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Synthesis of α–Amino and α–Alkoxy Aldehydes via Oxoammonium Oxidation

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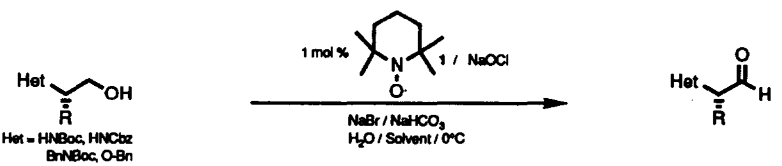
Abstract: Oxoammonium oxidation (TEMPO, 1) of various optically active α-amino and α-alkoxy alcohols affords the corresponding aldehydes in good yield and high enantiomeric purity.

The growing importance of chiral α-hetero-substituted aldehydes in organic synthesis has stimulated the development of numerous useful methods for the oxidation of optically active α-amino and α-alkoxy alcohols.[1] For example, chromium-based oxidants have been used for this purpose, although in certain cases racemization of the resultant aldehydes has been reported.[2] Other methods most often involve activated forms of dimethylsulfoxide (DMSO), e.g. DMSO-oxalyl chloride,[3] DMSO-trifluoroaceticanhydride,[4] and DMSO-dicyclohexylcarbodiimide,[5] and typically afford α-amino and α-alkoxy aldehydes in good to excellent yields. The success of the latter methods requires the use of low reaction temperatures and strict adherence to the documented reaction conditions in order to avoid racemization.[6] In addition, the co-production of dimethylsulfide (stench) and toxic gaseous side products (DMSO-oxalyl chloride → carbon monoxide) further limits their use on an industrial scale.

Recently, there have been several reports of oxoammonium-promoted oxidation of alcohols to aldehydes and ketones.[7] This oxidation utilizes a catalytic nitroxyl radical species (e.g.. 2,2,6,6-tetramethyl-1-piperidinyloxy free radical , TEMPO, 1) with commercial bleach as the net oxidant. Attracted by the mildness of these reaction conditions, coupled with our interest in the synthesis of α-hetero-substituted aldehydes,[8] we decided to investigate its application towards the oxidation of the corresponding alcohols (Scheme 1). Herein, we report on the successful utilization of this methodology for the general preparation of optically active α-amino and α-alkoxy aldehydes.



Scheme 1

Under our experimental conditions, suitably protected α-amino alcohols are smoothly oxidized to the corresponding aldehydes in good to excellent yields (Table I). Thus, treatment of a rapidly stirred biphasic (toluene / H_2O)[9] mixture of Cbz-L-Phenylalaninol with buffered commercial bleach solution in the presence of catalytic amounts of TEMPO free radical (1-2 mol %) and stoichiometric amounts of NaBr[10] gave clean and rapid oxidation to the desired aldehyde as a white solid in nearly quantitative yield. To determine the enantiomeric purity, the aldehyde was reduced back to the alcohol (LAH / THF, 0°C) and then derivatized with 3,5-dinitrobenzoyl chloride (Et_3N, DMAP / CH_2Cl_2) . Gratifyingly, HPLC analysis of the benzoate thus obtained utilizing a Pirkle D-2-naphthylalanine column[11] indicated that no detectable amount of racemization had occurred.

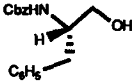
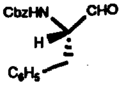
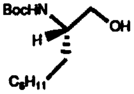
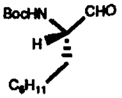
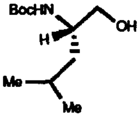
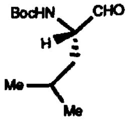
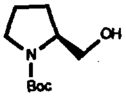
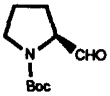
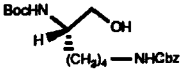
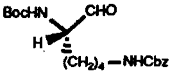
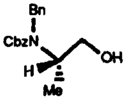
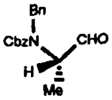
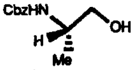
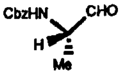
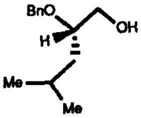
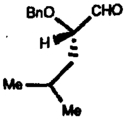
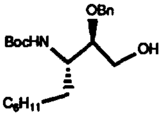
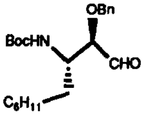
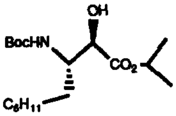
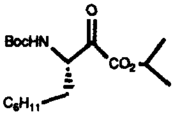
Other simply protected α-amino aldehydes are also readily prepared utilizing this methodology in high chemical yield and optical purity (Table I, entries 2-5). The previously described routes to these compounds are generally less efficient.[12] The only detectable side products were varying amounts of the corresponding acids which were easily removed by aqueous extraction during workup. It should be noted that over oxidation can be minimized by utilizing very vigorous stirring (>1000 rpm) of the biphasic reaction mixtures.[13] For example, the oxidation of Cbz-L-Phe-ol and Boc-L-Cha-ol with less efficient stirring afforded increased amounts of acid (Table I, entries 1 and 2). It would appear that efficient mixing of the reaction phases is *essential* to ensure rapid and selective oxidation of the nitroxyl radical to the intermediary oxoammonium salt.[7] From our limited study, carbamoyl (Boc and Cbz) protecting groups are preferred.[14] In the case of substrates possessing less hydrophobic side chains, bis-protection of the amino functionality appears to be advantageous in terms of chemical yield (Table I, entry 6 vs. 7). It should be noted that α-amino ketones can also be prepared under these conditions (Table I, entry 10).

Under identical experimental conditions, chiral α-alkoxy alcohols[14] are smoothly transformed into the corresponding α-alkoxy aldehydes in excellent yields and without loss of optical purity (Table I, entries 8 and 9). Once again the only detectable side products were small amounts of the corresponding acids and purification of the isolated reaction products was deemed unnecessary.

In summary, the oxoammonium (TEMPO) oxidation of optically active α-amino and α-alkoxy alcohols affords the corresponding aldehydes in good yield and high optical purity. This method is characterized by mild reaction conditions, non-toxic by-products, short reaction times, good to excellent chemoselectivity and ease of reaction workup, making it ideal for both lab and industrial scale.

The following procedure is representative. A 1-L 3-necked Morton flask containing Cbz-L-Phenylalaninol (8.56 g, 0.03 mol), TEMPO free radical (0.042 g, 0.0003 mol)[15], and NaBr (3.19 g, 0.031 mol) in a bi-phasic mixture of toluene (90 mL) / ethyl acetate (90 mL) and water (15 mL) was immersed in a 0°C ice water bath. With rapid mechanical stirring (1200 rpm), an aqueous solution of 0.35 M NaOCl (94 mL, 0.033 mol) containing $NaHCO_3$ (7.35 g, 0.0875 mol) is added dropwise over a period of 1h and stirred for an additional 10 min. The aqueous layer was separated and washed with toluene (20 mL). The combined organic layers were washed with a solution of KI (0.25 g) dissolved in 10% aqueous $KHSO_4$ (40 mL). The iodine-colored organic layer was then washed successively with 10% aqueous sodium thiosulfate (20 mL), pH 7 phosphate buffer (0.2 M, 50 mL) and saturated brine. Drying (Na_2SO_4) gave after filtration and concentration 8.50 g

Table I: Oxoammonium oxidation of Protected α-Heterosubstituted Alcohols

Entry	Alcohol	Aldehyde	Yield[a]	ee[b]	Rotation
1			96 (81)[c]	>99	+ 73.6°
2			91 (65)[c]	97	+ 26.4°
3			77	>99	+ 18.7°
4			82	>98[d]	- 96.3°
5			89	> 99	+ 37.9°
6			90	g	+ 57.7°
7			51	>99	+ 47.1°
8			77	>98[e]	- 82.6°
9			92	>95[f]	- 20.4°
10			87	g	+ 43.7°

[a] Crude purity was > 97 % by G. C. determination. [b] Based on HPLC, see text. [c] Stirring rate was 200 rpm std flask. [d] Based on rotation.[ref.17] [e] Based on rotation.[ref.18] [f] de; based on NMR. [g] Not determined.

(96.6 %) of the desired aldehyde as a white solid which was judged to be >98 % pure by GC analysis and >99% ee (vide supra).

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6. (a) In our hands the enantiomeric purity of the DMSO-oxalyl chloride reaction products is highly dependent on the subsequent addition of base (usually Et_3N). Excess base or prolonged reaction times such as those experienced on large scale can lead to varying amounts of racemization. Unpublished results. (b) DMSO / SO_3 pyridine complex can be used for the oxidation of α-hetero-alcohols at ambient temperatures, see: Hamada, Y.;Shioiri, T. *Chem. Pharm, Bull.* **1982**, *30*, 1921-1924, and ref. 3.
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9. Toluene or mixtures of toluene-ethyl acetate appear to be the solvents of choice. If nessessary, minimal amounts of CH_2Cl_2 can be added in order to solubilize the substrate but pure CH_2Cl_2[7] in our hands led to emulsion problems during workup.
10. The use of stoichiometric amounts of NaBr resulted in slightly higher yields than trials using catalytic loads of NaBr.
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13. Good results can be obtained using vigorous magnetic stirring on small scale (<10 mmol). However, the use of a Morton flask with *vigorous* overhead mechanical stirring is recommended on larger scale.
14. Attempts of oxidation of 2,2-dimethl-4-alkyl-5-hyroxymethyloxazolines and 2,2-dimethyl-4-hydroxymethyl-5-alkyl-dioxolanes gave poor yields of aldehyde.
15. The use of the triphenylmethyl and benzoyl protecting groups led to reduced yields of the desired aldehydes. In addition, attempts directed toward the oxidation of protected tryptophanol led to complex reaction mixtures and trace quantities of desired aldehyde.
16. TEMPO free radical was purchased from the Aldrich Chemical Co. and used without further purification. Care should be taken when handling nitroxyl radicals as they are highly toxic!
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18. Unpublished result.

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