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Stoichiometric Asymmetric Oxidation with Hydrogen Peroxide Activated by a Chiral Phosphoryl Chloride

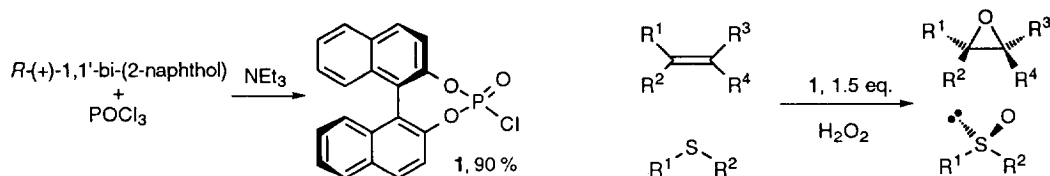
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Abstract: *R*-(-)-1,1'-Bi-(2-naphthoxy)phosphoryl chloride was used as a chiral activator for hydrogen peroxide. A variety of prochiral olefins and thioethers could be transformed to epoxides and sulfoxides, respectively, in moderate to good yields. The enantiomeric excesses obtained were up to 22 % for olefin epoxidation and up to 27 % for sulfoxidation.

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The development of methods for asymmetric oxidation is one of the most challenging fields in modern organic chemistry. Hydrogen peroxide is a very attractive terminal oxidant due to its ready availability and its high oxygen content¹. Furthermore, water is the only by-product. We have been addressing the question of whether peroxy derivatives of chiral dialkyl or diaryl phosphates may be useful reagents for stoichiometric asymmetric oxidations for some time. A recent publication by Kende et al.² on the use of related achiral or racemic phosphorus-based activators for hydrogen peroxide prompts us to disclose our own initial results. We herein report the first one-step procedure for the stoichiometric asymmetric oxidation of olefins and thioethers with hydrogen peroxide. The oxidant is activated by the *R*-(-)-1,1'-bi-(2-naphthoxy)phosphoryl chloride **1**, which is prepared in almost quantitative yield from *R*-(+)-1,1'-bi-(2-naphthol) and phosphoryl chloride³.



In a typical oxidation experiment, the phosphoryl chloride **1** (40.0 mg, 109 μmol, 1.5 eq.), anhydrous potassium carbonate (30.0 mg, 217 μmol, 3.0 eq.) and urea-hydrogen peroxide clathrate (48.0 mg, 509 μmol, 7 eq.) were dissolved in 0.5 ml abs. methanol at -5 °C. The substrate (72.7 μmol) and an internal standard were added immediately. The reaction mixture was stirred at -5 °C. The progress of the reactions was monitored by capillary GC or HPLC, using calibration curves for both starting materials and products. Enantiomeric excesses were determined either on chiral GC or HPLC columns. The results for a variety of substrates are summarized in the Table. As it turned out, the chiral activator **1** allowed for the asymmetric epoxidation of a variety of prochiral alkenes of different substitution pattern: conjugated *Z*-, *E*-, 1,2-disubstituted and terminal olefins (entries 1, 3 and 4) could be oxygenated as well as non-conjugated, terminal ones, using 1-octene as a prototype (entry 6). Interestingly, 1-methylcyclohexene, a trialkylsubstituted substrate was epoxidized rapidly and in good yield, but gave the epoxide as a racemate (entry 2). Finally, *E*-stilbene reacted only very sluggishly, affording a low yield of the epoxide in racemic form (entry 5). No oxidation occurred in the absence of the activator **1**. Thioethers like thioanisole gave the sulfoxide in reasonable yield and at moderate ees (entries 7-9).

A possible mechanistic interpretation of our preliminary results involves the intermediate formation of a chiral (RO)₂P(O)-OOH species, as already invoked by Kende² for achiral activators. In order to increase the enantioselectivity of this type of reagent, molecular modelling suggests that the major problem to be solved is

the efficient transformation of the chiral information present in the ester portion to the peroxy substructure. We are presently investigating variations of the activator structure for further optimizing this promising new type of stoichiometric asymmetric oxidation.

Table: Epoxidation of olefins and sulfoxidation of thioethers using hydrogen peroxide-urea clathrate and the chiral activator **1**^a.

Entry	Olefin/Thioether	Reaction	Yield	Enantiomeric Excess
		Time [h]	of Epoxide/Sulfoxide	of Epoxide/Sulfoxide
1	1,2-dihydronaphthalene	4	55 % ^b	20 % ^{b,g}
2	1-methylcyclohexene	2	60 % ^c	0 % ^c
3	<i>E</i> - β -methylstyrene	4	45 % ^d	16 % ^{d,i}
4	styrene	6	16 % ^c	22 % ^{c,h}
5	<i>E</i> -stilbene	12	ca. 5 % ^e	0 % ^e
6	1-octene	24	20 % ^c	10 % ^{c,i}
7	thioanisole	1	54 % ^f	14 % ^{f,i}
8	2-bromothioanisole	1	50 % ^f	20 % ^{f,i}
9	2-iodothioanisole	1	56 % ^f	27 % ^{f,i}

^aReactions were carried out as described in the text. ^bGC on heptakis-2,6-di-O-methyl-3-O-pentyl- β -CD, 25 m, 1,2-dibromobenzene as internal standard. ^cGC on heptakis-2,6-di-O-methyl-3-O-pentyl- β -CD, 25 m, bromobenzene as internal standard. ^dGC on octakis-2,6-di-O-pentyl-3-O-butyryl- γ -CD, 25 m, 1,2-dibromobenzene as internal standard. ^eHPLC on Daicel OD-H, bromobenzene as internal standard. ^fGC on octakis-2,6-di-O-pentyl-3-O-butyryl- γ -CD, 25 m, diphenylether as internal standard. ^gMajor enantiomer: (1*S*,2*R*), according to the elution profile (comparison with authentic samples). ^hMajor enantiomer: *S*, according to the elution profile (comparison with authentic samples). ⁱConfiguration of major enantiomer not determined.

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2. Kende, A. S.; Delair, P.; Blass, B. E. *Tetrahedron Lett.* **1994**, *35*, 8123-8126.
3. The reaction was carried out as described for racemic 1,1'-bi-(2-naphthol) in ref. 4. A colorless foam was obtained which was purified by column chromatography on silica gel (eluting with ether), affording **1** as a colorless solid (90 %); m.p.: 209 °C; CH-analysis: calcd. (found) C: 65.50 (65.31), H: 3.30 (3.36); HRMS: calcd. (found) 366.0213 (366.0184); $[\alpha]_D^{20} = -558$ ($c = 1.00$, CHCl₃); ¹H-NMR (300 MHz, CDCl₃): $\delta = 7.30$ -7.70 (m, 8H), 7.95-8.15 (m, 4 H); ¹³C-NMR (75 MHz, CDCl₃): $\delta = 119.88$, 119.93, 120.28, 120.32 (all d), 121.56, 121.66 (both s), 126.34, 127.06, 127.15, 127.26, 128.61, 128.65, 131.65, 131.87 (all d), 132.02, 132.19, 146.33, 146.48, 146.54, 146.71 (all s); ³¹P-NMR (30 MHz, CDCl₃): $\delta = 12.5$ (vs. external 85 % H₃PO₄).
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