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Catalytic Asymmetric Dihydroxylation of α-Methylstyrene by Air

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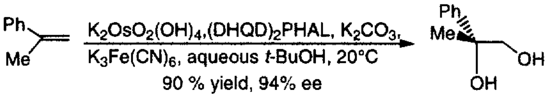
Abstract :Dioxygen is able, under visible irradiation, to promote the high yielding and highly asymmetric dihydroxylation of α-methylstyrene in the presence of catalytic amounts of Os(VI), phthalazine dihydroquinidine chiral ligand [$(DHQD)_2PHAL$].

Since its discovery by Sharpless the asymmetric dihydroxylation of C,C double bonds (AD reaction)[1] has attracted synthetic[1] and theoretical[2] interests because it constantly allows the high yield synthesis of almost enantiomerically pure diols (Scheme 1).

Scheme 1



Typically the reaction is performed in aqueous *t*-butanol (the solvent) using, per millimole of olefin to be oxidized, 1.4 g of a premix which contains catalytic amounts [% in weight] of (i) potassium osmate dihydrate [0.104 %] and (ii) one of the phthalazine linked to two chincona alkaloid ligands [$(DHQD)_2PHAL$ or $(DHQ)_2PHAL$, 0.552 %] which play the role of oxidant or of the chiral inductor respectively. Larger amounts of potassium ferricyanide [$K_3Fe(CN)_6$, 69.96 %] and potassium carbonate [29.39 %] are also required as the co-oxidant and as the base respectively.[1]

Several oxidants, such as N-methyl morpholine N-oxide (NMO),[1,3] sodium peroxodisulphate ($Na_2S_2O_8$)[1] and iodine (I_2)[4a] have been tested in place of the ferricyanide which account for the larger amount of matter in the premix, but none of them have been able to supplant it.

Dedicated with warm affection and deep admiration to Professor L. Ghosez at the occasion of his 65th Birthday

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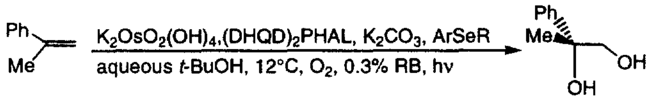
NMO give constantly lower ee's even if the co-oxidant is slowly added to the medium[1,3] and sodium peroxodisulphate is unable to perform the required process unless some potassium ferricyanide is present.[1] Iodine proved to be efficient but has not yet been used extensively.[4a] Electochemical versions which use catalytic amounts of iodine[4a] or potassium ferricyanide[4b] have been also disclosed.

Selective oxidation of organic molecule by air is one of the chemist dreams not only due to its great availability but also because it is clean and ecological compared to other oxidants especially those which are salts or heavy metals derivatives. We now report an efficient, high yielding (93%) and highly asymmetric (97%)[1b] dihydroxylation of α-methylstyrene (SOAD reaction)[5a] which is a variant of the Sharpless AD reaction[1] but which uses dioxygen rather than potassium ferricyanide [$K_3Fe(CN)_6$] as the co-oxidant.

Since dioxygen neither in its original triplet state nor in its activated singlet one is able to re-oxidize osmium (VI) to osmium (VIII), the effective oxidant, we use a catalytic amount of benzyl phenyl selenide (8.1 mol equiv. %) and visible light in the presence of a sensitizer (Scheme 2). We in fact described,[6] more than 20 years ago, that singlet oxygen is able to oxidize selenides to their oxides and Abatjoglou later used this reaction to re-oxidize osmium (VI) to osmium (VIII).[7]

The reaction is usually carried out in a cylindrical reactor linked to a balloon filled with dioxygen, equipped with an efficient mechanical stirrer, immersed in a water bath maintained at 12°C by external cooling and irradiated by two external garden projectors of 500 watts each (Osram 64702 R7s, 500 W-230 V, bought in a supermarket for 10 Euro each). It is best performed in aqueous *t*-butanol (the solvent), with potassium osmate dihydrate(1.25 mol eq % the oxidant), $(DHQD)_2PHAL$ (the chiral ligand, 2.3 mol eq %), potassium carbonate (the base, 0.30 mol eq %), benzyl phenylselenide (the oxygen carrier, 8.1 mol %) and trace amount of Rose Bengal (RB) (the sensitizer for $^3O_2$ to $^1O_2$ activation, 0.3 mol eq %) under a slight pressure of dioxygen (the co-oxidant, from 3.8 to 2.7 mmHg). After 24 hours of reaction the mixture is treated with an aqueous solution of sodium sulfite to reduce the remaining selenoxide and osmium tetroxide (Scheme 2, entry a).[8] Interestingly, the reaction can be carried out with air instead of dioxygen (Scheme 2, entry b) and although the reaction has been usually performed with higher amounts of osmium and chiral ligand than originally described by Sharpless,[1] it works with similar yields and ee's when the original amounts of these catalysts are used (Scheme 2, entry c).

Scheme 2



Entry	$K_2OsO_2(OH)_4$	K_2CO_3	$(DHQD)_2PHAL$	Co-oxidant	ArSeR [a]	Yield %[ee %]
a	1.25[a]	30[a]	2.30[a]	O_2	$PhSeCH_2Ph$ [8.1]	93 [97]
b	1.80[a]	30[a]	2.78[a]	air	$PhSeCH_2Ph$ [8.1]	87 [93]
c	0.40[a]	30[a]	1.06[a]	O_2	$PhSeCH_2Ph$ [8.1]	89 [96]
d	1.88[a]	72[a]	2.47[a]	O_2	MeSePh(*p*CO_2H) [8.0]	93 [95]

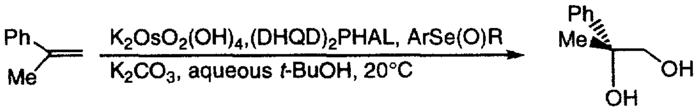
[a] In mol equiv. %

The reaction occurs similarly with different selenides[9] including potassium(*p*-carboxylate)-phenyl methyl selenide. The later offers the advantage to be easily separated from the diol and recycled (Scheme 2, entry d). It takes also place successfully in aqueous acetonitrile or cyclohexane and at temperatures ranging from 0°C to 30°C, but, under these conditions, the diol is usually produced with lower yields and ee.[9]

The reaction seems to be different from the one described by Abatjoglou[7] since it does not proceed with osmium tetroxide, requires much longer time (24 h instead of 2 h)[7] and takes place under much lower pressure of oxygen (3.8 instead of 2586 mmHg). We have verified that a selenoxide is effectively formed in this reaction. We have also assessed, in a separate experiment that selenoxides are efficient stoichiometric co-oxidants in the asymmetric dihydroxylation of α-methylstyrene (SeOAD reaction,[5b] Scheme 3), but we have not proved that they are the real oxidants in the singlet oxygen reaction reported above since any of the intermediates on the way to selenoxides could be able to play this role.

The reaction involving stoichiometric amounts of selenoxide (SeOAD reaction) possesses the same features than the one involving singlet oxygen (SOAD reaction) : it is best achieved in aqueous *t*-butanol, and although it is faster (2-3 h instead of 24 h), it produces the diol in very good yields and with high ee's. Specific results are gathered in Scheme 3.

Scheme 3



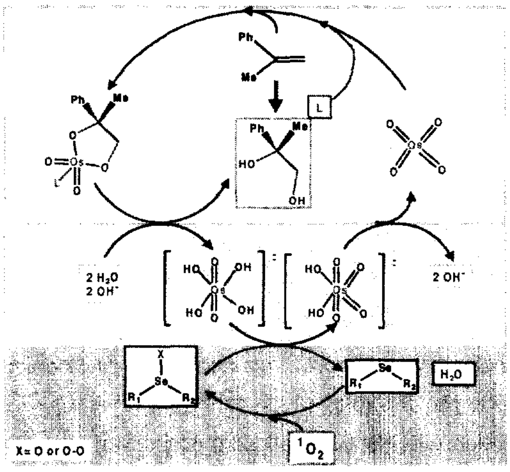
Entry	$K_2OsO_2(OH)_4$	K_2CO_3	$(DHQD)_2$PHAL	ArSe(O)R [a]	Yield %[ee%]
a	1.58[a]	30[a]	2.70[a]	PhSe(O)CH_2Ph [102]	96 [97]
b	1.70[a]	65[a]	2.12[a]	MeSe(O)Ph(*p*CO_2H) [102]	61 [97]

[a] In mol equiv. %

The last results are remarkable since we thought, in relation with the original work of Sharpless and Marko,[3] that the slow generation of the effective co-oxidant was the origin of the high enantioselectivity observed in the *SOAD reaction*. We now know that this is at least not the case in the *SeOAD reaction*. Apparently the second cycle of low enantioselectivity which is operative when NMO is used[3] and which lowers the overall enantioselectivity of the process does not take place with selenoxides.

Finally the reaction reported in Scheme 2 requires further comments. It is quite efficient when carried out potassium (*p*-carboxylate)-phenyl methyl selenide (Scheme 2, entry d). It also bring to new light the intimate mechanism of singlet oxygen oxidation of selenides which is quite different from the one of the related sulfides.[10] For example we have found, during this work, that $^{1}O_2$ quantitatively oxidizes diphenyl selenide although it is well known that diphenyl sulfide is inert under the same conditions.[10]

The presence of an hydrogen on the carbon linked to the sulfur atom which is apparently required for successful $^1O_2$ oxidation of diphenyl sulfide[10] is no longer required for its selenium analog.



In conclusion, we have demonstrated that selenides are able, in the presence of light, to promote the efficient dihydroxylation of α-methylstyrene. Not only this new version of the AD reaction uses a simpler, more available and more ecological co-oxidant but also it requires much less matter : 87 mg of matter is required to oxidize α-methylstyrene in the SOAD reaction instead of 1400 mg when Admix is used. *Three* cycles have to works in concert for that purpose and this is apparently the case (see beside).[11] We are extending this reaction to other examples especially those in which the olefin is known to react with singlet oxygen and we are trying to use oxygen, light and catalytic amount of selenides to effect various oxidation reactions.

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References and notes

1. a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483; b) These reactions can be performed using commercially available premixes which are available from Aldrich Chemical Co [AD-mix-α n° 39,275-8; AD-mix-β n° 39,276-6].
2. a) Corey, E. J. ; Noe, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 319; b) DelMonte, A. J.; Haller, J.; b) Sharpless, K. B.; Singleton, D. A.; Strassner, T.; Thomas, A. A. *J. Am. Chem. Soc.* **1997**, *119*, 9907; c) Rouhi, A. M. C&EN **1997**, November Issue, p23.
3. a) E.N. Jacobsen, I. Marko, W. S. Mungall, G. Schroder, K. B. Sharpless *J. Am. Chem. Soc.* **1988**, *110*, 1968; b) J. S. M. Wai, I. Marko, J. S. Svendsen, M. G. Finn, E. N. Jacobsen and K. B. Sharpless *J. Am. Chem. Soc.* **1989**, *111*, 1123; c) In the original work,[3a] the AD reaction has not been carried out on α-methylstyrene and NMO with the "bystander" methoxyquinoleine.[1] We have checked that the reaction provides, using $(DHQD)_2PHAL$ as the ligand and under normal conditions (no slow addition of NMO)[1,3b] results similar to those described in the original paper (ee 67%).[3a]
4. a) Torii, S.; Liu, P.; Bhuvaneswari, N.; Amatore, C.; Jutand, A. *J. Org. Chem.* **1996**, *61*, 3055 and references cited; b) Torii, S.; Liu, P.; Tanaka, H. *Chem. Lett.* **1995**, 319.
5. a) for "Singlet Oxygen mediated Asymmetric Diydroxylation"; b) for "SelenOxide mediated Asymmetric Diydroxylation".
6. L. Hevesi, A. Krief *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 381.
7. A.G. Abatjoglou, D. R. Bryant *Tetrahedron Lett.* **1981**, *22*, 2051.
8. a) H. Becker, K. B. Sharpless *Angew. Chem. Int. Ed. Engl. Ed.* **1996**, *35*, 448; b) $[\alpha]^{25}_D = -5.28$ (c = 0.97, EtOH)[8a] or $[\alpha]^{24}_D = -4.89$ (c = 3.9, EtOH).
9. These results will be described later.
10. F. Jensen, A. Greer, E. L. Clennan *J. Am. Chem. Soc.* **1998**, *120*, 4439.
11. The following amount of reagents (in mg) has been used to oxidize 1 mmol of α-methylstyrene in aqueous *t*-BuOH by the original Sharpless AD reaction using Admix or our SOAD reaction. (AD/SOAD) : $K_2OsO_2(OH)_4$ (1.45/ 4.6); $(DHQD)_2PHAL$ (7.7/17.9); K_2CO_3 (411/41); $K_3Fe(CN)_6$ (979/-); $PhSeCH_2Ph$ (-/20) rose bengale (-/3); overall (1400/87).