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Stereocontrolled Reductive Amination of 3-Hydroxy Ketones.

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Abstract: *syn*-1,3-Aminoalcohols are synthesized in high diastereomeric excess by reductive amination of 3-hydroxyketones with sodium cyanoborohydride in the presence of benzylamine. © 1997 Published by Elsevier Science Ltd.

Over the past years, there has been a great effort towards exploiting the presence of a proximal hydroxyl group to control the stereoselectivity of a new chiral center. For example, Narasaka[1] and Evans[2] have reported complementary reagent-based strategies for preparation of 1,3-*syn* and *anti* diols via reduction of acyclic 3-hydroxyketones. Since we were interested in the easy access to the 1,3-aminoalcohol fragment,[3] we tried to develop a methodology based on such a hydroxy-directed reduction. The reduction of 3-hydroxy oximine[4] or 3-hydroxy oximino benzyl ether have been reported.[5,6] In the latter case, the results obtained were highly dependent on the reducing agent. When lithium aluminium hydride was used, the stereochemistry of the 1,3-aminoalcohol was dependent on the (E/Z)-oxime geometry; however, the addition of sodium methylate allowed to isolate the 1,3-*syn* isomer mainly whatever the oxime geometry.[5] In contrast, with tetramethylammonium triacetoxyborohydride (TABH) the (*Z*)-oximino ether afforded the *syn* aminoalcohol while the *anti* isomer was obtained from the (*E*)-oxime.[6]

We report here an efficient and stereoselective route to 1,3-*syn* aminoalcohols by reductive amination of 3-hydroxyketones.

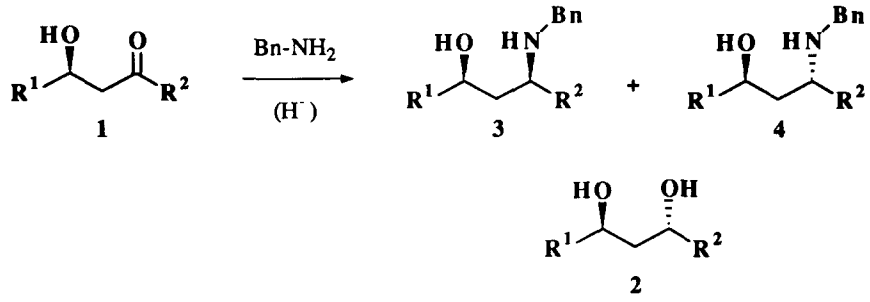
We have previously shown that the reductive amination[7] of ketoepoxides with tetramethylammonium triacetoxyborohydride in acidic medium stereoselectively afforded *anti* aminoalkylepoxides.[8]

However, when the same reaction was conducted with the 3-hydroxyketones protected as a MOM ether in the presence of benzylamine, we observed nearly no transformation into the corresponding 3-alkoxy amines.

We then decided to study the reduction of the 3-hydroxyketones **1**. So, compound **1** (R^1 = *i*-Bu, R^2 = C_6H_5) was treated with TABH under usual conditions.[8] However, in addition to a poor selectivity (a 3:2 mixture of 1,3-amino alcohols), an important fraction (16%) of 1,3-diol **2** was isolated. The same result was obtained when sodium triacetoxyborohydride was used (*syn*:*anti* 2:1). In order to decrease the amount of diol,

we changed the nature of the reducing agent and used sodium cyanoborohydride. We were pleased to observed, along with a decreased amount of diol (9%), an improved stereoselectivity.

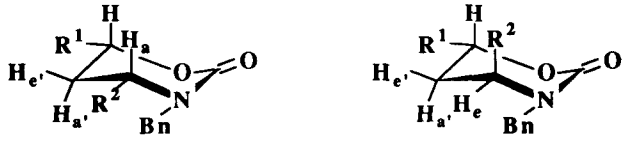
To prevent the formation of diols due to the reduction of ketone, we decided to use an excess of amine in order to favour the formation of the imine. By operating at -15° C, 3-hydroxyketones **1** afforded smooth conversion to the 1,3-*syn* product **3** which were obtained in good yields accompanied with a minor amount of the 1,3-diols **2** (Table 1).



Scheme 1

As expected, a lower temperature increased the amount of the major isomer (entries 1 and 2). The reaction was very sensitive to steric hindrance and it was necessary with 2,6-Dimethyl-5-hydroxy-heptan-3-one to operate at 0° C to obtain a satisfactory yield (entry 7). The same conditions were used with 2-substituted hydroxyketones such as **5** and **6** which showed a decreased reactivity due to the presence of the methyl substituent.[9] Moreover, a more hindered 3-hydroxyketone such as 5-hydroxy-2,4,6-trimethyl-3-heptanone was reduced in 1,3-diols only.

To determine the stereochemistry of the reduction, the aminoalcohols **3** and **4** were transformed into cyclic carbamates by reaction with phosgene and analyzed by ^{1}H NMR. The 1,3-*syn* isomer demonstrated the expected trans diaxial proton coupling ($J_{a,a'}$ = 11.6 Hz) whereas the corresponding *anti* isomer provided coupling constants in keeping with the usual data for vicinal axial-equatorial ($J_{a',e}$ = 5.8 Hz) and equatorial-



syn *anti*

Scheme 2

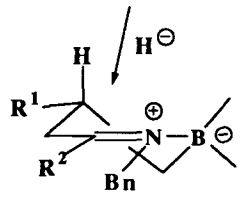
equatorial ($J_{e,e'}$ = 2.3 Hz) arrangements (Scheme 2).[10] Moreover, in all cases, the ^{13}C deplacements were in accordance with previous observations (δ *syn* > δ *anti* for the C_N and C_O carbons).[11]

Table 1 Diastereoselective reductive amination of 3-hydroxyketones **1**

Entry	3-Hydroxy ketone R1	R2	T°C	**3** *syn*:**4** *anti* Ratio[a] (% yield)[b]	**2** (% yield)
1	Benzyl	C_6H_5	20	81:19 (77)	12
2	Benzyl	C_6H_5	-15	98:2 (79)	4
3	C_6H_5	C_6H_5	0	84:16 (77)	11
4	*i*-Pr	C_6H_5	-25	91:9 (72)	6
5	*n*-Prop	Et	-15	87:13 (76)	3
6	*i*-Bu	C_6H_5	0	95:5 (79)	5
7	*i*-Pr	*i*-Pr	0	92:8 (75)	3
8[c]	*i*-Pr	*i*-Pr	-15	85:15 (40)	20

[a] Determined by 200 MHz ^1H and ^{13}C NMR spectroscopy. [b] Total yield of isolated 3 and 4 isomers [c] allylamine was used instead of benzylamine. Typical procedure: acetic acid (8 mmol) was added to a cooled (0°C) mixture of 3-hydroxyketone (1 mmol), benzylamine (4 mmol) and 4 Å molecular sieves (500 mg) in THF (10 mL). After stirring for ten minutes, sodium cyanoborohydride (2 mmol) was added and the mixture was stirred at - 15°C for 24 h before hydrolysis (NaOH 1M). The two diastereomers were separated by flash-chromatography on silicagel (cyclohexane/AcOEt/MeOH 55/44/1) and the *syn* isomer was eluted in first.

Although an internal hydride delivery after a ligand exchange between the free alcohol and the cyanoborohydride was not to exclude, excesses of borohydride necessary to the complete reduction would suggest that such internal reaction is not effective in these substrates. The stereochemistry of the reductions may be better interpreted by the formation of a cyclic adduct resulting from a ligand exchange followed by an external axial attack of a second molecule of hydride on the half-chair transition-state which favours the forma-



Scheme 3

tion of a chair conformation (Scheme 3). Such a model is consistent with the slow reactivity observed for the hydroxyketone **5** which affords a transition state where the methyl substituent is axial whereas the three substituents are in equatorial position for the diastereomer **6**.[9]

In summary, 1,3-*syn* aminoalcohols may be easily obtained in good yields by reductive amination of 3-hydroxyketones using a commercial reducing agent: sodium cyanoborohydride. The methodology described here should find numerous applications in the synthesis of functionally diverse enantiopure molecules.

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9. The hydroxyketone **6** was totally reduced in one day at 0°C (yield: 80 %; *syn/anti* ratio 88/12) whereas the hydroxyketone **5** necessitated three days at 15°C to be completely transformed into the correponding aminoalcohol (yield: 65 %; *syn/anti* ratio 78/22).
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