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Stereoselective Reductive Amination of Chiral *N,N*-Dibenzylamino Ketones

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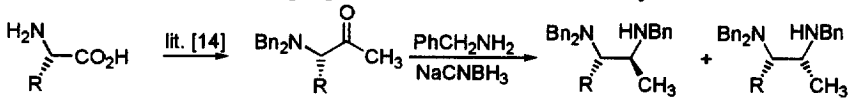
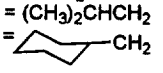
Abstract

N,N-Dibenzylamino ketones of the type $Bn_2N(R)CHC(O)CH_3$, prepared in enantiomerically pure form from α-amino acids, undergo stereoselective reductive amination using $PhCH_2NH_2/NaCNBH_3$ or $NH_4OAc/NaCNBH_3$ with formation of diastereo- and enantiomerically pure vicinal diamines $Bn_2N(R)CHCH(NHCH_2Ph)CH_3$ or $Bn_2N(R)CHCH(NH_2)CH_3$, respectively.

Keywords: Amino acids; Diamines; Asymmetric induction; reduction.

Vicinal diamines bearing two neighboring stereogenic centers constitute an important class of compounds found in nature and used as pharmaceuticals and/or as chiral ligands in asymmetric synthesis [1-10]. Many different synthetic methods for the preparation of these compounds have been developed during the last decade [1-10]. One approach is based on the use of the chiral pool of α-amino acids **1**, these being transformed into the corresponding α-amino aldimines which can then be subjected to a variety of different diastereoselective C-C bond forming reactions [11-13]. Here we describe an alternative strategy: The amino acids **1** are first transformed into the ketones **2** [14], which are then reductively aminated.



1 a: R = $PhCH_2$
b: R = $(CH_3)_2CHCH_2$
c: R = 

2

3 **4**

a: 84%; > 95 : < 5
b: 81%; > 95 : < 5
c: 86%; > 95 : < 5

Upon reacting ketones **2** with benzylamine in the presence of $NaCNBH_3$, exclusive formation of diamines **3** was observed.[1] Debenzylation with formation of diamines **5** allowed for

[1] Experimental procedure: The solution of an *N,N*-dibenzylamino ketone **2** [14] (3 mmol) in 20 ml of dry methanol is treated with benzylamine (2.6 ml; 24 mmol), $NaCNBH_3$ (230 mg; 3.6 mmol) and $MgSO_4$ (2 g). The mixture is heated under reflux for 16 h. Following the removal of $MgSO_4$ by filtration, the solution is concentrated i. vac. and the residue dissolved in diethyl ether (30 ml). The solution is washed with NaCl-solution, dried over $MgSO_4$ and concentrated i. vac. to provide > 95% of crude products **3**. In order to obtain analytically pure samples the residues are chromatographed.

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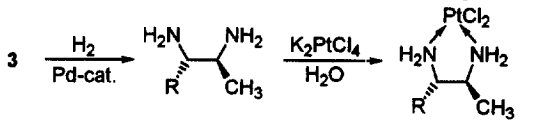
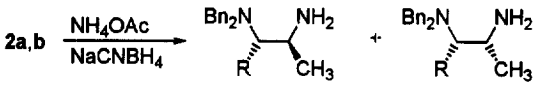
configurational assignment (by comparison with known compounds) [11] and also set the stage for the synthesis of platinum compounds **6** which are chiral analogs of *cis*-platinum [1-10].



5 a: Pd/C: 87%; **6 a**: 66%;
b: $Pd(OH)_2$/C: 72%; **b**: 62%
c: Pd/C: 90%; **c**: 73%

In order to see whether ammonia can also be used as the nitrogen component in the reductive amination, ketones **2a-b** were reacted with $NH_4OAc/NaCNBH_3$. Indeed, good yields of diamines **7** were observed, diastereoselectivity again being essentially complete. Compounds **7** can also be debenzylated with formation of diamines **5**. Control experiments based on the formation and HPLC analysis of the "double Mosher amides" of **5** demonstrated an optical purity of > 96% [15].



7 **8**

a: 76%; > 95 : < 5
b: 83%; > 95 : < 5

Although the present method is extremely simple and efficient, it has a clear limitation in that only methyl ketones of the type **2** can be reductively aminated. Ketones in which the methyl group is replaced by larger residues such as *n*-butyl or phenyl [14] do not undergo reductive amination, even if the reaction time is prolonged to 10 days [15]. Presumably, this is due to steric reasons. Mechanistically, the successful reactions of ketones **2** occur in two steps, namely ketimine formation (possibly in protonated form), followed by in situ non-chelation controlled reduction. Thus, this is yet another example in which protective group tuning [16] in the form of two benzyl groups at nitrogen exerts a strong stereochemically directing effect [13].

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