Enantioselective Oxidation of Secondary Alcohols Using a Chiral Nitroxyl (*N*-Oxoammonium salt) Catalyst

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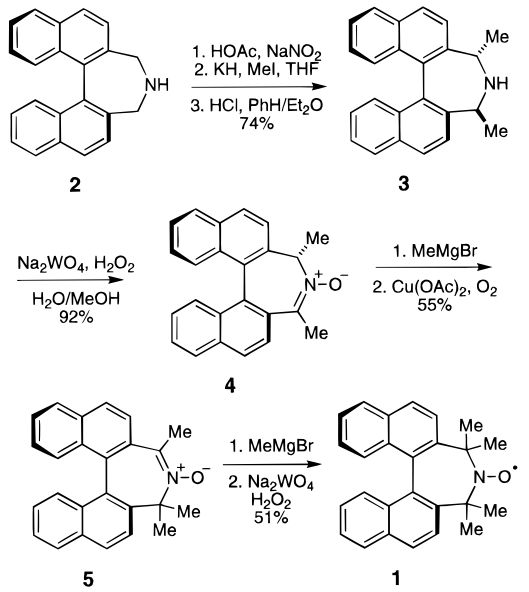
Optically pure secondary alcohols are some of the most important chiral intermediates in organic synthesis. They have been prepared by many methods, including enantioselective reduction of prochiral ketones[1] and enzymatic resolution of their racemates, usually by acetylation or deacylation.[2] Resolution of secondary alcohols has also been achieved by enantioselective oxidation using the redox enzyme horse liver alcohol dehydrogenase (HLADH).[3] Several other enantioselective chemical oxidations have been reported, but each one has been limited by modest selectivity and/or low turnover.[4,5] During the course of this investigation, Bobbitt reported the preparation of chiral nitroxides derived from (+)-dihydrocarvone and their use as enantioselective oxidants.[5] We report the first efficient, enantioselective oxidation of secondary alcohols using a nonenzymatic catalyst.

In designing an enantioselective oxidation, we were attracted to the very efficient catalytic oxidations mediated by nitroxyl radicals. In the presence of a bulk oxidant, nitroxyl radicals are oxidized to *N*-oxoammonium salts that in turn rapidly oxidize alcohols to aldehydes or ketones. The resulting hydroxylamines are reoxidized by the bulk oxidant to *N*-oxoammonium salts to complete the catalytic cycle.[6] A number of bulk oxidants have been used including *m*-CPBA[7] and an electrochemical oxidation,[8] but the most convenient system uses buffered, commercial bleach.[9] TEMPO or substituted TEMPO catalysts are normally used at 1 mol %, and the reactions are complete in less than 10 min at 0 °C.[9] Semmelhack has studied the reaction mechanism

Scheme 1



and concluded that the transition state for oxidation step is a cyclic fragmentation of the alkoxide−*N*-oxoammonium salt complex similar to a Cope elimination.[6,10] With their fast and efficient turnover using inexpensive oxidants, and their highly-ordered transition states for oxidation, *N*-oxoammonium salts are promising leads for the development of enantioselective catalysts.

The preparation of the optically pure nitroxide catalyst (−)-(*S*)-3,5-dihydro-3,3,5,5-tetramethyl-4*H*-dinaphth[2,1-*c*:1′,2′-*e*]azepine-*N*-oxyl (**1**) is shown in Scheme 1. Nitroxide **1** was identified as a promising lead because of its similarity to the many very selective transition metal−BINAP catalysts.[1] Azepine **2** (>92% ee)[11] was prepared by the procedure of Hawkins and Fu.[12] The permethylation was carried out in two phases: alkylation of an *N*-nitroso derivative followed by Grignard additions to nitrones **4** and **5**. Nitrosation of **2** proceeded in almost quantitative yield. Bisalkylation was carried out using KH and excess MeI in refluxing THF to give the dimethyl azepine **3** in 74% overall yield after hydrolysis.[13] All attempts to deprotonate the dimethyl *N*-nitroso intermediate failed, presumably due to poor proton alignment with the acidifying nitroso and aryl groups.[14] Oxidation of optically pure[15] **3** with sodium tungstate and H_2O_2 gave the nitrone **4**, and methyl Grignard addition followed by reoxidation gave the nitrone **5** in 51% overall yield. A final methyl Grignard addition and oxidation gave the desired nitroxide **1** in 51% yield. The optical purity of nitroxide (−)-(*S*)-**1** was assumed to be >97% ee on the basis of the optical purity of the dimethylazepine **3**.[15,16]

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(3) For a discussion of resolutions using HLADH, see: Danieli, B.; Lesma, G.; Passarella, D.; Riva, S. In *Advances in the Use of Synthons in Organic Chemistry*; Donodoni, S., Ed.; JAI Press: Greenwich, CT, 1993; Vol. 1, pp 143−219.

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(8) (a) Semmelhack, M. F.; Chou, C. S.; Cortes, D. S. *J. Am. Chem. Soc.* **1983**, *105*, 4492−4494. (b) Inokuchi, T.; Matsumoto, S.; Torii, S. *J. Org. Chem.* **1991**, *56*, 2416−2421.

(9) (a) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559−2562. (b) Anelli, P. L.; Montanari, F.; Quici, S. *Org. React.* **1990**, *69*, 212−219.

(10) For an alternate mechanistic proposal see: Ma, Z; Bobbitt, J. M. *J. Org. Chem.* **1991**, *56*, 6110−6114.

(11) **2**: $[\alpha]^{24}_D$ +574.4° (*c* = 0.79, $CHCl_3$); [lit. $[\alpha]^{20}_D$ +620° (*c* = 0.78, $CHCl_3$)[12a] and $[\alpha]^{20}_D$ +574.8° (*c* = 0.7, $CHCl_3$)]. Maigrot, N.; Mazaleyrat, J. P.; Welvart, Z. *J. Org. Chem.* **1985**, *50*, 3916−3918.

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(13) Meyers reported an independent synthesis of **3** using his enantioselective aryl coupling and alkylation: Meyers, A. I.; Nguyen, T. H. *Tetrahedron Lett.* **1995**, *36*, 5873−5876.

(14) Fraser, R. R.; Boussard, G.; Postescu, I. D.; Whiting, J. J.; Wigfield, Y. Y. *Can. J. Chem.* **1973**, *51*, 1109−1115.

(15) The hydrochloride salt of **3** was recrystallized twice to ensure optical purity. **3**: $[\alpha]^{24}_D$ +391.7° (*c* = 1.00, $CHCl_3$); [lit.[13] $[\alpha]^{23}_D$ +365° (*c* = 1.0, CH_2Cl_2)]. Mosher's analysis showed none of the minor enantiomer.

(16) **1**: $[\alpha]^{23}_D$ −610° (*c* 0.18, $CHCl_3$).

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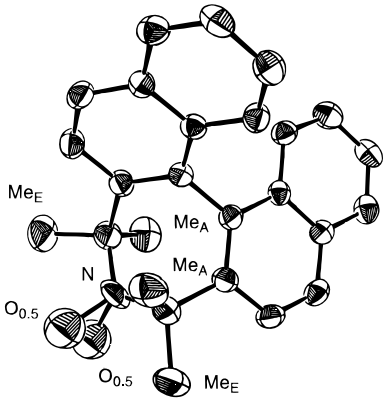
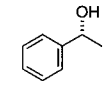
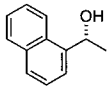
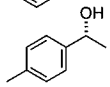
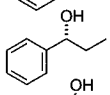
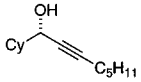
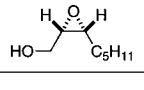


Figure 1. ORTEP representation of the nitroxide **1** (50% probability ellipsoids). The axial (Me_A) and equatorial (Me_E) methyl groups are labeled. The nitrogen atom is pyramidal, and the oxygen atom is disordered in the structure.

Table 1. Enantioselective Oxidations and Resolutions of Racemic Alcohols with (−)-(*S*)-1

Entry	Eq (*S*)-**1**[a]	Recovered Alcohol	Config.[a]	ee	Conversion	S
1[b]	0.5%		*R*	81%	69%	5.0
2[b]	1.0%		*R*	98%	87%	7.1[f]
3[e]	0.5%		*R*	57%	56%	4.5
4[b]	1.0%		*R*	73%	58%	6.8
5[c]	1.0%		*R*	64%	58%	5.1
6[b]	1.0%		*R*	89%	70%	6.0
7[b,g]	0.5%		*R*	57%	59%	3.9
8[b]	0.5%		–	<6%	58%	<1.2
9[c]	0.5%		*S*	41%	66%	2.2
10[b,d]	0.5%		2*S*,3*R*	19%	58%	1.5

[a] Eq (*S*)-**1** is the molar equivalent of the catalyst in each reaction. The configurations were determined by Mosher's ester analysis. [b] Enantiomeric excess determined by GC analysis with a Chiraldex G-TA (30 m × 0.32 mm) column. [c] Enantiomeric excess determined by Mosher's ester analysis. [d] Configuration determined by comparison to the Sharpless asymmetric epoxidation product. [e] Optical purity by rotation: observed $[\alpha]_D$ 44.6° (lit.[22] $[\alpha]_D$ 78°). [f] For greater accuracy, the *S* value was determined at lower conversion: 66% ee at 54% conversion. [g] Configuration assigned by analogy to the other examples.

The nitroxide oxidation catalyst (−)-(*S*)-**1** was characterized by X-ray crystallography, and its structure is shown in Figure 1.

Enantioselective oxidations of alcohols using nitroxide catalyst (−)-(*S*)-**1** are shown in Table 1. The TEMPO catalyst oxidizes primary alcohols faster than secondary alcohols under Anelli's conditions, but the oxidation still works with secondary alcohols.[9,17] Nitroxide **1** is both more hindered and more selective than TEMPO. While TEMPO rapidly oxidizes unsubstituted secondary alcohols, nitroxide **1** oxidizes only activated secondary alcohols to ketones at a convenient rate. The oxidations in Table 1 were carried out with 0.5−1.0 mol % of **1**, 0.6−0.7 equiv of NaOCl (0.35 M, pH 8.6), and 0.1 equiv of KBr in a rapidly stirred CH_2Cl_2/H_2O mixture for 30 min at 0 °C. The efficiency of the resolution is characterized by S ($= k_S/k_R$), the selectivity factor.[18] The S values range from 3.9 to 7.1 for simple benzylic alcohols with a reproducibility of about ±0.5. There is a slow uncatalyzed oxidation[19] that reduces the apparent S value, but this can be overcome by increasing the amount of catalyst (entries 1 and 2) from 0.5 to 1.0% which increases S from 5.0 to 7.1. Further increasing the catalyst concentration to 2.0% does not improve S. The optical purity of the recovered alcohol is dependent on the conversion; an S value of 6.0, for example, leads to recovered starting material with an ee of 89% at 70% conversion (entry 6). Alkynyl alcohols are also resolved under these conditions, but with modest S values (e.g., entry 9). A single example using a primary alcohol with an adjacent chiral center shows that resolution is possible,[5] but the S factor is too low to be useful (entry 10).[20] Among the aromatic substrates, entries 1−8, ortho-substituted benzyl alcohols are a bit more selective than unsubstituted rings, and the 1,2,3,4-tetrahydro-1-naphthol (entry 8) is unselective. The selectivity in this series correlates well with the ground state conformation of the benzyl alcohol: substrates where the benzyl hydrogen eclipses the aromatic ring are oxidized selectively, whereas substrates with the benzyl hydrogen perpendicular to the aromatic ring are less selective or unselective. The *S* enantiomer is oxidized preferentially with each aromatic alcohol. The identity of the fast reacting enantiomer is not obvious from inspection of molecular models. However, the transition state for the fast *S* reacting isomer is predicted to be 0.57 kcal/mol more stable than for the slow reacting *R* isomer using an AM1 approximation, in good agreement with the experimental results.[21]

We have described the first efficient, enantioselective oxidation of secondary alcohols using a nonenzymatic catalyst. The system is both rapid and chemically efficient, using ca. 1 mol % nitroxide catalyst (−)-(*S*)-**1** with bleach as the bulk oxidant. The selectivity factors are good for a first-generation system. We are investigating other catalysts to improve the selectivity and to extend the oxidation to other classes of substrates.

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Supporting Information Available: Experimental procedures for a typical oxidation and for the preparation of nitroxide catalyst (−)-(*S*)-**1** (7 pages).

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(17) Anelli, P. L.; Banfi, S.; Montanari, F.; Quici, S. *J. Org. Chem.* **1989**, *54*, 2970−2972.

(18) $S = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$ where ee is the fractional enantiomeric excess and C is the conversion. For an excellent discussion of kinetic resolutions, see: Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249−330.

(19) Lee, G. A.; Freedman, H. H. *Tetrahedron Lett.* **1976**, 1641.

(20) We thank Mr. Timothy Richardson for performing this experiment.

(21) The transition state for the oxidation of methoxide with dimethyl-*N*-oxoammonium cation was located at 6-31G*. The transition state atoms were frozen, and the complete transition state for the reaction of (*R*)- and (*S*)-1-phenylethanol with the *N*-oxoammonium salt of **1** was assembled around this frozen core and minimized at the AM1 level. The calculated TS energy for (*S*)-1-phenylethanol was 161.70 kcal/mol, while the TS energy for (*R*)-1-phenylethanol was 162.27 kcal/mol. Details of these calculations will be presented elsewhere.

(22) Balfe, M. P.; Downer, E. A. W.; Evans, A. A.; Kenyon, J.; Poplett, R.; Searle, C. E.; Tarnoky, A. L. *J. Chem. Soc.* **1946**, 787−803.