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α′-BENZOYLOXY AND α′-METHOXYMETHOXY LITHIUM ENOLATES GIVING OPPOSITE DIASTEREOFACIAL SELECTIVITIES IN ALDOL REACTIONS. USE OF (PROBABLE) EXTENDED CHELATION FOR REVERSAL OF STEREOSELECTIVITIES

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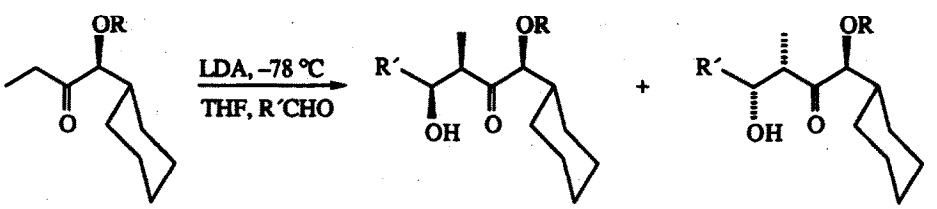
Key Words: aldol; lithium enolate; chelation; nonchelation; high facial selectivity

Abstract: *The Li enolates of α-benzoyloxy and α-methoxymethoxy ketones* ***1a*** *and* ***1c*** *afford nonchelation and chelation aldol products, respectively, both with usefully high diastereofacial selectivities. Evidence suggests that transition state chelation of the benzoyl C=O is responsible for the observed "nonchelation" stereoselectivity of* ***1a****.*

In aldol reactions of lithium enolates, good stereocontrol frequently correlates with a preference for the product expected from a chelation-controlled pathway—a pathway involving additional Li---O coordination to an oxygen present in the aldehyde or enolate. High selectivity for nonchelation stereochemistry is more difficult to obtain. A plausible strategy for obtaining "nonchelation" products should then be to design a *chelating* group capable of reversing the usual chelation stereoselectivity. Chelation would thus be exploited to give the selectivity normally associated with nonchelation control.

We wish to report the successful application of this strategy using α-benzoyloxy ketone **1a**, which gives a rare[1] example, the first with a chiral lithium enolate, of lithium-mediated aldol reactions having high facial selectivity for nonchelation products, **2**. Use of this lithium enolate has advantages of simplicity and cost as an alternative to titanium-[2,3] and boron-mediated[4] aldol reactions of **1e**. Also, ketone **1c** gives improved levels of chelation-control products, **3**, in representative cases, compared with **1d**. Thus, either syn aldol configuration, **2** or **3**, can now be obtained in a lithium-mediated aldol reaction directed by a single enolate chiral center.

Preferential ligation of the benzoate *carbonyl* oxygen to Li in the transition structure is indicated to be the origin of the preference for **2** over the product, **3**, expected via chelation of the α ether oxygen.



(1)

1 **2** **3**

a R = –COPh **b** R = –CH_2Ph **c** R = –CH_2OMe **d** R = –$SiMe_3$ **e** R = –$SiMe_2$*t*-Bu

It is established that α-OR group size controls stereoselectivity in lithium-mediated aldol reactions.[5-7] While the Me_3SiO group in **1d** is believed to permit lithium–oxygen chelation in the transition structure, the *t*-$BuMe_2SiO$ group in **1e** apparently inhibits chelation as a result of its larger size.[2,3,5] We previously reported that low selectivity favoring nonchelation product results from **1e** (3:2 = 44:56, 24:76, and 17:83 for R′ = Ph, iPr, and Et, respectively).[3] Until now, this problem has been solved by use of boron or titanium enolates. The successful design of **1a** and **1c** allows synthesis of either **2** or **3** from a single enantiomer of starting ketone **1**.

Our design is based on extended chelation to provide alternative ligation sites to the metal atom.[8–10] We selected benzoate **1a** and MOM-ether **1c** for this purpose. To test the consequences of absence of the benzoate C=O present in **1a**, we also examined benzyl ether **1b**. Ketones **1a–1c** were prepared by modification and combination of literature protocols.[11–14] We have examined representative aldehydes CH_3CH_2CHO and $(CH_3)_2CHCHO$, which have been used extensively as synthons[15] for polypropionate chains and macrolide antibiotics, along with PhCHO for comparison with literature results and to test the generality of the process.

Aldol reactions of lithium enolates of **1a–d** (Table I) were carried out according to literature procedure.[6] Product ratios, chelation:nonchelation (3:2), were determined by integration of resolved resonances of the diastereomers in 500 MHz ^1H NMR spectra of the crude product mixture. The major product isomers[14] from **1a**, **1c**, and **1d** were separated and fully characterized.

Table I. Diastereofacial Selectivities for Aldol Reactions of Lithium Enolates of Chiral Ketones (*S*)-$CH_3CH_2COCH(OR)c$-C_6H_{11} With Representative Aldehydes R´CHO

Entry	Substrate		R´	Stereoselectivity (3:2)[a]	Yield (%)[b]
		R			
1	**1a**	COPh	CH_3CH_2	4:96	80
2	**1a**	COPh	CH_3CH_2	3:97 (TMEDA)	96
3	**1a**	COPh	$(CH_3)_2CH$	4:96 (TMEDA)	67
4	**1a**	COPh	C_6H_5	14:86 (TMEDA)	72
5	**1b**	CH_2Ph	CH_3CH_2	74:26	57
6	**1b**	CH_2Ph	$(CH_3)_2CH$	75:25	59
7	**1b**	CH_2Ph	C_6H_5	79:21 (TMEDA)	60
8	**1c**	CH_2OCH_3	CH_3CH_2	92:8 (TMEDA)	70
9	**1c**	CH_2OCH_3	$(CH_3)_2CH$	93:7 (TMEDA)	67
10	**1c**	CH_2OCH_3	C_6H_5	80:20 (TMEDA)	65
11	**1d**	$Si(CH_3)_3$	CH_3CH_2	89:11	84
12	**1d**	$Si(CH_3)_3$	CH_3CH_2	91:9 (TMEDA)	94
13	**1d**	$Si(CH_3)_3$	$(CH_3)_2CH$	80:20	64
14	**1d**	$Si(CH_3)_3$	$(CH_3)_2CH$	88:12 (TMEDA)	70
15	**1d**	$Si(CH_3)_3$	C_6H_5	90:10 (TMEDA)	84
16	**1d**	$Si(CH_3)_3$	$(CH_3)_3C$	88:12 (TMEDA)	54

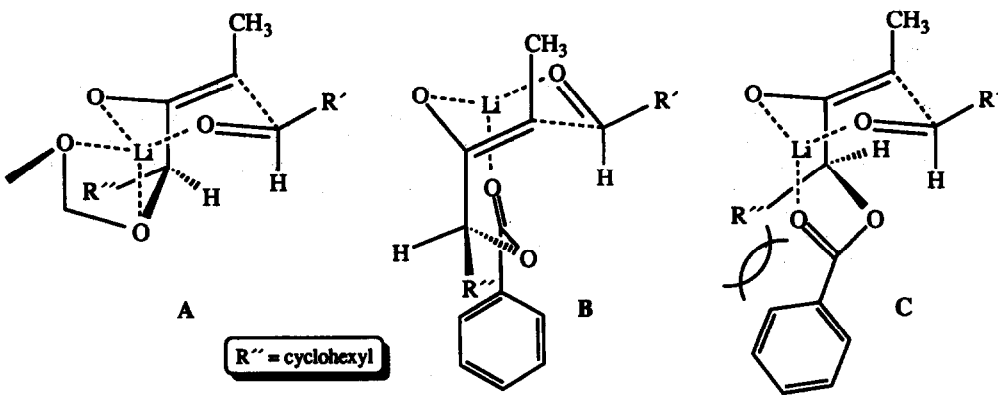
[a]Ratios determined by 500 MHz ^1H NMR analysis of the crude reaction mixture. [b]Isolated yield of the mixture of diastereomers.

Benzoyl ketone **1a** and MOM-ether ketone **1c** give high nonchelation[16] and chelation[17] selectivities, respectively, with CH_3CH_2CHO and $(CH_3)_2CHCHO$ (entries 1, 3, 8, 9). Benzyl ether **1b**, in which the C=O of **1a** is replaced by CH_2, gives reversed stereochemistry[18] and greatly reduced stereoselectivity compared with **1a** (entries 5, 6, 7). This dramatic reversal implicates the C=O as the cause of the high "nonchelation" selectivity of **1a**. Addition of TMEDA increases both nonchelation[19] and chelation selectivity (entries 1, 2, 11, 12, 13, 14). Ketone **1d** shows a major bias toward chelation stereochemistry.[20]

These results have very interesting parallels with recent work on chelation vs. nonchelation in addition of Me_2Mg to α-OR-substituted ketones.[21,22] It is surprising, however, that Me_3Si ketone (**1d**) gives stronger aldol chelation control than benzyl (**1b**), whereas, in the Me_2Mg reactions, benzyl is stronger than Me_3Si.

The stereochemical preference of MOM-ether ketone **1c** appears to result from chelation of the ether oxygens, analogous to that believed to operate with the TMSO ketone **1d**.[5,6] On the other hand, the experimental evidence implicating the benzoyl C=O of ketone **1a** suggests that reaction takes place with chelation at a new site, *the C=O*, to produce a strong stereochemical preference opposite to that of **1b**, **1c**, and **1d**. These lithium enolates are likely aggregated,[23] and may well remain so at the transition state. Therefore, transition state chelation may conceivably involve more complex coordination with more than one lithium within the aggregate.

However, a consistent, if schematic, explanation of the results can be given, based on Zimmerman–Traxler six-membered ring transition states involving coordination to only a single lithium.[24] The MOM ether conformation is subject to anomeric preference.[25] In the most favorable chelated transition structure for **1c** (**A**), the oxygen atom of the chiral center remains proximal to Li, and the conformational preference of the MOM ether group (C–O bonds anti to oxygen lone electron pairs) permits extended chelation to the metal. The length of Li–O bonds (typically 2.0 Å)[26] would allow the coordination here (and in **B** and **C** as well) to be essentially strain-free. The most favorable transition structure for **1a** is postulated to be **B**, which incorporates the inherent *Z* ester conformational preference[27] and places R″ anti to the benzoyl group, minimizing steric repulsions. The benzoyl *carbonyl* oxygen is then readily able to chelate.[28] A-type chelation would be disfavored for **1a** (cf. **C**) because R″ is, at best, gauche to the benzoate group and suffers repulsive interactions with both the carbonyl oxygen and the phenyl ring of the benzoate group. To avoid these repulsions would require a boat-like conformation of the 7-membered chelate ring. The present results, including the lower selectivities observed with **1b**, indicate that involvement of the benzoyl carbonyl of **1a**, probably through chelation as postulated in **B**, is sufficient to favor highly the facial selectivity normally labeled "nonchelation"—but through introduction of an extended C=O chelation interaction!



As discussed above, comparison of **1a** and **1b**, and especially the exceptionally high selectivity with **1a**, implicates the carbonyl oxygen in **1a**. We have also noted that in a titanium-mediated aldol reaction of the benzoyloxy ketone, the time for Li–Ti exchange upon addition of $ClTi(OiPr)_3$ to the lithium enolate of **1a** was considerably longer compared with that for **1e**, consistent with tighter coordination of lithium in the enolate of **1a**.[16] It might be argued that the stereochemical outcome is a consequence of steric bulk of the benzoate rather than the postulated C=O chelation. However, the poor selectivity with lithium in the case of **1e** (which has a bulky TBDMS group) and the stereochemical reversal with benzyl ether **1b** provide rather strong support for the C=O chelation hypothesis. Use of this type of extended chelation has interesting possibilities for other reactions as well.

Whether this hypothesis is mechanistically exact or not, the very high "nonchelation" selectivities found for benzoyloxy substrate **1a** are both unusual and potentially useful in synthetic operations.

In conclusion, we have achieved highly synthetically useful facial selectivities, which are novel in lithium-mediated aldol reactions. We have also provided mechanistic indications (especially the dramatic reversal of stereoselectivity between **1a** and **1b**) that C=O chelation is responsible for a high selectivity with **1a**. Taking advantage of this concept, preliminary success has been achieved with the rational design of an amide system which shows very high selectivity in aldol reactions.[29]

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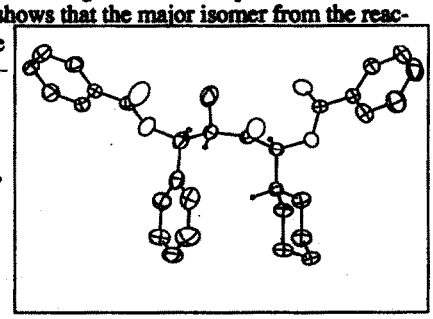
17. The MOM protecting group was cleaved, and the resulting diol was analyzed by HPLC. The retention times of the two major isomers are equal within experimental error to the retention times under the same experimental conditions of the diols obtained from desilylation of the aldol adducts of the corresponding aldehydes with **1d**. Single crystal X-ray analysis of the major diols from propionaldehyde and pivalaldehyde prove the absolute configurations in these cases. X-ray analysis of the dibenzoate prepared by benzoylation of the adduct from reaction of ketone **1a** with PhCHO proves the absolute configuration of the minor adduct from TMS substrate **1d**, since comparison of the high-field NMR spectra of the dibenzoates prepared from the adducts of PhCHO with **1a** and **1d** shows that the major isomer from the reaction of **1a** is identical to the minor isomer from **1d**, and, vice versa, the major isomer from **1d** is identical to the minor isomer from **1a**. This same reverse NMR correlation of major and minor isomers from **1a** and **1d** was found for all other aldehydes studied as well. We have not been able to obtain an X-ray structure for an isobutyraldehyde adduct; however, analogy with the other three adducts from **1d** strongly indicates that the absolute configuration is the same for the isobutyraldehyde adduct as well. The crucial structure of the dibenzoate resulting from monobenzoylation of the major aldol adduct from ketone **1a** with benzaldehyde is shown.



18. Debenzylation of the adducts was achieved in all three cases with H_2 using 5% Pd/C catalyst. HPLC analysis of the resulting diols and comparison of the retention times with those of authentic, known diols determined the absolute stereochemistry of the adducts.
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