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ALDOL CONDENSATIONS OF CHIRAL α-HALOIMIDATES. A CHIRAL DARZENS CONDENSATION PROCEDURE.

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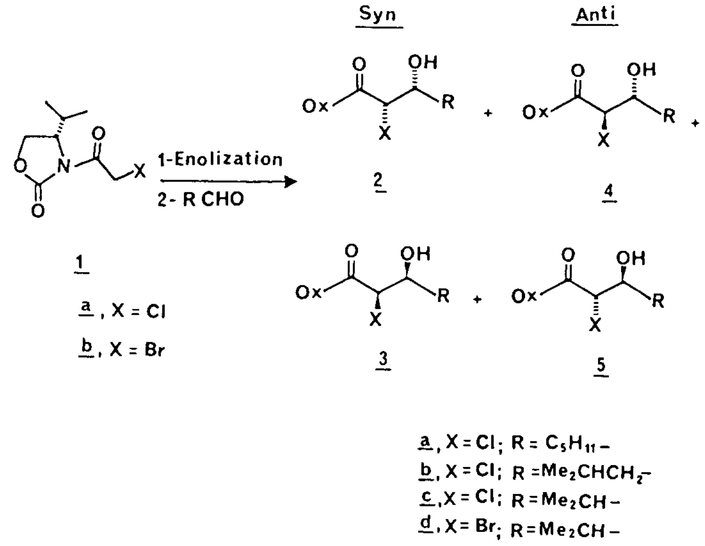
Summary: Enantiomerically pure benzyl cis-α,β-epoxycarboxylates were prepared by a modified Darzens procedure utilizing aldol condensation reactions of chiral α-haloimidates with various aldehydes. A unique chirality reversal was observed using Zinc-enolates.

The epoxide functionality has proved to be one of the most versatile bifunctional synthons in organic synthesis.[1] Its utility in synthesis has been further enhanced by the newly discovered procedure of Sharpless and Katsuki[2] which greatly simplifies the formation of chiral epoxides in predictable absolute stereochemistry and high enantiomeric excess. Other methods[3] currently in the literature for chiral epoxide formation miss their mark by a wide margin in terms of the enantiomeric excess achieved or simplicity of application. To fill the need for complimentary methodologies that deliver the epoxide functionality in a highly enantioselective fashion, we have been developing in our laboratories a chiral modification of the Darzens condensation[4] procedure which is the subject of this report. Inherent in this method is the utilization of chiral α-haloimidates in typical aldol reactions via Zn, Sn (II) and $(n\text{-Bu})_2B$ enolates, along lines similar to the studies of Evans and coworkers,[5] and the elaboration of the resultant chiral 1,2-halohydrins to α,β-epoxy esters. Accordingly, the first part of this investigation examined the behavior of the α-haloimidates under kinetically controlled aldol conditions since such studies have not been reported in the literature.

Imidates 1a, mp 48-49°C, $[\alpha]_D$ +97.9° (c 1.0, $CHCl_3$) and 1b, mp 55-57°C, $[\alpha]_D$ +83° (c 1.0, $CHCl_3$) were readily available from α-haloacetyl halides and (+)-4-isopropyloxazolidinone.[5a] The aldol condensations (Scheme I) were carried out according to the following procedure, except in those cases specifically noted in the table. Z-Enolates were kinetically generated with LDA (Et_2O or THF solvent, -78°C), and were treated with

Scheme 1



the chelating metal [ZnCl$_2$[6] or Sn(OTf)$_2$[7]] followed by the aldehyde. Once the reaction reached completion at -20°C, the product composition was assayed by ^{1}H NMR for diastereomeric ratios. The results are presented in Table I.

Table I: Comparative Aldol Condensations of Metal Enolate of 1 with Aldehydes:

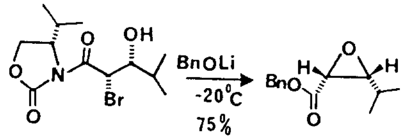
	Reactants			Product Distribution[a]			
Entry	Aldehyde	X	Metal[b]	diastereo-selection Syn:anti	Enantioselection 2:3	4:5	Yield[8] %
1	$C_5H_{11}CHO$	Cl	Zn (1 eq.)	3:1	1:5	4:1	61
2	"	"	Zn (1/2 eq.)	5:1	1:3	4:1	60
3	"	"	SnII[c]	3:1	2:1	1:3	84
4	"	"	SnII	6:1	6:1	2:3	73
5	"	"	B[d]	>20:1	>20:1	-[e]	62
6	$(CH_3)_2CHCH_2CHO$	"	Zn	5:1	1:3	1:1	60
7	"	"	SnII[c]	4.5:1	3:1	1:1	68
8	"	"	SnII	8:1	7:1	2:3	73
9	"	"	B[d]	>20:1	>20:1	-[e]	55
10	$(CH_3)_2CHCHO$	"	Zn	>20:1	1:5	-[e]	63
11	"	Br	Zn	7:1	1:9	1:3	72
12	"	Cl	SnII[c]	3:1	2:1	2:3	64
13	"	"	SnII	13:1	4:1	1:1	77
14	"	Br	SnII	15:1	6:1	1:1	65
15	"	Cl	B[d]	>20:1	>20:1	-[e]	52
16	"	Br	B[d]	>20:1	>20:1	-[e]	51

(a) Ratios determined by 90 MHz ^{1}H NMR; (b) Zn, SnII and B refer to $ZnCl_2$, $Sn(OSO_2CF_3)_2$ and $(n\text{-}Bu)_2BOSO_2CF_3$ respectively; (c) Condensation ran by the method of Mukaiyama[9]; (d) Condensation ran by the method of Evans[5a]; (e) No antiproducts could be detected.

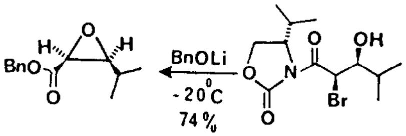
As seen from the results, and in agreement with previous findings,[5] the formation of the *syn* adducts is favored over the *anti* in the reaction. It is also apparent that increased steric bulk on the aldehyde consistently improves this diastereoselectivity. The highest degree of selectivity was obtained with the $(n\text{-Bu})_2$BOTf reagent, first used by Mukaiyama[10] and later explored by Evans.[5,11]

Interesting results were observed in the $ZnCl_2$ and $Sn(OTf)_2$ mediated reactions. It is seen from entries 1 and 2 that employment of a full equivalent of $ZnCl_2$ was not necessary to achieve diastereoselection in the condensation, a finding previously paralleled by Widdowson.[12] With respect to the $Sn(OTf)_2$ mediated reactions, both diastereo and enantioselectivities were greatly improved (entries 4, 8, 13 vs. 3, 7, 12) when the tin reagent was added to preformed Li-enolates at -78°C as described by our procedure. A comparison of the 2:3 ratios from the Zn reactions vs. those obtained with SnII or B reveals a most intriguing chirality reversal of the adducts (2 vs. 3). In fact this finding allowed us to prepare both enantiomeric epoxides from the same chiral precursor (*vide infra*). Evans[5] has made a similar observation in Li enolate reactions, although in that instance the major product of the reaction was *anti*. We believe that additional sites of ligation on the Zn^{2+} cation may be responsible for this reversal of enantiofacial preference although work with additional metals will be required before the complete mechanism can be elucidated.

At the outset of this study we had envisaged the eventuality that the reaction would provide diastereomeric epoxides directly. This obviously did not materialize; in fact attempts to carry out the desired conversion on chloro compounds 2 and 3 were frustrated with various degrees of epimerization. On the other hand, two of the bromo adducts, 2d and 3d have been converted to the *cis* α,β-epoxy esters 6 without epimerization,[13] on treatment with lithium benzyloxide (THF, -78 → -20°C). Thus we have obtained both antipodes of 6 [$[\alpha]_D$ + 35.7° (C 1.0, $CHCl_3$) and -36.6° (C 1.0, $CHCl_3$) respectively], whose absolute stereochemical assignment rests on an X-ray structural determination of the halohydrin starting material. We further anticipate that this transformation offers an opportunity for a one pot chiral epoxidation procedure and this will be reported on shortly.



2d (+)-6(R,R)



(-)-6(S,S) 3d

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