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Tin (IV)-Mediated Stereoselective Synthesis of Epoxides with Concomitant Alkyl Peroxide Formation

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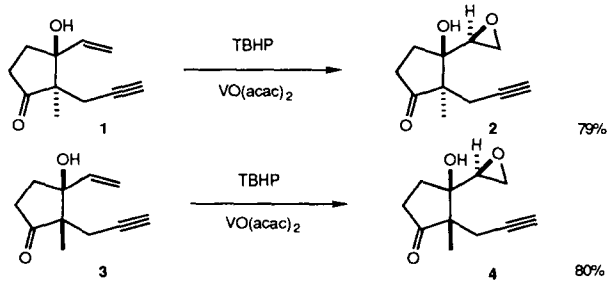
Abstract: Epoxy alkyl peroxides are formed stereoselectively by the action of *t*-butyl hydroperoxide-$SnCl_4$ upon allylic alcohols containing an amido group, and with reversal of the diastereoselectivity shown by the action of *t*-butyl hydroperoxide-$VO(acac)_2$ upon analogous carbocyclic alcohols.

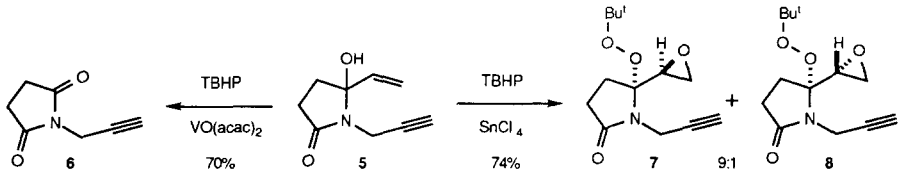
Epoxides are key intermediates in synthesis, principally because of their ability to undergo stereoselective nucleophilic displacement.[1] 2,3-Epoxy alcohols and their derivatives possess additional advantages including their ready asymmetric synthesis by Katsuki-Sharpless epoxidation,[2] and also the possibility of the hydroxyl group coordinating to a metal and thereby directing the site of nucleophilic attack, sometimes with reversal of normal chemoselectivity. Intramolecular nucleophilic displacements on 2,3-epoxy alcohols by carbon nucleophiles afford efficient, convergent and stereoselective routes to polyhydroxylated fused carbocyclic systems.[3]



Scheme 1. Diastereoselective epoxidations of 1-vinyl-1-cycloalkanols

The diastereoselective epoxidations shown in Scheme 1 are prerequisite to Lewis acid mediated cyclizations that furnish polyfunctionalized fused carbocycles.[4] The π-face selectivity exhibited by **1** and **3** (Scheme 1) is notable and we sought to examine epoxidation of lactam analogues such as **5**. Whereas **1** and **3** can be epoxidized using either *m*-CPBA in $CHCl_3$, or by *tert*-butyl hydroperoxide (TBHP) (1.5 eq., catalytic $VO(acac)_2$, benzene, 18 h reflux), neither of those methods was successful for **5**; instead, imide **6** was obtained from both reactions (80% and 70%, respectively). The formation of **6** presumably reflects the increase in electron richness of the quaternary centre due to the nitrogen atom; this evidently leads to fragmentation of a retro-aldol type, possibly *via* an *N*-acyliminium species.

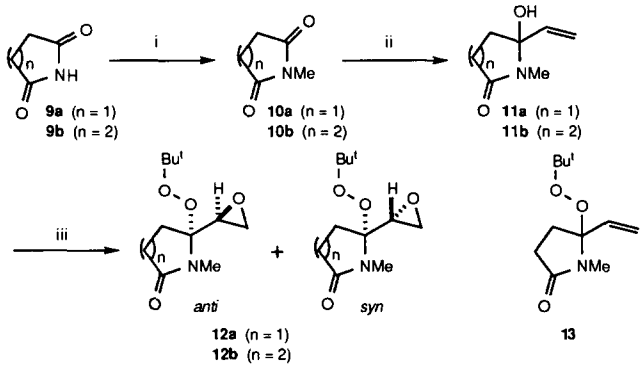
In an attempt to overcome the fragmentation, the use of other Lewis acids were investigated. Remarkably, *the use of TBHP in the presence of $SnCl_4$ was found to effect not only epoxidation, but also displacement of the hydroxyl group by an alkyl hydroperoxy group* (Scheme 2) *with reversal of diastereoselectivity as compared with carbocyclic analogues* (Scheme 1). ^1H NMR spectroscopy[5] of the reaction mixture showed a 9:1 ratio of diastereoisomers, subsequently shown to be **7** and **8** respectively.[3,6] The major diastereoisomer **7** crystallized from ethyl acetate - 40-60 °C petroleum ether as cubes, m.p. 98-99 °C.[7] Its relative configuration was confirmed by an X-ray determination on a single crystal.[8] The TBHP-$SnCl_4$ system is of particular significance, since *m*-CPBA (1.5 eq.) and $SnCl_4$ (2.0 eq.) (CH_2Cl_2, 0 °C, 0.5 h) gave **6** (85%).



Scheme 2. Epoxidation-peroxidation of an unsaturated hydroxylactam

The epoxidation with concomitant hydroperoxidation was found to apply to other hydroxylactams (Scheme 3). *N*-Methylsuccinimide **10a** and *N*-methyglutarimide **10b** were reacted with vinylmagnesium bromide to give respectively the hydroxylactams **11a** and **11b**.[9] To hydroxylactam **11a** (0.5 g, 3.54 mmol) in CH_2Cl_2 (60 mL) at -78 °C was added TBHP (1.70 eq.) followed by $SnCl_4$ (2.31 g, 8.85 mmol) and the mixture stirred for 1 h, from which was obtained a 9:1 mixture (62%) of *anti*:*syn* **12a**. Similarly, **11b** was converted by TBHP (2.2 eq.) and $SnCl_4$ (2.0 eq.) (-78 °C, 2.5 h) into a 7:1 mixture (64%) of *anti*:*syn* **12b**. Interestingly, from the reaction of **11a** at -78 °C with TBHP (2.2 eq.) and a catalytic quantity of $SnCl_4$ (8 mol%) in CH_2Cl_2 the peroxide **13** (59%) was isolated. A similar reaction conducted in the absence of $SnCl_4$ gave a quantitative recovery of **11a**.

To our knowledge, these are the first examples of epoxidation with concomitant formation of a dialkyl peroxide. It is notable that unsymmetrical dialkyl peroxides are formed in good yields, in contrast to other methods limited by substrate or modest yields.[10] For example, although alkyl bromides react with potassium superoxide to give di-*n*-alkyl peroxides, unsymmetrical dialkyl peroxides could not be prepared efficiently by that method.[11] Further studies are required to determine whether tin(IV) affords different products to other Lewis acids. Tertiary alcohols have been converted into the corresponding *t*-butyl peroxides by reaction with trichloroacetonitrile followed by TBHP and $BF_3.OEt_2$, but low yields were obtained.[12] $Ti(Oi\text{-}Pr)_4$ has been shown to effect epoxidation by oxygen atom transfer from a neighbouring hydroperoxide group, or intermolecularly from 2-hydroperoxy-2-phenylpropan-1-ol.[13]



Scheme 3. Epoxidation-peroxidation of hydroxylated γ- and δ-lactams
Reagents and conditions: i, MeI (1.5 eq.), K_2CO_3 (1.5 eq.), acetone; reflux 4 h (**9a**) or 16 h (**9b**) ii, vinylmagnesium bromide (1.5 eq.) in THF, 20 °C iii, TBHP (2.2 eq.) in CH_2Cl_2; $SnCl_4$ (2.2 eq.), -78 °C for 1.5 h (**11a**) or 2 h (**11b**).

The mechanism and scope of these novel tin(IV)-mediated epoxidations of allylic alcohols are being studied. The epoxidation-peroxidation reactions are notable for the absence of competing reactions including semi-pinacol rearrangements,[14] or attack of the epoxide by chloride. Selective deoxygenation of the peroxy group would afford the *anti*-epoxy alcohols[10] and hence in principle a route to the diastereoisomers complementary to the *syn*-epoxy alcohols[14] which usually predominate in metal-catalyzed peroxidations. That possibility is being investigated.

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5. For epoxy peroxide **7** the methine hydrogen atom of the epoxide unit resonated at δ 3.32 (dd, J = 4.5 and 2.8 Hz) for the *anti*-diastereoisomer and at δ 3.37 (dd, J = 4.1 and 3.0 Hz) for the *syn*-diastereoisomer. For epoxy peroxide **12a** the methine hydrogen atom of the epoxide unit resonated at δ 3.11 (dd, J = 4.0 and 2.5 Hz) for the *anti*-diastereoisomer and at δ 3.18 (dd, J = 3.8 and 2.5 Hz) for the *syn*-diastereoisomer.
6. New compounds gave satisfactory elemental analyses or high resolution mass spectral data, and exhibited spectroscopic data (IR, ^{1}H NMR, and ^{13}C NMR) in agreement with their structures.
7. *Representative peroxidation experiment:* To a stirred solution of **5** (0.15 g, 0.91 mmol) in CH_2Cl_2 (30 mL) at -78 °C $SnCl_4$ (0.31 mL, 2.66 mmol) was added dropwise over 5 min. When the addition was complete, *t*-butyl hydroperoxide (0.42 mL, 2.0 mmol, 5.46 M) in CH_2Cl_2 was added dropwise over 5 min. The resulting solution was stirred at -78 °C for 2 h, then poured onto ice (50 g). The aqueous layer was extracted with diethyl ether (2X15 mL) and the ethereal extracts were combined with the CH_2Cl_2 layer to give a solution which was dried ($MgSO_4$) and evaporated to give an oil that was subjected to column chromatography (silica gel; 20:80 V/V ethyl acetate: 40-60 °C petroleum ether) to give **7** as a white solid (0.16 g, 74%). Recrystallization from ethyl acetate-petroleum ether afforded **7** as cubes, m.p. 98-99 °C.
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9. *N*-Propargyl succinimide was prepared (97%) by heating a mixture of succinimide, propargyl bromide (1.2 eq.) and K_2CO_3 in acetone at reflux for 6 h. This procedure was easier and superior to a Mitsunobu-type alkylation: Schoemaker, H. E.; Boer-Terpstra, T.; Dijkink, J.; Speckamp, W. N. *Tetrahedron*, **1980**, *36*, 143. 5-Ethenyl-5-hydroxy-1-propargyl-2-pyrrolidinone **5** (80%) was prepared by addition of vinylmagnesium bromide (1.3 eq.) in THF to *N*-Propargyl succinimide in THF at -78 °C, followed by removal of the coolant and stirring 2 h at ambient temperature. The mixture was worked up by treatment with saturated aqueous ammonium chloride and extraction with ether. A similar procedure was used to prepare lactams **11a** and **11b**: Drage, J. S.; Earl, R. A.; Vollhardt, K. P. C. *J. Heterocycl. Chem.*, **1982**, *19*, 701.
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