DMF for 20 h at 70 °C.<sup>15</sup>



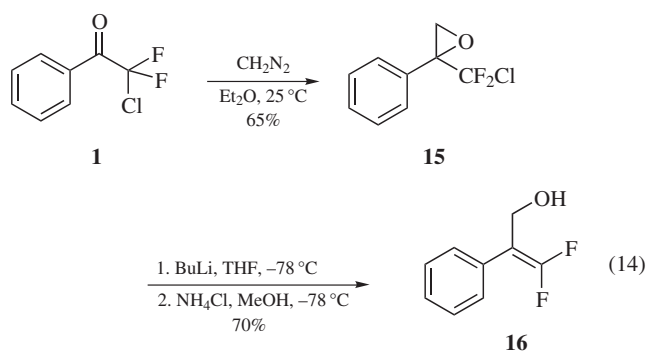
**Use in the Preparation of *gem*-Difluoromethylene-containing Compounds Via C–Cl Bond Cleavage.** The chlorine atom in 2-chloro-2,2-difluoroacetophenone (**1**) can be replaced by other nucleophiles. For example, the reaction of compound **1** with NaN<sub>3</sub> in DMSO at 100 °C for 5 min gives 2-azido-2,2-difluoroacetophenone (**12**) in 81% yield (eq 10).<sup>16</sup> Tetrakis(dimethylamino) ethylene (TDAE) was found to be an effective reductant of 2-chloro-2,2-difluoroacetophenone (**1**), and the generated  $\alpha,\alpha$ -difluoroacetyl anion can be trapped with a variety of aldehydes under mild reaction conditions to give the corresponding 2,2-difluoro-3-hydroxy ketone **13** in moderate yield (eq 11).<sup>17,18</sup> Compound **1** can also be used in the synthesis of  $\alpha$ -(heteroarylthio)- $\alpha,\alpha$ -difluoroacetophenone derivatives **14** (eq 12), which are good candidates for further chemical elaboration.<sup>19,20</sup> The reaction mechanism is believed to be an S<sub>RN</sub>1 process (eq 13).<sup>19</sup> By the use of a single



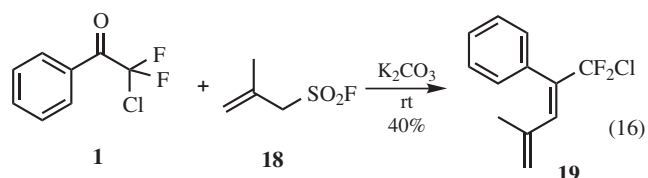
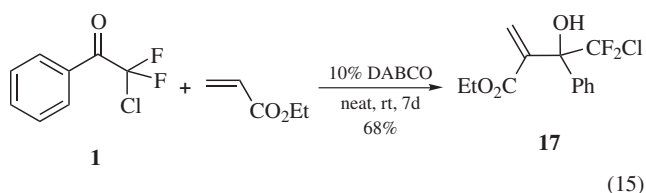


electron transfer (SET) approach with organic reductants such as sodium hydroxymethanesulfinate, sodium dithionite, and TDAE, 2-chloro-2,2-difluoroacetophenone (**1**) can be reductively dehalogenated to give the corresponding difluoromethylated (CF<sub>2</sub>H-containing) derivatives.<sup>21</sup> Furthermore, compound **1** was also used in the TDAE-mediated difluoromethylation reactions of ethyl pyruvate, which is a mild approach to the synthesis of 3,3-difluoro-2-hydroxy-2-methyl-4-oxo-butyric ethyl ester derivatives.<sup>22</sup>

Compound **1** can react with diazomethane to afford epoxide **15** in 65% yield. Upon treatment with butyllithium, the epoxide undergoes efficient ring opening to give the 3,3-difluoro-2-phenyl-alken-1-ol **16** (eq 14).<sup>23</sup> Compound **16** is a suitable substance for sigmatropic rearrangement leading to compounds containing a CF<sub>2</sub> group in mid-chain.



**Other Miscellaneous Reactions.** 2-Chloro-2,2-difluoroacetophenone (**1**) can be applied in the Baylis–Hillman reaction, and the corresponding chlorodifluoromethyl-containing BH product **17** can be obtained in 68% yield (eq 15).<sup>24</sup> Furthermore, treatment of **1** with 2-methylprop-2-ene-1-sulfonyl fluoride (**18**), in the presence of potassium carbonate, gives exclusively the corresponding trisubstituted (*Z*)-alkene **19** in 40% yield (eq 16).<sup>25</sup>



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