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A PREDOMINATELY *ANTI*-STEREOSELECTIVE CHIRAL METAL DIRECTED ALDOL CONDENSATION WITH AROMATIC ALDEHYDES

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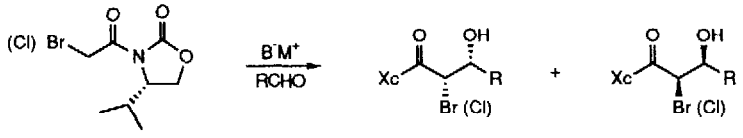
Abstract: *Chiral haloacetyl oxazolidinones were reacted with aromatic aldehydes via their kinetically generated Z-enolates to yield predominately anti aldol adducts. The reaction is postulated to proceed thru a boat-like transition state. A unique reversal of chirality was observed in using stannous enolates.*

Earlier we reported the highly stereoselective synthesis of *syn*--chiral α-haloimidates obtained *via* a metal directed, stereocontrolled aldol-type condensation of chiral α-haloacetyl oxazolidinones with ***aliphatic*** aldehydes under kinetically controlled conditions.[1,2] In that report we described in detail the dependence of product stereochemistry on choice of metal counterion during or after enolate generation. Our exploitation of that dependence allowed us total control of *syn* enantio product selectivity, without having to change the chiral auxillary. We were able to rationalize our results nicely by employing the well-known Zimmerman-Traxler chair-like transition state model.[3]



Syn-B (M = B, Sn^{II}) Syn-Li (M = Li, Zn, Sn^{IV})

However, we have since found that the chair-like transition state (TS) does not always apply to ***aromatic*** aldehydes, particularly when it is *ortho* substituted.

Although the literature contains earlier reports of *anti* aldol additives with chiral oxazolidinones using boron,[4] lithium,[5] and titanium,[6] a systematic study of the effects of different metals on these same substances in the aromatic aldehyde series has not been reported to date. **Scheme I** and **Table I** show our results with aromatic aldehydes where predominately *anti* isomers were obtained from Z-enolates with a high degree of stereoselectivity in most of the examples shown. *Syn* isomers usually result from Z-enolates in the aldol reaction *via* the chair-like model. However, in all our cases where the *anti* isomers were obtained, only the configuration at the β-hydroxy carbon had been changed when compared to the expected *syn* isomer.[3] For example, in our previous work with aliphatic aldehydes, isomer **3** *(syn-Li)* **(Scheme I)** was obtained from a lithium mediated reaction, but in this work mainly *anti* **4** *(anti-Li)* was obtained. Thus, epimerization at the α-halo carbon or reaction involving the E-enolate may be ruled out.

Scheme I

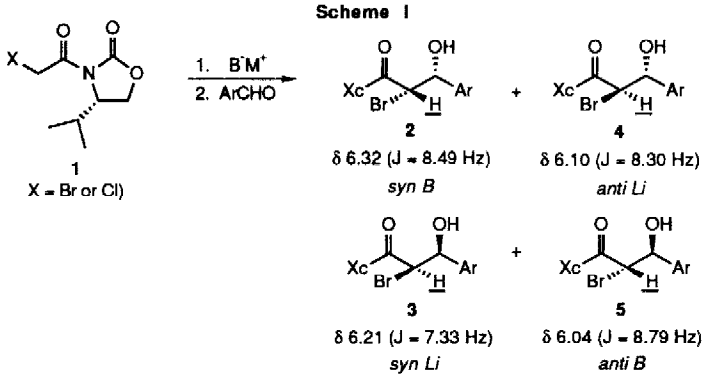


Table I[a]

Comparative Aldol Condensations of Metal Enolates of ***1*** *with Aromatic Aldehydes*

Entry	Ar	X	Metal	Diastereoselection[b] *Syn:Anti* **(2+3):(4+5)**	Enantioselection *Syn* **2:3**	Enantioselection *Anti* **4:5**	Yield[c] %
1	Ph	Br	Li	25:75	18:7	70:5	61
2	"	"	Sn^{IV}	21:79	9:12	76:3	77
3	"	"	Zn	33:67	15:18	66:1	73
4	"	"	Sn^{II}	**85:15**	**79:6**	**6:9**	67
5	"	"	B[d]	98:2	98:0	2:0	63
6	Ph	Cl	Li	24:76	17:7	70:6	70
7	"	"	Sn^{IV}	22:78	15:7	78:0	73
8	"	"	Zn	33:67	19:14	67:0	67
9	"	"	Sn^{II}	**96:4**	**92:4**	**4:0**	56
10	"	"	B[d]	>99:0	>99:0	0:0	68
11	Ar[e]	Br	Li	13:87	5:8	79:8	65
12	"	"	Sn^{IV}	9:91	0:9	82:9	78
13	"	"	Zn	33:67	4:9	54:33	76
14	"	"	Sn^{II}	**27:73 (5:95)**[f]	**6:21 (0:5)**	**0:73 (0:95)**	67 (79)
15	"	"	B	98:2	93:5	2:0	60

[a] All reactions were carried out according to ref 2, except where noted. X-ray crystallography was used in structure determinations.

[b] Isomer ratios were determined by GLC and 400 MHz ^1H NMR. The elution order on a DB-1 capillary column for the benzaldehyde adducts after treatment with "Tri-Sil" is: **5**:**2**:**3**:**4**.

[c] Isolated chromatographed yields. All compounds were fully characterized by either a CHN (+0.3%) or Hi-Res. mass spec.

[d] Only diethylboron triflate prepared *in situ* [8] in CH_2Cl_2 was effective with benzaldehyde. Di-*n*-butyl and diethylboron triflates were effective with *o*-(8-phenyloctyl)benzaldehyde.

[e] Ar refers to *o*-(8-phenyloctyl)benzaldehyde.

[f] Data in parentheses prepresents results from a phenylglycine derived chiral auxillary.

All metal enolates were generated from **1** as previously reported,[2,7,8] except where noted, and similarly reacted with the appropriate aldehyde. Our results indicate that, unlike the aliphatic series, there is very little discernible difference in diastereoselectivities between the bromo and chloro acetyloxazolidinones. However, very substantial differences were discovered in the metals studied.

As in our previous study,[1,2] Li, Zn, and Sn^{IV} behaved similarly, but this time *via* a chelated boat-like TS **6** to yield predominately *anti* aldol product. Stannous and di-*n*-butylboron triflates mediated reactions still yielded mainly *syn* products for benzaldehyde *via* the unchelated chair-like model.[2] However, when the very sterically encumbered *o*-(8-phenyloctyl)benzaldehyde was used, a markedly overall improvement in selectivities was observed. In addition, *the Sn^{II} mediated reaction now gave the anti product which is enantiomeric at the halohydrin carbons to the anti adduct from the Li, Zn and Sn^{IV} examples, presumably by the unchelated boat TS model 7.* This represents a continuation of the chirality reversal that we have already reported.[2] Boat-like transition states in certain cases are known to be the principle pathway in aldol reactions.[6,9,10,11]

Scheme II

Enolate Facial Attack

6 **7**

Apparently, the steric congestion introduced by the large ortho-substituent has now forced the Sn^{II} mediated reactions to react in a non-chelated manner *via* the boat-like TS, as compared to the chelated boat of the Li, Zn, and Sn^{IV} examples, *vide supra*. Boron enolates in our case still, however, react *via* the chair non-chelated model (compare entries 14 and 15 to entries 4,5 and 9,10). Further study aimed at advancing our understanding of the steric and electronic factors[12] that control the chair versus boat transition states in this system will be forthcoming.

References and Notes

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11. The unfavored chair or "skewed-transition state"[9] may also be invoked to explain our results. However, we observed no difference in selectivity between the chloro and bromo examples (entries 1-10) which is predicted to be the case only for the "boat alternative".[9]

12. In a preliminary unpublished result we have employed cyclohexane carboxaldehyde in the lithium mediated aldol reaction to yield a 1:1 ratio of the two *syn* isomers. This aldehyde is just as sterically demanding, if not more so, than benzaldehyde. Thus, one variable which must influence product stereochemistry is the *pi* electron cloud of the aromatic ring system, possibly through secondary orbital interactions[13,14,15] with the oxazolidinone carbonyl or the α-halogen. This result will be further discussed in a future publication.

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