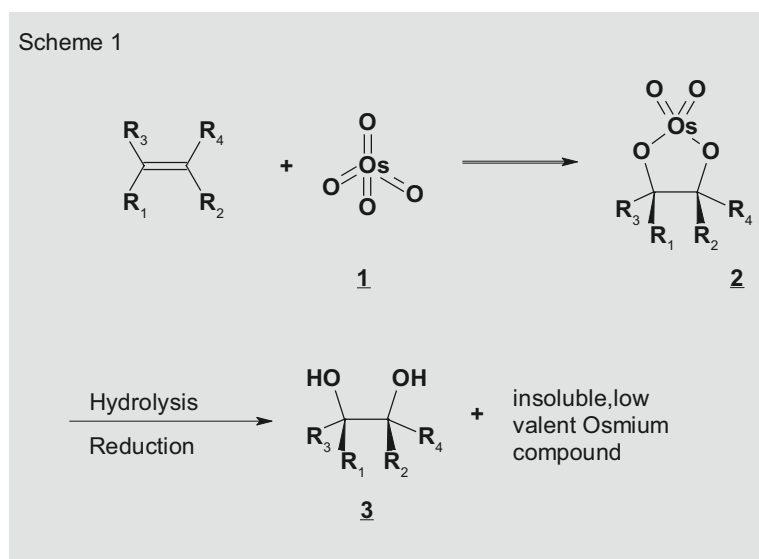




## 3 - Osmium based oxidation reagents

Osmium tetroxide (**1**), a colorless to slightly yellow solid, has a melting point of 40°C and a boiling point of 132°C. It sublimes at room temperature and forms **highly toxic fumes** that have an ozone-like odor (*osme* = greek: smell). It is somewhat soluble in water but easily soluble in carbon tetrachloride, alcohol, ether, benzene and other solvents.

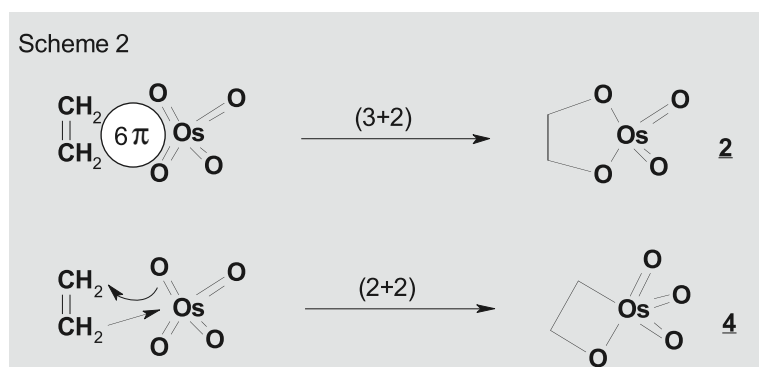
The first use of stoichiometric amounts of osmium tetroxide for the cis-hydroxylation of alkenes was described by Rudolf Criegee in 1936<sup>1</sup>, but the reactivity of osmium tetroxide towards unsaturated compounds had been observed earlier<sup>2</sup>.



Osmium tetroxide is a very reliable reagent for the cis-hydroxylation of alkenes<sup>3,4</sup>. The reaction proceeds through the formation of a cyclic osmate ester (**2**), which is then (mostly reductively) hydrolyzed to form the cis-diol (**3**) (Scheme 1).

Common reducing agents for this reductive cleavage are lithium aluminum hydride<sup>5</sup>, potassium or sodium sulfite<sup>6</sup>, and hydrogen sulfide. Hydrolysis of the ester can also be achieved with alkaline mannitol or catechol.

The reaction is usually run in aqueous acetone, but substrate solubility may require the use of other solvents. Aqueous tert-butanol, tetrahydrofuran, and mixtures of these solvents have also been used successfully.



The formation of the osmate ester has been proposed to proceed via a (3+2)<sup>7,8</sup> or (2+2) cycloaddition<sup>9</sup> mechanism (Scheme 2).

The structures of the osmate esters are more complex (Schemes 1 and 2<sup>10</sup>).

Архангельск (8182)63-90-72  
Астана (7172)727-132  
Астрахань (8512)99-46-04  
Барнаул (3852)73-04-60  
Белгород (4722)40-23-64  
Брянск (4832)59-03-52  
Владивосток (423)249-28-31  
Волгоград (844)278-03-48  
Вологда (8172)26-41-59  
Воронеж (473)204-51-73  
Екатеринбург (343)384-55-89  
Иваново (4932)77-34-06

Ижевск (3412)26-03-58  
Иркутск (395)279-98-46  
Казань (843)206-01-48  
Калининград (4012)72-03-81  
Калуга (4842)92-23-67  
Кемерово (3842)65-04-62  
Киров (8332)68-02-04  
Краснодар (861)203-40-90  
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Нижегород (831)429-08-12  
Новокузнецк (3843)20-46-81  
Новосибирск (383)227-86-73  
Омск (3812)21-46-40  
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Самара (846)206-03-16  
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Саратов (845)249-38-78  
Севастополь (8692)22-31-93  
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Смоленск (4812)29-41-54  
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Сургут (3462)77-98-35  
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Тула (4872)74-02-29  
Тюмень (3452)66-21-18  
Ульяновск (8422)24-23-59  
Уфа (347)229-48-12  
Хабаровск (4212)92-98-04  
Челябинск (351)202-03-61  
Череповец (8202)49-02-64  
Ярославль (4852)69-52-93

Киргизия (996)312-96-26-47

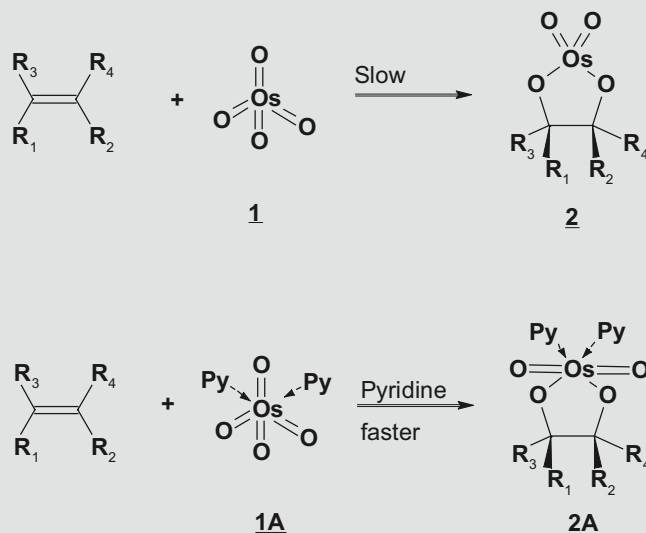
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Osmium tetroxide is electrophilic and adds more easily to electron-rich double bonds than to electron deficient alkenes<sup>11</sup>. Even extremely electron-poor polyfluorinated alkenes, though, can react<sup>12</sup>.

Scheme 3



The reaction of osmium tetroxide with alkenes is strongly accelerated by tertiary amines, especially pyridine<sup>4,1,13</sup> (Scheme 3), but a decrease in reaction speed has also been observed in some cases<sup>14</sup>. The reaction of tertiary amines with osmium tetroxide is an early example of *Ligand Accelerated Catalysis* (LAC)<sup>15</sup>.

Since osmium tetroxide is expensive and toxic, the development of procedures where the reagent could be used in catalytic amounts was a major advantage<sup>16,17,18,19</sup>.

Several methods with different co-oxidants have been developed recently. The most common co-oxidants are hydrogen peroxide, metal chlorates, tert-butylhydroperoxide, potassium ferricyanide, N-methylmorpholine-N-oxide, and trimethylamine-N-oxide (Scheme 4)<sup>20</sup>. Recent use of molecular oxygen<sup>21</sup>, selenoxides<sup>22</sup> and a cascade of re-oxidants (Hydrogen peroxide → Methyltrioxorhenium → Amine Ligand N-oxide → Osmium tetroxide) have been reported<sup>23</sup>.

41188 Hydrogen peroxide, 30% reagent ACS  
20246 Hydrogen peroxide, 35%  
30286 Hydrogen peroxide, 50%  
41819 Potassium chlorate, ACS reagent  
20886 Potassium chlorate, 99%  
22322 Sodium chlorate, 99+%  
18034 tert-Butyl hydroperoxide, 70% in water  
20834 N-Methylmorpholine-N-oxide, monohydrate  
42189 Trimethylamine-N-oxide, dihydrate  
34696 Methyltrioxorhenium

11 H.B.Henbest, W.R.Jackson, B.C.G.Robb, J.Chem.Soc. (B) (1966) 803. (.X9..)

12 W.A.Herrmann, S.J.Eder, W.Scherer, Angew.Chem. 104 (1992) 1371.

13 E.Erdik, D.S.Matteson, J.Org.Chem. 54 (1989) 2742.

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15 D.J.Berrisford, C.Bolm, K.B.Sharpless, Angew.Chem 107 (1995) 1159.

16 K.A.Hofmann, O.Erhard, O.Schneider, Chem.Ber. 46 (1913) 1657.(.X15..)

17 N.A.Milas, S.Sussman, J.Am.Chem.Soc. 58 (1936) 1302 (...X1...); N.A.Milas, S.Sussman, J.Am.Chem.Soc. 59 (1937) 2345.

18 V.van Rheenen, R.C.Kelly, D.Y.Cha, Tetrahedron Lett. 23 (1976) 1973(...X3..); V.van Rheenen, D.Y.Cha, W.M.Hartley Org.Synth.Coll.Vol. 6 (1988) 342 (.X5..)

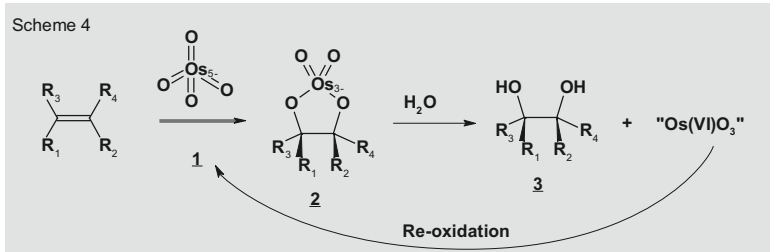
19 K.Akashi, R.E.Palermo, K.B.Sharpless J.Org.Chem 43 (1978) 2063. (.X4..)

20 M.Minato, K.Yamamoto, J.Tsuji, J.Org.Chem. 55 (1990) 766.

21 Ch.Döbler, G.Mehltretter, M.Beller, Angew.Chem 111 (1999) 3211.

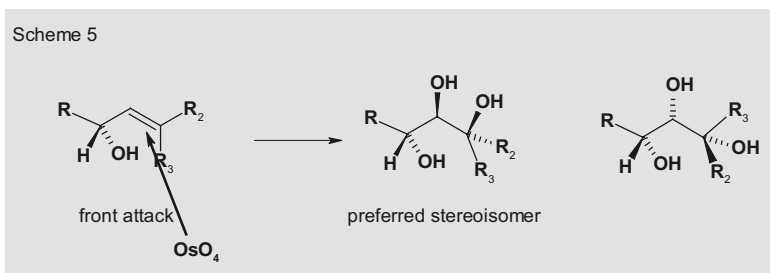
22 A.Krief, C. Colaux-Castillo, Pure Appl.Chem 74 (2002) 107. (.X31..)

23 S.Y.Jonsson, H.Adolfson, J.E.Bäckvall, Chemistry (2003) 2783 (.X34..)

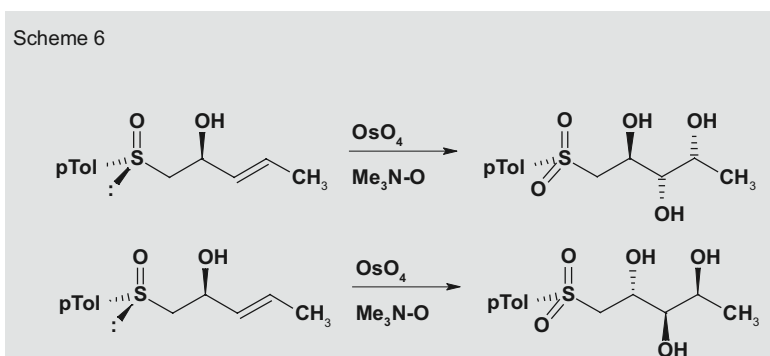


The choice of co-oxidant is important, because over-oxidation of the cis-diol to the  $\alpha$ -ketol can cause workup problems and lower yields<sup>18</sup>.

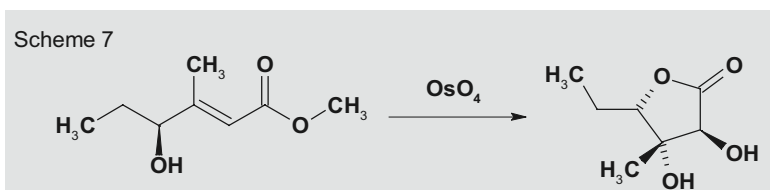
The problems of the high cost and toxicity of osmium tetroxide were also addressed by using encapsulated<sup>24,25</sup> or immobilized<sup>26</sup> osmium tetroxide.



The hydroxylation reaction shows remarkable **diastereoselectivity** in cases where the double bond is attached to a stereocenter carrying an oxygen. The stereochemistry shows that osmium tetroxide preferably attacks from the face away from the alcohol (Scheme 5). The selectivity is even higher with Z-double bonds ( $R_2=H$ )<sup>27,28,29,30</sup>.



A similar observation was made by Solladié on allylic  $\beta$ -hydroxysulfoxides (Scheme 6)<sup>31</sup>.



A different diastereoselectivity was reported by Stork<sup>32</sup> for  $\gamma$ -hydroxy- $\alpha,\beta$ -unsaturated esters; in this case, the osmium tetroxide has apparently attacked from the face containing the alcohol (Scheme 7).

The high chemo- regio- and diastereoselectivity of the osmylation reaction has led K. Barry Sharpless<sup>33</sup> to the **catalytic enantioselective asymmetric dihydroxylation (AD)** reaction<sup>34</sup>. The AD-reaction is probably the most reliable method for the generation of asymmetry from prochiral alkenes, and many chemists have used this method for their synthesis<sup>35</sup>.

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25 S. Nagayama, M. Endo, S. Kobayashi, J. Org. Chem., 63, 6094-6095 (1998).

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27 J.K.Cha, W.J.Christ, Y.Kishi, Tetrahedron Lett. 24 (1983) 3943; J.K.Cha, W.J.Christ, Y.Kishi, Tetrahedron 40 (1984) 2247 (.X10..)

28 D.A.Evans, S.W.Kaldor, J.Org.Chem. 55 (1990) 1698.

29 S.Seito, Y.Morikawa, T.Moriwake, J.Org.Chem 55 (1990) 5424.

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31 G.Solladié, C.Fréchou, G. Demailly, Tetrahedron Lett. 27 (1986) 2867 (.X13..)

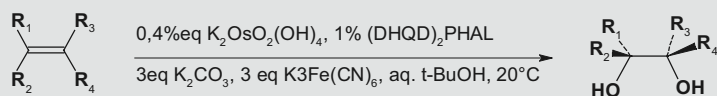
32 G.Stork, M.Kahn, Tetrahedron Lett. 24 (1983) 3951. (.X14..)

33 K.Barry Sharpless won together with Ryoji Noyori and William S. Knowles the Nobel price for chemistry 2001 for their achievements in asymmetric synthesis.

34 H.C.Kolb, M.S.VanNieuwenhze, K.B.Sharpless, Chem. Rev. 94 (1994) 2485.

35 Some recent examples: C.Choi, S.K.Tian, L.Deng, Synthesis 11 (2001) 1737; S.H.Krishna Reddy, S.Lee, A.Datta, G.I.Georg, J.Org.Chem 66 (2001) 8211; R.Sadyandy, R.A.Fernandes, P.Kumar, Arkivoc (2005) 36.

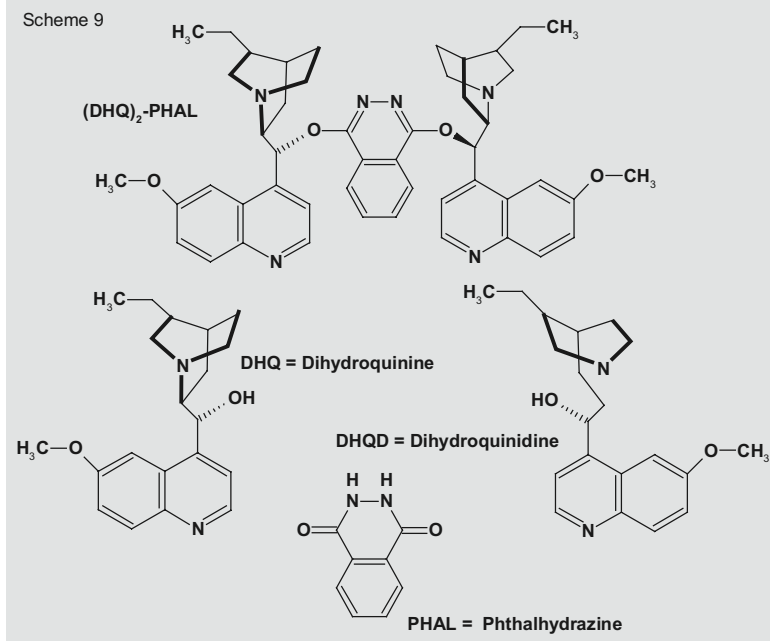
Scheme 8



The AD-reaction uses derivatives of cinchonaalkaloids such as (DHQ)2-PHAL (the bis-ether of phthalhydrazine with dihydroquinidine) as carriers for the asymmetric information **and** as accelerators for catalytic activity<sup>36,37,38</sup>.

Many synthetic procedures for asymmetric dihydroxylation with different chiral ligands are published<sup>39,40,41</sup>.

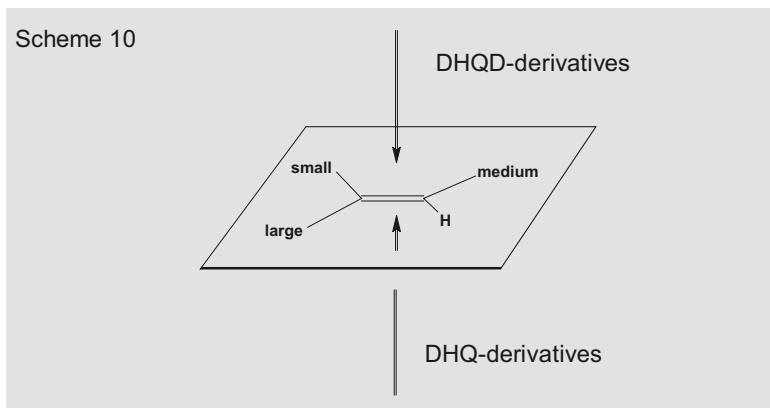
Scheme 9



The following catalytic cycle has been proposed for the AD-reaction<sup>42,43,44,45,46</sup> (Scheme 11). Cycle A results in high enantioselectivity due to participation of the chiral ligand; the competing cycle B shows only low enantioselectivity.

The stereochemical outcome of the AD-reaction with the two cinchona-alkaloids DHQ and DHQD is predictable<sup>47</sup>:

Scheme 10

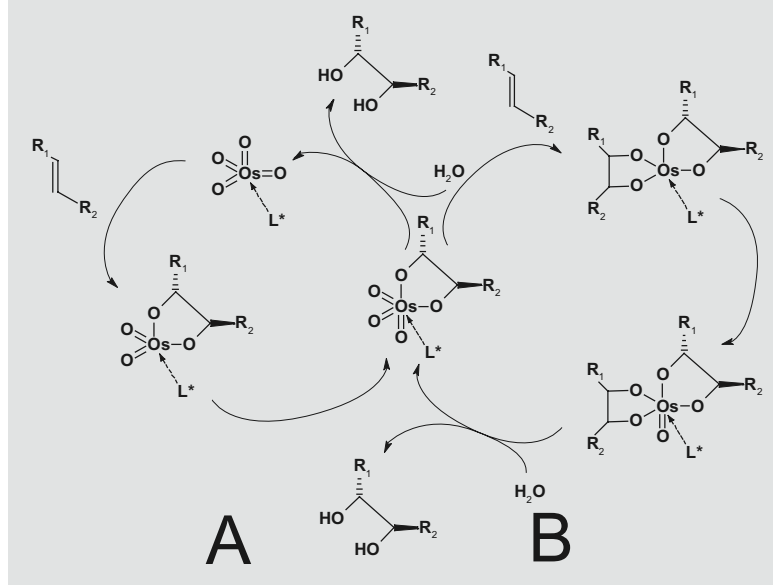


36 E.N.Jacobsen, I.Marko, W.S.Mungall, G.Schröder, K.B.Sharpless, *J.Am.Chem.Soc.* 110 (1988) 1968.  
 37 D.W.Nelson, A.Gypser, P.T.Ho, H.C.Kolb, T.Kondo, H.-L. Kwon, D.V.McGrath, A.E.Rubin, P.-O. Norrby, K.B.Gable, K.B.Sharpless, *J.Am.Chem.Soc.* 119 (1997) 1840. (...X22...)  
 38 E.N.Jacobsen, I.Marko, M.B.France, J.S.Svedsen, K.B.Sharpless, *J.Am.Chem.Soc.* 111 (1989) 737.  
 39 J.Gonzalez, C.Aurigemma, L.Truesdale, *Org.Synthe. Coll.Vol.* 10 (2004) 603. (...X26...)  
 40 B.H.Mc.Kee, D.G.Gilheany, K.B.Sharpless, *Org.Synt. Coll.Vol.* 9 (1998) 383. (...X27...)  
 41 R.Oi, K.B.Sharpless, *Org.Synt.Coll.Vol.* 9 (1998) 251. (...X28)

42 J.-S.M.Wai, I.Marko, J.S.Svedsen, M.G.Finn, E.N.Jacobsen, K.B.Sharpless, *J.Am.Chem.Soc.* 111 (1989) 1123. (...X25...)  
 43 H.Becker, K.B.Sharpless *Angew.Chem.* 108 (1996) 447  
 44 H.C.Kolb, M.S.Van Nieuwenhze, K.B.Sharpless, *Chem.Rev.* 94 (1994) 2483  
 45 M.A.Andersson, R.Epple, V.V.Fokin, K.B.Sharpless *Angew.Chem* 114 (2002) 389.  
 46 P.-O.Norrby, T.Rasmussen, J.Haller, T.Strassner, K.N.Houk, *J.Am.Chem.Soc.* 121 (1999) 10186.  
 47 A.C.Spivey, R.Hanson, N.Scorah, S.J.Thorpe, *J.Chem.Ed.* 76 (1999) 655

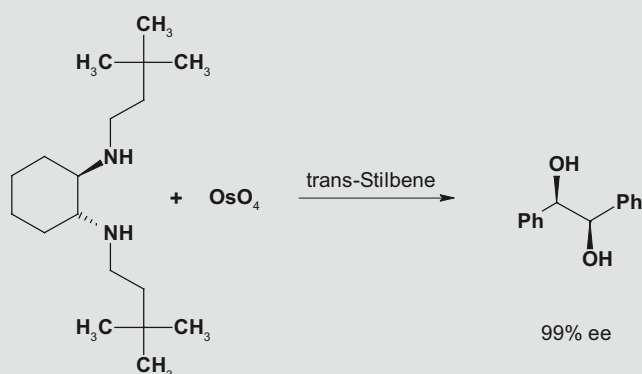


Scheme 11



Besides cinchona-derived ligands, other C<sub>2</sub>-asymmetrical ligands have been used successfully for the AD-reaction<sup>48</sup>.

Scheme 12

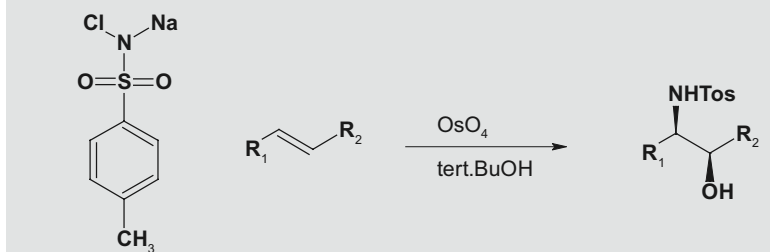


36464 (1R,2R)-(-)-1,2-Diaminocyclohexane 98%  
 31022 (1S,2S)-(+)-1,2-Diaminocyclohexane 98%  
 24867 (±)-trans-1,2-Cyclohexanediamine  
 16104 trans-Stilbene 96%



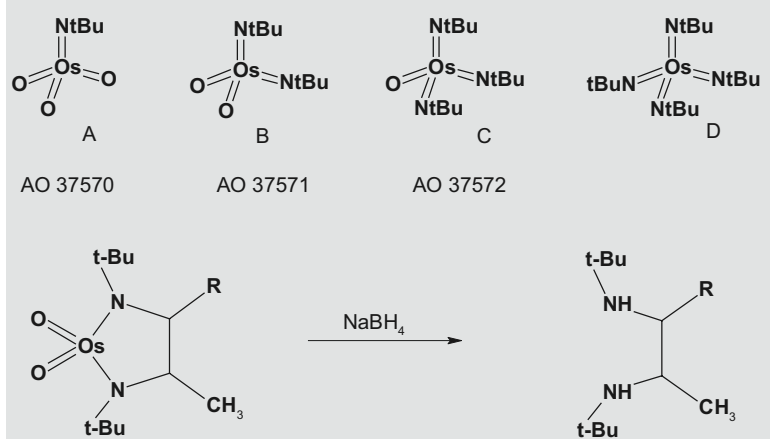
The reaction of osmium tetroxide with olefins is not only limited to dihydroxylation. Valuable  $\beta$ -hydroxyamines can be synthesized in the presence of electrophilic nitrogen-sources like Chloramine T<sup>49,50</sup> or others<sup>51</sup>:

Scheme 13



In the presence of (DHQ)2PHAL and related cinchona-derived ligands, aminohydroxylation is also enantioselective<sup>52</sup>.

Scheme 14



The use of the imido-osmium (VIII) compounds (A-D, Scheme 14) allows an excellent approach to vicinal amino alcohols and vicinal diamines with a high preference for cis-addition to terminal or E-alkenes and regioselectivity placing the amino group at the sterically least-hindered or terminal carbon<sup>53,54</sup>. The addition of the bis(imido)osmium complex leads to a remarkably stable osmimidazolidine, from which the vicinal diamine can be liberated by reductive cleavage with sodium borohydride.

49 K.B.Sharpless, A.O.Chong, K.O'Shima, 41 (1976) 177.

50 E.Hernanz, K.B.Sharpless, Org.Synth. Coll.Vol. 7 (1990) 375. (..X37..)

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53 K.Muniz, Chem.Soc.Rev. 33 (2004) 166.

54 K.Muniz, M.Nieger, H. Mansikkamäki, Angew.Chem 115 (2003) 6140.



## Osmium products from Acros Organics

- 19118 ..... Osmium(VIII)-tetroxide 99.9+%
- 19745 ..... Osmium tetroxide, 2.5 wt% solution in t-butanol, stabilized
- 31901 ..... Osmium tetroxide, 4 wt% solution in water
- 19762 ..... Osmium(III) chloride, 63.2% to 65.2% Os
- 19766 ..... Potassium osmate(VI) dihydrate, 51.0-52.0% Os
- 38516 ..... Osmium powder
- 19763 ..... Ammonium hexachloroosmate(IV), 42.5 to 44.5% Os
- 19765 ..... Potassium hexachloroosmate(IV), min 39% Os
- 31862 ..... Sodium hexachloroosmate(IV)hydrate, 38.0-41.0% Os
- 31870 ..... Osmium(III) chloride hydrate
- 31871 ..... Triosmium dodecacarbonyl 98%
- 36353 ..... Bis(cyclopentadienyl)osmium
- 20319 ..... Manganese(IV) oxide 88%, precipitated active

Архангельск (8182)63-90-72  
 Астана (7172)727-132  
 Астрахань (8512)99-46-04  
 Барнаул (3852)73-04-60  
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 Вологда (8172)26-41-59  
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 Калуга (4842)92-23-67  
 Кемерово (3842)65-04-62  
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 Краснодар (861)203-40-90  
 Красноярск (391)204-63-61  
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