Homochiral Amine Oxides in the Enantioselective Reduction of Ketones

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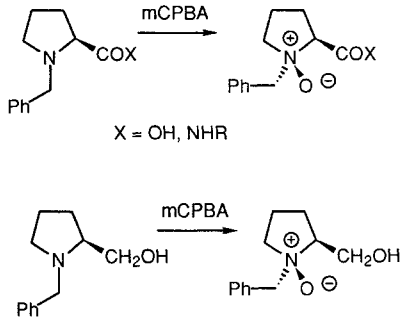
Abstract: The synthesis of a number of novel homochiral prolinol *N*-oxide derivatives is described. Several of these were found to catalyse the borane reduction of α-chloroacetophenone to (S)-2-chloro-1-phenylethanol in excellent chemical yield and in 96% ee.

The synthesis of organic compounds in optically pure or enriched form is one of the major themes of modern organic chemistry[1]. A substantial number of chiral ligands based on amines, sulfides, sulfoxides, phosphines and phosphine oxides have been reported over recent years and several have emerged as powerful controlling elements in asymmetric synthesis[2]. However, there have been virtually no examples of asymmetric synthesis using homochiral tertiary amine *N*-oxides[3], despite the excellent metal binding properties of this functional group[4]. This is very suprising given the widespread use of achiral amine oxides such as *N*-methylmorpholine *N*-oxide in synthesis, exemplified by the osmium mediated *cis*-hydroxylation of alkenes[5] and the Ley-Griffith TPAP oxidation of alcohols to aldehydes and ketones[6].

A handful of transformations employing chiral amine *N*-oxides have been reported, notably by Kerr[7] and Marchetti[8] but these reactions exhibit only modest enantioselectivity at best. Perhaps the major reason that homochiral amine oxides have not been exploited is the lack of methods for their preparation. We have recently reported the preparation of a series of homochiral amine *N*-oxides derived from *N*-alkylated derivatives of the α-amino acid L-proline[9]. If a hydrogen bonding carboxylate side chain is present (such as a primary/secondary amide, carboxylic acid or alcohol) oxidation occurs to give the *N*-oxide *syn* to this side chain (Scheme 1). The resulting amine *N*-oxides are stabilized by intramolecular hydrogen bonding. As a consequence of the hydrogen bonding they are highly stable, crystalline, non hydrated solids.



Scheme 1

The ease of preparation of these *N*-oxides and their stability has promoted us to investigate their use as ligands in asymmetric synthesis. In this letter we report the preliminary results of these investigations. We chose to study the enantioselective reduction of ketones since this is one of the most important transformations in organic synthesis[10]. The pioneering work of Itsuno[11] utilised amino alcohols (A) in the presence of borane to effect this key transformation with modest to good enantioselectivity. This was extended by Corey and coworkers[12] who introduced the use of oxazaborolidines based on α,α-diphenylpyrrolidinemethanol (B) as catalysts in the borane reduction of ketones. More recently Wills and colleagues[13] have reported the use of chiral phosphinamide catalysts (C) in this process (Figure 1).

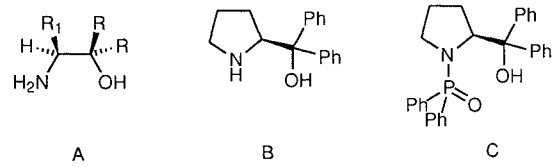


Figure 1

The ease with which we could prepare homochiral amine oxides and the enormous potential of these compounds has led us to investigate them in asymmetric transformations. In particular, the hydroxymethyl functionalised proline derivatives appeared attractive given their success in previous asymmetric reductions. Given mechanistic interpretations of the reaction we also elected to synthesise a number of amine *N*-oxides which bore additional metal binding sites. In particular, a 2-pyridylmethyl substituent on the proline ring nitrogen was attractive given the known ability of the basic nitrogen to coordinate boron species. The ligands we chose to prepare are shown in Figure 2.

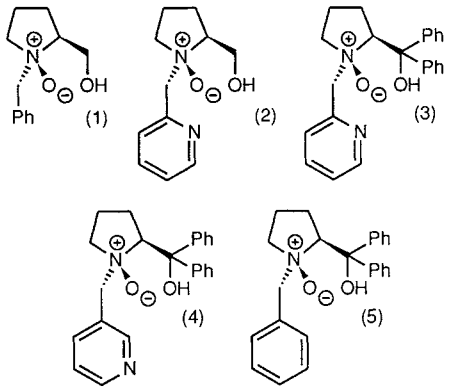
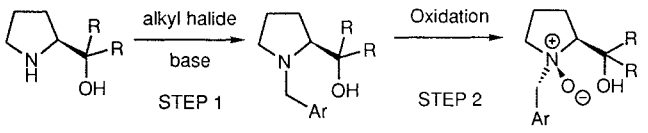


Figure 2

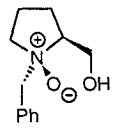
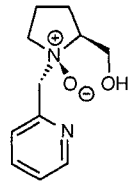
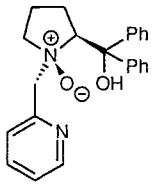
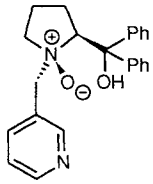
We anticipated that *N*-oxides (1) to (4) would be prepared from the precursor tertiary amine by oxidation with a peracid (such as *m*CPBA)(Scheme 2, STEP 2) and the *N*-oxide would be formed *syn* to the side chain hydroxyl group in accordance with our previous observations. The tertiary amines were readily available by *N*-alkylation of the appropriate prolinol derivative (prolinol or (S)-α,α-diphenylpyrrolidinemethanol[14]) with the appropriate alkyl halide (Scheme 2, STEP 1). The synthesis of *N*-oxide (5) has been reported previously[9].



Scheme 2

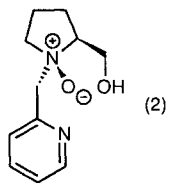
The results of this study are shown in table 1. In general the yields are excellent and all of the *N*-oxides are stable, crystalline solids. ^{1}H and ^{13}C NMR clearly showed that the *N*-oxides had been formed as a single

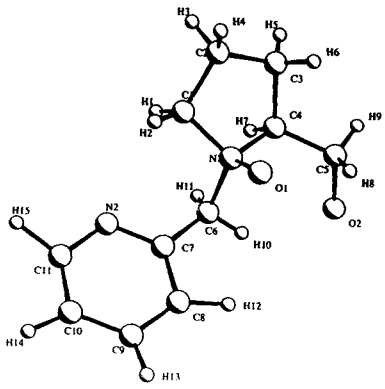
Table 1. Preparation of tertiary amine *N*-oxides

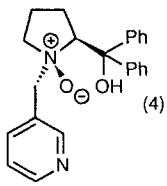
Entry	Step 1 conditions	% yield	Step 2 conditions	% yield	Amine Oxide
1	N/A*	–	*m*CPBA K_2CO_3, CH_2Cl_2, -78°C	94	
2	2-picolyl chloride, DBU, CH_2Cl_2	92	*m*CPBA K_2CO_3, CH_2Cl_2, -78°C	95	
3	2-picolyl chloride, DBU, CH_2Cl_2	96	*m*CPBA K_2CO_3, CH_2Cl_2, -78°C	98	
4	3-picolyl chloride, DBU, CH_2Cl_2	56	*m*CPBA K_2CO_3, CH_2Cl_2, -78°C	63	

* Commercially available *N*-benzylprolinol was used.

diastereoisomer in each case, with the *N*-oxide *syn* to the side chain hydroxyl group. The structures of (2) and (4) were verified by x-ray crystallography (Figure 3)[15].


(2)




(4)

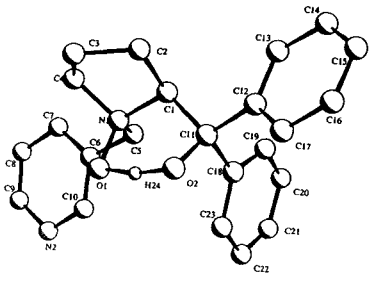
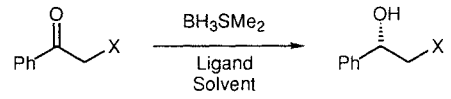


Figure 3

The oxidations of the tertiary amines were both highly chemo- and diastereoselective. We observed none of the pyridine *N*-oxides for ligands (2), (3) and (4) when one equivalent of *m*CPBA was used, although if two equivalents of *m*CPBA were used the bis-(*N*-oxides) could be isolated. Having established a reliable route to these amine *N*-oxides we then investigated their use as catalysts in the borane reduction of ketones (Scheme 3).



Scheme 3

The general conditions described by Wills and coworkers were used[13]. Thus, the amine oxide catalyst was dissolved in the appropriate solvent and one equivalent of borane dimethylsulfide was added. The solution was heated to reflux and the ketone was added. The reduction was complete in five minutes. After cooling, aqueous work up gave the corresponding alcohol in essentially quantitative yield. The amine oxides were stable to these conditions and we observed no reduction of the *N*-oxides to the parent tertiary amine. The amine oxide could be recovered from the reaction mixture in >90% yield. The enantiomeric excess of the product was determined by converting them to their trifluoroacetates and analysing by chiral GC. The results are summarised in table 2.

The first ligand we investigated, *N*-benzylprolinol *N*-oxide (1) gave virtually no measurable enantioselectivity. This prompted us to investigate the *N*-(2-pyridylmethyl)prolinol *N*-oxide catalyst (2),

Table 2: Reduction of ketones using borane dimethyl sulfide and chiral amine *N*- oxides.

Entry	X =	Catalyst	mol% Catalyst	Solvent	% Yield	% ee
1	Me	1	5	toluene	99	3(R)
2	Me	2	5	toluene	99	20(R)
3	Me	2	10	toluene	99	13(R)
4	Me	2	5	thf	99	9(R)
5	Me	3	5	toluene	99	58(R)
6	Me	3	10	toluene	99	53(R)
7	Me	3	5	thf	99	68(R)
8	OMe	3	5	thf	99	48(R)
9	Cl	3	5	thf	99	**96(S)**
10	Me	4	5	thf	99	79(R)
11	Cl	4	5	thf	99	**96(S)**
12	Me	5	5	thf	99	12(R)

bearing the additional borane binding site in the form of the pyridine nitrogen. The ee of the product alcohol immediately increased. We then examined the effect of increasing the steric bulk adjacent to the alcohol by using the *N*-oxides derived from α,α-diphenylpyrrolidinemethanol. It was highly gratifying to observe a dramatic increase in the ee of the product alcohols with both catalyst 3 and 4. In particular, the reduction of α-chloroacetophenone in the presence of catalysts 3 and 4 gave (S)-2-chloro-1-phenylethanol in an excellent 96% ee. This chloro alcohol can be readily converted through to the homochiral epoxide which is a versatile building block in organic synthesis. The importance of the pyridine nitrogen to the success of this reaction is illustrated by the dramatic fall in enantioselectivity when amine oxide (5) is used. Although this compound bears the bulky diphenyl substituents it does not possess a pyridine nitrogen and the ee falls to a meagre 12%.

In summary, we have synthesised a number of new homochiral amine oxides and demonstrated their use as catalysts in enantioselective reductions. We are currently evaluating these and other related *N*-oxides in a range of enantioselective transformations.

Acknowledgments:

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15. Full crystallographic data will be deposited at the Cambridge Crystallographic Data Centre. We would like to thank Mr J. V. Barkley (University of Liverpool) for carrying out these structure determinations.
16. The amine oxide catalyst (0.05 mmol) was dissolved in the dry solvent (5 ml) under nitrogen and borane dimethylsulfide complex (10M (BH_3), 0.10 ml, 1.0 mmol) was added. The reaction mixture heated at reflux for 5 minutes. A solution of the ketone (1.00 mmol) in 1 ml of dry solvent was added over 5 minutes. The reaction mixture was heated at reflux for a further 5 minutes and then allowed to cool to room temperature. Distilled water (5 ml) was added and the mixture extracted with CH_2Cl_2 (3 x 5 ml). The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo* to give the alcohol in essentially quantitative yield. Conversion to the trifluoroacetate was accomplished by addition of excess trifluoroacetic anhydride (1.0 ml) to a solution of the

alcohol in dry CH_2Cl_2. The solvent was allowed to evaporate overnight. Each reaction was run in triplicate and the ee given is an average of the three runs. Analysis was performed on a Phillips PU 4600 gas chromatograph using a Lipodex A column (25m x 0.25 μm, 0.6 bar, 75°C), or a Chiraldex GTA column (0.6 bar, 70°C). On the Lipodex A column, the retention time for (R)-2-chloro-1-phenyl-1-ethanol trifluoroacetate is 46.05 minutes and for (S)-2- chloro-1-phenyl-1-ethanol trifluoroacetate is 45.17 minutes. All compounds gave correct spectroscopic and analytical data.