The first efficient bovine serum albumin catalyzed asymmetric oxidation of tertiary amines to the corresponding *N*-oxides *via* kinetic dynamic resolution

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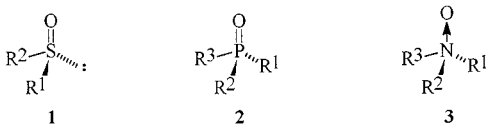
Unsymmetrical teriary amines were oxidized with a few oxidants in the presence of bovine serum albumin to give the corresponding *N*-oxides of the highest optical purity ever reported (up to 66%) for the reaction of asymmetric oxidation of amines *via* their kinetic dynamic resolution.

During the last three decades chiral sulfoxides **1**[1] and phosphine oxides **2**[2] have found widespread application in the stereochemistry of heteroorganic compounds and especially in asymmetric synthesis. In a sharp contrast, the nitrogen analogues of **1** and **2**, *i.e.* chiral tertiary amine *N*-oxides **3**, are much



1 **2** **3**

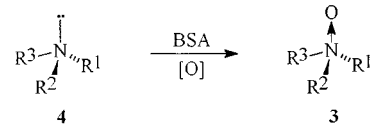
less known and without practical use in asymmetric synthesis. This results mainly from the fact that access to optically active tertiary *N*-oxides is very limited[3] in comparison to the sulfur and phosphorus analogues. Until now a few optically active tertiary *N*-oxides of high optical purity have been obtained *via* classical resolution of the corresponding racemates. At the beginning of this century Meisenheimer[4] resolved some asymmetric *N*,*N*-dialkylarylamine oxides *via* diasteromeric salts with α-bromocamphoric acid and tartaric acids. More recently, the enantiomers of *N*-methyl-*N*-phenyl-4-methylcyclohexylamine *N*-oxide[5] and *N*-methyl-*N*-neopentyl-4-methylcyclohexylamine *N*-oxide[6] were resolved using (−)-dibenzoyltartaric acid. Very recently, Toda *et al.*[7] reported nonclassical resolution of some asymmetric *N*,*N*-dialkylarylamine *N*-oxides with optically active host compounds. Simultaneously a report[8] appeared on partial resolution of the enantiomers of *N*-benzyl-*N*-methylpropynylamine *N*-oxide using the chiracal OD and chiralpark AD CPS columns.

Asymmetric oxidation of unsymmetrical tertiary amines has also been used for the preparation of optically active *N*-oxides. However, all the reported procedures gave the required oxidation products in very low optical yield. Thus, when *N*-methyl-1,2,3,4-tetrahydroquinoline was treated[9] with percamphoric acid at −70 °C in $CHCl_3$ the corresponding *N*-oxide obtained as the hydrochloride had an ee value of only 0.6%. Similar oxidation of a series of *N*-alkyl-*N*-methylanilines produced *N*-oxides with germinal optical rotation.[10] (+)-*N*-*trans*-crotyl-*N*-ethyl-*p*-toluidine *N*-oxide having an ee of 16% was derived from the parent amine by oxidation with dibenzoyl-L-pertartaric acid.[11]

As part of our program involving biologically-mediated reactions of prochiral heteroorganic substrates[12] we became interested in the asymmetric protein catalyzed oxidation of unsymmetrical tertiary amines **4** to the corresponding optically active *N*-oxides **3**.

Our interest in this oxidation results not only from the still existing need for an efficient procedure for the preparation of optically active *N*-oxides, but mainly from the fact that this conversion fulfils at least one of the conditions which characterise an ideal dynamic kinetic resolution procedure.[13] Indeed the starting material enantiomers (tertiary amines) are always in equilibrium due to a very fast pyramidal inversion on the stereogenic nitrogen atom of the substrates.

Here we report that a number of optically active *N*-oxides **3** of considerably higher enantiomeric excess than these reported until now were obtained from the direct oxidation of the corresponding amines **4** in the presence of bovine serum albumin (BSA) [eqn. (1)]. BSA, the most abundant protein in



4 **3** (1)

blood plasma, acts as a transport protein and forms adducts with various kinds of hydrophoboic compounds.[14] Effective discrimination of the substituents bonded to the nitrogen atom in amine **4** should be achievable by fixing the amine in the chiral environment of BSA, thus making asymmetric induction in the subsequent oxidation possible. Here we report that BSA can be used in catalytic amounts to afford the corresponding optically active *N*-oxides. The reactions were carried out by stirring at room temperature a heterogeneous mixture of substrate (1 mmol) and oxidant (2 mmol) in the presence of BSA (0.05 mmol; the molecular weight of the BSA was taken as 66 000) in a borate buffer solution (pH 9). (These conditions were found to afford the highest enantioselectivity in the BSA—catalyzed sulfoxidation of functionalized sulfides.[12])

The results collected in Table 1 show the oxidations always produced optically active *N*-oxides in chemical yields ranging from 10% to quantitative. It should be noted that in many cases, when chemical yields are low, a substantial amount of the starting amine was recovered during the chromatographic purification of the crude reaction products. The extent of asymmetric induction was determined by ^{1}H NMR spectroscopy using optically active *tert*-butylphenylphosphinothioic acid as a chiral solvating agent.[15] Analysis of the ee values indicates that optically active *N*-oxides of high opitcal purity (*ca.* 65%) were produced in two cases (**3d** and **3e**).

Modest enantiomeric excesses were observed in other cases. In general higher selectivity is observed with increased length of the alkyl chain of *N*-alkyl-*N*-methylbenzylamine *N*-oxides. The highest ee values in the oxidation with $NaIO_4$ were observed for *n*-butyl oxide **3d** (64.6%) and *n*-pentyl homologue **3e** (63.5%). Similar behaviour has already been observed in the BSA catalyzed sulfoxidation of sulfides with $NaIO_4$[12*a*] and dioxiranes.[12*b*] In this context it was interesting to check the influence of the nature of the oxidant on the stereochemical outcome of the oxidation of amines to *N*-oxides. As a model compound amine **4e** was selected. Analysis of the observed relationship indicates that the stereoselectivity change dramatically with MCPBA as oxidant instead of $NaIO_4$, the ees being

Table 1 The bovine serum albumin catalyzed oxidation of tertiary amines $R^1R^2R^3N$ **4** to the corresponding *N*-oxides, $R^1R^2R^3N \rightarrow O$ **3**

Amine						*N*-Oxide			
4	R^1	R^2	R^3	Oxidant	*t*/h	**3**	Yield (%)	$[\alpha]_{589}$[a]	Ee[b] (%)
4a	Me	Bn	Et	$NaIO_4$	48	**3a**	35[c]	−2.5	20.0
4b	Me	Bn	Pr	$NaIO_4$	24	**3b**	30[c]	−3.9	48.5
4c	Me	Bn	Pr^i	$NaIO_4$	24	**3c**	30[c]	−3.6	41.7
4d	Me	Bn	Bu	$NaIO_4$	24	**3d**	30[c]	−4.9	64.6
4e	Me	Bn	C_5H_{12}	$NaIO_4$	42	**3e**	87	−4.8	63.5
4e	Me	Bn	C_5H_{12}	Oxone	72	**3e**	40	−3.0	40.0
4e	Me	Bn	C_5H_{12}	H_2O_2	72	**3e**	100	−7.1	66.8
4e	Me	Bn	C_5H_{12}	MCPBA	72	**3e**	100	+0.5	4.0
4f	Me	Bn	C_7H_{15}	$NaIO_4$	48	**3f**	83	−2.5	48.0
4g	Me	Ph	Et	$NaIO_4$	72	**3g**	25[c]	−3.2	18.0[d]
4h	Me	Ph	Pr	$NaIO_4$	72	**3h**	13[c]	−4.1	44.0
4h	Me	Ph	Pr	MCPBA	24	**3h**	48[c]	+0.7	10.0
4i	Me	Ph	C_5H_{12}	$NaIO_4$	72	**3i**	24	−2.1	28.0
4j	Me	*p*-Tol	Et	$NaIO_4$	60	**3j**	35[c]	−3.2	24.0[e]

[a] All rotations were measured in $CHCl_3$. [b] Determined by ^1H NMR spectroscopy with *tert*-butylphenylphosphinothioic acid as a chiral solvating agent (ref. 15). [c] Substantial amount (20–30%) of the starting amine was recovered during chromatographic purification of the produced *N*-oxide. [d] Maximum value reported for this *N*-oxide is $[\alpha]_D$ +16.4 ($CHCl_3$) (ref. 7). [e] Maximum value reported for this *N*-oxide is $[\alpha]_D$ +13.0 ($CHCl_3$) (ref. 7).

4 and 63.5%, respectively. This shows the great sensitivity of this method to changes in the reaction conditions.

In conclusion we would like to stress that although our method did not always give very high stereoselectivity, it constitutes the first procedure for effective asymmetric oxidation of unsymmetrical amines to the corresponding *N*-oxides. It also constitutes the first example of a dynamic kinetic resolution procedure, which is based on the inherent ability of the substrate enantiomers to be in equilibrium under the reaction conditions. The results presented above demonstrate moreover that the use of a catalytic amount of BSA is not limited to the oxidation of prochiral organosulfur derivatives, but can be extended to substrates containing other heteroatoms. Work is in progress to extend the applicability of this dynamic kinetic resolution procedure and to determine the absolute configuration at the nitrogen stereogenic center in the formed optically active *N*-oxides by spectroscopic techniques.

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