

Alkene Syn Dihydroxylation with Malonoyl Peroxides

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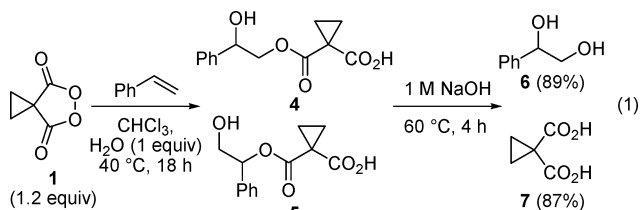
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Abstract: Cyclopropyl malonoyl peroxide (**1**), which can be prepared in a single step from the commercially available diacid, is an effective reagent for the dihydroxylation of alkenes. Reaction of **1** with an alkene in the presence of 1 equiv of water at 40 °C followed by alkaline hydrolysis leads to the corresponding diol (40–93%). With 1,2-disubstituted alkenes, the reaction proceeds with syn selectivity (3:1 to >50:1). A mechanism consistent with the experimental findings that is supported by oxygen-labeling studies is proposed.

The dihydroxylation of alkenes is a fundamental transformation in organic synthesis. A range of methods have been reported for the preparation of *syn*-1,2-diols;¹ however, the OsO₄-catalyzed procedure developed by Sharpless and co-workers is most commonly employed.² Despite the widespread popularity of this reaction, the toxicity of osmium and high levels of inorganic waste represent important limitations that have hindered its application on an industrial scale.³ For these reasons, the development of a metal-free dihydroxylation procedure provides a challenging and highly attractive target.

Peroxides are known to be highly reactive and serve as versatile reagents in synthesis.⁴ Examples of a peroxide reagent capable of *syn* dihydroxylation are rare.⁵ Isolated reports have shown that phthaloyl peroxide dihydroxylates a limited number of alkenes, but the explosive nature of this compound has limited its use in synthesis.^{5a} We reasoned that a class of stable cyclic acyl peroxides may provide the basis of a metal-free dihydroxylation procedure. Herein we report that cyclopropyl malonoyl peroxide (**1**) is an effective reagent for alkene *syn* dihydroxylation.

Development of the reaction between peroxides **1–3** and styrene was initially examined by varying the solvent, time, temperature, additive, and peroxide stoichiometry. Optimized conditions involved addition of **1** (1.2 equiv) to styrene in the presence of 1 equiv of water to give two intermediate esters **4** and **5** in a roughly 1:1 ratio. Removal of the solvent followed by hydrolysis of the crude reaction mixture provided diol **6** (89%) and diacid **7** (87%) (eq 1). Recovered **7** can be converted to peroxide **1** (77%) in a single step.



Several features of this novel dihydroxylation procedure deserve comment. The reaction proceeds under mild conditions in the presence of air and moisture. For the majority of alkenes examined, the diol product required no column chromatography, and diacid **7** was recycled through workup. Although we recommend safe working procedures for peroxides, in our hands **1** proved to be insensitive to shock and direct heating and was bench-stable. The combination of easily handled reagent and mild reaction conditions renders the overall process highly practical.

The relative rates of reaction of peroxides **1–3** with styrene are shown in Figure 1. Interestingly, this revealed a marked change in reactivity through simple modification of the peroxide structure, with cyclopropyl malonoyl peroxide **1** emerging as the most effective.

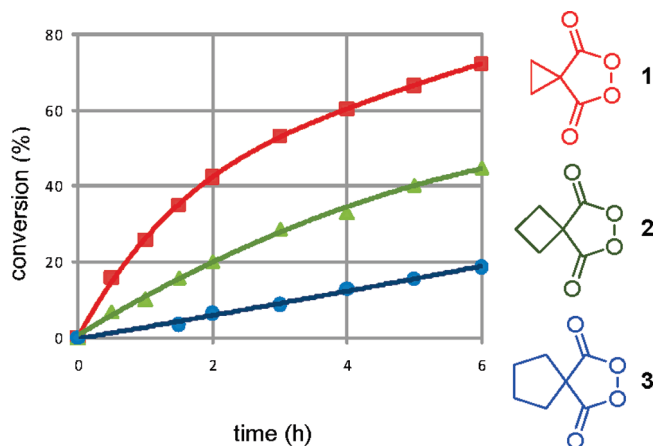


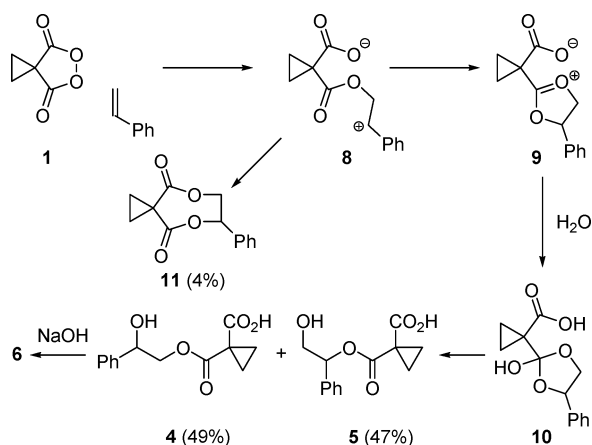
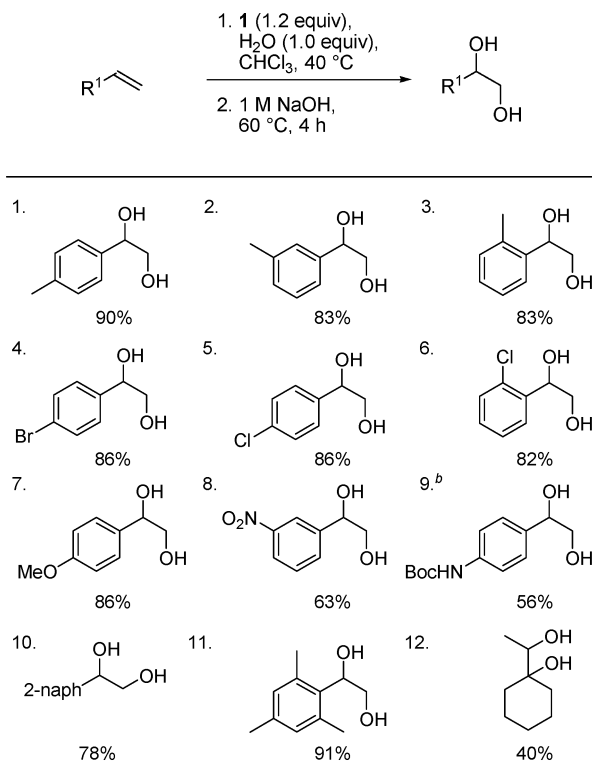
Figure 1. Relative rates for the reaction of peroxides **1–3** with styrene. All of the reactions were performed in CHCl₃ (0.6 M) at 40 °C in the presence of H₂O (1.0 equiv). (■) peroxide **1**; (▲) peroxide **2**; (●) peroxide **3**.

An explanation for the enhanced rate observed with **1** came from X-ray crystallography (Figure 2). For each peroxide **1–3**, the five-membered cyclic peroxide unit adopts a planar conformation with nearly identical O–O bond lengths. The major difference among **1–3** is the OC–C–CO bond angle. As the size of the spirocyclic ring decreases from five to four to three, the OC–C–CO bond angle increases from 102.34(17)° (**3**) to 107.56(19)° (**1**). This increases the ring strain of the peroxide and is manifested by the

	1	2	3
O–O bond (Å)	1.476(2)	1.476(2)	1.471(2)
OC–C–CO angle	107.56(19)	104.01(13)	102.34(17)

Figure 2. X-ray structural data for peroxides **1–3**.

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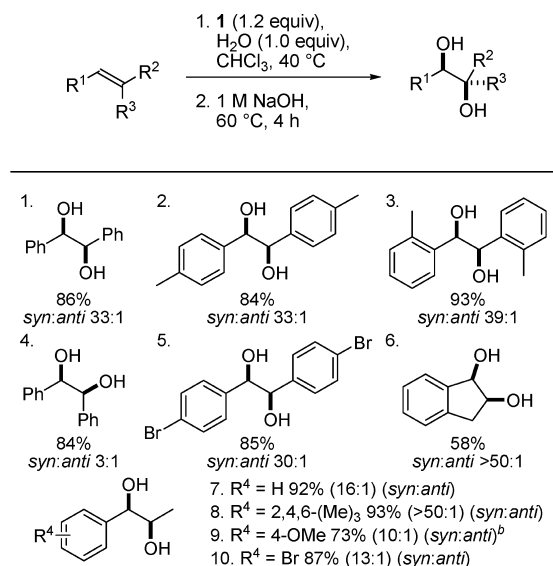
Scheme 1. Possible Mechanistic Course of the Reaction**Table 1.** Scope of the Dihydroxylation^a

^a Yields quoted are isolated yields. All reactions were run in duplicate. ^b Reaction was performed with peroxide 2.

increased reactivity of **1**, consistent with differential scanning calorimetry (DSC) analysis (Supporting Information).

Mechanistically, we believe that reaction of alkene with peroxide **1** leads to **8**, which undergoes ring closure to form dioxonium species **9** (Scheme 1).⁶ Hydrolysis with the molecule of water necessary to bring about reaction explains the 1:1 ratio of esters **4** and **5**. Additionally, a small amount (4%) of **11** resulting from direct cyclization of **8** was present in the crude reaction mixture. Consistent with this proposal, a preliminary investigation using H₂¹⁸O showed incorporation of the label in the intermediates **4** and **5** and the diacid **7** but not in the final diol product **6**.

Pleasingly, the conditions developed above were effective for the dihydroxylation of a range of alkenes in up to 91% isolated yield (Table 1). For each reaction, diacid **7** could easily be recovered through workup.

Table 2. Stereoselectivity of the Dihydroxylation^a

^a Yields quoted are isolated yields. All reactions were run in duplicate. Stereoselectivities were determined by ¹H NMR spectroscopy of the crude reaction mixture, with relative stereochemistries determined by comparison to material prepared by Sharpless dihydroxylation. ^b Reaction was conducted at 0 °C.

Diastereoselectivity was examined with a series of 1,2-disubstituted alkenes (Table 2). *trans*-Stilbene substrates gave selectivities in excess of 30:1 (entries 1–3 and 5). Consistent with the proposed mechanism (i.e., **8**), *cis*-stilbene gave the syn-dihydroxylated product in a lower 3:1 ratio (entry 4), whereas incorporation of the alkene within a ring resulted in exclusive formation of the syn product (entry 6). β-Methylstyrene derivatives also gave the products with excellent stereoselectivity (≥ 10:1) (entries 7–10), providing a powerful and versatile method for selective alkene functionalization.

We have described an effective and highly practical method for the syn dihydroxylation of alkenes. The reaction is operationally simple and transition-metal-free and does not require the rigorous exclusion of moisture or air. Current efforts are focusing on a catalytic variant of this transformation.

Caution! Peroxides are particularly dangerous. These procedures should be carried out only by knowledgeable laboratory workers.

Acknowledgment. The authors thank Leverhulme Trust, EPSRC, and GlaxoSmithKline for financial support and the Mass Spectrometry Service, Swansea, for high-resolution spectra. We are indebted to Professor Barry Carpenter for enthusiastic and insightful discussions and Dr. John Brazier for stimulating debate.

Supporting Information Available: Experimental procedures, characterization data, NMR spectra for all compounds, DSC data, and CIF files for **1**–**3**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (6) At this stage, it is not clear whether the reaction of alkene with peroxide **1** occurs via an ionic, SET, or radical chain mechanism.

JA1066674