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Highly diastereoselective reduction of α-alkyl-β-hydroxy ketones with sodium and lithium boron hydrides *via* their titanium alcoholates.

Giuseppe Bartoli[a*], M. Cristina Bellucci[a], Marcella Bosco[a], Renato Dalpozzo[b], Enrico Marcantoni[c] and Letizia Sambri[a].

a)Dipartimento di Chimica Organica "A. Mangini", v.le Risorgimento, 4 I-40136 Bologna, Italy,
b) Dipartimento di Chimica, Università della Calabria, 87030 Arcavata di Rende (CS), Italy
c)Dipartimento di Scienze Chimiche, Via S.Agostino 1, I-62032 Camerino (MC), Italy

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Abstract

The reduction of α-alkyl-β-hydroxy ketones is highly *syn*-selective if carried out in THF on their Ti-alcoholate complexes with $LiBH_4$ or L-Selectride® or N-selectride® depending on the bulkiness of the group bound to the carbonyl group.

Keywords: reduction; ketols; diols; $TiCl_4$; diastereoselection.

Diastereoselective synthesis of 1,3-diols is an important target in organic chemistry because this unit is found in the structure of a large variety of natural products [1]. At present several general protocols for 1,3-diol synthesis are available in the literature. In particular, extensive studies have been devoted to the direct hydride reduction of β-hydroxy ketones having a stereogenic center near to a prochiral carbonyl group. However, only in the case of 1,3-induction it was possible to organize an efficient stereocontrol which allowed various general protocols, directed to the preparation of both *syn* [2] and *anti*-1,3-diols [3], to be set up. On the contrary, analogous general procedures showing 1,2-induction, (a stereogenic center in α-position),

* Corresponding author. Phone: (+)39-051-6443624; fax: (+)39-051-6443654; e-mail : bartoli@ms.fci.unibo.it

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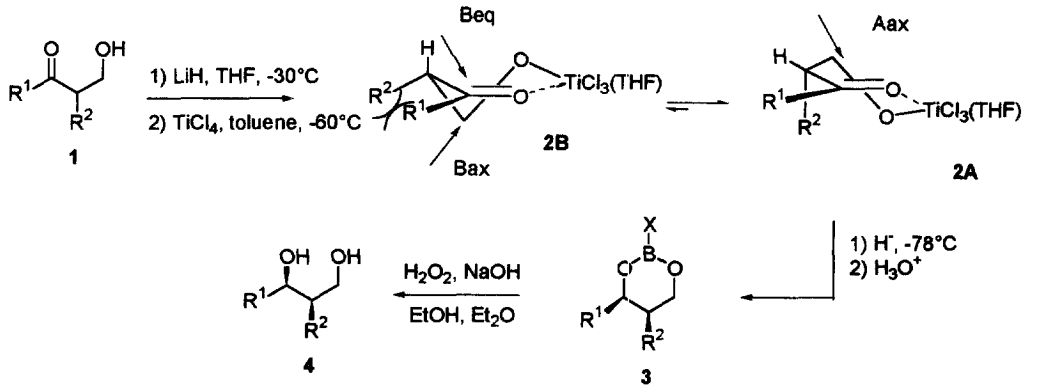
are not available so far. In fact, the reduction of simple α-alkyl-β-hydroxy ketones like **1** with both $Zn(BH_4)_2$ in Et_2O [4] and $TiCl_4$-BH_3·py complex, in CH_2Cl_2 [5], gives excellent results only when R^1 is a bulky group such as t-Butyl or a sp^2 hybridized centre such as phenyl or the sterically hindered vinyl fragment. When R^1 is a linear carbon chain, a dramatic decrease in selectivity is observed.

In this work we wish to report that highly diastereoselective reduction of **1** can be successfully accomplished by reacting the corresponding titanium alcoholate [6] with a variety of reducing agents with different steric requirements. In particular, the steric hindrance of boron hydrides such as L-Selectride® and N-selectride® has been advantageously exploited to ensure highly stereoselective reduction of substrates with linear chains substituents. A typical procedure follows: a THF solution of Ti-alcoholate **2** was prepared by treatment of ketone **1**, dissolved in THF, with LiH (1.2 eq) at -30°C, followed by transmetallation with $TiCl_4$ in CH_2Cl_2 (1.2 eq) at -60°C. The solution was cooled at -78°C and then the appropriate hydride was added. After 2 hrs the reaction was quenched with aqueous HCl 1 M. The usual work-up gave a crude material which was treated with H_2O_2/NaOH in a EtOH/Et_2O solvent mixture [7]. The oxidizing treatment was necessary to hydrolize stable cyclic boron derivatives **3** formed upon acidic quenching, (Scheme 1). In fact, in the reaction of **1a** with $LiBH_4$ we were able to isolate and characterize the dioxaborinanol **3a**, X=OH [8]. Although in the reactions with L-Selectride® and N-selectride® compounds **3** could not be purified, ^1H NMR analysis of the crude products indicated the presence of a *s*-butyl chain bound to the boron atom (X=*s*-Bu).



Scheme 1

As shown in Table 1, the reduction of **1** with the small $LiBH_4$ gives excellent results when R^1 group is a phenyl (**1a-c**). On the contrary, moderate selectivity is observed when R^1 group is a

linear carbon chain such as ethyl or propyl (**1d-e**). However when the reduction is performed with a sterically hindered hydride, such as L- selectride®, an effective increase in *syn*-selectivity is observed, (Table 1, entry 5, 8); N-selectride® afforded a further improvement [9], (Table 1, entry 6, 9).

Table 1 : Reduction of α-alkyl-β-hydroxy ketones **1a-e** in THF at -78°C with metal hydrides (H^-) *via* their titanium alcoholates.

Entry	Starting material	R^1	R^2	H^-	Product	Yields(%)	de(%)
1	**1a**	Ph	Me	$LiBH_4$	**4a**	95	98
2	**1b**	Ph	Et	$LiBH_4$	**4b**	95	98
3	**1c**	Ph	Ph	$LiBH_4$	**4c**	95	98
4	**1d**	Et	Me	$LiBH_4$	**4d**	90	30
5	**1d**	Et	Me	L-selectride®	**4d**	90	80
6	**1d**	Et	Me	N-selectride®	**4d**	92	86
7	**1e**	Pr	Et	$LiBH_4$	**4e**	90	40
8	**1e**	Pr	Et	L-selectride®	**4e**	91	90
9	**1e**	Pr	Et	N-selectride®	**4e**	93	98

On account of the strong internal coordination action of the Lewis acid, the titanium alcoholate **2** preferentially assumes a rigid and stable half chair conformation **2A** with the α-alkyl substituent in a pseudo axial position, so as to avoid the destabilizing $A^{(1,2)}$-like interaction present in **2B**. This structural arrangement facilitates the entry of the attacking hydride ion on the carbonyl group opposite to the α-substituent (Aax attack). The low selectivity observed when R^1 is a linear carbon chain can be ascribed to a decrease in $A^{(1,2)}$-strain in the cyclic intermediate **2** with consequent increase in stability of conformer **2B**: the attack on **2B** of a small metal hydride will be not selective.

Present results indicate that the use of sterically hindered reducing agents makes again the reaction highly selective, by ensuring a high stereofacial discrimination. In other words, with L-selectride® and N-selectride® only the poorly sterically hindered axial attack (Aax) on **2A** should be preferred.

In conclusion, the reduction of α-alkyl-β-hydroxy ketones *via* Ti-alcoholates presents an actual improvement with respect to previous reported methods, since it is based on the formation of a rigid intermediate, stable in a coordinating solvent, such as THF. This feature allows the use of L-selectride® and N-selectride®, as reducing agents, which can ensure high diastereomeric excesses when a high stereofacial discrimination is required.

Studies are in progress in our laboratory to extend this protocol to more complex α-substituted systems having α' or β-stereocenters.

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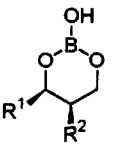
[8] The following procedure allows to obtain pure compound **3a**. The reaction mixture was poured in diluted HCl and extracted with Et_2O. The organic layer was dried and evaporated to small volume until compound **3a** crystallizes. Spectroscopical data follow: ^1H NMR (300MHz, $CDCl_3$): 0.73 (d, 3H, CH_3, J_{HH}=7.2), 2.20-2.40 (m, 1H, CH), 3.81 (dd, 1 H, $C\underline{H}_2O$, J_{HH}=5.5, J_{HH}=11.0), 4.12 (dd, 1 H, $C\underline{H}_2O$, J_{HH}=3.6, J_{HH}=11.0), 5.21 (d, 1 H, $C\underline{H}O$, J_{HH}=3.6), 7.20-7.45 (m, 5H, Ph); HRMS: calcd for $C_{10}H_{13}BO_3$: 192.0958; found: 192.0950.



3a

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