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A CONVENIENT "ONE-POT" SYNTHESIS OF EPOXY ALCOHOLS VIA PHOTOOXYGENATION OF OLEFINS IN THE PRESENCE OF TITANIUM(IV) CATALYST

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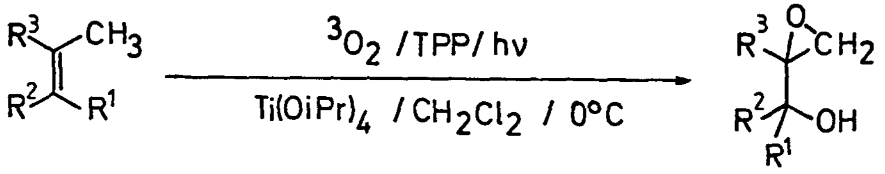
SUMMARY: The ene reaction of singlet oxygen with alkenes in the presence of titanium alkoxides was employed to prepare epoxy alcohols in high diastereoselectivity; enantioselectivity could be achieved by use of diethyl tartrate as chiral auxiliary.

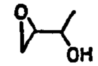
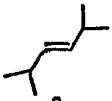
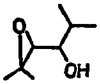
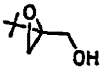
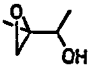
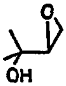
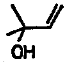
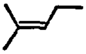
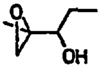
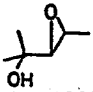
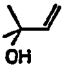
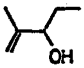
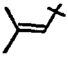
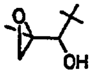
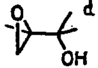
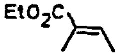
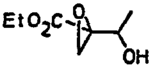
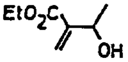
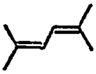
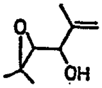
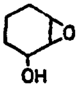
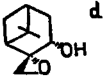
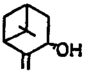
In the Sharpless epoxidation(1) allylic alcohols are converted into epoxy alcohols by Ti(IV)-catalyzed oxygen transfer using hydroperoxides as the extraneous source of oxygen, an especially attractive transformation because in the presence of diethyl tartrate (DET) as chiral auxiliary, synthetically valuable products(2) are obtained in high enantiomeric excess. Since allylic alcohols are readily accessible via singlet oxygenation of olefins and subsequent reduction of the allylic hydroperoxides(3), and since the latter can be converted into the respective epoxy alcohols via metal catalyzed oxygen transfer(4), the "one pot" synthesis of epoxy alcohols from olefins via oxygenation under transition metal catalysis is especially valuable(5) (eq. 1).



(eq. 1)

As Table I reveals, this novel and convenient oxygen functionalization of olefins has broad scope. Thus, disubstituted (1,2,3), trisubstituted (4,5,6) and tetrasubstituted (7) acyclic olefins, carboethoxy-substituted olefin 8, diene 9, and cyclic (10) and bicyclic (11) olefins are readily converted into their respective epoxy alcohols. For some cases (1,2,3,6,7,9), the epoxy alcohols were the only oxidized products, as confirmed by 400 MHz ^{1}H-NMR analysis directly of the crude reaction mixture. For other cases (4,5,8,10,11) appreciable amounts of the corresponding allylic alcohols are formed as by products. A particularly serious case is ethyl tiglate (8), for which as much as 25% of the reduction product 8b was observed. Presumably in the first step of this mechanistically complex oxygen transfer reaction the intermediary allylic hydroperoxide is reduced to the allylic alcohol by the Ti(IV)-catalyst and in a second step intermolecular epoxidation affords the epoxy alcohol.

TABLE I: Reaction of Singlet Oxygen in the Presence of Titanium Tetraisopropoxide

Olefins	Products (Yield[b]; Diastereomeric Ratio[c]) Epoxy Alcohols	 Allylic Alcohols	 Enones
 1	 1a (68%; 53:47)		
 2	 2a (75%; 90:10)		
 3	 3a (87%)		
 4	 4a (38%; 83:17)  4a' (47%)	 4b (3%)	
 5	 5a (28%; 79:21)  5a' (42%)	 5b (3%)  5b' (3%)	
 6	 6a (84%; 95:5)		
 7	 7a (84%)[d]		
 8	 8a (68%; 90:10)	 8b (25%)	
 9	 9a (74%; 93:7)		
 10	 10a (62%; 98:2)[e]	 10b (7%)	 10c (5%)
 11	 11a (81%)[d]	 11b (7%)	 11c (3%)

a) All reactions were carried out using 0.1 M substrate solutions and varying amounts of Ti(OiPr)$_4$ in methylene chloride [(5·10^{-4} M tetraphenylporphine (TPP) as sensitizer)] at 0°C. The reactions were monitored by ^{1}H-NMR and TLC. After completion the reaction mixture was diluted with ether and stirred vigorously for 1-2 h with saturated aqu. Na_2SO_4 solution (1 mL per mmol Ti used) at 20°C, followed by filtration over Celite and Kugelrohr distillation. b) Yields are reported for isolated, purified materials. All new compounds gave appropriate spectral and analytical data. c) Diastereomeric ratios were determined by 400 MHz ^{1}H-NMR. d) cf. Lit. 5. e) cis-trans ratio of 98:2 determined by capillary GC.

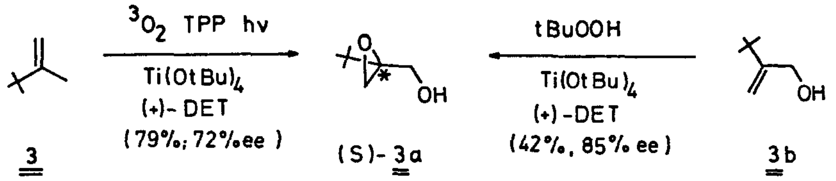
When the latter step is slow, as would be expected for 8b, allylic alcohol accumulates as by-product. In this context it is significant to mention that larger amounts of $Ti(OiPr)_4$ (up to 40%) had to be employed to drive the reaction to completion.

Olefin 4 was chosen to examine whether the regioselectivity in the oxygen transfer was dependent on the concentrations of $Ti(OiPr)_4$ catalyst. In the concentration range of 5-150 mol% catalyst the ratio of regioisomers 4a and 4a' remained constant in the experimental error (Table I). Furthermore, a kinetic analysis(6) of the photooxygenation gave β-values ranging between 0.0053 and 0.0066 mol/L for the above concentrations of $Ti(OiPr)_4$, which are within experimental error the same as without Ti(IV)-catalyst. Thus, under these conditions quenching of singlet oxygen by $Ti(OiPr)_4$ is negligible.

For cyclohexene (10) and α-pinene (11), in addition to the reduction products 10b and 11b, respectively, the corresponding enones 10c and 11c were formed as by-products. Moreover, in the case of α-pinene, control experiments showed that the epoxy alcohol 11a was converted quantitatively into the enone 11c when stoichiometric amounts of Ti(IV)-reagent were used. Fortunately, application of catalytic quantities (5%) of $Ti(OiPr)_4$ afforded the epoxy alcohol 11a in 81% yield (Table I).

Gratifying is the high degree of diastereoselection of the Ti(IV)-catalyzed oxygen functionalization of olefins. As Table I exhibits, except for *trans*-2-butene (1), the diastereomeric ratios range from 79:21 for 5 to 98:2 for 10, but are mostly 90:10 and above (2,6,8,9). The ratio of diastereomers were determined by integration of the respective signals in the 400 MHz ^1H-NMR-spectra. To establish the configurations of the epoxy alcohols, the epoxy alcohol 8b(7) was epoxidized by means of $VO(acac)_2$/*tert.*BuOOH(1c) compared with the diastereomeric mixture derived from the direct Ti(IV)-catalyzed oxygen functionalization of the tiglate 8. 400 MHz ^1H-NMR showed the same qualitative pattern of diastereomer signals, indicating preferential formation of the (RS,SR)-diastereomer(8). In the case of olefins 2 and 9 the NMR data are also consistent with unlike(ul)-selectivity(9). In the case of 9 it is noteworthy that only oxygen transfer to the trisubstituted double bond took place, leading to the epoxy alcohol 9a. This unusually high degree of diastereoselectivity in the oxygen transfer should prove of synthetic value.

Of utmost significance for synthetic purposes was to test the degree of optical induction of the present Ti(IV)-catalyzed "one pot" synthesis of epoxy alcohols from olefins using diethyl tartrate (DET) as chiral auxiliary. The results are summarized in eq. 2(10). Clearly, the epoxy alcohol (S)-3a(11) was formed in good chemical and optical yield. Enantiomeric excess (e.e.) was determined by 400 MHz ^1H-NMR analysis of the corresponding MTPA-ester(12) and of the $Eu(tfc)_3$-shifted epoxy acetate.



3 (S)-3a 3b (eq. 2)

We emphasize the following practical advantages for the "one pot" synthesis of epoxy alcohols directly from olefins via Ti(IV)-catalyzed oxygen transfer: 1. the potentially dangerous hydroperoxides that serve as oxygen donors are formed in situ and thus do not require handling; 2. catalytic amounts of Ti(IV)-reagent suffice; 3. the chemical yields are high; 4. the diastereoselectivity is high; 5. with the help of DET optically active product is obtained in high enantiomeric excess.

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