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Palladium(II)-Catalyzed Cyclization of Unsaturated Hydroperoxides for the Synthesis of 1,2-Dioxanes

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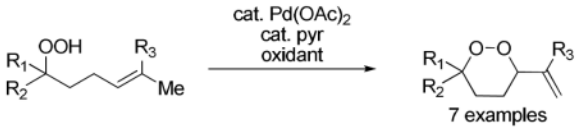
Abstract



The cyclization of γ,δ-unsaturated tertiary hydroperoxides in the presence of a palladium(II) catalyst afforded 1,2-dioxanes resembling biologically active natural products. A variety of substrates were screened, and synthetic manipulations were accomplished to construct compounds with structural similarity to antimalarial targets.

The discovery of peroxide-containing natural products as active agents against malaria[1] and various cancers[2] has led to an increased effort to synthesize these compounds and their derivatives.[3] As a class, cyclic peroxides are the most common peroxide-containing motifs isolated.[4] The structures in Figure 1 represent three important types of endoperoxides: 1,2-dioxolanes (as found in plakinic acid C);[5] 1,2,4-trioxanes (as represented by artemisinin);[3a] and 1,2-dioxanes (as exemplified by peroxyplakoric acid A_1 methyl ester).[6]

In light of the pharmaceutical potential of peroxides, the development of methods to prepare these compounds would aid in the discovery of new peroxide-containing drugs.[1c] The lability of the weak O–O bond makes installation and functionalization of peroxides particularly challenging, however.[3d,7] The synthesis of 1,2-dioxanes has been accomplished in various ways. The intramolecular nucleophilic displacement of leaving groups, such as halides[8] or mesylates[9], has been employed. The use of peroxides as nucleophiles for the intramolecular attack on epoxides is another method for the synthesis of 1,2-dioxanes.[10] While these methods are useful, they require preformation of the desired leaving group. A common strategy for the synthesis of endoperoxides is the cyclization of pendant hydroperoxides onto activated alkenes. For example, conjugate additions of peroxide nucleophiles onto electron-deficient alkenes have been used.[11] These conditions also facilitate formation of epoxide side products, arising from Weitz-Scheffer oxidation,[12] resulting in diminished yields of the desired endoperoxide. In addition, peroxyl radical cyclizations onto olefins are well established in the literature.[13] Methods involving intramolecular attack of peroxide nucleophiles onto halonium[14] and mercuronium ions,[15] generated *in situ* from alkenes, have been used to yield 1,2-dioxanes. The potential drawback to these reactions is that residual iodine and mercury atoms may need to be removed by a subsequent transformation.[15c]

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Supporting Information **Available:** Complete experimental procedures and product characterization. This material is available free of charge via the Internat at http://pubs.acs.org.

Given the large number of cyclic peroxides containing the 1,2-dioxane moiety, we sought to develop a complementary approach to synthesize this important structural motif. We reasoned that a late transition metal could combine alkene activation, intramolecular attack of the peroxide, and subsequent removal of the activating species in a single transformation. Related heteroatom nucleophiles, such as alcohols[16] and amines,[17,18] have been widely demonstrated to undergo cyclization onto olefins activated by electrophilic transition metal catalysts, including palladium(II) complexes. In contrast, only one example of a transition metal-catalyzed reaction resulting in peroxide-containing products has been reported.[19] Nonetheless, the formation of isomeric products limits the reaction's utility. In this Letter, we report the palladium-catalyzed synthesis of cyclic peroxides that can be functionalized to give compounds structurally related to biologically active natural products.

Our first experiments were focused on the feasibility of catalyzing the intramolecular addition of hydroperoxides onto pendant olefins. The model substrate, unsaturated tertiary hydroperoxide **1a**, was synthesized from the corrresponding alcohol.[20] Next, hydroperoxide **1a** was treated under Corey's conditions,[19] but only decomposition products were observed. It was reasoned that a sacrificial oxidant could oxidize an intermediate palladium(0) species to prevent premature degradation of the free hydroperoxide. Addition of one equivalent of benzoquinone (BQ) gave a mixture of products including the desired 1,2-dioxane, as identified by ^{1}H and ^{13}C NMR spectroscopy. Alcohol **4a**, which was likely formed by reduction of the peroxide, was observed, as was its cyclized product, furan **3a**.[16]

Additional screening of reaction conditions with unsaturated hydroperoxide **1b** provided a set of standard conditions for peroxycyclization. From these studies, it was clear that employing catalytic $Pd(OAc)_2$ afforded higher conversions and yields than when using $Pd(OCOCF_3)_2$, $[(NHC)Pd(allyl)Cl]_2$,[21] $Pd(PPh_3)_2Cl_2$, $Pt(PPh_3)_2Cl_2$, or $PdCl_2$. Exchanging NaH_2PO_4 with pyridine suppressed furan formation, simplifying isolation of the endoperoxide. In contrast to the success with benzoquinone, some oxidants (*N*-chlorosuccinimide, 2,3-dichloro-5,6-dicyanobenzoquinone, $K_2S_2O_8$, O_2, Re_2O_7, Ag_2CO_3/O_2) gave mostly decomposition products, while others ($HOAc/MnO_2$, cumene hydroperoxide, Ag_2O) provided the desired 1,2-dioxane, albeit in lower yields. When used as an oxidant in 1,4-dioxane, the combination of catalytic benzoquinone and stoichiometric Ag_2CO_3 (or AgOAc)[22] gave comparable yields to the reaction using stoichiometric benzoquinone (Scheme 2). Other viable solvents include toluene and 1,2-dichloroethane.[23] As observed previously, reduction of peroxide **1b** to alcohol **4b** was a major side product of the reaction when 1,2-dichloroethane was used as the solvent. Using Ag_2CO_3 suppressed reduction, but promoted oxidation to other unidentified products.

The application of this peroxypalladation to various unsaturated hydroperoxides is displayed in Table 1. Yields for these reaction are generally consistent among substrates. The alkyl tertiary hydroperoxides afforded modest diastereoselectivities, where the major diastereomer was assigned by comparing ^{13}C NMR chemical shifts of the methyl group on the endoperoxide ring.[24] Cyclization of mixed peroxyacetals (entries 2 and 6) gave higher diastereoselectivities, which could result from placing the methoxy group in the axial position due to the anomeric effect.[25] Products that resemble known biologically active natural products, such as peroxyplakoric acid A_1 methyl ester (Figure 1), were obtained from α,β-unsaturated esters (entries 5 and 6). The reaction appears to be specific for tertiary γ,δ-unsaturated hydroperoxides, because substrates with different substitution did not cyclize (entries 7 and 8).

A mechanism can be proposed by consideration of other reactions of peroxides with alkenes (Scheme 3).[19,26,27] Ligand exchange of peroxide **1** for the acetate and coordination of the alkene would give peroxypalladium species **5**.[26] *Syn*-addition across the double bond and subsequent β-hydride elimination affords the 1,2-dioxane **2** and liberates a palladium(II)

hydride, which reductively eliminates acetic acid.[26,27] Reoxidation of the palladium(0) species with benzoquinone provides the requisite palladium(II) catalyst.[28]

The stability of cyclic peroxides allowed further manipulation of the products to provide structures that are analogous to those found in biologically active compounds (**9**). In particular, the 1,2-dioxane core with an acetic acid side chain is a common structural motif in naturally occuring peroxides, such as peroxyplakoric acid A_1 methyl ester (Figure 1) and its derivatives. We were particularly interested in structures **2f** and **2g** because the ester functional group provided a convenient synthetic handle (Scheme 4). Given that many of the bioactive structures are saturated, hydrogenation of the C–C double bond is an essential transformation. Attempts to hydrogenate in the presence of Pd/C failed to produce the desired product, likely promoting cleavage of the O–O bond. A procedure using diimide, which was generated *in situ*, reduced the double bond smoothly to afford the saturated endoperoxide **7f** in good yield.[29,30] Hydrolysis to the carboxylic acid was achieved using 1 M LiOH in MeOH,[31] and the chloroquine derived amide **8f** was then formed using *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbo-diimide hydrochloride (EDC). Endoperoxide **8f** resembles the previously reported five-membered analog (**9**), which has demonstrated potent antimalarial activity against chloroquine-resistant strains of *Plasmodium falciparum*, the most virulent form of the malaria parasite.[32,33]

In conclusion, palladium-catalyzed cyclization of unsaturated tertiary hydroperoxides gives rise to 1,2-dioxane products. Following cyclization, further functionalization was achieved without degradation of the peroxide. This method is tolerant of functional groups that can be manipulated in subsequent transformations to afford biologically significant products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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20. Complete synthetic details are provided as Supporting Information. Peroxides can be explosive and appropriate safety measures should be taken (avoid light, heat and run on small scale).
21. NHC = *N*-heterocyclic carbene ligand (1,3-bis(2,4,6-trimethylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene).
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23. Calculation of the yield by NMR, based on an internal standard, affords a 41% yield of the observed 1,2-dioxane products. See Supporting Information for details. Resubjecting products to chromatographic conditions gave quantitative recovery of the product.
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30. The stereochemistry of the major diastereomer, as shown in Scheme 4, was assigned based on correlations of ^{1}H and ^{13}C chemical shifts to similar compounds reported in the literature: Ibrahim SRM, Ebel R, Wray V, Müller WEG, Edrada-Ebel R, Proksch P. J Nat Prod 2008;71:1358–1364.1364 [PubMed: 18672931]
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33. The covalent attachment of the endoperoxide to a chloroquine moiety has been shown to enhance antimalarial activity as compared to either of these components individually: Walsh JJ, Coughlan D, Heneghan N, Gaynor C, Bell A. Bioorg Med Chem Lett 2007;17:3599–3602.3602 [PubMed: 17482816]

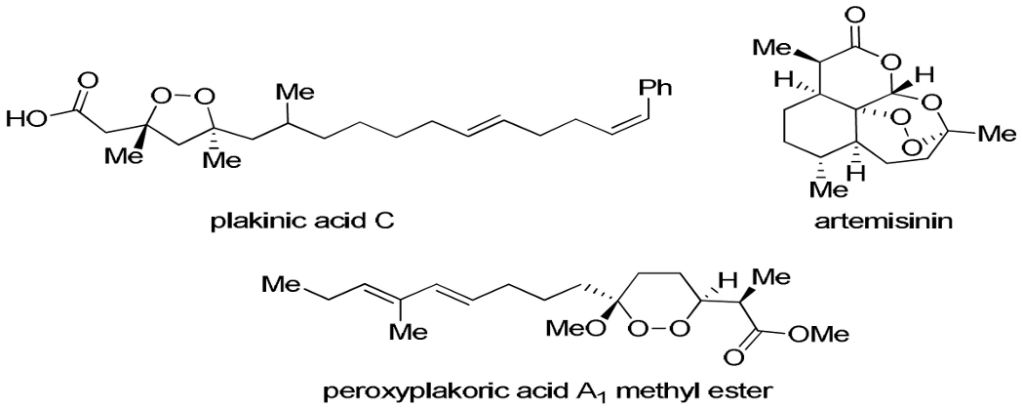
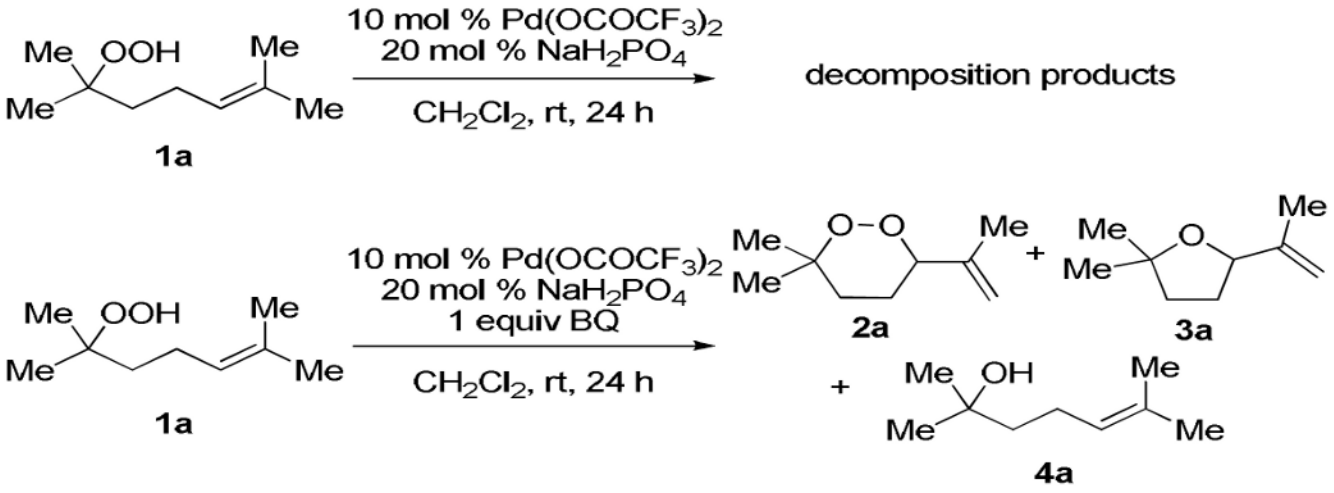
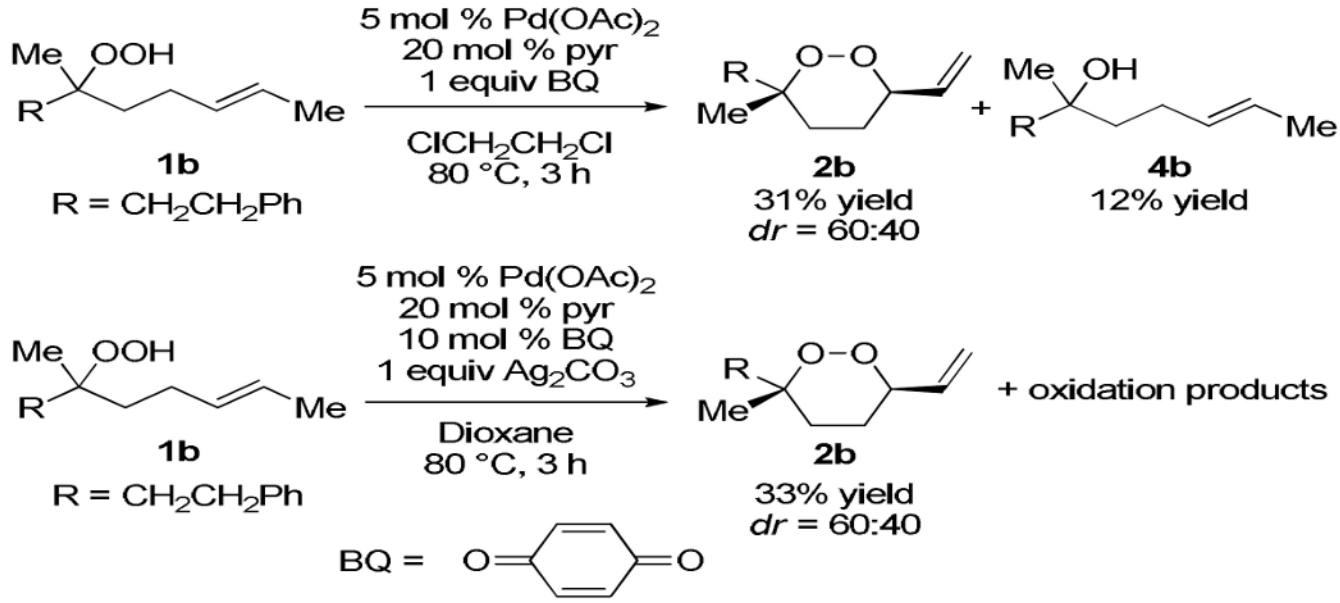


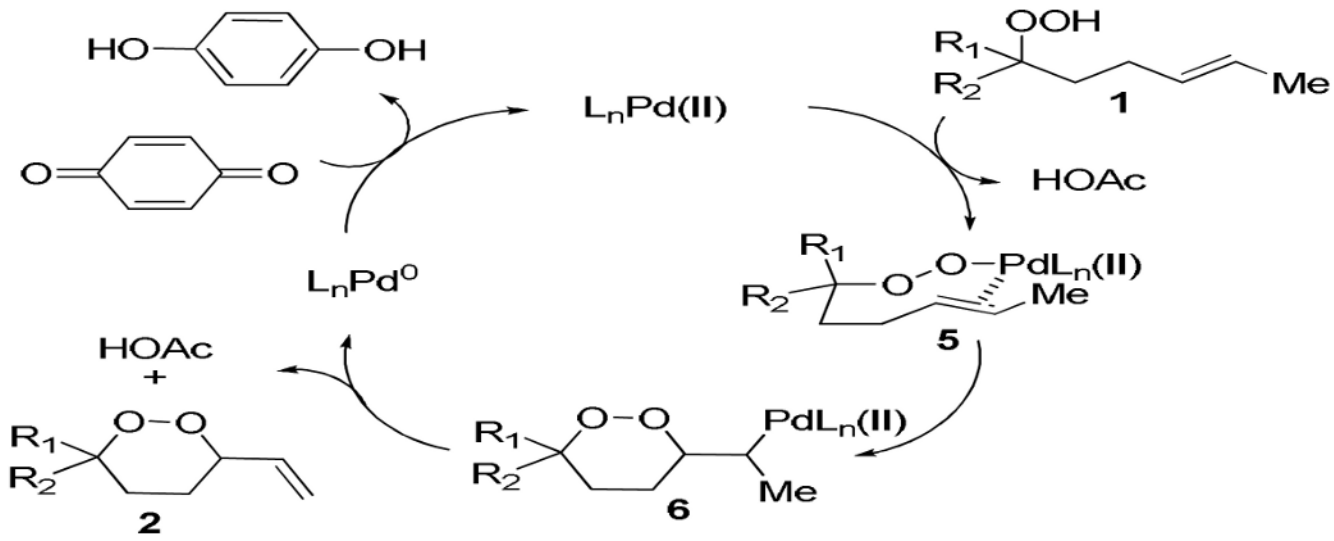
Figure 1.
Cyclic Peroxide Natural Products



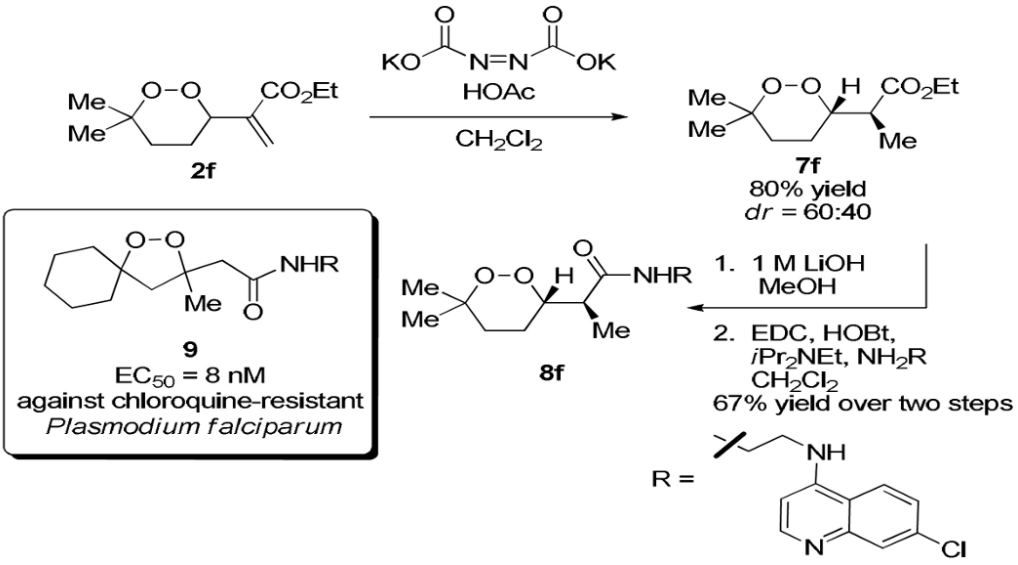
Scheme 1.
Initial Conditions for Peroxycyclization



Scheme 2.
Optimized Reaction Conditions



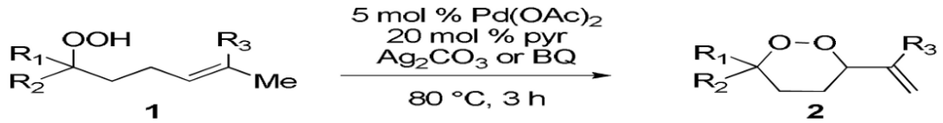
Scheme 3.
Proposed Mechanism for Peroxypalladation



Scheme 4.
Synthetic Manipulation of Endoperoxide **2f**

Table 1

ated Peroxides



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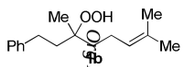
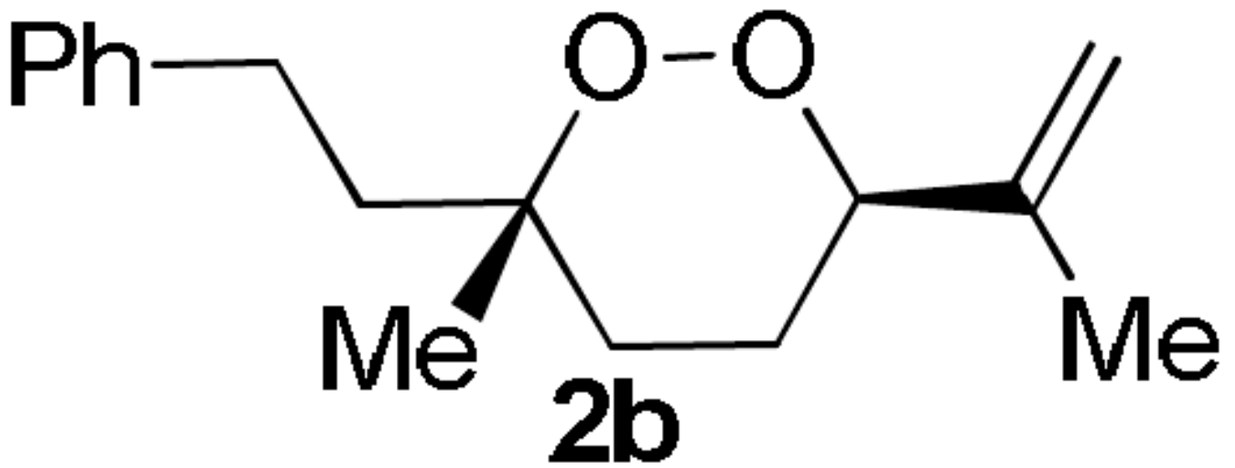
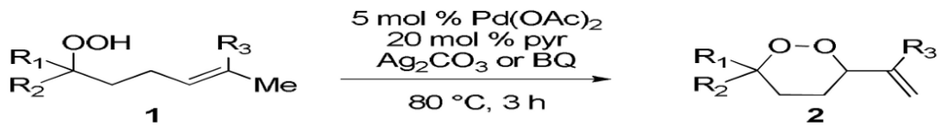
		35 (75:25)[a]



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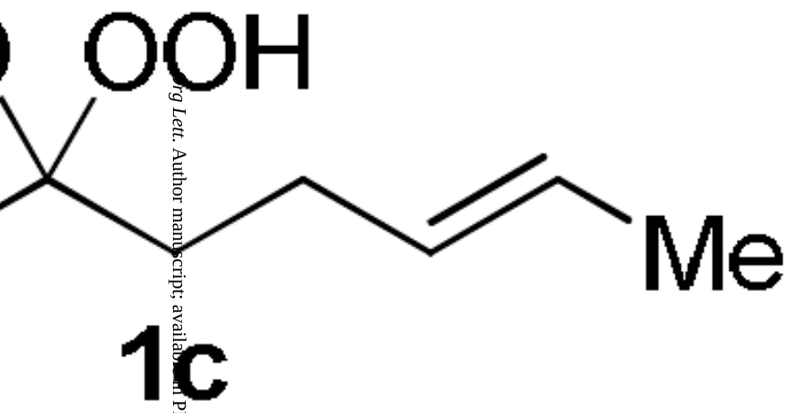	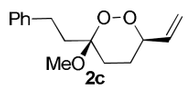	34 (>97:3)[b]

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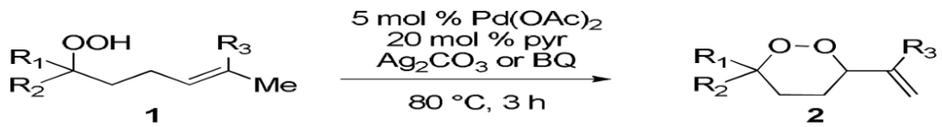

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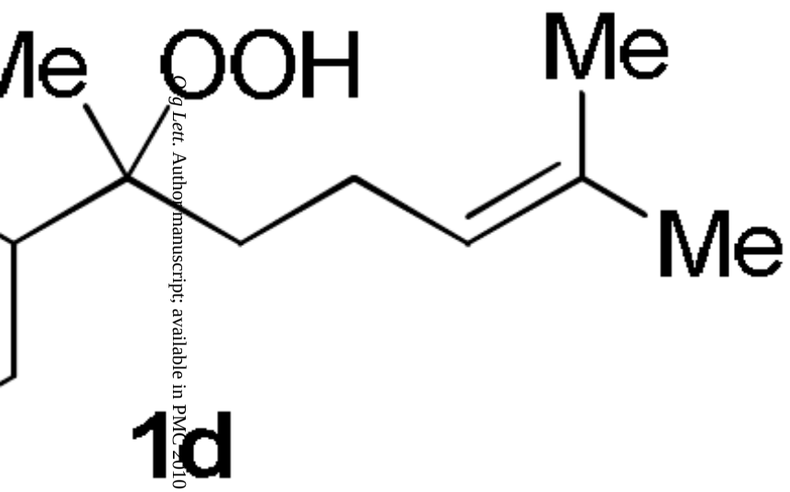
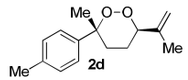
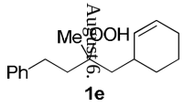
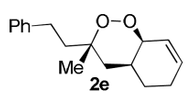
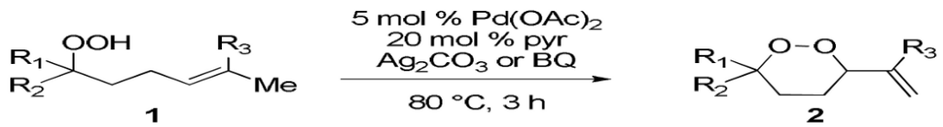
		30 (75:25)[a]
		35 (48:30:16:6)[a,c]



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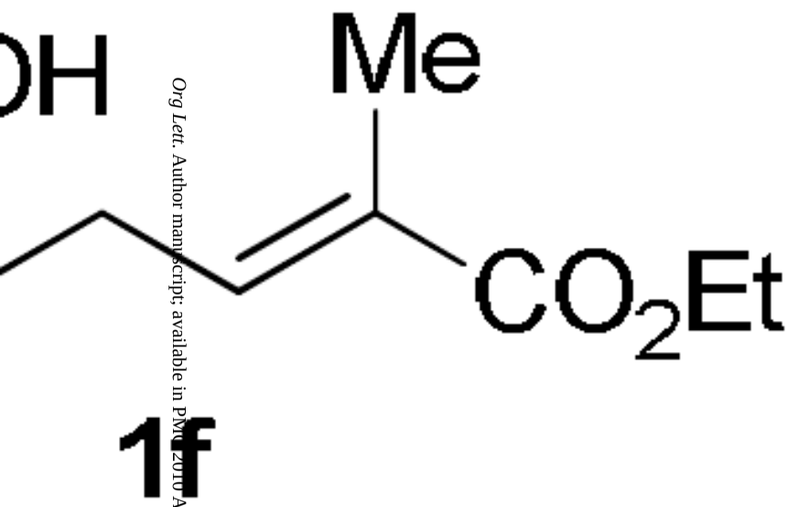	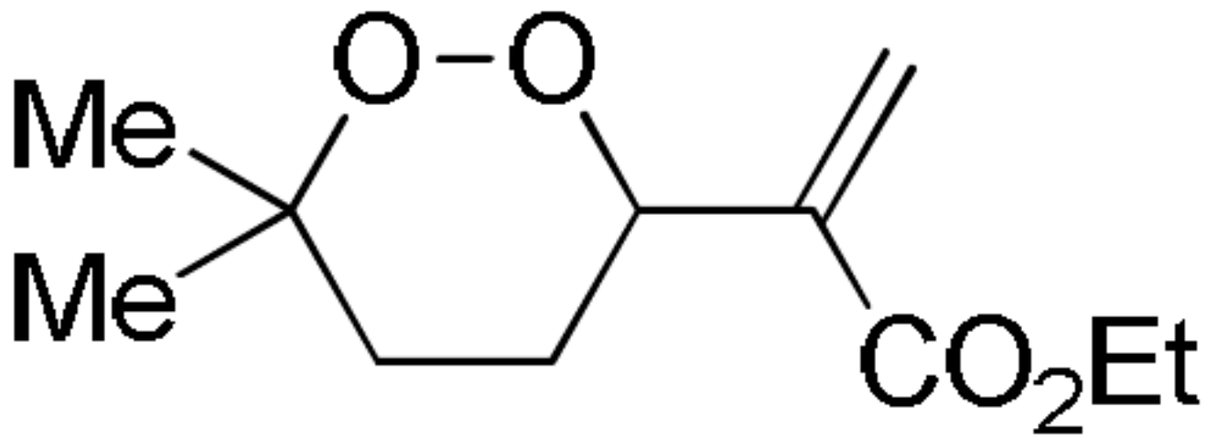	31[b]

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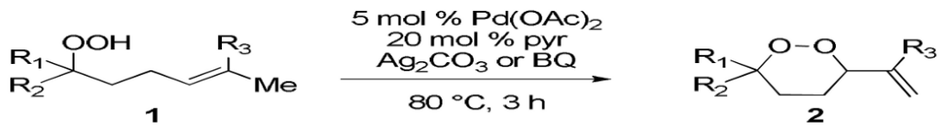
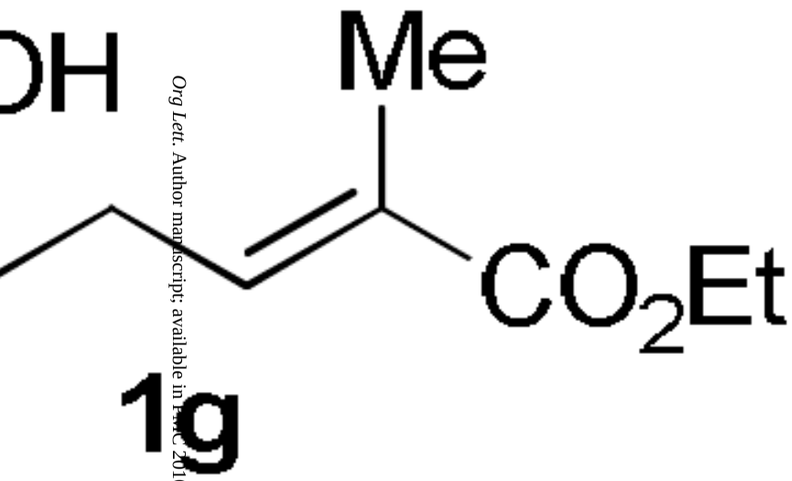
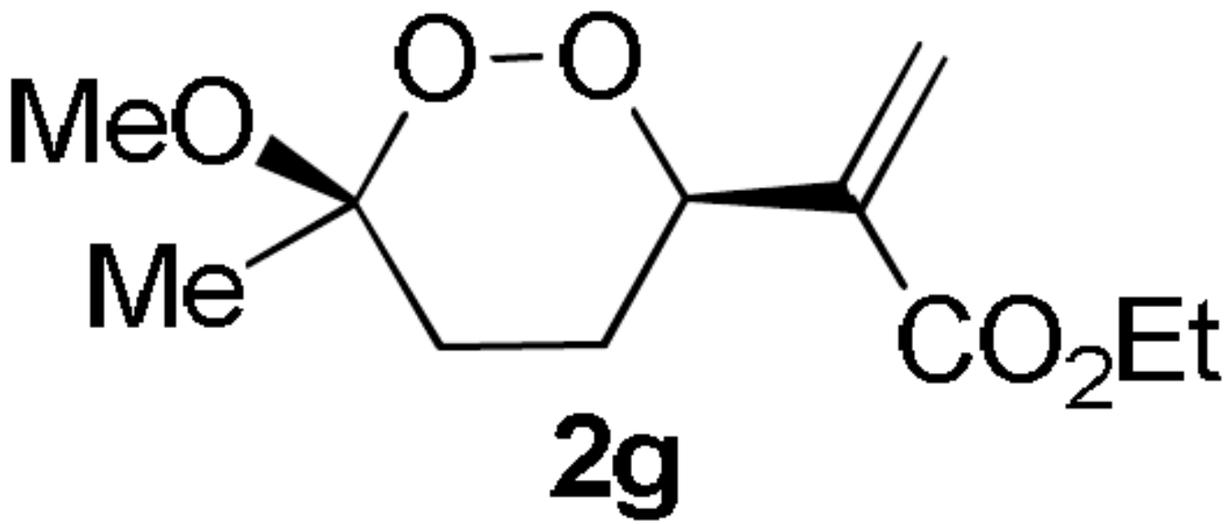


substrate	product	% yield (dr)
		30 (90:10)[b]

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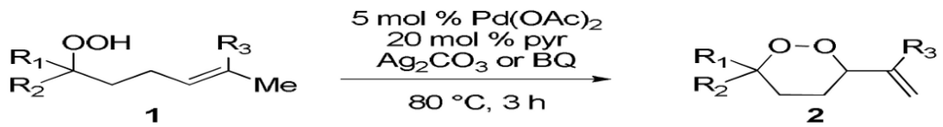
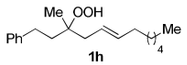
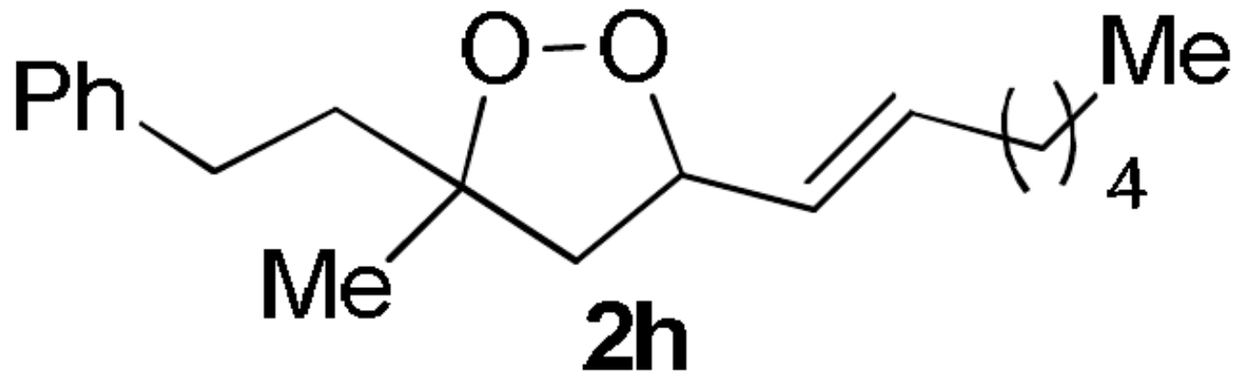


substrate	product	% yield (dr)
		NR[d]

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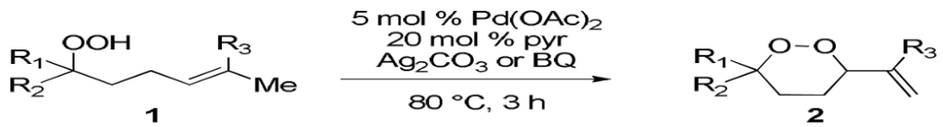
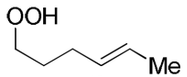
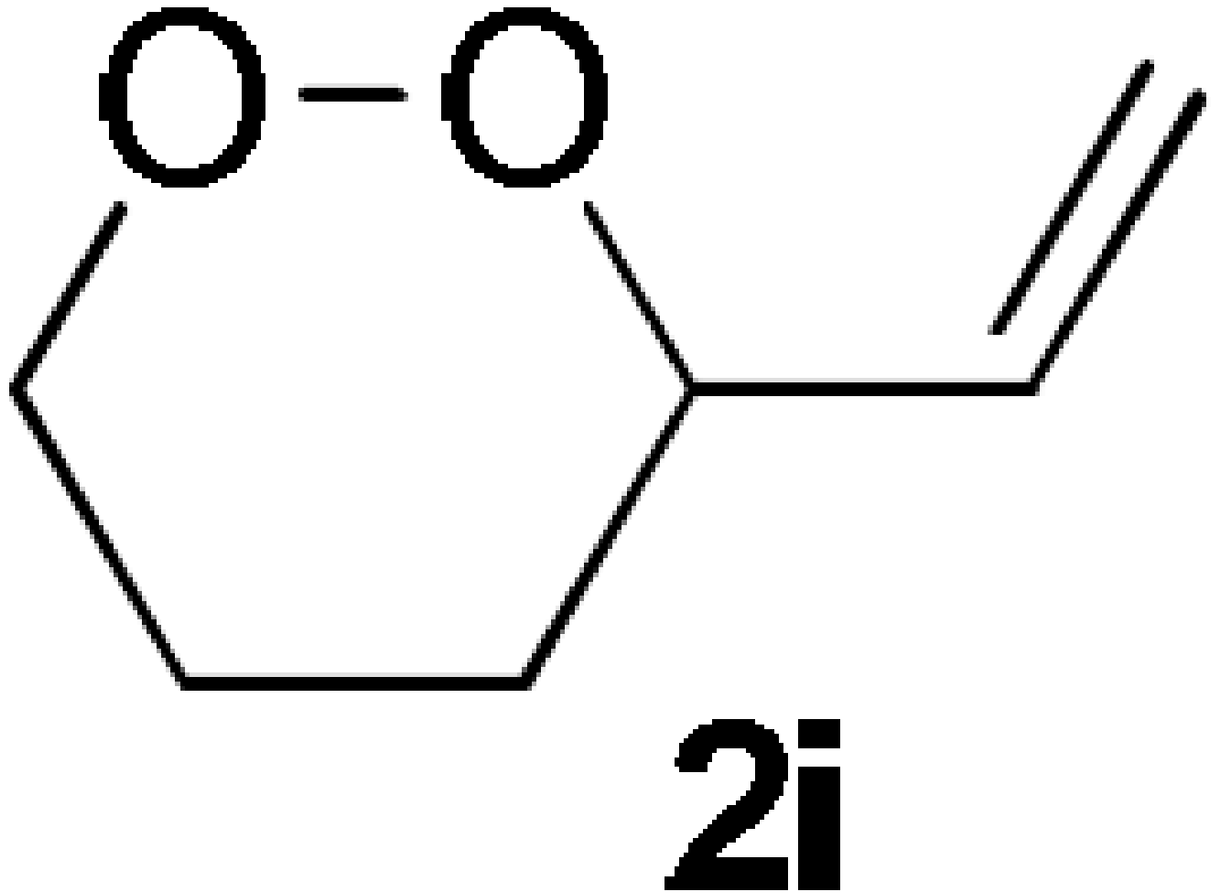
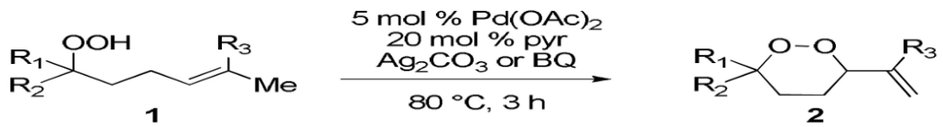


substrate	product	% yield (dr)
 **1i**	 **2i**	NR[d]



substrate	product	% yield (dr)

ne, 0.050 mmol BQ, 1.0 mmol Ag_2CO_3.

ne, 0.50 mmol BQ.