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Remote Stereocontrol in Acyclic Systems. Hydride Addition to 1,5- and 1,6-Hydroxy Ketones Mediated by Metal Chelation

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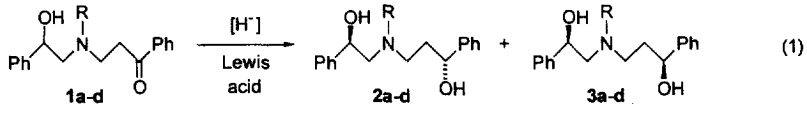
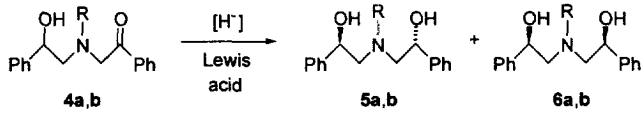
Abstract: Acyclic 1,6-hydroxy amino ketones can be reduced to either the *anti* or *syn* diols with high 1,6 diastereoselectivity by sequential treatment with a Lewis acid and a borohydride reagent, with the direction of stereocontrol depending on the Lewis acid complexant used. For example, with **1a** *anti*:*syn* ratios of >100:1 [$Ti(OiPr)_4$/K-Selectride] and 1:7 [$Al(OEt)_3$/K-Selectride] were realized. 1,5-Hydroxy amino ketone **4a** was reduced with high *syn* 1,5 diastereoselectivity [*anti*:*syn* = 1:18 with $Al(OEt)_3$/K-Selectride].

Metal chelation has proven to be an effective means for achieving high 1,2- and 1,3-stereocontrol in acyclic systems.[1] Some especially notable cases where chelation has played a major role are aldol reactions[2] and the addition of organometallic reagents to aldehydes and ketones,[3] with Lewis acids of various types serving as critical components. For example, by employing chelation control Reetz obtained high 1,2- and 1,3-diastereoselectivity in Mukaiyama-type aldol reactions of α- and β-alkoxy aldehydes[2a,3b] and Keck obtained high 1,2-diastereoselectivity in the addition of crotyl(tributyl)stannane to α-alkoxy aldehydes.[3c,d]

Complementary to the diastereoselective addition of carbon nucleophiles to aldehydes, hydride reagents have been used for the diastereoselective reduction of ketones to secondary alcohols. Lewis acid-mediated chelation control has been effective in the stereoselective reduction of β-hydroxy ketones with metal borohydrides,[4] as well as in the stereoselective reduction of β-diketones,[5] α-[6a] and β-hydroxy[6b-d] ketones, 3-keto-2-alkylesters,[7] β-keto sulfoxides,[8] and 3-keto-2-alkylphosphine oxides.[9] However, there are limited examples of more remote (>1,3) asymmetric induction of this kind.[10] We have been interested in achieving high stereocontrol for the hydride reduction of acyclic ketones with a distant hydroxyl directing group.[11] Indeed, we found[11] that the reduction of hydroxy amino ketones **1a** and **4a** with *R*-Alpine-Hydride®[12] occurs with high (>10:1) *anti* stereoselectivity and proposed that lithium participates in a bicyclic metal chelate with the substrate. Thus, we decided to explore the potential usefulness of Lewis acids with our hydroxy amino ketone substrates. Herein, we report the ability to attain high 1,5 and 1,6 diastereoselectivity in the reduction of **1** and **4**, respectively, with borohydride reagents via Lewis acid-based chelation control (Eqs. 1 and 2).



(1)



(2)

a: R = $PhCH_2$; **b**: R = Me; **c**: R = H; **d**: R = PhC(O)

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In an extension of our prior work, lithium was examined for pre-complexation with 1,6-hydroxy amino ketone **1a**.[11b,c] Reduction with the bulky hydride reagent K-Selectride® *subsequent* to deprotonation with either BuLi or *t*-BuLi gave low stereocontrol (Table 1, entries 1 and 2). Use of Bu_3B, $SnCl_4$, and $Zr(OiPr)_4$ for pre-complexation also afforded low diastereoselectivity (entries 3-5), while $Yb(OTf)_4$ showed a modest preference for the *anti* isomer (*anti*:*syn* = 4.8:1), albeit with low chemical conversion (entry 6). Despite these discouraging results, we proceeded to examine $Ti(OiPr)_4$ as a Lewis acid complexant in the reduction of **1a** because, in coordination studies of **1a** by ^1H NMR, this agent delivered the most significant change in the NMR spectrum of **1a**, whereas $LiBF_4$ had little effect.[11c] Pre-coordination of **1a** with $Ti(OiPr)_4$, followed by reduction by $Zn(BH_4)_2$, gave an 18.5:1 ratio of *anti*:*syn* diols with a 90% isolated yield (entry 7). Under this protocol, reduction with either $LiBH_4$ (entry 8) or NB-Enantride™ (entry 10) gave a strong preference for the *anti* diol of 24:1 and 21:1, respectively (90% and 82% yields). When the reduction was performed with K-Selectride (entry 11), the *anti* diastereoselectivity became an impressive >100:1 (91% yield)! As the reaction temperature was increased, the *anti*:*syn* selectivity decreased (entries 9 and 12). Relative to different metal cations in the Selectride reagent under $Ti(OiPr)_4$-complex conditions (entries 11, 13, and 14), the diastereoselectivity increased in the order Li < Na < K.

Table 1. Reduction of 1,6-Hydroxy Amino Ketone **1a**.

entry	Lewis acid	reducing agent[a]	temp, °C	time, h	2:3	yield, %[b]
1	BuLi	K-Selectride	-78	24	1:1.7	40 (50 addn)
2	*t*-BuLi	K-Selectride	-78	24	1:1	45 (50 addn)
3	Bu_3B	K-Selectride	-78	24	1:1.1	90
4	$SnCl_4$	K-Selectride	-78	24	1.1:1	40 (60 SM)
5	$Zr(OiPr)_4$	K-Selectride	-78	24	1.8:1	57 (27 SM)
6	$Yb(OTf)_3$	K-Selectride	-78	22	4.8:1	51 (44 SM)
7	$Ti(OiPr)_4$	$Zn(BH_4)_2$	-78	18	18.5:1	90
8	$Ti(OiPr)_4$	$LiBH_4$	-78	0.3	24:1	90
9	$Ti(OiPr)_4$	$LiBH_4$	-20	0.3	3.7:1	89
10	$Ti(OiPr)_4$	NB-Enantride[c]	-78	2	21:1	82
11	$Ti(OiPr)_4$	K-Selectride	-78	0.25	**>100:1**	91
12	$Ti(OiPr)_4$	K-Selectride	-20	0.3	13.4:1	92
13	$Ti(OiPr)_4$	N-Selectride	-78	0.5	52:1	90
14	$Ti(OiPr)_4$	L-Selectride	-78	0.5	33:1	88

a. Selectride = tri-*sec*-butylborohydride (1.0 M in THF; K = potassium, N = sodium, and L = lithium); NB-Enantride = lithium hydrido (9-borabicyclo[3.3.1]nonane-nopol benzyl ether adduct (0.5 M in THF). Source: Aldrich Chemical Co. b. addn = addition of either butyl or *t*-butyl to the ketone (diastereomeric ratio = 1:1). SM = recovered starting material.[11c] c. *R*-Alpine-Hydride also gave a high preponderance of the *anti* isomer, but purification of the product for NMR analysis was problematic.

At this point, the effect of the substituent of the nitrogen was also examined. With the nitrogen as a tertiary amine, the size of the substituent had little effect on diastereoselectivity or yield. Substitution of benzyl (**1a**) with a methyl (**1b**) group resulted in *anti* diol in 90% yield with a diastereoselectivity of >100:1. However, placement of a hydrogen on nitrogen (**1c**) decreased the stereoselectivity to *anti*/*syn* = 2:1 (85% yield), and a benzoyl group (**1d**) decreased the stereoselectivity to *anti*/*syn* = 1:1.

These results are consistent with our proposed model of a "5,6-bicyclic" metal chelate that experiences external hydride addition (Fig. 1).[11c] However, we found that the *syn* isomer can be formed preferentially, as well, depending on the Lewis acid used for pre-complexation (Table 2). With $Al(OEt)_3$ as the Lewis acid and K-Selectride as the reducing agent, we obtained a 1:7.1 *anti*:*syn* ratio with 88% yield (entry 6). Interestingly, $Yb(OiPr)_3$ gave mainly the *syn* isomer compared with $Yb(OTf)_3$, which gave the *anti* isomer. Figure 2 depicts a proposed model to account for this *syn* selectivity, which may arise from a change in

coordination geometry with different Lewis acids. Such a change in coordination could account for the difference in selectivity between $Yb(OiPr)_3$ and $Yb(OTf)_3$, as one of the isopropyl ligands in $Yb(OiPr)_3$ could exchange with the hydroxyl group in the substrate to produce a trigonal bipyramidal intermediate, whereas $Yb(OTf)_3$ might not undergo exchange and thereby produce an octahedral intermediate.

Table 2. Reduction of 1,6-Hydroxy Amino Ketone **1a**.[a]

entry	Lewis acid	2:3	yield, %
1	$Cu(OTf)_2$	1:2.1	83
2	$Mg(OTf)_2$	1:2.3	87
3	$Zn(OTf)_2$	1:3.3	83
4	$Y(OiPr)_3$	1:3.5	86
5	$Yb(OiPr)_3$	1:4.3	90
6	$Al(OEt)_3$	1:7.1	88

a. Conducted in CH_2Cl_2 at -78°C with K-Selectride.

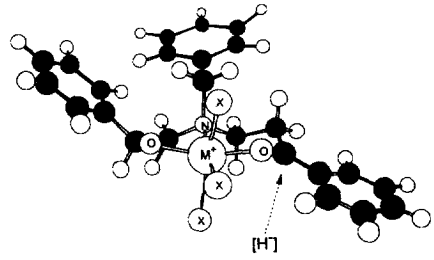


Figure 1

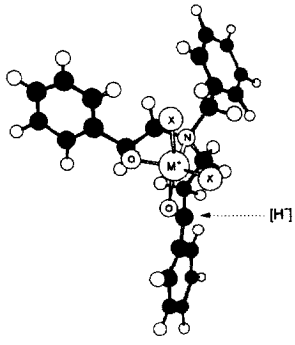


Figure 2

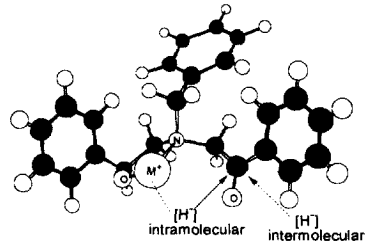


Figure 3

Reduction of 1,5-hydroxy amino ketone **4a** with *R*-Alpine Hydride gave mainly the *anti* isomer;[11c] however, pre-coordination of **4a** with a Lewis acid followed by reduction can well furnish the *syn* isomer with high stereoselectivity, with K-Selectride (Table 3). In the case of 1,6-hydroxy amino ketone **1a**, $Ti(OiPr)_4$ was the most effective Lewis acid, but $Ti(OiPr)_4$ was ineffective with **4a** (entry 1). Lithium coordination, by deprotonation of the alcohol with BuLi, followed by reduction with K-Selectride gave the *syn* isomer as the major product (entry 6). No addition of butyl to the ketone was observed, although this occurred in the reduction of **1a**. The highest *syn* preference was realized with $Al(OEt)_3$, which gave an *anti*:*syn* ratio of 1:18.5 (entry 7). The size of the substituent on nitrogen had a substantial effect on diastereoselectivity with a methyl group affording an *anti*:*syn* ratio of just 1:2.1 (cf. entries 7 and 8).

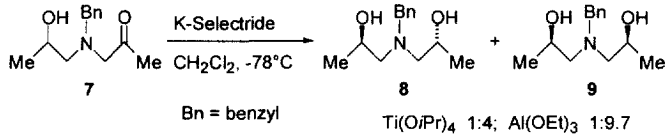
In the reduction of 1,5-hydroxy amino ketone **7**, both $Ti(OiPr)_4$ and $Al(OEt)_3$ produced *syn* diol **9** as the major product (Eq. 3). This is in sharp contrast to the corresponding 1,6-hydroxy amino ketone, **1a**, where $Ti(OiPr)_4$ produced the *anti* diol and $Al(OEt)_3$ produced mainly the *syn* diol.

Previously, we proposed a five-membered-ring metal complex with an intramolecular reduction, using 2 mol equiv of a metal borohydride, to arrive at the *anti* 1,5-diol (Fig. 3).[11a,c] The same type of model with a five-membered-ring metal complex can be applied to these results, but reduction would have to occur via intermolecular addition of hydride to form the *syn* diol (Fig. 3).

Table 3. Reduction of 1,5-Hydroxy Amino Ketone 4.[a]

entry	ketone	Lewis acid	time, h	5:6	yield, %
1	**4a**	$Ti(OiPr)_4$	21	1:1	14 (80 SM)
2	**4a**	$Zn(OTf)_2$	23	1:1.6	50 (38 SM)
3	**4a**	Bu_3B	21	1:2	60 (29 SM)
4	**4a**	$Y(OiPr)_3$	24	1:2	51 (44 SM)
5	**4a**	$Mg(OTf)_2$	23	1:9	70 (20 SM)
6	**4a**	BuLi	23	1:11	60 (40 SM)
7	**4a**	$Al(OEt)_3$	23	1:18.5	65 (30 SM)
8	**4b**	$Al(OEt)_3$	23	1:2.1	65 (30 SM)

a. Reactions were conducted in CH_2Cl_2 at -78°C with K-Selectride. SM = recovered starting material.[11c]



(3)

In summary, reduction of 1,6-hydroxy amino ketones by sequential addition of a Lewis acid and a borohydride reagent can afford either *syn* or *anti* diol products with high 1,6 diastereoselectivity, depending on the Lewis acid pre-complexing agent. This reduction may proceed via a "5,6-bicyclic" metal chelate and external hydride addition, with the choice between *anti* and *syn* diols possibly related to the coordination geometry of the metal. Although we have reported obtaining only *anti* diols with high 1,5 diastereoselectivity from the reduction of 1,5-hydroxy amino ketones,[11a,c] we have now obtained the *syn* diol, by sequential addition of a Lewis acid and a borohydride reagent. Thus, chelation control can be an effective means for achieving high remote stereocontrol in the reduction of 1,5- and 1,6-hydroxy amino ketones.

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