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Hydroperoxide-Mediated C-C Bond Formation: Synthesis of 1,2-Dioxolanes from Alkoxyhydroperoxides in the Presence of Lewis Acids

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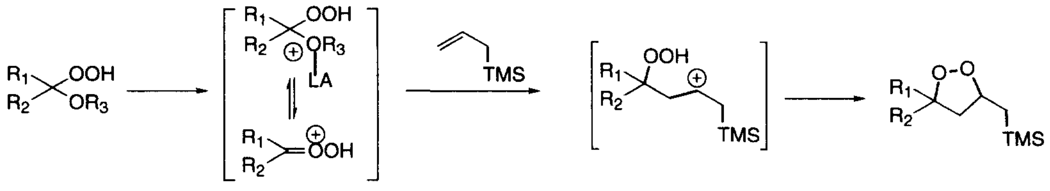
Abstract: *Lewis-acid activation of ozonolysis-derived hydroperoxyketals affords intermediate hydroperoxycarbenium ions (protonated carbonyl oxides) which undergo addition of allyltrimethylsilane to directly afford 1,2-dioxolanes.*

Five-membered ring peroxides, 1,2-dioxolanes, are found in prostaglandins, oxidized lipids, and antifungal marine natural products.[1-3] Traditional methods for dioxolane synthesis rely upon cyclization of a functionalized hydroperoxide or dioxygenation of a cyclopropane.[4-6] The direct 1,3-dipolar addition of carbonyl oxides and alkenes is an attractive strategy for dioxolane synthesis,[7-10] but one which is limited by the incompatibility of nucleophilic alkenes with ozonolytic generation of the carbonyl oxide.[11] The decomposition of ozonides (1,2,4-trioxolanes) in the presence of strong acid has been used to generate protonated carbonyl oxides capable of 1,3-dipolar addition.[10] We now report a new and convenient approach to dioxolanes based upon nucleophilic attack of allyltrimethylsilane on hydroperoxycarbenium ions generated through activation of alkoxyhydroperoxides with Lewis acids.(Scheme 1)

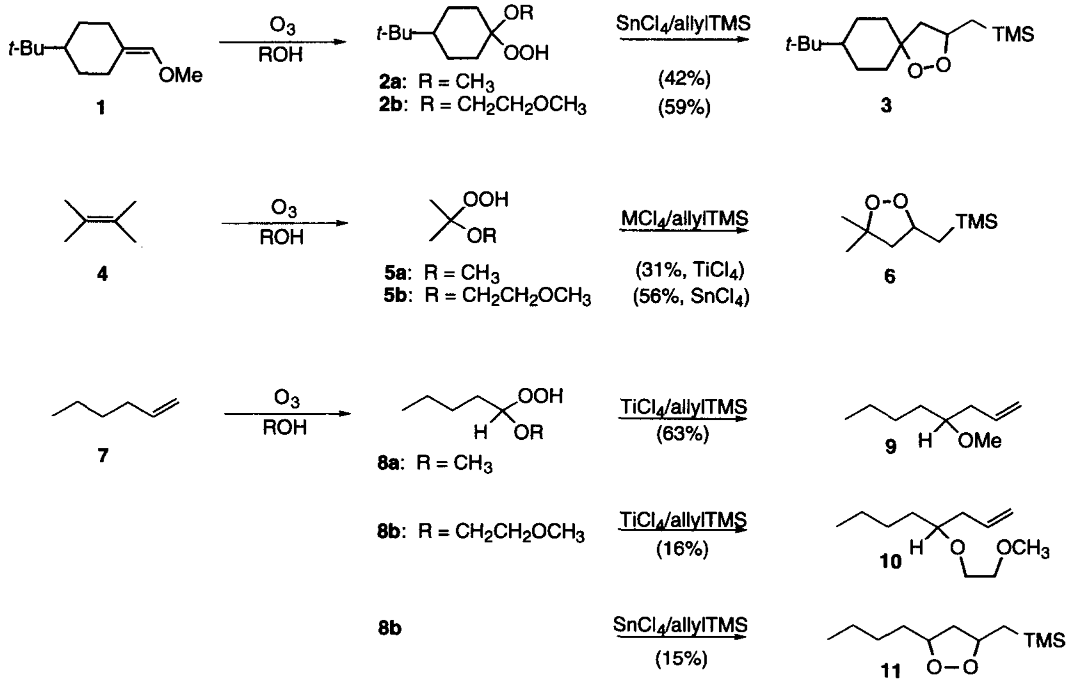
Scheme 1



We recently discovered a new method for synthesis of dialkyl peroxides based upon activation of monoperoxyketals with Lewis acids; the derived peroxycarbenium ion underwent reaction with electron-rich alkenes to produce a new C-C bond.[12] Given the direct availability of monohydroperoxyketals (alkoxyhydroperoxides) from ozonolysis, we wondered if the application of the same bond-forming sequence might allow for a direct synthesis of dioxolanes (Scheme 1). Oxygen-assisted expulsion of the complexed alkoxide would provide an intermediate hydroperoxycarbenium ion, identical to either a protonated or metallated carbonyl oxide.[10] Attack of allyltrimethylsilane or a similar nucleophile would produce an intermediate β-trimethylsilyl cation which would partition between loss of trimethylsilyl cation to produce an unsaturated hydroperoxide or intramolecular trapping by the hydroperoxide to produce a trimethylsilyl-substituted dioxolane.

Alkoxyhydroperoxide substrates were easily prepared through ozonolysis of alkenes in the presence of an alcohol.(Scheme 2)[13] Hydroperoxy ketal **2a** was prepared in high yield upon ozonolysis of enol ether **1** in methanol. Addition of $SnCl_4$ to a chilled mixture of **2a** and allyltrimethylsilane afforded a 42% yield of 1,2-dioxolane **3**, which was a single diastereomer according to the ^{13}C NMR spectrum.[14] Although we have been unable to conclusively assign the product stereochemistry, attack of an alkyl nucleophile would be anticipated to occur from the equatorial face. Reaction of **2** with allylsilane in the presence of $TiCl_4$ furnished only an allylated peroxide dimer, presumably arising from attack on an intermediate dimeric peroxyketal.[12] Alkoxyhydroperoxide **5a**, obtained upon ozonolysis of 2,3-dimethyl-2-butene, underwent similar addition of allyltrimethylsilane in the presence of $TiCl_4$, but not $SnCl_4$, to furnish a 31% yield of 1,2-dioxolane **6**.[15] The reported yields were obtained upon rapid addition of Lewis acid to the chilled mixture of alkoxyhydroperoxide and allylsilane; slow addition of Lewis acid or premixing of the hydroperoxide and Lewis acid gave much lower yields, presumably due to disproportionation or formation of tetroxides. No significant products were isolated upon reaction of either **2a** or **5a** with allyltributylstannane in the presence of $TiCl_4$.

Scheme 2

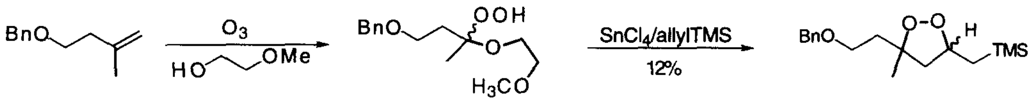


Assuming that reduced selectivity between hydroperoxide and alkoxide complexation might be responsible for the modest yields from substrates **2a** or **5a**, we investigated the use of a more Lewis basic leaving group, a strategy which has been successfully employed during analogous displacements of acetals.[16] Ozonolysis of enol ether **1** in the presence of 2-methoxyethanol afforded **2b**, the methoxyethyl analog of **2a** and alkoxyhydroperoxide **5b**, the analog of **5a**, was similarly available from 2,3-dimethyl-2-butene.[15] Reaction of **2b** with $SnCl_4$ and allyltrimethylsilane under the same conditions as had been employed for the non-chelating analog **2** produced an improved yield of dioxolane **3**. Similarly, whereas hydroperoxide **5a** failed to furnish products upon reaction with allyltrimethylsilane and $SnCl_4$, displacement of **5b** produced dioxolane **6** in 59% yield.

We also investigated the Lewis acid-mediated reaction of allyltrimethylsilane with hydroperoxyacetals (Scheme 2). Acetal **8a** was prepared from the ozonolysis of 1-hexene in methanol. Surprisingly, reaction with allylsilane in the presence of $TiCl_4$ produced methyl ether **9** in 63% yield, implying Lewis acid-mediated activation of the hydroperoxide towards displacement. Alkoxyhydroperoxide **8b**, prepared by ozonolysis of 1-hexene in 2-methoxyethanol, reacted with allyltrimethylsilane in the presence of $TiCl_4$ to produce the methoxyethyl ether **10**; reaction in the presence of $SnCl_4$ afforded dioxolane **11** in 15% yield.

Finally, a more highly functionalized hydroperoxyketal was prepared as a model for synthetic approaches to plakinic acid, a 1,2-dioxolane natural product.[1] (Scheme 3) Addition of allyltrimethylsilane in the presence of $SnCl_4$ afforded the desired 1,2-dioxolane, albeit in low yield.

Scheme 3



In summary, we have demonstrated that the activation of alkoxyhydroperoxides with Lewis acids provides a convenient two-step route from alkenes to dioxolanes via a synthetic equivalent of a protonated carbonyl oxide. Further investigations into the scope and mechanism of hydroperoxycarbenium-mediated reactions are in progress and will be reported in due course.

Caution. Standard precautions (use of safety shields, avoidance of heat, light, or metal salts, reactions on minimal scale) should always be observed in any reactions involving low molecular weight peroxides.[17-19]

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(14) All new compounds have been characterized by ^{1}H, ^{13}C, and IR spectroscopy. Satisfactory elemental analyses (± 0.4 % for C and H) have been obtained for compounds **2ab**,**3**, **5b**, **6**, **8ab**, **9**, and **10**. Typical experimental: To a -78° C solution of freshly prepared alkoxyhydroperoxide **2** (280 mg, 1.39 mmol) and allyltrimethyl silane (427 mg, 3.74 mmol) in CH_2Cl_2 (30 mL) was rapidly added $SnCl_4$ (1.39 mL of a 1 M solution in CH_2Cl_2). Upon completion (90 min, monitored by TLC), the reaction was quenched with water (20 mL), and allowed to warm to RT. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (1 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography on silica gel with 2% ethyl acetate/hexane afforded 165 mg (42%) of dioxolane **3**.

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