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Enantioselective Synthesis of Optically Active β-Aminoalcohols *via* Asymmetric Reduction

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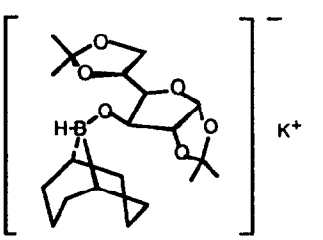
Abstract: Optically active β-aminoalcohol derivatives were prepared by asymmteric reduction of the corresponding aminoketones with a chiral borohydride, K glucoride (**1**).

Optically active β-amino-α-aryl(or alkyl)ethanol derivatives are not only important in phamaceuticals such as β-adrenergic blocking agents,[1] but are also used as useful catalysts for asymmetric carbon-carbon bond formation reactions.[2] One of the most convenient methods for the preparation of the amino alcohols may be the asymmetric reduction of the corresponding α-amino ketones. Several successful achievements for such reduction have been accomplished by asymmetric hydrogenation using chiral phosphine-rhodium[3] or ruthenium[4] catalysts. However, only one example of the reduction with a chiral hydride reagent has been reported.[5] Recently, we reported that a new chiral borohydride, K glucoride (**1**)[6] provided high optical yields in the reduction of alkylaryl ketones, relatively hindered aliphaticketones and α-keto esters.

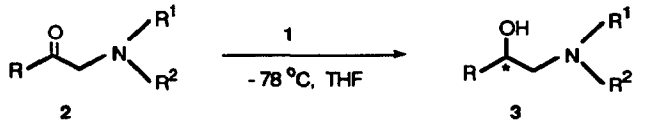


1

In the course of our study on asymmetric reduction of some functionalized ketone derivatives with **1**, we found that this reagent reduced α-aminoketones (**2**) in high yields to the corresponding β-aminoalcohols (**3**) with good enantioselectivities. We now report our preliminary results for the reaction.

The aminoketones were prepared by reaction of the corresponding α-bromoketones and amines. The reduction was carried out with 1.1 equiv of **1** at -78 ℃ in THF. As shown in Table 1, all of the aminoketones (**2**) examined are smoothly reduced to give **3** in high yields. In the case of aromatic α-aminoketones (**2a-2f**), the corresponding β-aminoalcohols (**3a-3f**) were obtained with 44 - 73 % ee. It is noteworthy that all of the aminoalcohols obtained are consistently enriched in the S enantiomers and increasing the steric bulk of R^1 and R^2 groups in **2a-2f** leads to higher optical induction. However, the reduction of aliphatic aminoketones afforded low optical induction (9 - 33 % ee). Using this methodology, the study of the enantioselective synthesis of optically active β-amino-α-arylethanol derivatives having pharmacological activities is in progress.

Table 1. Asymmetric Reduction of α-Amino Ketones with 1 in THF at -78°C.[a]



2 3

entry	2			time	yield[b]	3		
	R	R^1	R^2	h	%	$[\alpha]_D^{22}$, deg.	% ee	abs. config.
a	Ph	Bn	H	3	83[c]	8.96 (*c* 4.78, H_2O)	32[d](48)[e]	S
b	Ph	Bn	Me	6	82	29.33 (*c* 2.36, EtOH)	51[f](56)[e]	S
c	Ph	Me	Me	3	87	29.24 (*c* 1.19, MeOH)	58[g]	S
d	Ph	Et	Et	3	81[c]	47.41 (*c* 5.02, H_2O)	73[h]	S
e	Ph	$-(CH_2)_5-$		3	82	31.86 (*c* 1.13, EtOH)	60[i]	S
f	Ph	$-(CH_2OCH_2)-$		3	91	27.55 (*c* 3.02, MeOH)	(44)[e]	S
g	Me	Me	Me	3	90	-2.06 (*c* 0.99, MeOH)	9[j]	R
h	Me	Et	Et	3	92	-10.95 (*c* 4.07, EtOH)	24[k]	R
i	t-Bu	$-(CH_2)_5-$		24	89	24.14 (*c* 1.96, EtOH)	33[l]	S

[a] [H⁻ / Cpd] = 1.1. [b] Isolated yields after silica gel column chromatography. [c] HCl salt. [d] Based on $[\alpha]_D^{25}$ 27.8 (*c* 5.0, H_2O) ; ref. 3. [e] The figures in parentheses indicate % ee determined by HPLC chiral column (Chiralcel OD, Daicel Co.) [f] Based on the calculated $[\alpha]_D^{20}$ -57.21 (*c* 2.3, EtOH) ; ref. 7. [g] Based on the calculated $[\alpha]_D^{20}$ -50.27 (*c* 1.61, MeOH) ; ref. 7. [h] Based on $[\alpha]_D^{23}$ 64.6 (*c* 5.0, H_2O); ref. 3. [i] Based on the calculated $[\alpha]_D^{20}$ 52.89 (*c* 1.12, EtOH) ; ref. 7. [j] Based on $[\alpha]_D^{22}$ 22.85 (*c* 1.02, MeOH) ; ref. 8. [k] Based on $[\alpha]_D^{24}$ - 46.2 (*c* 4, EtOH) ; ref. 9. [l] Based on the calculated $[\alpha]_D^{22}$ - 72.96 (*c* 1.91, EtOH) ; ref. 2.

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