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Facile Perhydrolysis of Oxetanes Catalyzed by Molybdenum Species

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Supporting Information

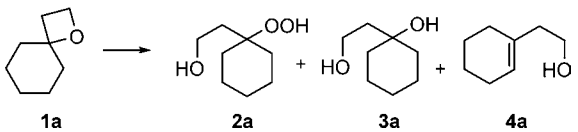
ABSTRACT: Perhydrolysis of a range of tertiary oxetanes was achieved in synthetically useful yields under mild conditions. Different functional/protecting groups were tolerated. Similar ring-opening of secondary oxetanes, which had been unfeasible to date, was also realized with ease. With the aid of optically active substrates the perhydrolysis was shown to proceed with significant stereoselectivity.

Incorporation of peroxy bonds into carbon frameworks is an essential step in the synthesis of organic peroxides. Because of the limited existing methods and the intrinsic instability of peroxy linkages, such a step is often also a critical/most difficult step in the whole synthetic sequence. The known sources of the peroxy bonds include dioxygen species in either singlet state ($^1O_2$) or triplet ($^3O_2$), ozone (O_3), or hydrogen peroxide (H_2O_2). Among these, the $^1O_2$[1,2] and O_3[3] are highly reactive species and thus have found numerous successful applications. $^3O_2$ can be used only when carbon-centered radicals are present.[4] As for H_2O_2, its incorporation into organic molecules in useful yields is achieved mainly via perhydrolysis of ketals/ketones or epoxides to date.[5,6]

Oxetanes are less reactive than epoxides in general and often show significantly lower reactivity toward most nucleophiles.[7] In 2002, perhydrolysis of oxetanes was explored for the first time by Dussault.[8] Using an acid catalyst such as TMSOTf they achieved successful perhydrolysis of several alkyl oxetanes in H_2O_2/Et_2O. However, after that pioneering work no other protocols appeared in the literature to date; further studies on use of oxetanes (especially multifunctionalized ones) as substrates for incorporation of peroxy functionalities thus remain highly desirable.

In continuation of our studies[9] on synthesis of organic peroxides, we also examined the reaction of oxetanes with H_2O_2. Using **1a**[10] as a model (Scheme 1), we first tested the

Scheme 1



transformation in ethereal[5l] H_2O_2 in the presence of PMA[9a] (phosphomolybdic acid). To our surprise, despite the similarity of **1** to the corresponding epoxide, the desired **2a** was obtained in only 22% yield while **3a** and **4a** were isolated in 12% and 50%, respectively (Table 1, entry 1). Comparable results were also observed in *t*-BuOMe (Table 1, entry 2), a solvent much

Table 1. Perhydrolysis of 1a leading to 2a, 3a and 4a[a]

entry	conditions	**2a** (%)	**3a** (%)	**4a** (%)
1	Et_2O/PMA/6 h	22	12	50
2	*t*-BuOMe/PMA/7 h	23	14	46
3	Et_2O/Na_2MoO_4.gly/12 h	58	11	traces
4	*t*-BuOMe/Na_2MoO_4.gly/12 h	61	10	traces

[a]All runs were performed at ambient temperature in the indicated solvent saturated with H_2O_2 in the presence of 10 mol % (with respect to **1a**) of the indicated catalyst.

safer than Et_2O because of its lower tendency[11] to form hydroperoxides by autoxidation and higher boiling point.

However, when Na_2MoO_4-gly (prepared[9c] from Na_2MoO_4 and glycine) was used, the yield for the desired **2a** was raised to 58% (Table 1, entry 3). In *t*-BuOMe, 61% yield was recorded for **2a**. And in both cases, the previously dominating elimination product **4a** became negligible.

Oxetanes **1b**–**h** also reacted smoothly under the same conditions, although the required time varied from 1 to 48 h depending on the structure. The yields and product distribution pattern differed slightly when the ring size of the cyclic ketone residue (Table 2, entries 1–2, also Table 1, entry 4) changed. In the case of **1d** (Table 2, entry 3), where the elimination product **4d** was not possible to form, the composition of the product mixture became rather simple. Nonspirooxetanes also afforded the expected hydroxy-hydroperoxides in yields comparable to those observed with the spiro- substrates (Table 2, entries 4–7). In particular, those benzylic oxetanes led to apparently cleaner reactions and better material balance (Table 2, entries 5–7).

The alcohols **3** (probably due to hydrolysis) were formed in all cases, although in later experiments they were not collected (because of their small quantities and/or inseparability from other side-products) and thus are not included in Tables 3 and 4.

Oxetanes[10] with two stereogenic centers were next tested under our standard conditions (H_2O_2/*t*-BuOMe/Na_2MoO_4–

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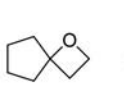
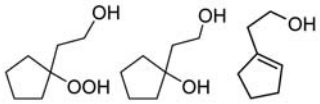
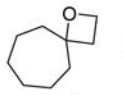
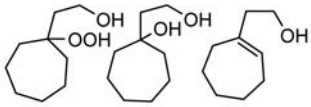
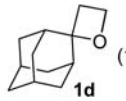
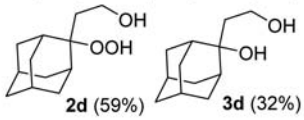
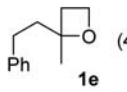
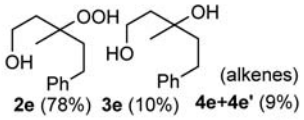
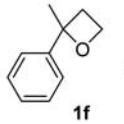
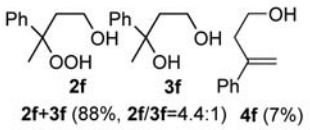
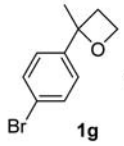
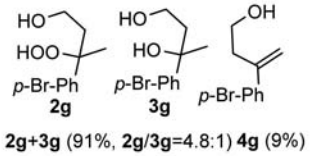
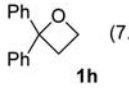
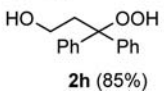
Table 2. Results of Perhydrolysis of 1b–h[a]

entry	substrate (time[b])	identified products (yield)
1	 (5 h) **1b**	 **2b** (48%) **3b** (17%) **4b** (13%)
2	 (4 h) **1c**	 **2c** (50%) **3c** (16%) **4c** (28%)
3	 (16 h) **1d**	 **2d** (59%) **3d** (32%)
4	 (48 h) **1e**	 **2e** (78%) **3e** (10%) **4e+4e'** (9%) (alkenes)
5[c]	 (1 h) **1f**	 **2f+3f** (88%, **2f/3f**=4.4:1) **4f** (7%)
6[c]	 (4 h) **1g**	 **2g+3g** (91%, **2g/3g**=4.8:1) **4g** (9%)
7	 (7.5 h) **1h**	 **2h** (85%)

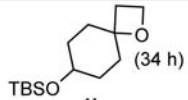
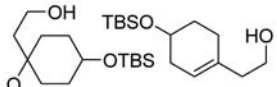
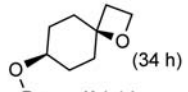
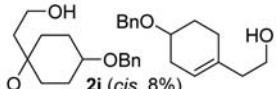
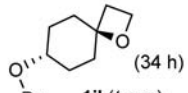
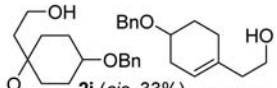
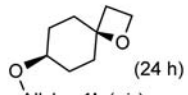
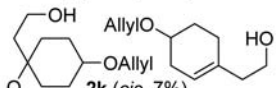
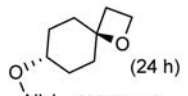
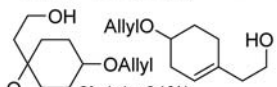
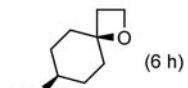
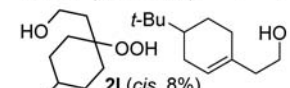
[a]Performed under the standard conditions. [b]The reaction time. [c]The **2f**/**3f** and **2g**/**3g** ratios were determined by ^{1}H NMR.

gly (10 mol %)/rt, with [oxetane] = 0.2 M). The TBS protected **1i** (an inseparable *cis*/*trans* isomers) afforded **2i** (an inseparable *cis*/*trans* isomers, Table 3, entry 1) in 54% isolated yield along with 13% of **4i**, providing the first successful protecting group compatible example for the oxetane perhydrolysis. The separated diastereomers such as **1j**,[12] **1j**′, **1k**[13] and **1k**′ showed distinct differences in stereoselectivity (Table 3, entries 2–5) of the hydroperoxyl group substitution and thus provided important clues to the stereochemical course of the reaction. The isolated *t*-Bu substituted oxetane **1l** also afforded similar results (entry 6).

A group of racemic substrates[14] with two adjacent stereogenic centers were then examined (Table 4), which (**1m**–**q**[15]) all afforded the expected hydroperoxides under the above-mentioned standard conditions in 37–41% yields. The sterically less hindered side chain oxetane **1r** (Table 4, entry 6) seemed much more reactive, providing **2r** (inseparable diastereomers) in a 57% isolated yield.

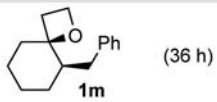
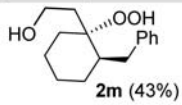
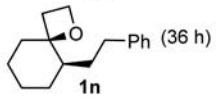
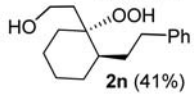
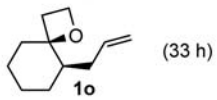
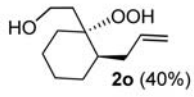
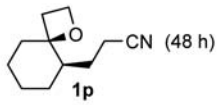
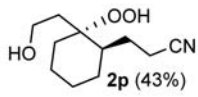
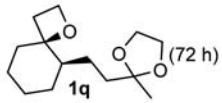
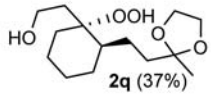
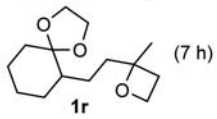
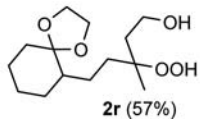
Secondary oxetanes **1s**,**t** were also tested. Interestingly, these sterically less crowded oxetanes turned out to be completely resistant to the H_2O_2/*t*-BuOMe/Na_2MoO_4-gly/rt conditions. However, with the more acidic PMA as the catalyst, the anticipated perhydrolysis eventually occurred smoothly, affording **2s** and **2t**, respectively, but along with the primary hydroperoxides **2s**′ and **2t**′ (Scheme 2).

Table 3. Results of Perhydrolysis of 1i–l[a]

entry	substrate (time[b])	identified products (yield)
1	 (34 h) **1i**	 **2i** (54%) **4i** (13%)
2	 (34 h) **1j** (*cis*)	 **2j** (*cis*, 8%) **2j'** (*trans*, 34%) **4j** (12%)
3	 (34 h) **1j'** (*trans*)	 **2j** (*cis*, 33%) **2j'** (*trans*, 23%) **4j** (14%)
4	 (24 h) **1k** (*cis*)	 **2k** (*cis*, 7%) **2k'** (*trans*, 35%) **4k** (10%)
5	 (24 h) **1k'** (*trans*)	 **2k** (*cis*, 31%) **2k'** (*trans*, 13%) **4k** (10%)
6	 (6 h) **1l** (*cis*)	 **2l** (*cis*, 8%) **2l'** (*trans*, 45%) **4l** (27%)

[a]Performed under the standard conditions. [b]The reaction time.

Table 4. Results of Perhydrolysis of 1m–r[a]

entry	substrate (time[b])	product (yield)
1[c]	 (36 h) **1m**	 **2m** (43%)
2[d]	 (36 h) **1n**	 **2n** (41%)
3	 (33 h) **1o**	 **2o** (40%)
4	 (48 h) **1p**	 **2p** (43%)
5[e]	 (72 h) **1q**	 **2q** (37%)
6[f]	 (7 h) **1r**	 **2r** (57%)

[a]Performed under the standard conditions; minor/inseparable products were not shown. [b]The reaction time. [c]14% of **1m** was recovered. [d]16% of **1n** was recovered. [e]Performed at 10 °C; 25% of **1q** was recovered. [f]Along with 22% of **4r** (inseparable alkene isomers).

The failures under the above-mentioned standard conditions, along with the documented[8] similar case under the previous conditions, reveal that secondary oxetanes are far less reactive

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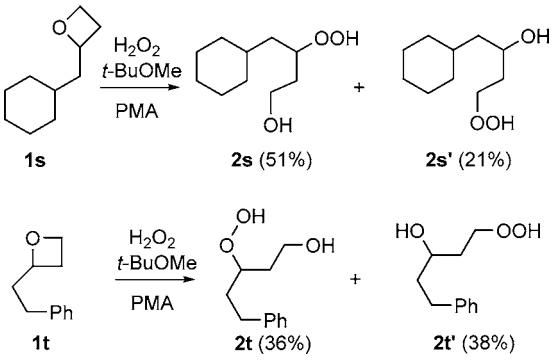
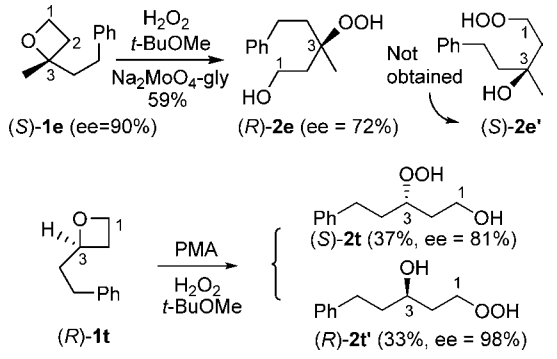
Scheme 2



than corresponding tertiary oxetanes. It follows that the S_N2 route must be negligible in the perhydrolysis of tertiary oxetanes. Otherwise, **1s,t** would have reacted easier than **1a−r** because of their much less steric crowdedness around the reaction centers compared with that in **1a−r**.

To gain further mechanistic insights, we next examined the perhydrolysis with optically active **1e**[16] and **1t**[16] (Scheme 3).

Scheme 3

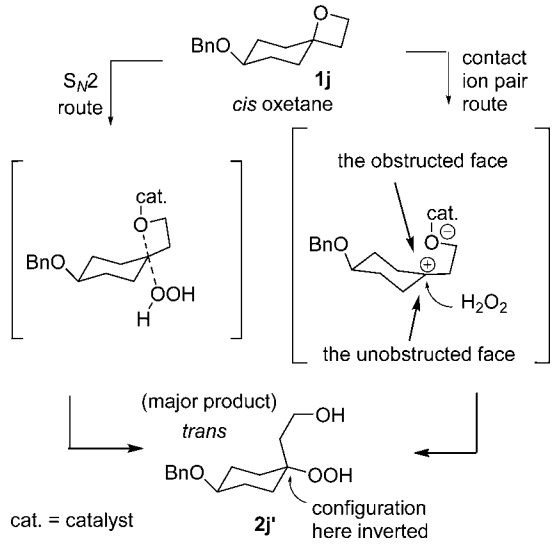


Under the standard conditions, the expected (*R*)-**2e** (75% ee, along with 17% of unreacted starting (*S*)-**1e**) was isolated in 73% yield (cf. also Table S1 in the Supporting Information).

The outcome for the perhydrolysis of (*R*)-**1t** (affording (*S*)-**2t** with poorer regioselectivity yet a higher level of inversion along with substantial amounts of **2t′**) is fully consistent with the preceding reasoning that the S_N2 path predominated in the perhydrolysis of the secondary oxetanes yet was nearly negligible in the tertiary cases. It is also compatible with the result with (*S*)-**1e**: If the S_N2 path contributed substantially in the formation of (*R*)-**2e**, it would have also occurred at the much less congested C-1 and afforded the primary hydroperoxide (*S*)-**2e′** (which was not observed) in significant quantities.

An issue that remains to be addressed here is why the tertiary oxetanes still showed significant stereoselectivity in the transformation? A plausible explanation that can reconcile an S_N1 type mechanism and the significant levels of configuration inversion in the facile perhydrolysis of the tertiary oxetanes is that the leaving group stayed rather close to the reaction center (so-called "contact ion pair"[17]) and thus partially blocked that face of the intermediate carbocation; the attacking H_2O_2 could enter mainly from the opposite face leading to hydroperoxide with an inverted configuration as illustrated in Scheme 4.

Scheme 4



If the ring substituent and the leaving group are *trans* to each other (e.g., **1j′**), formation of the hydroperoxides with an inverted configuration is expected to be reduced because the backside (opposite to the leaving group) is now partially blocked by the ring substituent. The observations with **1j′** and **1k′** were indeed compatible with this deduction.

In summary, facile perhydrolysis of tertiary oxetanes was achieved in the presence of Na_2MoO_4-gly. A range of functional/protecting groups were well tolerated. Even secondary oxetanes (resistant to previous conditions) reacted smoothly if using PMA as the catalyst. Some insights about the perhydrolysis mechanism were also thus gained. The mildness of conditions, broadened substrate scope and improved yields make the present protocol a beneficial alternative to the so far only[8] entry to the useful/desirable[8,18] γ-hydroxyhydroperoxides.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data/scanned spectra for products (new compounds), chiral HPLC. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(13) The relative configurations of **1k** and **1k**′ (separable from each other, with distinct differences in ^1H NMR) were established by comparison with an authentic **1k** prepared from **1j** by debenzylation and allylation.

(14) For relative configurations, cf. Supporting Information.

(15) Prepared using the method of ref 10. It is noteworthy that the epoxides obtained in these cases were a single diastereomer (by comparison with the authentic samples obtained through derivatization as previously mentioned in ref 9c above). The relative configurations were not changed during the transformation to oxetanes according to ref 10 above. For other synthetic accesses to oxetnes, see refs 7 and 8 above.

(16) For syntheses, see the Supporting Information.

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