

Synthetic Methods

Oxidation

Vol. 5 No. 1

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Other Reagents for Oxidation

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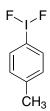
## Introduction

Sigma-Aldrich is proud to offer a new series of *ChemFiles*—called Synthetic Methods—to our Organic Chemistry and Drug Discovery customers. Each piece will highlight a specific motif or selected organic transformation, and the range of products Sigma-Aldrich offers in this area. Our first installment focuses on oxidation chemistry. In the future, we will highlight other synthetic methods such as asymmetric synthesis and reduction. We trust you will find these pieces useful, and we welcome your comments for future installments. If you cannot find a product for your specific research in organic synthesis or drug discovery, we encourage your input to help us increase our product range. "Please bother us" at **mredlich@sial.com** with your suggestions.

Oxidation is one of the most common transformations in all of organic chemistry. As a result, the number of oxidizing agents and reactions at the research chemist's disposal number in the hundreds; however, few provide extended utility across a broad range of substrates while remaining able to selectively oxidize one group over another. Fewer yet remain effective under mild conditions. At Sigma-Aldrich, we are committed to being your preferred supplier for reagents used in oxidation—and we'd like to highlight some new, popular, and versatile oxidation reagents in this *ChemFile*.

Listed on the following pages is a selection of oxidation reagents available from Sigma-Aldrich. For a complete listing of oxidation reagents, please visit **sigma-aldrich.com/oxidation**. For a regular update on the latest products from Sigma-Aldrich, please visit **sigma-aldrich.com/newprod**.

# NEW lodotoluene difluoride



The importance of selectively fluorinating compounds in medicinal chemistry, biology, and organic synthesis is well appreciated and provides a major impetus to the discovery of new fluorinating agents that can operate according to an efficient, safe, and mild criteria. Elemental fluorine, and many electrophilic fluorinating agents have been used in synthesis; however, most of these fluorinating

agents are highly aggressive, unstable, and require special equipment and care for safe handling. By contrast, iodotoluene difluoride (tol- $IF_2$ ) is easy to handle, and is less toxic than many fluorinating agents. Sigma-Aldrich is pleased to introduce this new reagent for oxidation and fluorination.

A new methodology for the synthesis of fluorinated cyclic ethers was recently reported, which utilized tol-IF $_2$  to achieve a fluorinative ring-expansion of four-, five-, and six-membered rings, an example of which is illustrated in **Scheme 1**. $^1$ 

Selective monofluorination of  $\beta$ -ketoesters,  $\beta$ -ketoamides, and diketones takes place without requirement of HF-amine complexes under mild conditions (**Scheme 2**). The formation of difluoro products were not detected in these reactions.<sup>2</sup>

When one equivalent of tol-IF<sub>2</sub> is reacted with phenylsulfanylated esters, the  $\alpha$ -fluoro sulfide results through a Fluoro-Pummerer reaction. In contrast to diethylaminosulfur trifluoride, two equivalents produces the  $\alpha$ , $\alpha$ -difluoro sulfide, and three equivalents of tol-IF<sub>2</sub> produces the  $\alpha$ , $\alpha$ -difluoro sulfoxide. This behavior was exploited in the one pot synthesis of a 3-fluoro-2(5*H*)-furanone (**Scheme 3**).<sup>3</sup>

Treatment of phenylsulfanylated lactams with one equivalent of tol-IF<sub>2</sub> results in the unsaturated heterocycle in moderate to good yields. When two equivalents of the reagent were used, the lactams were fluorinated in the  $\alpha$  - and  $\beta$ -positions resulting in the diastereomeric difluoride (**Scheme 4**).<sup>4</sup>

4-lodotoluene difluoride	
65,111-7	1 g 5 g

$$C_5H_{11} \underbrace{\hspace{1cm} 0}_{\text{I}} \underbrace{\hspace{1cm} \frac{\text{tol-IF}_2}{\text{Et}_3\text{N-5HF, CH}_2\text{Cl}_2}} \underbrace{\hspace{1cm} C_5H_{11}}_{\text{C}_5H_{11}} \underbrace{\hspace{1cm} 0}_{\text{C}_5H_{11}}$$

Scheme 1

Scheme 2

Scheme 3

# Diethylaminosulfur trifluoride (DAST)



DAST has proven itself to be an extremely popular reagent for nucleophilic fluorination, due to its ease of handling and versatility. It has regularly been employed in a myriad selective fluorinations of alcohols, alkenols, carbohydrates, ketones, sulfides, epoxides,

thioethers, and cyanohydrins. In addition some novel organic cyclizations are possible when DAST is employed as a reagent.<sup>5</sup>

Fluorodeoxygenation was achieved using DAST in a preparatively simple synthesis of 5,5-difluoropipecolic acid from glutamic acid (**Scheme 5**).<sup>6</sup>

1,2,2-Trifluorostyrenes can be synthesized using a sequential reaction on the parent  $\alpha$ -(trifluoromethyl)phenylethanol with DAST, followed by dehydrohalogenation with lithium bis(trimethylsilyl)amide (LHMDS). This method achieves the trifluorostyrene without requirement of palladium coupling (**Scheme 6**).<sup>7</sup>

DAST was recently used to obtain fluorinated analogues of 3,6-dibromocarbazole piperazine derivatives of 2-propanol (**Scheme 7**). A series of these analogues are described as the first small and potent modulators of the cytochrome *c* release triggered by Bid-induced Bax activation in a mitochondrial assay.<sup>8</sup>

The synthesis of  $\alpha$ , $\alpha$ -difluoroamides via direct fluorination was recently reported using DAST as the fluorinating reagent in a one-pot reaction (**Scheme 8**). Decreasing the molar ratio of DAST to substrate resulted in the formation of the respective  $\alpha$ -ketoamide.

 $\alpha\text{-Fluorosulfides}$  and secondary alcohols were coupled by Yb(OTf)\_3 to generate O,S-acetals, which are key intermediates in the assembly of ciguatoxins. In their synthesis, hydrogen was directly converted to fluorine using DAST and a catalytic amount of SbCl\_3 to make the  $\alpha\text{-fluorosulfide}$  (Scheme 9).10

Diethylaminosulfur trifluoride (DAST)	
23,525-3	1 g 5 g 25 g 125 g 250 g

Scheme 5

Scheme 6

Scheme 7

1.832

2 3

Scheme 8



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# Selectfluor™

Selectfluor™ (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate), or F-TEDA) is a user-friendly, mild, air- and moisturestable, non-volatile reagent for

electrophilic fluorination. Selectfluor<sup>m</sup> is capable of introducing fluorine into organic substrates in one step, with a remarkably broad scope of reactivity.<sup>11</sup> Many of these reactions display excellent regioselectivity.

Recently, the synthesis of a potent and noncytotoxic nucleoside inhibitor of Hepatitis C virus RNA replication was accomplished using Selectfluor™ (**Scheme 10**). This ribonucleoside shows a significantly improved enzymatic stability profile compared to the parent 2′-C-methyladenosine.¹²

Allylic fluorides can be prepared via a sequential cross-metathesis/ electrophilic fluorodesilylation route (**Scheme 11**). This route avoids the formation of by-products that result from allylic transposition, which is observed when nucleophilic displacement or ring-opening reaction with DAST is attempted.<sup>13</sup>

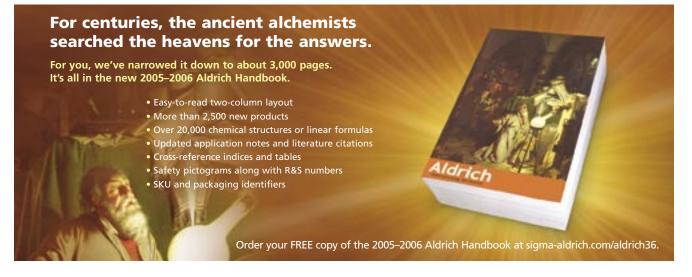
Selectfluor<sup>T</sup> is also capable of effecting other transformations. One recent example uses Selectfluor<sup>T</sup> as an alternative to silver or mercury salts in the rearrangement of iodides to alcohols (**Scheme 12**). In the case of an iodochloride (X=CI), substitution only occurs at the iodide and not the chloride. <sup>14</sup>

Selectfluor<sup> $^{\text{TM}}$ </sup> has even been employed as an efficient catalyst for the preparation of  $\beta$ -hydroxy thiocyanates using ammonium thiocyanate under mild conditions (**Scheme 13**). In all cases, the reactions proceed rapidly at room temperature without the formation of the corresponding thiiranes, which are generally the exclusive products when Lewis acids such as  $Sc(OTf)_3$  and  $InCl_3$  are used.<sup>15</sup>

Scheme 10

Scheme 11

Scheme 12



1 g 5 g

# Ishikawa's Reagent

Ishikawa's reagent (*N*,*N*-diethyl-1,1,2,3,3,3-hexafluoropropylamine) has also demonstrated utility in fluorination. In a recent example, Ishikawa's reagent has been used in a clean and reproducible fluorination protocol on an intermediate

in the total synthesis of 26-fluoroepothilone B (Scheme 14).16

Ishikawa's reagent also displays the ability to insert a fluoro(trifluoromethyl)methylene moiety in unsaturated alcohols (**Scheme 15**).<sup>17</sup>

Ishikawa's Reagent	
56,499-0	25 g 100 g

$\begin{array}{cccccccccccccccccccccccccccccccccccc$		
HO SON SON SON SON SON SON SON SON SON SO		
26-Fluoroepothilone B		

Scheme 14

Scheme 15

# Other Reagents for Fluorination

Cesium fluoride, 99%		
19,832-3	25 g 100 g	
Cesium fluoride, 99.9%		
28,934-528,934-5	5 g 25 g 100 g	
(Dimethylamino)sulfur trifluoride		
24,821-5	5 g 25 g	
N-Fluorobenzenesulfonimide, 97%	6	
39,271-5	1 g 5 g	
1-Fluoropyridinium tetrafluorobo	rate, 97%	
37,726-0	1 g 5 g	
1-Fluoropyridinium triflate, 99%		
32,365-9	1 g 5 g	
1-Fluoro-2,4,6-trimethylpyridinium tetrafluoroborate, 95+%		
43,931-2	1 g 5 g	
11-Fluoro-2,4,6-trimethylpyridiniu	m triflate, tech., 85%	
37,821-6	1 g 5 g	
Hydrogen fluoride-pyridine		
18,422-5	25 g 100 g	
Morpholinosulfur trifluoride		
33,891-5	1 g 5 g	

Poly[4-vinylpyridinium poly(hyd	rogenfluoride)]	
37,705-8	5 g 25 g	
Potassium fluoride, 99+%, a.c.s.	reagent	
40,293-1	5 g 100 g 500 g 12 kg	
Potassium fluoride, spray-dried,	99%	
30,759-9	50 g 250 g 1 kg	
Tetrabutylammonium difluorotri	phenylstannate, 97%	
41,862-5	250 mg 1 g	
Tetrabutylammonium fluoride, 1 containing ca. 5 wt. % water	.0M solution in THF	
21,614-3	5 mL 100 mL 500 mL 2 L 2.5 L 20 L	
Tetrabutylammonium fluoride, 7	5 wt. % solution in water	
36,139-9	25 g 100 g 500 g	
Tetrabutylammonium fluoride, on silica gel		
35,867-3	5 g 25 g	
Triethylamine trihydrofluoride, 9	98%	
34,464-8	5 g 25 g 100 g	
Tris(dimethylamino)sulfur (trime	thylsilyl)difluoride, tech.	
25,060-0	250 mg	



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## **Dess-Martin Periodinane**

Dess–Martin Periodinane (DMP) is among the most widely used reagents for the mild oxidation of alcohols to aldehydes and ketones.<sup>18</sup> The neutral conditions of the oxidation reaction make it a suitable choice in syntheses of sensitive, functionally complex intermediates. When used in

hydrophilic ionic liquids, DMP oxidations proceed even faster than in conventional solvents.<sup>19</sup> Other advantages such as selectivity, avoiding the use of toxic (i.e. chromium-based) chemicals, using stoichiometric amounts of reagent, and ease of work-up make the Dess–Martin periodinane a reliable and easy-to-use oxidizer in organic synthesis.

DMP has been employed in a practical and efficient route for the one-step conversion of aromatic and aliphatic aldehydes to acyl azides (**Scheme 16**). The acyl azides are able to be isolated without rearrangement to the alkyl isocyanate due to the mild reaction conditions.<sup>20</sup>

Intramolecular competition between a dihydropyridine and isoxazolyl alcohols has also been reported. When oxidation was performed using one equivalent of DMP, the keto-isoxazole-dihydropyridine was produced in 93% isolated yield, with no detectable oxidation of the dihydropyridine (**Scheme 17**).<sup>21</sup>

A recent report describes a useful procedure for the removal of thioacetals and thioketals using DMP, displaying compatibility with a wide range of functional groups (**Scheme 18**). A direct route to the corresponding acetals is also possible when the transformation is performed in the presence of an alcohol (**Scheme 19**).<sup>22</sup>

Rare, complex, and diverse polycycles and heterocycles can be rapidly obtained through DMP-mediated cascade cyclization (**Scheme 20**). <sup>23,24</sup>

A slight modification in the reaction conditions allows for the generation of p-quinones from anilides. This approach was then used as a key step in concise and efficient syntheses of epoxyquinomycin B (**Scheme 21**) and topoisomerase-II inhibitor BE-10988 (**Scheme 22**).<sup>25</sup>

Dess–Martin periodinane was found to be a superior oxidant for the efficient preparation of epimerization-sensitive, optically active N-protected  $\alpha$ -amino aldehydes with high enantiomeric excess (**Scheme 23**). <sup>26</sup>

DMP-mediated oxidation also provides a convenient route to the preparation of highly reactive acyl nitroso compounds. These products can be trapped by dienes to form cycloadducts (**Scheme 24**).<sup>27</sup>

Dess-Martin periodinane, 97%		
27,462-3	1 g 5 g	
Dess-Martin periodinane, 0.3M solution in dichloromethane		
55,987-3	1 mL 5 mL 25 ml	

Scheme 16

Scheme 17

$$\begin{array}{c|c} & & \\ S & S \\ R' & \\ \end{array} \begin{array}{c} DMP, CH_3CN, CH_2CI_2, H_2O \\ up to 99\% \end{array} \begin{array}{c} O \\ R \end{array}$$

Scheme 18

TBDMSO 1) TBAF 1) TBAF 2) DMP 
$$R_1$$
  $R_2$   $R_3$   $R_4$   $R_4$   $R_4$   $R_5$   $R_8$   $R_2$   $R_8$   $R_8$   $R_8$   $R_9$   $R_9$   $R_9$ 

Scheme 20

Scheme 21

Scheme 22

Scheme 23

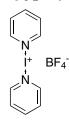


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# Bis(pyridine)iodonium tetrafluoroborate

### (Ipy<sub>2</sub>BF<sub>4</sub>, Barluenga's Reagent)



This mild iodinating and oxidizing reagent is capable of selectively reacting with a wide range of unsaturated substrates and tolerates a variety of functional groups. Ipy<sub>2</sub>BF<sub>4</sub> reacts with acetonides derived from simple terpenes to accomplish selective iodofunctionalization with excellent regioand diastereofacial control (**Scheme 25**).<sup>28</sup>

When added to 2-alkynyl-substituted benzaldehydes, Ipy<sub>2</sub>BF<sub>4</sub> produces substituted naphthalene products upon treatment with either an alkene or alkyne (**Scheme 26**).<sup>29</sup> Alternatively, subsequent treatment with primary alcohols affords oxygen containing heterocycles (**Scheme 27**).<sup>30</sup>

Recently, tetracyclic tetrahydrofurans were produced using Ipy<sub>2</sub>BF<sub>4</sub> in a key step of the synthesis of a series of potential broadspectrum psychotropic agents (**Scheme 28**).<sup>31</sup>

Additionally, Ipy<sub>2</sub>BF<sub>4</sub> has been reported to be useful in general iodinations (**Scheme 29**)<sup>32</sup> and oxidation of alcohols to carbonyls.<sup>33</sup> Photolytic reactions of cycloalkanols produced ring-cleaved products, while thermal reactions left the ring intact during oxidation (**Scheme 30**). Thermal reactions of primary alcohols were capable of producing either aldehydes in dilute conditions or esters in more concentrated solutions (**Scheme 31**).

#### Bis(pyridine)iodonium tetrafluoroborate

53,163-4

1 g

Scheme 26

Scheme 27

Scheme 28

Scheme 29

Scheme 30

Ipy<sub>2</sub>BF<sub>4</sub> , I<sub>2</sub>, MS 4Å K<sub>2</sub>CO<sub>3</sub>, CH<sub>3</sub>CN, 60°C

14h

Ipy<sub>2</sub>BF<sub>4</sub> , I<sub>2</sub>, MS 4Å

K<sub>2</sub>CO<sub>3</sub>, CH<sub>3</sub>CN, 40°C

Scheme 31

# Safer, Amine-Stabilized BH<sub>3</sub>-THF Solutions for Hydroboration and Reduction

Scheme 25

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- Enhanced safety
- Shipment for all pack sizes at room temperature providing greater cost savings
- Excellent reactivity and selectivity vs. BH<sub>3</sub>-THF (17,619-2; NaBH<sub>4</sub>stabilized)

(*R*)-Me-CBS cat. 1M in toluene (10 mol %) 17,619-2: 97%; 90.3%e

65,039-0
 BH<sub>3</sub>THF, 1.0M solution in THF, 1,2,2,6,6-Pentamethylpiperidine (PMP)-stabilized
 65,041-2
 BH<sub>3</sub>THF, 1.0M solution in THF, N-Isopropyl-N-methyl-tert-butylamine (NIMBA)-stabilized
 17,619-2
 BH<sub>3</sub>THF, 1.0M solution in THF, NaBH<sub>4</sub>-stabilized

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# Magnesium bis(monoperoxyphthalate) hexahydrate

$$\begin{bmatrix} O & O^{-} \\ O & O^{-} \\ O & O^{-} \end{bmatrix} Mg^{2+} \cdot 6H_2O$$

Magnesium bis(monoperoxyphthalate) hexahydrate (monoperoxyphthalic acid magnesium salt, or MMPP) is a mild, general oxidizing agent which is a suitable replacement for peroxycarboxylic acids. This

versatile reagent is capable of effecting many types of general oxidation reactions.<sup>34</sup> In addition, MMPP displays low toxicity, and is safer to use in larger-scale reactions, compared to common peroxycarboxylic acids. The reaction by-product, magnesium bisphthalate, is water soluble, and generally easy to separate during work-up.

Recently, the difficult oxidation of glycosyl sulfides to the sulfoxide has been achieved using moist MMPP and microwave irradiation (MW) (**Scheme 32**). The yields using MMPP were superior to those achieved using other oxidants such as oxone or sodium periodate, and no over-oxidation to the sulfone was observed.<sup>35</sup>

MMPP was also used in the formation of a unique alkenyl tricarbonyl, which was used as a common precursor in the synthesis of a series of heterocyclic substituted amino acids (**Scheme 33**).<sup>36</sup>

MMPP was used in conjunction with ultrasound stimulation to produce 2-aryl-3-hydroxysultams and 2-aryl-3-alkoxysultams in one step from the isothiazolium salt (**Scheme 34**).<sup>37</sup>

Whereas most aromatic aldehydes are oxidized to the corresponding carboxylic acids, it has been reported that o- and p-methoxybenzaldehydes can be converted to the analogous phenols in presence of MMPP (**Scheme 35**).<sup>38</sup>

Magnesium bis(monoperoxyphthalate) hexahydrate

28,320-7

5 g 100 g

Scheme 32

$$H_3CO \xrightarrow[N(Boc)_2]{PPh_3} \underbrace{MMPP}_{N(Boc)_2} H_3CO \xrightarrow[N(Boc)_2]{N(Boc)_2} \underbrace{O}_{N(Boc)_2} \underbrace{O}$$

Scheme 33

Scheme 34

$$\begin{array}{c|c} O \\ H \\ OCH_3 \end{array} \begin{array}{c} MMPP \\ MeOH \end{array} \begin{array}{c} OH \\ OCH_3 \end{array}$$

Scheme 35

#### **New Piperazine Building Blocks from Sigma-Aldrich** 65.167-2 65.238-5 1-(3-Hydroxyphenyl)piperazine, 97% 1-Boc-4-(4-methoxycarbonylphenyl)piperazine, 97% MW 178.24 1 g MW 320.19 1 g $C_{17}H_{24}N_2O_4$ $C_{10}H_{14}N_2O$ 5 g 5 g 65,237-7 65,142-7 1-Boc-4-(2-methoxycarbonylphenyl)piperazine 1-Boc-4-(4-Formylphenyl)piperazine, 97% MW 308.38 MW 290.36 1 g 1 g $C_{16}H_{24}N_2O_4$ 5 g C<sub>16</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub> 5 g 65.015-6 1-(2-Chloro-6-fluorobenzyl)piperazine, 98% 4-(Boc-piperazin-1-yl)-3-nitrobenzoic acid, 97% 1 g MW 351.35 MW 228.69 C<sub>16</sub>H<sub>21</sub>N<sub>3</sub>O<sub>6</sub> 10 g 5 g C<sub>11</sub>H<sub>14</sub>CIFN<sub>2</sub>



## **Chloramine-T**

Although the aziridinations<sup>39</sup> and aminohydroxylations<sup>40</sup> of olefins using chloramine-T as a commercially-available and inexpensive nitrene source have been well documented, the use of chloramine-T in other capacities as an oxidizing agent is less well-known.

When a solution of chloramine-T in acetonitrile was added to thioglycosides, it resulted in their chemoselective hydrolysis into glycosyl hemiacetals under neutral conditions (**Scheme 36**). The reaction is carried out without requiring any additive, and is tolerant of a variety of functional groups. Furthermore, neither oxidation of sulfur atoms, nor formation of aziridines was observed during the course of the reaction.<sup>41</sup>

Chloramine-T is also capable of oxidative cyclization to produce various heterocycles. A recent report details the synthesis of 1,2,4-triazolo[4,3-a][1,8]naphthyridines using chloramine-T under microwave irradiation (**Scheme 37**). The reaction proceeds cleanly in minutes, and requires a simple mild work-up to obtain the desired product.<sup>42</sup>

Fused cyclic ethers have been obtained through oxidation by chloramine-T. Pyranocyclohexane derivatives were synthesized starting from 1,2:5,6-di-O-isopropylidene- $\alpha$ -D-glucofuranose, using chloramine-T in a key step on an oxime derivative (**Scheme 38**).  $^{43}$ 

Scheme 36

Scheme 37

Scheme 38

# **Other Reagents for Oxidation**

<i>N</i> -Bromosuccinimide, 99%		
B8,125-5	5 g 100 g 500 g 1 kg 2.5 kg	
1,1'-Carbonyldiimidazole		
11,553-3	5 g 10 g 25 g 100 g 1 kg 25 kg	
3-Chloroperoxybenzoic acid, 77% Ma	x.	
27,303-1	25 g 100 g 500 g	

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone, 98%		
D6,040-0  Dithiothreitol	5 g 10 g 100 g	
15,046-0	250 mg 1 g 5 g 25 g 100 g 1 kg 5 kg 10 kg	
Osmium tetroxide, 99.8%		
20,103-0	250 mg 500 mg 1 a	

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Osmium tetroxide, 98+%, a.c.s. reage	nt	
41,949-4	250 mg 1 g	
Osmium tetroxide, 4 wt. % solution is	n water	
25,175-5	2 mL 5 mL 10 mL	
Osmium tetroxide, 2.5 wt. % solution	in 2-methyl-2-propanol	
20,886-8	1 mL 5 mL 25 mL	
Oxalyl chloride, 98%		
O8801	25 g 100 g 1 kg 2.5 kg 50 kg	
OXONE®, monopersulfate compound		
22,803-6	5 g 100 g 1 kg 5 kg 25 kg	
Peracetic acid, 32 wt. % solution in di	ilute acetic acid	
26,933-6	5 mL 100 mL 500 mL	
Phosphorus pentachloride, 95%		
15,777-5	5 g 100 g 1 kg	
Phosphorus tribromide, 99%		
25,653-6	5 g 100 g 500 g	
Phosphorus tribromide, 97%		
15,778-3	5 g 100 g 500 g	
Phosphorus trichloride, ReagentPlus™	, 99%	
32,046-3	1 L	
Phosphorus trichloride, ReagentPlus™		
15,779-1	50 g 250 g 1 kg	
Pyridinium chlorochromate, 98%		
19,014-4	25 g 100 g 500 g	
Triphosgene, 98%		
33,075-2	5 g 25 g 100 g	

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