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Cr(Salen)-Catalyzed Addition of 1,3-Dichloropropene to Aromatic Aldehydes. A Simple Access to Optically Active Vinyl Epoxides

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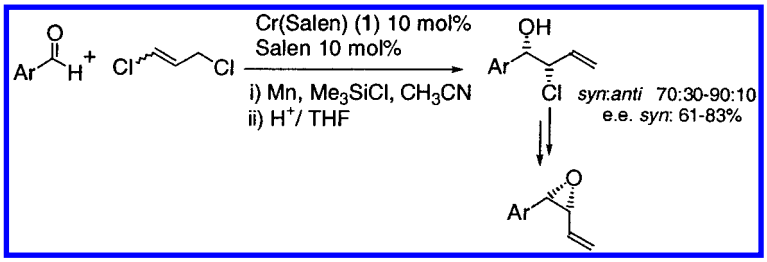
ABSTRACT



Chiral Cr(Salen) complex (1) prepared in situ from $CrCl_3$ promotes the enantioselective addition of 1,3-dichloropropene to aromatic aldehydes in the presence of Mn as the stoichiometric reductant and Me_3SiCl as a scavenger. The resulting 1,2-chlorohydrins obtained in good enantiomeric and diastereoisomeric excesses can be easily transformed into the corresponding chiral vinyl epoxides.

Vinyl epoxides are important starting materials for the preparation of a variety of biologically active products and are useful intermediates for synthesis.[1] Several metal-catalyzed ring opening reactions of vinyl epoxides were recently described.[2] Optically active vinyl epoxides can also being employed as chiral carbonyl synthons, affording protected alcohols in high ee's.[3] Since 1,2-halohydrines are key intermediates for the preparation of vinyl epoxides, a direct synthesis of optically active 1,2-chlorohydrins is highly desirable.[4] Toward this goal an enantioselective boron-mediated stoichiometric addition of chloropropene to aldehydes was recently reported.[5]

Here we describe a catalytic diastereo- and enatioselective approach to optically active chlorohydrins based on a stereoselective redox process.[6] Recently, we have developed the first enantioselective Nozaki-Hiyama (NH) reaction catalyzed by Cr(Salen) complex **1** operating at room temperature (Figure 1).[7a] This procedure appears also to be effective in promoting the addition of prochiral allyl bromides

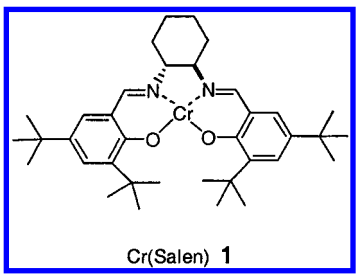


Figure 1.

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(1) (a) Lindström, U. M.; Olofsson, B.; Somfai, P. *Tetrahedron Lett.* **1999**, *40*, 9276−9279. (b) Solladié-Cavallo, A.; Bouérat, L.; Roje, M. *Tetrahedron Lett.* **2000**, *41*, 7309−7312.

(2) Taylor, S. K. *Tetrahedron* **2000**, *56*, 1149−1163 and references therein.

(3) Lautens, M.; Ouellet, S. G.; Raeppel, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 4079−4082.

(4) α-Halohydrines are easily converted to oxyranes, see: Marshall, J. A. *Chem. Rev.* **1989**, *89*, 1503−1511.

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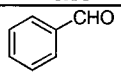
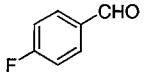
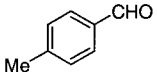
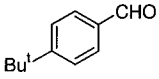
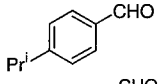
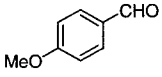
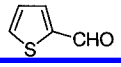
Table 1

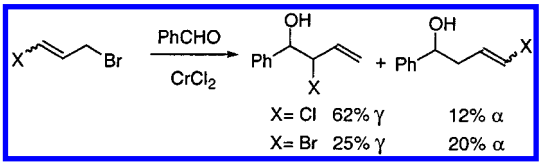
ArCHO	% 3γ[a]	% 4α[a]	*syn*:*anti*[b]	% e.e. *syn*[c]	% e.e. *anti*[c]
	**3a** (44)	**4a** (5)	90:10	81	44
	**3b** (35)	**4b** (15)	90:10	83	30
	**3c** (43)	**4c** (10)	84:16	71	--[d]
	**3d** (40)	**4d** (10)	77:23	73	--[d]
	**3e** (40)	**4e** (10)	87:13	82[e]	--[d]
	**3f** (30)	**4f** (10)	76:24	61	--[d]
	**3g** (30)	**4g** (15)	70:30	74[e]	0

[a] Isolated yield after chromatography. [b] The *anti*:*syn* ratio was evaluated by chiral HPLC (Chiralcel-OD) and ^{1}H and ^{13}C NMR. [c] The ee's of the products were evaluated by chiral HPLC (Chiralcel-OD) (see Supporting Information). [d] The *anti* diastereoisomer was not separated in the HPLC analysis. [e] The ee was evaluated by chiral CG (Megadex-5) analysis performed on the corresponding epoxide (see Supporting Information).

to aromatic aldehydes.[7b] In particular, we have observed a peculiar and unique switch of simple diastereoselection (*anti* → *syn*) if an excess of Salen ligand is utilized.[8] As an extension to other prochiral substrates, the commercially available 1,3-dichloro- and 1,3-dibromopropenes were employed.

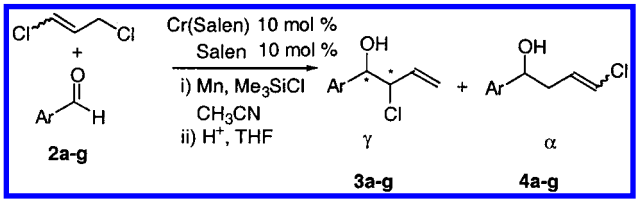
Until now, the Nozaki−Hiyama reaction with 1,3-dihalopropenes was rarely employed in organic synthesis, and the few examples reported required stoichiometric amounts of $CrCl_2$.[9] In 1-chloro-3-bromopropene, moderate yields of the desired γ-adduct were obtained due to the formation of side products such as the dienes (Scheme 1). Moreover, it is noteworthy that commercially available 1,3-dichloropropene is not reactive under the reported conditions.[9]

Scheme 1. Addition of 1,3-Dihalopropene to PhCHO Mediated by $CrCl_2$



On the other hand, we found that 1,3-dichloropropene[10] smoothly reacted with aromatic aldehydes in the presence of a catalytic amount of Cr(Salen) complex (Scheme 2).[11]

Scheme 2. Addition of 1,3-Dichloropropene to Aromatic Aldehydes Catalyzed by Cr(Salen)



Our protocol uses 10 mol % of Cr(Salen) complex prepared in situ[7a] by mixing $CrCl_2$[12] and Salen.[13] Free Salen ligand (10 mol %) is added[7b] in order to ensure a good *syn* simple stereoselection. Good levels of simple stereoselection (de 40−80%) and high enantioselectivity for the *syn* product (ee up to 83% with *p*-F-C_6H_4CHO) were recorded with a number of aromatic aldehydes as reported in Table 1.[14]

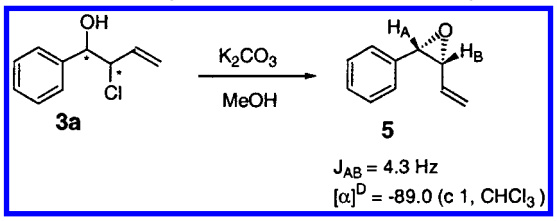
In contrast to the previously cited boron strategy, our protocol adopts very mild experimental conditions[5] and uses commercially available reagents.

(5) Hu, S.; Jayaraman, S.; Oehlschlager, A. C. *J. Org. Chem.* **1996**, *61*, 7513−7520.
(6) Fürstner, A. *Chem. Eur. J.* **1998**, *4*, 567−570.
(7) (a) Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 3357−3359. (b) Bandini, M.; Cozzi, P. G.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 2327−2330.
(8) It is worth noting that the addition of crotyl halides to aldehydes promoted by catalytic or stoichiometric amount of Cr salts normally gives the *anti* diasteroisomer in high yields, see: Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 12349−12357.
(9) Wender, P. A.; Wisniewski Grissom J.; Hoffmann, U.; Mah, R. *Tetrahedron Lett.* **1990**, *46*, 6605−6609.
(10) Commercially available 1,3-dichloropropene is a 55:45 diastereoisomeric mixture (*E*/*Z*). However, the simple diastereoselectivity of the reaction is not affected by the diastereoisomeric ratio of the starting halide (see ref 7b). 1,3-Dibromopropene gave only byproducts in the Cr(Salen)-catalyzed reaction.
(11) For applications of Cr(Salen) complexes in asymmetric catalysis, see: Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421−431.
(12) $CrCl_2$ is obtained by reducing anhydrous $CrCl_3$ by the excess of Mn in the reaction flask.

The desired γ-adducts were obtained in satisfactory chemical yields considering the formation of byproducts derived from process (α-adducts, eliminated products) and from side reactions connected to the redox nature of the catalytic cycle (such as the pinacol coupling).

The γ-adducts **3a**−**g**, purified by flash chromatography, were analyzed by chiral HPLC (Chiralcel-OD) and fully characterized by spectroscopic analysis (see Supporting Information). Relative and absolute configurations of the 1,2-chlorohydrins were established by transforming **3a** in the corresponding vinyl epoxide **5** (Scheme 3) and comparing

Scheme 3. Determination of the Absolute Configuration for the Chlorohydrin Derived from Benzaldehyde



the optical rotation value ($[\alpha]_D = -89.0$, *c* 1, $CHCl_3$) with the reported value.[15] The stereochemistry of the chlorohydrins **3b**−**g** was assigned by analogy. It is worth noting that the (1*S*,2*S*) absolute configuration of **3a**, obtained with (*R*,*R*)-Salen, was the same as obtained by the addition of other crotyl reagents to aromatic aldehydes,[7b] showing the generality of our methodology. Mechanistically, this redox system appears to be quite complex since specific cooperative effects between different Cr(Salen) molecules seem to be involved in this enantioselective reaction. In fact, a working model for the catalytic redox cycle implicates the synergistic action of one molecule of [Cr(Salen)allyl] and one of [Cr(Salen)X] in the stereodifferentiating step of the reaction mechanism.[16]

In conclusion we have described a simple and effective approach toward the synthesis of optically active 1,2-*syn*-chlorohydrins, key intermediates for the preparation of *cis*-vinyl epoxides. Investigations concerning the stereoselective addition of other hetero-substituted crotyl halides to carbonyl compounds mediated by Cr(Salen) catalyst are in progress in our laboratory.

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Supporting Information Available: Typical reaction procedure for the Cr(Salen)-mediated reaction and analytical data for the isolated compounds (chlorohydrins and epoxides). This material is available free of charge from the Internet at http://pubs.acs.org.

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(13) $CrCl_3$ (0.1 mmol) was suspended in anhydrous CH_3CN; then Mn powder (3 mmol) was added. The mixture was kept at room temperature without stirring for 5−8 min. After that, the mixture was vigorously stirred and a green-white precipitated was formed in 10−15 min. Salen (0.2 mmol) and anhydrous Et_3N (0.2 mmol) were added. The resulting heterogeneous mixture was stirred at room temperature during 1 h; then 1,3-dichloropropene (1.5 mmol) was added. The mixture turned maroon-red, and the resulting suspension was stirred during 1 h at room temperature. After that time, the aldehyde (1 mmol) and Me_3SiCl (1.5 mmol) were added. After complete consumption of the aldehyde (checked by GC, 24−48 h), the reaction was quenched with a saturated solution of $NaHCO_3$ (5 mL) and filtered over Celite. After usual workup the crude *O*-protected chlorohydrin was desilylated under acid conditions (HCl 2 N, THF, checked by TLC). Finally the product was purified by flash chromatography.

(14) Other aromatic aldehydes were screened, giving the desired product in lower yield: *p*-Ph-C_6H_4CHO (yield 12%; *syn*:*anti* 64:36; ee *syn* = 58%), *p*-MeS-C_6H_4CHO (yield 15%; *syn*:*anti* 90:10; ee *syn* = 47%), *o*-F-C_6H_4-CHO (15% yield; *syn*:*anti* 65:35; ee *syn* = 72%). Aliphatic aldehydes were found to be unreactive. α,β-Unsaturated aldehydes furnished a complex mixture of 1,2 and 1,4 adducts.

(15) Reported value: cis-(1*R*,2*S*)-1,2-epoxy-1-phenyl-3-butene $[\alpha]_D$ = +97.4 (**c** 2.65, EtOH): see ref 5.

(16) An acyclic transition state has been proposed on the basis of detailed mechanistic studies, see: Bandini, M.; Cozzi, P. G.; Umani-Ronchi, A. *Tetrahedron* **2001**, *57*, 835−843.