

## ASYMMETRIC SYNTHESIS WITH CHIRAL HYDROGENOLYSABLE AMINES: A NEW ROUTE TO ENANTIOPURE ETHANOLAMINES\*\*

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**Abstract** - Enantiopure ethanolamines have been obtained via diastereoselective reduction of chiral 2,3-dihydro-6H-1,4-oxazin-2-ones

Chiral  $\beta$ -aminoalcohols form an important class of compounds due to their usefulness in modern organic chemistry as chiral auxiliaries<sup>1</sup> or chiral building blocks.<sup>2</sup>

Preparation of  $\beta$ -ethanolamines (**1**) has been described by chemical reduction of natural  $\alpha$ -aminoacids,<sup>3</sup> enzymatic resolution<sup>4</sup> or synthetic approaches.<sup>5</sup>

The literature reports two general homochiral amines syntheses: addition reaction of organometallic reagents<sup>5-7</sup> or hydrogen<sup>8</sup> to chiral imines or iminiums.

This last strategy has been applied to  $\alpha$ -hydroxyketones (**2a**), using  $\alpha$ -methylbenzylamine,  $\alpha$ -phenylglycinol and methyl  $\alpha$ -phenylglycinate as chiral hydrogenolysable amines, but we never observed the  $\alpha$ -hydroxyimine formation. However, catalytic reductive amination of ketone (**2a**, R=CH<sub>3</sub>) with the same chiral amines leads to a diastereomeric mixture (d.e.= 80%). Unfortunately, the results obtained with other substituents are not satisfactory.

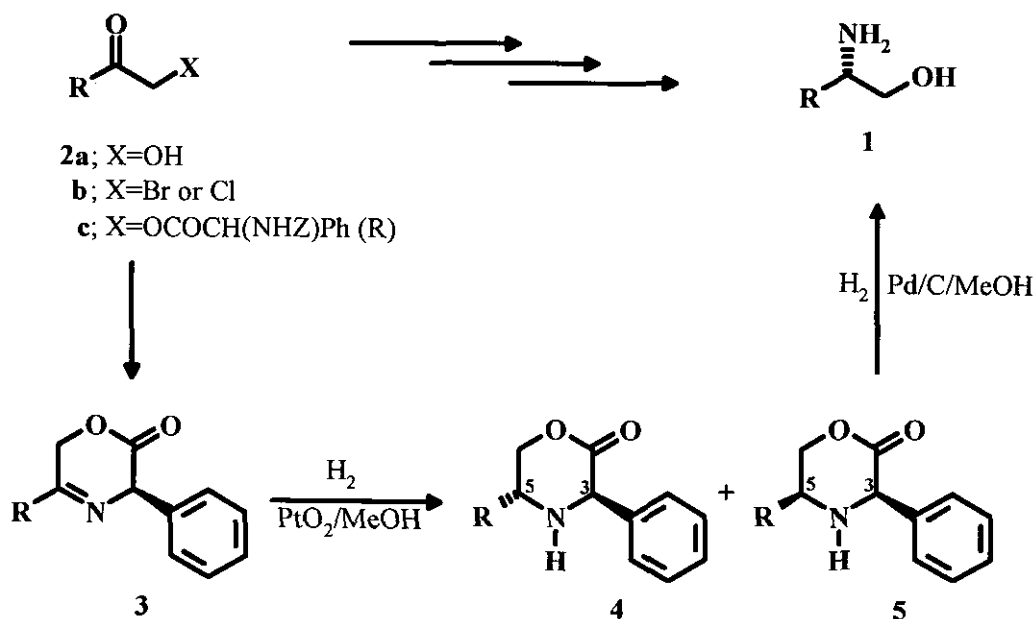
Here we report preparation and diastereoselective reduction of cyclic imines (**3**) which have permitted to obtain optically pure ethanolamines (**1**) after reduction and debenylation.

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\*\* Dedicated to Professor Alan R. Katritzky on the occasion of his 65th birthday.

Chiral oxazinones (**3**) were readily obtained in two steps from  $\alpha$ -halomethyl ketones (**2b**)<sup>9</sup> and potassium (R)-N-carbobenzyloxy- $\alpha$ -phenylglycinate by nucleophilic substitution in DMF,<sup>10</sup> leading to esters (**2c**) in good yields (83-98%).

Then cleavage of Cbz-protecting group using 33% hydrobromic acid in acetic acid and subsequent neutralisation of the resulting hydrobromides in water provided chiral oxazinones (**3**) in quantitative yields (Scheme 1).



Scheme 1

Reduction of oxazinones (**3**) was achieved by catalytic hydrogenation leading to morpholinones (**4**)+(5) with diastereomeric excesses between 66 and 86%. Best diastereoselectivity and chemical yields were obtained over  $PtO_2$  in methanol at atmospheric hydrogen pressure (Table 1). Isolation of the major *cis*-morpholinone (**5**) was performed by flash chromatography on silica gel using a  $CHCl_3$ - $Me_2CO$  mixture as an eluent.

**Table 1. Catalytic oxazinones (3) reduction.**

Oxazinones	R	Time (h)	<i>Cis</i> (5) / <i>trans</i> (4)	Morpholinones (5) (%) <sup>a</sup>
<b>3a</b>	Me	4	91 : 9	73
<b>3b</b>	Et	4	86 : 14	82
<b>3c</b>	iPr	4	90 : 10	84
<b>3d</b>	nBu	5	83 : 17	78
<b>3e</b>	iBu	5	85 : 15	76
<b>3f</b>	tBu	6	93 : 7	89

<sup>a</sup> Yields refer to chromatographed products.

Finally, hydrogenolysis of morpholinones (5) over 10% Pd/C (150 bars) for 72 h in methanol gave chiral  $\beta$ -ethanolamines (1) in good chemical yields (Table 2).

**Table 2.  $\beta$ -Ethanolamines (1) formation.**

Ethanolamines	R	Yields (%)	bp (°C/torr)		[ $\alpha$ ] <sub>D</sub> <sup>20</sup> (c, solvent)	
			Found	Ref.	Found	Ref.
<b>1a</b>	Me	89	76 / 16	12	+18.2 (neat)	14
<b>1b</b>	Et	84	87 / 22	12	+10.2 (neat)	14
<b>1c</b>	iPr	88	50 / 0.01	12	+17.1 (11.0, EtOH)	15
<b>1d</b>	nBu	78	70 / 0.01	12	+12.2 (8.7, EtOH)	12
<b>1e</b>	iBu	86	136 / 56	12	+01.2 (neat)	16
<b>1f</b>	tBu	82	60 / 0.01	13	+37.2 (3.0, EtOH)	13

As conclusion, we have developed a direct and general synthesis of enantiopure ethanolamines using  $\alpha$ -phenylglycine as chiral auxiliary.

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