Stereoselective Synthesis of Protected Ketohexoses via Aldol Reaction of Chiral Dioxanone Enolate

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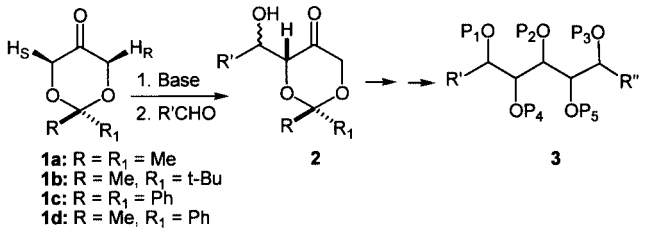
Abstract: Lithium and boron enolates of 2,2-dialkyl-1,3-dioxa-5-ones react with aldehydes to give aldol products in high diastereoselectivity and, when chiral lithium enolates are generated using optically pure chiral lithium amide bases, in high enantioselectivity. Dioxanone lithium enolates react readily with protected glyceraldehyde affording protected ketohexoses in high diastereo- and enantiomeric purity.

Keywords: dioxanone, enantioselective deprotonation, chiral lithium amides.

A few years ago we initiated a study of 2,2-dialkyl-1,3-dioxa-5-ones hoping that these compounds could be used as building blocks for synthesis of polyoxygenated natural products.[1] In particular, a double aldol reaction of 2,2-dialkyldioxanone **1** could lead to a polyhydroxyalkane **3** having a number of stereogenic centers. If relative and absolute stereochemistry of the process could be controlled chiral polyoxygenated natural products could be constructed quickly and efficiently (Scheme 1). This approach could also provide a quick entry into synthesis of carbohydrates. Although the main themes in carbohydrate synthesis involve manipulation of readily available monosaccharides and synthesis of oligosaccharides the stereoselective total synthesis of 'rare' sugars is a topic of current interest.[2]



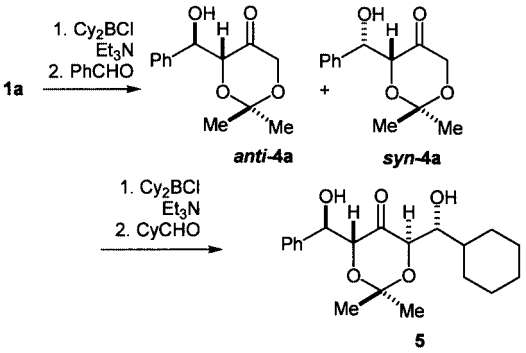
Scheme 1

Lithium enolates of cyclic ketones, being by necessity *E*-isomers, normally react with aldehydes to give predominantly *anti* aldols in agreement with the Zimmerman-Traxler model.[3] However, dioxanone lithium enolates, generated by treatment of the dioxanones with LDA, afforded the corresponding aldols (**2**) with low diastereoselectivity. The outcome was dependent on the structures of both the dioxanone and the aldehyde. Selected results are presented in Table 1. Larger groups in the acetal moiety of the dioxanone increased the diastereoselectivity (c.f., entries 1 and 3, 5 and 6). Of several aldehydes tested, only aliphatic aldehydes having an α-substituent were diastereoselective (c.f., entries 1, 4 and 5). In particular, cyclohexanecarboxaldehyde reacted with lithium enolate of 2-*tert*-butyl-2-methyl-1,3-dioxa-5-one **1b** to give only one product which was identified by NMR and X-ray crystallography as the *anti-cis* isomer **2b**. Boron enolates are well known to be more diastereoselective than the corresponding lithium enolates in aldol reactions.[4] We synthesized several boron enolates of dioxanone **1a** and examined briefly their reactions with benzaldehyde. Dicyclohexylboron enolate was the most diastereoselective and afforded the corresponding aldols *anti*-**4a** and *syn*-**4a** in a 96 : 4 ratio (Scheme 2). Two consecutive aldol reactions could be done in 'one pot' and yielded 4 diastereoisomeric bisaldols in a 83 : 09 : 06 : 02 ratio. After column chromatography a single isomer **5** was isolated in 64 % yield.

Table 1 Reactions of Li-enolates of **1** with aldehydes.

Entry	R	R_1	R'	anti : syn	% yield[a]
1	Me	Me	Ph	65 : 35	55
2	Me	t-Bu	Ph	77 : 23	70
3	Ph	Ph	Ph	72 : 28	77
4	Me	Me	Hexyl	62 : 28	62
5	Me	Me	Cy[c]	91 : 09	61
6	Me	t-Bu	Cy	anti[b]	61
7	Me	Ph	Cy	anti[b]	55

a. Yields refer to purified products and are the sum of *syn* and *anti* yields. b. Only one isomer (*anti-cis*) was detected in each case. c. Cy = cyclohexyl

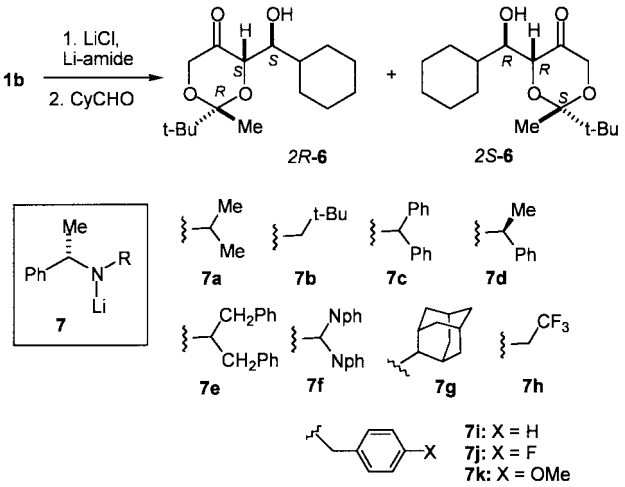


Scheme 2

*Enantioselective deprotonation of **1b**:* Dioxanones having C_S symmetry can be deprotonated enantioselectively with chiral lithium amides to give non-racemic mixture of two enantiomeric enolates.[5] These enolates can be trapped with electrophiles. We have undertaken a systematic study aimed at finding the most effective (in this system) lithium amide base derived from α-methylbenzylamine (general structure **7**). Since we had determined earlier that addition of LiCl was beneficial to selectivity,[1b] all reactions were run with one equivalent of LiCl and one equivalent of Li-amide. Fortunately, the reaction of lithium enolate of dioxanone **1b** with cyclohexanecarboxaldehyde proved very diastereoselective and only one diastereoisomer of the aldol **6**, namely the *anti-cis* isomer, was obtained in each reaction. The relative stereochemistry of this product was determined by x-ray crystallography on a derivative. The enantiomeric ratio was measured by NMR in the presence of the optically active shift reagent $Eu(hfc)_3$. The absolute stereochemistry of deprotonation was determined by degrading a sample of the non-racemic product **6** to a derivative of glyceraldehyde of known absolute configuration.[9] It was established that lithium amides of general structure **7** having the *R* configuration abstracted preferentially the H_R proton in **1b**, whereas analogous amides having the *S* configuration preferred the H_S proton. Overall, the aldol reaction of dioxanone enolate with cyclohexanecarboxaldehyde provided a good model system for our studies.

The parameter to which we paid most attention in this study was the structure of the lithium amide. In the group of lithium amides that were investigated there seemed to be a correlation between the size of the substituent on nitrogen (c.f., structure **7** in Scheme 3) and enantioselectivity. As the group R was changed from isopropyl to neopentyl to diphenylmethyl to bis-naphtylmethyl the enantioselectivity increased (Table 2, entries 1, 2, 3 and 6). Bases **7f** and **7h**, having a large (and, in the latter case, electron-withdrawing) substituent on nitrogen, were especially selective.[6] The contribution of electronic effects was clearly visible in the series **7i**, **7j** and **7k** – the presence of electron-withdrawing fluorine substituent on the benzene ring in **7j** led to a more selective deprotonation, whereas the electron-donating methoxy group in **7k** caused the decrease in enantioselectivity.[10] Reactions of dioxanone **1d** with chiral lithium amides were much less enantioselective than the corresponding reaction of **1b** (c.f., entries 3 and 12, 8 and 13). It seems that a fairly large conformational bias is necessary for the reaction to proceed with high enantioselectivity, this is a general trend in chemistry of cyclic ketones.[5]

Synthesis of carbohydrate derivatives: After developing the conditions for efficient and stereoselective deprotonation of C_S symmetrical dioxanones the stage was set for applying the method to carbohydrate synthesis. Isopropylidene *R*-glyceraldehyde **8** reacted readily with the achiral lithium enolate of dimethyldioxanone **1a** and afforded a mixture of four diastereoisomers. The two major products were identified as protected D-tagatose (**9**) and protected



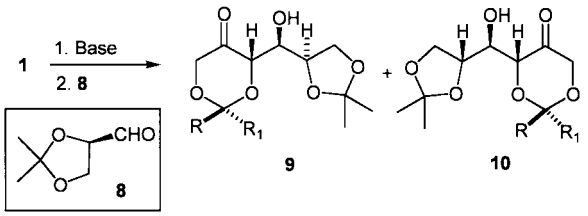
Scheme 3

D-psicose (**10**)[9] and it was noted that the reaction was not overly stereoselective (Scheme 4 and Table 3, entry 1). The corresponding boron enolate, generated with dicyclohexylboron chloride, reacted much more selectively to give a mixture of only two isomers with the D-tagatose derivative **9** predominating (entry 2). Chiral dioxanone lithium enolate, generated from **1b** by using the chiral base **7h**, combined with *R*-**8**, resulted in a system capable of double stereodifferentiation.[7] Isopropylidene glyceraldehyde is known to have rather low diastereotopic face selectivity in reactions with nucleophiles.[8] In our system the enolate clearly exerts much more control than the aldehyde with a small 'matched-mismatched' effect (Table 3, entries 3 and 4). Overall, enantioselective deprotonation of dioxanones followed by a reaction of the resulting lithium enolate with a chiral aldehyde provided an easy entry into carbohydrate derivatives.

Table 2 Enantioselective deprotonation of dioxanone **1b** with Li-amides **7a-k**.

Entry	Ketone	Li-amide	% ee[a]	% yield[b]
1	**1b**	*R*-**7a**	16 (-)	55
2	**1b**	*S*-**7b**	19 (+)	63
3	**1b**	*S*-**7c**	72 (+)	60
4	**1b**	*S*-**7d**	60 (+)	51
5	**1b**	*S*-**7e**	60 (+)	76
6	**1b**	*S*-**7f**	90 (+)	95
7	**1b**	*S*-**7g**	80 (+)	91
8	**1b**	*S*-**7h**	90 (+)	86
9	**1b**	*R*-**7i**	37 (-)	76
10	**1b**	*R*-**7j**	50 (-)	77
11	**1b**	*R*-**7k**	30 (-)	99
12	**1d**	*S*-**7c**	53 (+)	68
13	**1d**	*S*-**7h**	54 (+)	64

a. The sign in brackets indicates if the levorotatory (-) or the dextrorotatrory (+) isomer of the product **6** was formed predominantly. b. Yields refer to chromatographically purified **6**.



Scheme 4

Table 3 Reactions of dioxanone enolates with (**8**).

Entry	Ketone	Base	9 : 10	% yield[a]
1	**1a**	LDA	62 : 38[b]	70
2	**1a**	Et_3N/Cy_2BCl	85 : 15	59
3	**1b**	*R*-**7h**/LiCl	89 : 11[c]	77
4	**1b**	*S*-**7h**/LiCl	3 : 97	81

a. Combined yield of all products after chromatography. b. Two additional products were formed in 8% combined yield. c. One additional diastereoisomer was isolated in 5% yield.

In summary, we have demonstrated that lithium and boron enolates of dioxanones react with aldehydes with useful diastereselectivity. Dioxanones having C_S symmetry could be deprotonated with chiral lithium amides with high enantioselectivity. Aldol reaction of a chiral dioxanone lithium enolate with protected glyceraldehyde provided a stereoselective method of synthesis of protected ketohexoses.

Acknowledgement

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References and Notes

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(9) These studies will be described in the full paper
(10) The differences in ee reported in Table 2, entries 9-11 are small but statistically significant. Each experiment was repeated 3-5 times and with careful control of experimental conditions reproducibility within 2% was obtained.

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