Asymmetric dihydroxylation of C,C double bonds using catalytic amounts of osmium tetroxide, selenides, and air*

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Abstract: Selenides, selenoxides, osmium tetroxide, and potassium osmate dihydrate are in equilibrium in aqueous *tert*-butanol containing potassium carbonate. We took advantage of this feature to withdraw the equilibrium in each of the two directions to produce allylalcohols from allylselenides and diols from olefins. The latter reaction performed in the presence of catalytic amounts of Cinchona alkaloids and osmium tetroxide allows the enantioselective dihydroxylation of C,C double bonds.

Sharples AD reaction [1] is extremely useful and efficient for the asymmetric dihydroxylation of olefins (Scheme 1). It only requires [% in weight] catalytic amounts of (i) the pre-oxidant: potassium osmate dihydrate [0.104%] and of (ii) the chiral inductor derived from Cinchona alkaloid: often $(DHQD)_2PHAL$ or $(DHQ)_2PHAL$ [0.552%] to produce diols in extremely good yields and enantiomeric excesses. A series of selected ligands, all belonging to the Cinchona alkaloid family but attached to different linkers, are available for borderline cases [1a].

In fact, two premixes are commercially available under the name of AD-mix [2]. Although the amount of active ingredients is negligible, the amount of reagent required is important (1.4 g of AD-mix per mmole of olefin), mainly due to the excess of cooxidant {potassium ferricyanide, $K_3Fe(CN)_6$ [69.96%]} and of base [potassium carbonate, K_2CO_3 (29.39%)].
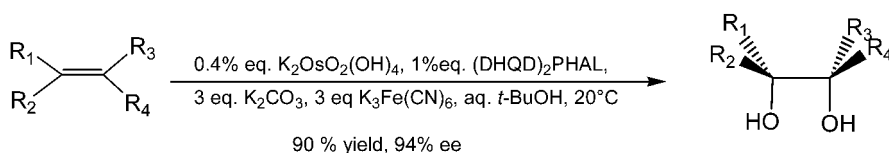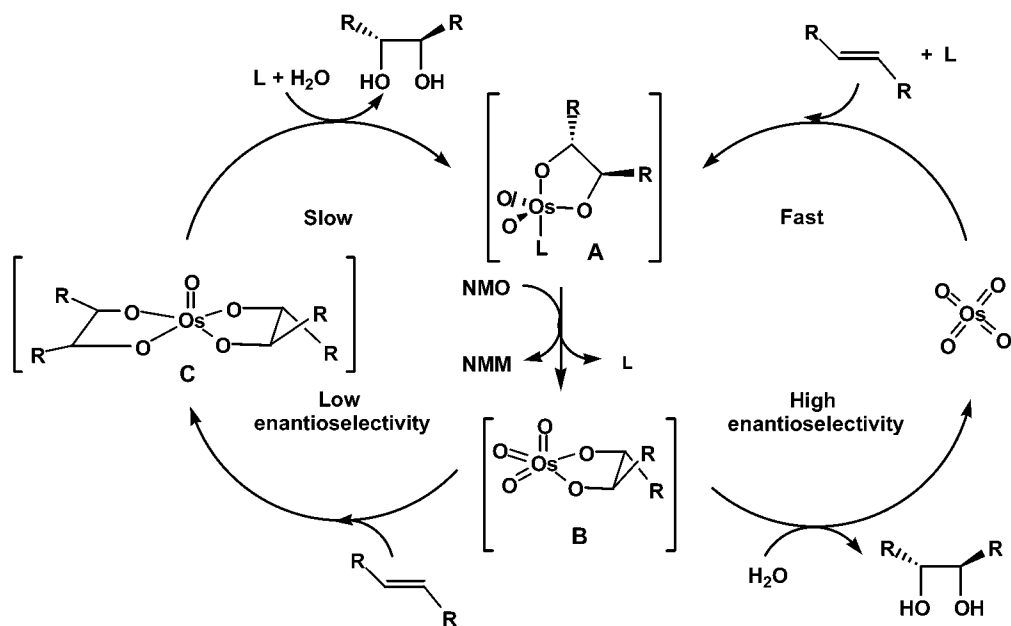

Scheme 1

Several oxidants, such as *N*-methyl morpholine *N*-oxide (NMO) [1a], sodium peroxodisulphate $(Na_2S_2O_8)$ [1a], and iodine (I_2) [2], which have been used in place of the ferricyanide, proved to be much less efficient or less practicable. This is the case of NMO [3], which constantly allows the high yield synthesis of diols from olefins but which did not provide the high ee's obtained with potassium

ferricyanide. All the efforts, including slow addition of the cooxidant to the medium [1] or performing the reaction at a specific pH [4] did not lead to substantial improvements.

The lower ee's observed with NMO was attributed [1] to the presence of a second cycle of "poor enantioselectivity" involving a trioxoglycolate complex which competes with the usual "high enantioselectivity" cycle in which liganded osmium tetroxide is operative (Scheme 2). Anyhow, the intimate mechanism by which NMO is regenerating osmium tetroxide has not been yet clearly established. For example, the way *N*-methyl morpholine is produced and even the nature of the substrate from which it is expelled has not been described.
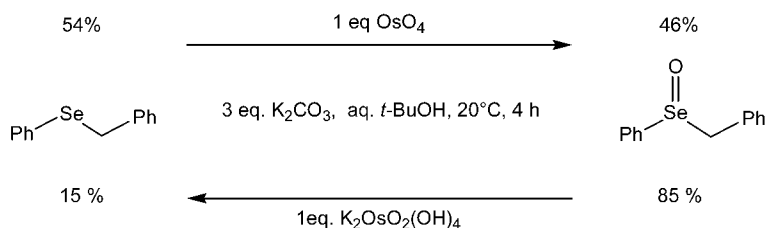

Scheme 2

Selenoxides belong to the same class of compounds as aminoxides and have been already successfully used as cooxidants in osmium tetroxide dihydroxylation of olefins [5]. We therefore thought that they could advantageously not only replace both potassium ferricyanide and NMO, but that they will provide the ee's of the former reagent and the low-weight amount of matter used with the later. Other expected advantages will be to avoid the large quantities of metal salt thrown in the waste and the easy recycling of the resulting selenides to selenoxides [6].

We first checked the aptitude of selenoxides to oxidize potassium osmate dihydrate, as well as the capacity of osmium tetroxide to oxidize selenides.

In fact, selenides are good reducing agents since they are oxidized by a large array of reagents (such as ozone, hydrogen peroxide, sodium perborate, *tert*-butyl hydroperoxide, peracids, dioxiranes, oxaziridines, selenenic anhydrides, perseleninic acids, and singlet oxygen) to selenoxides [6]. These reactions are usually faster than those of the corresponding sulfides. Moreover, they usually stop cleanly at that stage and do not lead to the over-oxidized product (the selenone) [63,7], as it proved often to be the case with sulfides which produce, on oxidation, quite large amounts of sulfones besides the sulfoxide.

We found that benzyl phenyl selenide reacts in basic media, with osmium tetroxide, to produce, after 4 h, benzyl phenyl selenoxide besides quite a large amount of the starting material (Scheme 3). We
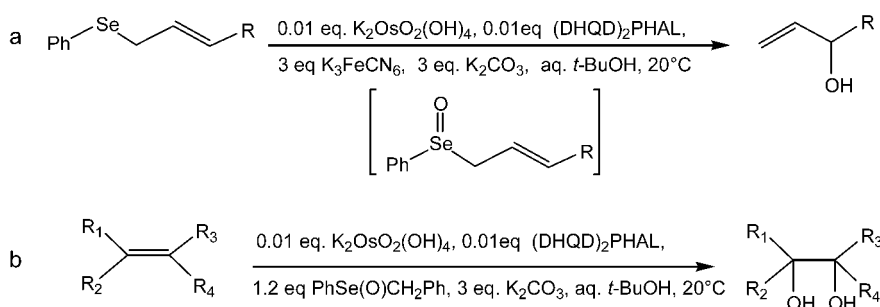
Scheme 3

also found some phenyl benzyl selenide on reaction of the same selenoxide with potassium osmate dihydrate, suggesting that all four products are part of an equilibrium (Scheme 3).

Accordingly, this equilibrium could be withdrawn toward each of the two directions if followed by a nonequilibrated reaction (Scheme 4). This proved to be effectively the case when:

1)   allylphenylselenides are reacted in place of benzyl phenyl selenide with AD-mix (Scheme 4, entry a)
2)   olefins are present in the medium besides catalytic amount of potassium osmate dihydrate and stoichiometric quantities of benzyl phenyl selenoxide (Scheme 4, entry b).
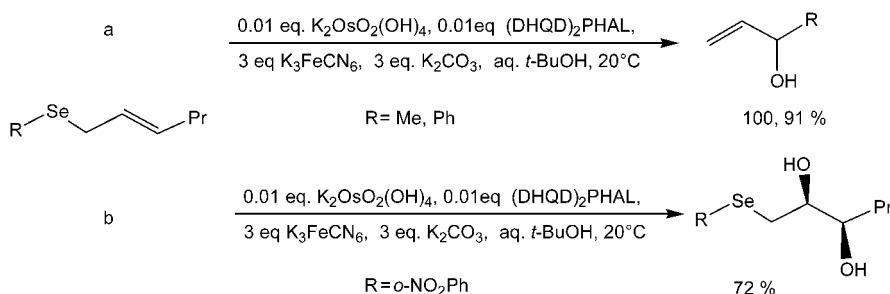

Scheme 4

OXIDATION OF SELENIDES TO SELENOXIDES BY OSMIUM(VIII) SPECIES: APPLICATION TO SYNTHESIS OF ALLYLALCOHOLS AND β,γ-DIHYDROXYALKYL SELENIDES

Although the comparative ability of allylselenides and related alkyl- or phenylselenides to be oxidized were unknown when we started this work, the aptitude of these selenoxides to rearrange to allylalcohols was well established [6d,e,8]. The equilibrium between allylselenoxides and allylseleninates lies toward the later and the presence, in the medium, of selenophilic species withdraw it to produce allylalcohols.

We first found that methyl- as well as phenyl-(2-hexenyl) selenides rearrange to the corresponding allylalcohols on reaction with AD-mix [9]. Their *p*-nitrophenyl analogs behave, however, differently as and produce β,γ-dihydroxyalkyl selenides resulting from the exclusive oxidation of their C,C double bond (Scheme 5, entry a) [9]. This is reminiscent of the reactivity of related allyl phenyl ethers and sulfides that are selectively oxidized to the corresponding β,γ-dihydroxyalkyl ethers and sulfides [1].

The enantioselectivity of the former process (Scheme 5, entry a) is insignificant [9] due either to a poor enantioselectivity of the oxidation step or because desymmetrization of the selenoxide via its hydrate is faster than the rearrangement. The formation of the diol from the related *p*-nitrophenyl

-(2-hexenyl) selenide takes however place with high enantioselection [9] as it is usually the case in the Sharpless AD reaction (Scheme 5, entry b) [1a].

a   0.01 eq. K$_2$OsO$_2$(OH)$_4$, 0.01eq (DHQD)$_2$PHAL,

3 eq K$_3$FeCN$_6$, 3 eq. K$_2$CO$_3$, aq. t-BuOH, 20°C

R= Me, Ph

100, 91 %

b   0.01 eq. K$_2$OsO$_2$(OH)$_4$, 0.01eq (DHQD)$_2$PHAL,

3 eq K$_3$FeCN$_6$, 3 eq. K$_2$CO$_3$, aq. t-BuOH, 20°C

R = o-NO$_2$Ph

72 %

Scheme 5

REDUCTION OF SELENOXIDES TO SELENIDES BY OSMIUM(VI) SPECIES: APPLICATION TO THE ENANTIOSELECTIVE SYNTHESIS OF DIOLS FROM OLEFINS

We also found that selenoxides are efficient stoichiometric cooxidants in the asymmetric dihydroxylation of olefins. The reaction (SeOAD reaction) [9] is best achieved in aqueous t-butanol (1-1 in volume), using the same (i) chiral ligand ((DHQD)$_2$PHAL, 0.016 mol equiv) and (ii) oxidant [K$_2$OsO$_2$(OH)$_4$, 0.016 mol equiv] as used in AD-mix as well as stoichiometric amounts of benzyl phenylselenoxide (Scheme 6). We also used potassium carbonate (0.3 equiv), but we only needed one-tenth of the amount present in AD-mix.

The reaction has been first carried out on α-methylstyrene leading to the corresponding diol in yield (93%) and ee (97%) almost identical to those described by Sharpless using the AD-mix method [1a].
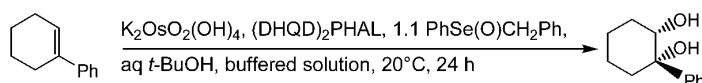
Ph   K$_2$OsO$_2$(OH)$_4$,(DHQD)$_2$PHAL, ArSe(O)R

Me   K$_2$CO$_3$, aqueous t-BuOH, 20°C, 3 h
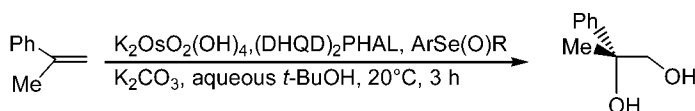
Scheme 6

The reaction has been also performed using a methyl phenylselenoxide bearing a carboxylic acid moiety on the aromatic ring. The yield in diol is lower (61%, ee 97%) because the reaction is slower but the use of this selenoxide offers the advantage of easy recovery of both the diol and the selenide in pure form using an acid-base treatment.

Results similar to those published by Sharpless using AD-mix [1a] method have been also obtained [4] using SeOAD reaction [0.016 mol equiv K$_2$OsO$_2$(OH)$_4$], 0.03 mol. equiv (DHQD)$_2$PHAL, 0.3 equiv K$_2$CO$_3$ and benzyl phenyl selenoxide (1.1 equiv) in aqueous $tert$-butyl alcohol [1-1 in volume]): from styrene (yield %, ee %, time h: 93,97,12), β-methyl styrene (92,99,20) stilbene (84,99,72), 1-phenyl cyclohexene (95,99,96), 4-decene (60,70,20), 2-methyl-1-octene (82,50,2.5), 4-t-decene (60,97,3), 2-methyl-2-heptene (85,99,20), and allyl phenyl sulfide (80,59,20).

As general trends, the reaction is highly pH-dependent and is usually substantially faster if carried with aryl selenoxides bearing an electron-withdrawing group on the phenyl group. Typical results are gathered in Schemes 7 and 8 and in Fig. 1 [4].
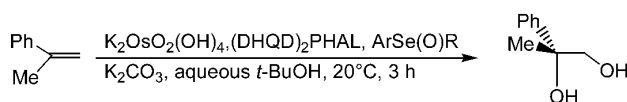
We also found, by performing the SeOAD reaction on 1-phenyl cyclohexene as a model, that the pH of the medium has an important impact both on the yield and the enantioselectivity of the diol formed. The reaction is very slow or even does not take place at pH under 9.5 [4]. Furthermore, our preliminary results, gathered in Scheme 7, tend to show that the pH at which the highest yield is found

Scheme 7 reaction: 1-phenyl cyclohexene with $K_2OsO_2(OH)_4$, $(DHQD)_2PHAL$, 1.1 $PhSe(O)CH_2Ph$, aq *t*-BuOH, buffered solution, 20°C, 24 h → cyclohexane-1,2-diol with Ph substituent.

Entry	$K_2OsO_2(OH)_4$ 10^{-2} mmol	$(DHQD)_2$ PHAL 10^{-2} mmol	pH	Yield % [ee%]	Entry	$K_2OsO_2(OH)_4$ 10^{-2} mmol	$(DHQD)_2$ PHAL 10^{-2} mmol	pH	Yield % [ee%]
a	0.93	2.10	6.4	0	d	1.53	2.93	10.4	90 [86]
b	1.58	2.90	9.56	47 [74]	e	1.43	2.89	11.5	83 [96]
c	1.60	3.18	10.0	86 [73]	f	1.25	3.00	12.1	77 [89]

Dependence of the yields and ees of the diols obtained from the SeOAD of 1-phenyl cyclohexene over the pH of the medium.

Scheme 7

Scheme 8 reaction: α-methyl styrene (Ph, Me) with $K_2OsO_2(OH)_4$, $(DHQD)_2PHAL$, $ArSe(O)R$, K_2CO_3, aqueous *t*-BuOH, 20°C, 3 h → diol (Ph, Me, OH, OH).

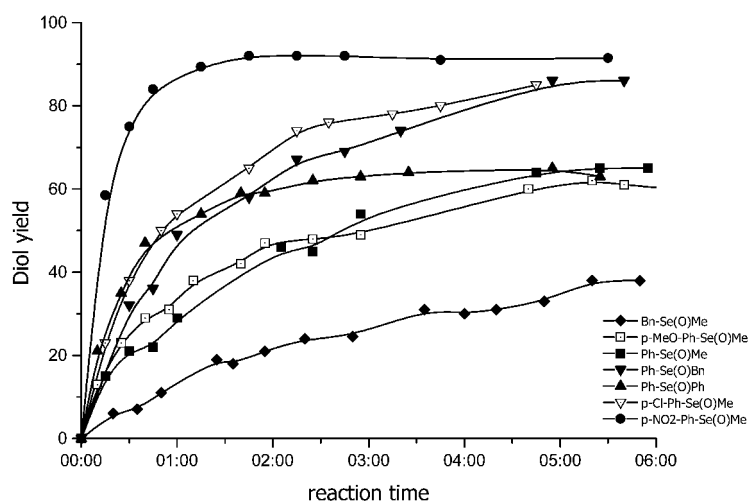| Entry	Selenoxide	Half-time (min.)	e.e of the diol	Entry	Selenoxide	Half-time (min.)	e.e of the diol
a	$PhCH_2Se(O)Me$	810	94 %	e	$PhSe(O)Ph$	56	90 %
b	*p*-MeO-$PhSe(O)Me$	163	90 %	f	*p*-Cl-$PhSe(O)Me$	50	90 %
c	$PhSe(O)Me$	163	88 %	g	*p*-NO_2-$PhSe(O)Me$	16	91 %
d	$PhCH_2Se(O)Ph$	70	91 %				

Scheme 8

Fig. 1 Relative rate of AD of α-methyl styrene under SeOAD conditions involving different selenoxides performed in the presence of K_2CO_3 (% of diol formed vs. reaction time in hours).

(pH 10.4, 90% yield, ee 86%), is different from the one that allows to get the highest enantioselectivity (pH 11.5, yield 83%, ee 96%).

We also found that the reaction is much faster when carried out with diaryl selenoxides than with related aryl methylselenoxides (Scheme 8, compare entry e with entry c; entry d with entry a, Fig. 1) and when the aryl group bears electron-withdrawing groups (Scheme 8, compare entry g with entry c).

Surprisingly the presence of an electron-donating group on the phenyl group does not seem to effect the rate of the dihydroxylation reaction (Scheme 8, compare entry b with entry c). Furthermore, the ee of the diols obtained after completion of each reaction do not markedly differ one from the other. The reported trends seem to be general, since similar results have been obtained when the reaction is carried out on 1-phenyl cyclohexene.

ENANTIOSELECTIVE AIR OXIDATION OF OLEFINS TO DIOLS

The same reactions can be achieved using catalytic amount of selenides (SeAD reaction). In such case, the selenide should be constantly oxidized *in situ* to the corresponding selenoxide until all the olefin present is transformed to the corresponding diol. Singlet oxygen which we used for that purpose long ago [10], was selected. Under the conditions described above, but using: (i) 8% of benzyl phenyl-selenide instead of 110% benzyl phenylselenoxide; (ii) trace amount of rose bengal (RB, 0.3%) as sensitizer for $^3O_2$ to $^1O_2$ activation; (iii) under a slight pressure of dioxygen as the cooxidant (from 3.8 to 2.7 mmHg); and (iv) light (2x 500 watts Osram 64702 R7s, 500 W-230 V, bought in a supermarket for 10 Euro each), the dihydroxylation of α-methylstyrene was achieved [8] after 24 h in yield (93%) and ee (97%) almost identical to those reported in the stoichiometric version (Scheme 9 entry a, compare to Scheme 6). Similar results were obtained using air instead of oxygen (87% yield, 93% ee, Scheme 9, entry b).

a	Oxygen	Yield 93 %, ee 97%
b	Air	Yield 87 %, ee 93%
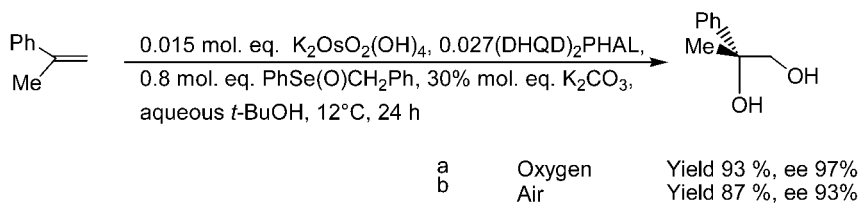
Scheme 9

CONCLUSION

We have demonstrated that phenylbenzylselenide is able, in the presence of light, to promote the efficient dihydroxylation of α-methylstyrene. Not only this new version of the AD reaction uses air as simpler, more available and more ecological cooxidant than those previously used, but also it requires much less matter (87 mg/mmol instead of 360 mg/mmol in the SeOAD reaction or 1400 mg/mmol in the AD-mix reaction). Nevertheless, this variant of the Sharpless AD reaction is at present more theoretical than practical.

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