Alkene Dihydroxylation

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Metal or No Metal: That Is the Question!**

*Michael Schwarz and Oliver Reiser**

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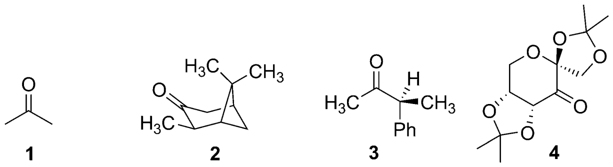
The oxidative functionalization of alkenes is among the most extensively investigated synthetic transformations in organic chemistry. Simple oxidative cleavage,[1a–d] halogenation,[1e] halohydrin formation,[1f] and Wacker oxidation[1g] are widely applied in academia and industry. Moreover, transition-metal-catalyzed epoxidation,[2a–e] dihydroxylation,[2f–h,3] and aminohydroxylation[2i,j] reactions, for which enantioselective variants with broad scope have been developed, serve as the cornerstone of many complex-molecule syntheses.

A stunning example of the progress in organocatalytic oxidation is the development of the epoxidation of alkenes with dioxiranes. Early examples with simple dimethyldioxirane generated from acetone (**1**) and Oxone (potassium peroxymonosulfate) in situ were reported in 1979 by Edwards et al.,[4a] and the scope of the reaction was expanded by Curci et al. in 1980.[4b] The same group developed the first asymmetric epoxidation in 1984 with dioxiranes derived from chiral ketones **2** and **3**;[4c] however, only low asymmetric induction could be achieved at this time (Figure 1).



1 Edwards et al., 1979 Curci et al., 1980

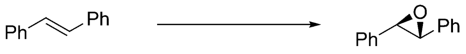
2 Curci et al., 1984

3 Curci et al., 1984

4 Shi et al., 1996

Figure 1. Representative ketones used for the epoxidation of alkenes with dioxiranes.

Quite a number of other chiral ketones were subsequently investigated[4d,e] to improve the enantiomeric excess until in 1996 the readily available fructose-derived ketone **4** was introduced by Shi et al.[4f] While stoichiometric amounts of **4** were initially necessary to achieve high enantioselectivity, only one year later the same group was able to establish a catalytic variant by adjusting the pH of the reaction;[4g] under these conditions the reaction rivalled the efficiency of metal-based asymmetric epoxidations (Scheme 1).



a) pH ca. 7-8, **4** (3 equiv), Oxone (5 equiv): 73 %, 95% *ee*
b) pH ca. 10.5, **4** (0.3 equiv), Oxone (1.4 equiv): 75 %, 97% *ee*

Scheme 1. Demonstration of the pH dependence of the asymmetric Shi epoxidation.[4g,5]

Another class of organic compounds, organic acyl peroxides, could potentially break the dominance of metal-catalyzed processes for the oxidative functionalization of alkenes. So far, the primary oxidant OsO$_4$ is still the reagent of choice for the *syn* dihydroxylation of alkenes[2f–h,3] for both asymmetric and non-asymmetric metal-catalyzed reactions.[2f–h] However, because of the high cost, volatility, and toxicity of OsO$_4$, its use in large-scale industrial processes is not viable, although significant efforts have been made in this area.[6] For safety and ease of handling, OsO$_4$ is typically prepared in situ from K$_2$[OsO$_2$(OH)$_2$].[2h] Nevertheless, the rare occurrence of "reactive metals" in the earth's crust is a severe restriction: the supply of osmium is even more limited than that of the other platinum group metals ruthenium, rhodium, palladium, and platinum.[7] The problem of the poor availability of these metals is obviated by organocatalytic processes, since these catalysts are composed of highly abundant elements.

The dihydroxylation of simple alkenes such as stilbene with phthaloyl peroxide (**5**) was established already in the late 1950s and early 1960s by Greene.[8] However, phthaloyl peroxide (**5**) is unstable in aromatic solvents and also decomposes slowly in carbon tetrachloride. Furthermore, it is explosive at high temperatures and very shock-sensitive.[8a] For the synthesis of phthaloyl peroxide (**5**), Greene prepared an anhydrous solution of hydrogen peroxide in diethyl ether with sodium carbonate.[8a,9] A safer and more convenient method for the preparation of phthaloyl peroxides was published recently by Siegel et al.,[10] in which hydrogen peroxide is replaced by sodium percarbonate, which also facilitates the synthesis of other phthaloyl peroxide derivatives. Among the derivatives synthesized, 2,3-dichlorophthaloyl peroxide (**6**) was found to be the most reactive although its stability is comparable to that of phthaloyl peroxide (**5**).

When *trans*-stilbene was subjected to **5**, followed by base hydrolysis, the diols **9** and **10** were liberated in good diastereomeric ratio (20:1) and yield, whereas the more

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[*] Dipl.-Chem. M. Schwarz, Prof. Dr. O. Reiser
Universität Regensburg, Institut für Organische Chemie
Universitätsstrasse 31, 93053 Regensburg (Germany)
E-mail: oliver.reiser@chemie.uni-regensburg.de
Homepage: http://www-oc.chemie.uni-regensburg.de/reiser

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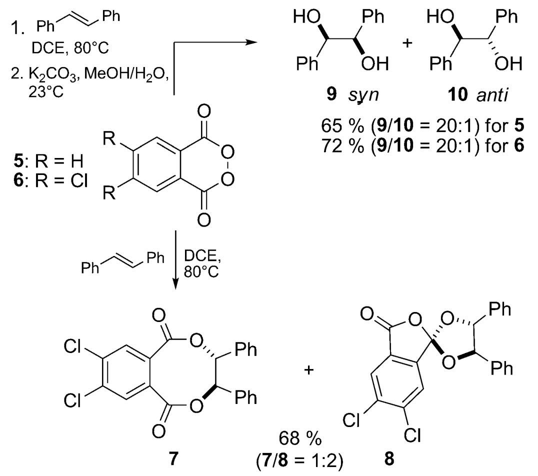


Scheme 2. Reactions of **5** and **6** with *trans*-stilbene. DCE = 1,2 dichloroethane.[10]

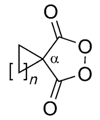
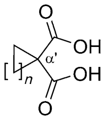
reactive 2,3-dichlorophthaloyl peroxide (**6**) led to improved yields (72 % versus 65 %). As intermediates, the cyclic phthalate **7** and lactonic *ortho*-ester **8** were identified (Scheme 2).

This process was amenable to various linear and cyclic alkenes which when treated with **6** gave rise to the corresponding *syn* diols in moderate to good yields (30–72 %). The enhanced reactivity of reagent **6** relative to that of **5** was especially apparent when aliphatic alkenes were employed as substrates (Scheme 3, diol **20**).

Despite the improved facile access to phthaloyl peroxides, a major drawback remains the instability of these compounds, which prevents their use in large-scale processes. As a possible solution to this problem, Tomkinson et al. investigated the use of malonyl peroxide derivatives for the dihydroxylation of alkenes.[11] Cyclopropylmalonyl peroxide (**11**) was found to be the most reactive peroxide in the series of three-, four-, and five-membered spirocyclic malonyl peroxides **11**–**13** for the dihydroxylation of styrene.

X-ray structure analysis of **11**–**13** revealed that all three compounds have similar peroxide bond lengths; however, the bond angles α are significantly different (Table 1). The authors reason that the increased reactivity of **11** over that of **12** and **13** is based on the higher ring strain in the five-membered acyl peroxide ring, which is reflected by the largest α bond angle in this series.[12] On the other hand, since the α angle found in the X-ray structure of **11** is closest to the ideal tetrahedral angle and is thus the least distorted, an alternative argument could be considered. By comparison of calculated α angles from the closed acyl peroxides (α value) and their corresponding open dicarboxylic acids (α' value), the strain release ($\alpha'-\alpha$) increases from **13** to **11** (Table 1),[13] which is also consistent with the higher reactivity of **11**.

Table 1: Comparison of calculated α angles of the closed acyl peroxides and their corresponding open dicarboxylic acids.[a]

			
n	α	α'	$\alpha'-\alpha$
11 $n=1$	105.2° (107.6°)[b]	119.6°	14.4°
12 $n=2$	102.3° (104.0°)[b]	116.2°	14.1°
13 $n=3$	101.5° (102.3°)[b]	104.6°	3.1°

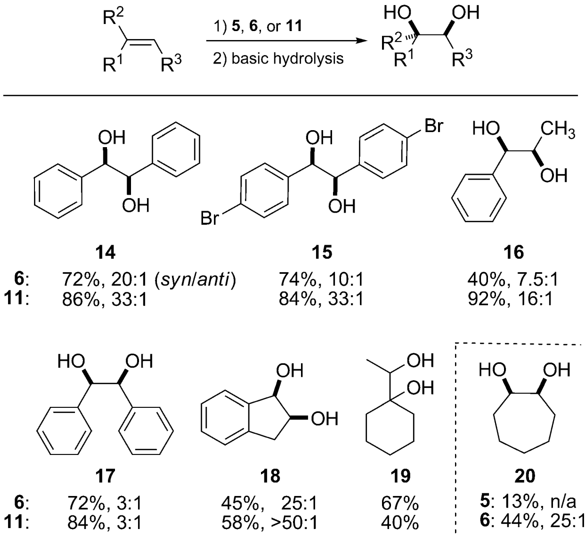
[a] Hartree–Fock 6-31G* calculation; equilibrium geometry at ground state.[13] [b] Bond angles α derived from X-ray structure analysis.[11]

Despite the increased reactivity of **11**, Tomkinson et al. point out that **11** "*proved to be insensitive to shock and direct heating and was bench-stable*".[11] Nevertheless, because of the reactive nature of peroxides, special precaution must always be exercised in handling such compounds.

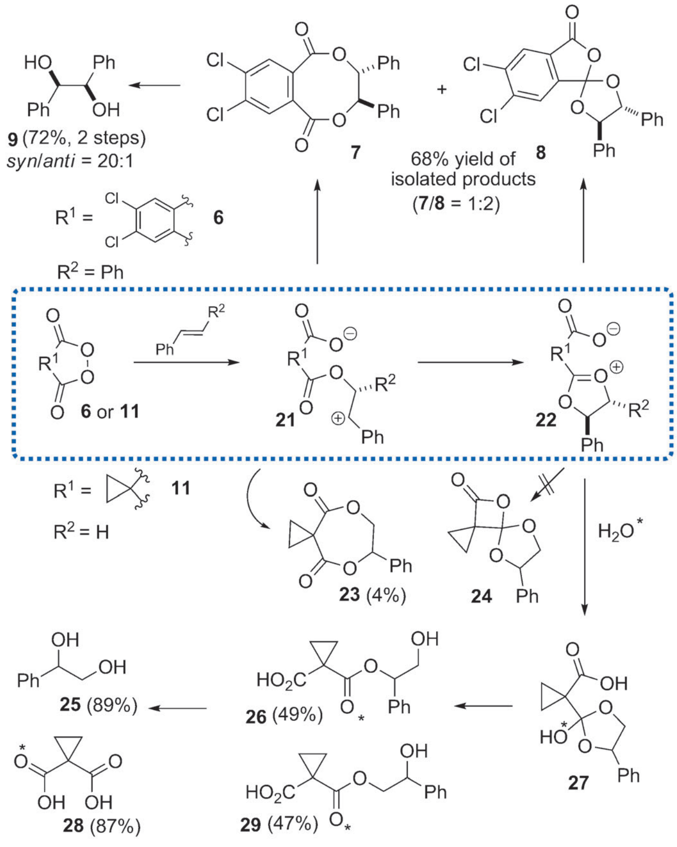
Aryl-substituted alkenes were dihydroxylated with **11** to yield the desired diols in 56–93 % yield and high *syn* selectivity (Scheme 3). In general, reactions of aryl-substituted alkenes with **11** resulted in higher stereospecificity and yield than with 2,3-dichlorophthaloyl peroxide (**6**). Alkyl-substituted alkenes appear to be more challenging; only one example was reported, the synthesis of diol **19** in only moderate yield (40 %). With this class of substrates 2,3-dichlorophthaloyl peroxide (**6**) seems to provide better results than reagents **5** and **11** (Scheme 3, diols **19** and **20**).

A plausible mechanism for the title transformation involves the ionic intermediates **21** and **22** proposed by Tomkinson et al. (Scheme 4). However at this time, a radical or a single-electron-transfer pathway also cannot be ruled out.[11] The occurrence of **21** and **22** is supported by the isolation of **7** and **8** by Siegel et al. in a ratio of 1:2;[10] this is consistent with the faster formation of five-membered over eight-membered rings. Tomkinson et al. isolated the seven-membered lactone **23** analogous to **7**, but the highly strained spiro compound **24** analogous to **8** was not observed.

In experiments with ^{18}O-labeled water Tomkinson et al. found ^{18}O in both compounds **26** and **29** as well as in the open carboxylic acid **28** (Scheme 4). The absence of labeled oxygen in diol **25** suggests the presence of oxonium intermediate **22** derived from **21** by an intramolecular ring closure.

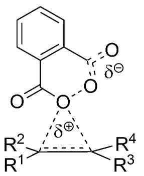


Scheme 3. Comparison of the stereospecifity and reactivity of **5**, **6**, and **11** in the reactions of selected alkenes.[10,11] n/a = not available.



Scheme 4. Possible mechanistic pathway for the dihydroxylation of alkenes. $O^* = {}^{18}O$.

Greene and Rees found second-order kinetics[8b,c] for the reaction between phthaloyl peroxide **5** and stilbene, and consequently dismissed a biradical mechanism proceeding through homolytic O–O cleavage.[8d] They also considered **21** as a possible intermediate, but nevertheless regarded it as an "electronic extreme".[8e] Hence, **30** was proposed as a potential intermediate undergoing charge redistribution during the formation of the products.[8e]



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Acyl peroxides could open the way to a process for the metal-free dihydroxylation of alkenes; however, many challenges must be overcome before the reaction is preparatively useful. Catalytic and asymmetric variants need to be developed, and conditions must be found that tolerate a wide range of functional groups in the substrates. Nevertheless, the developments discussed here show that organocatalytic processes are further advancing into areas that seemed to be traditionally in the realm of metal catalysis.

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[5] For detailed reaction conditions, see Ref. [4g]. Shi et al. were also able to improve the asymmetric induction slightly by changing both the temperature and the solvent. As this modification had no effect on the catalytic efficiency it is not shown in Scheme 1.

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