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Enantioselective catalytic addition of allyl organometallic reagents to aldehydes promoted by [Cr(Salen)]: the hidden role played by weak Lewis acids in metallo-Salen promoted reactions

Marco Bandini, Pier Giorgio Cozzi* and Achille Umani-Ronchi*

Dipartimento Chimico 'G. Ciamician', Università di Bologna, Via Selmi 2, 40126 Bologna, Italy

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Abstract—In this paper, we present the data obtained from kinetic analysis and from NLE study in the [Cr(Salen)] catalysed addition of allyl halides to aldehydes. The results show the key role played by weak Lewis acids in the catalytic system. Weak Lewis acids such as manganese salts and the [Cr(Salen)X] complex drive the stereochemistry of the reaction toward a high level of diastero- and enantioselectivity. Therefore, the Lewis acids and their properties must be taken into account in the rational design of metallo-Salen mediated processes.

1. Introduction

Chiral Schiff bases have become increasingly more important in modern organic and inorganic chemistry.[1] In fact, they are capable of complexing late and early transition metals stabilising them in high and low oxidation states. In this respect, a key feature is the presence of nitrogen and oxygen donor atoms in the coordination core, which act cooperatively. Another important characteristic is the possibility to prepare a large variety of structurally correlated Schiff bases by simple chemistry, modifying the stereo-electronical properties of the ligand. Moreover, the possibility to expand the coordination sphere by inserting additional donor atoms or groups improves the flexibility of such ligands. A particular class of Schiff bases, the Salen ((*R*,*R*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicydene)-1,2-cyclohexanediamine, **1**, Fig. 1), has started to attract considerable interest in the organic and organometallic chemistry community.[2] Chiral Salen Schiff bases have been used in interesting applications in asymmetric catalysis, in particular, metallo-Salen complexes were found to promote many important reactions.[3] Recently we have described the first enantioselective version of the Nozaki–Hiyama reactions promoted by a catalytic amount (10 mol%) of [Cr(Salen)] complex (Scheme 1).[4] Our chromium mediated redox reactions were based on two crucial features previously presented by Fürstner:[5] (a) the use of Mn powder (50 mesh) as the stoichiometric reductant; (b) the use of Me_3SiCl as the scavenger. Moreover, we discovered that in the addition of stereogenic allyl halides to aromatic aldehydes, the presence of Salen (chromium:Salen ratio 1:2) completely switches the simple diastereoselection from *anti* to *syn*.[4b] Such behaviour gave us a strong indication that the methodology was more than an application of classical redox chemistry in chromium mediated reactions. The unusual properties of our reactions prompted us to pursue more detailed mechanistic studies. We report here the results of 'nonlinear effect' (NLE) and kinetic studies on the [Cr(Salen)] mediated addition of stereogenic and non stereogenic organo halides to carbonyl compounds. On the basis of these results, the basic and subtle role played by weak Lewis acids in these reactions is suggested. Moreover, we would like to stress how the presence of weak Lewis acids can significantly affect the stereoselectivity in many fascinating Salen mediated reactions.

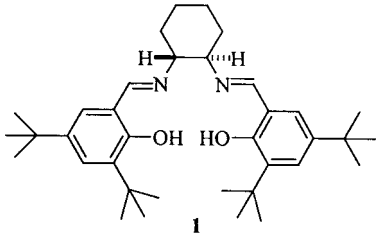

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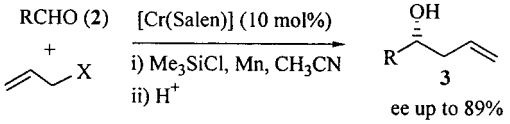
Figure 1. Salen Schiff base ligand.



Scheme 1. Asymmetric allylation reaction of aldehydes promoted by [Cr(Salen)] complex.

Keywords: allylation; catalysis; Lewis acids; Schiff bases.
* Corresponding authors. Tel.: +39-51-259509; fax: +39-051-2099456; e-mail: umani@ciam.unibo.it; cozzi@ciam.unibo.it

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Table 1. Asymmetric allylation of aldehydes in the presence of [Cr(Salen)] as the catalyst (all the reactions were carried out following the general procedure [see the Experimental])

Entry	RCHO-**2**	Yield (%)-**3**	Ee (%)-**3**
1	PhCHO-**2a**	67	84
2	4Me–C_6H_4CHO-**2b**	67	78
3	4Ph–C_6H_4CHO-**2c**	54	82
4	4F–C_6H_4CHO-**2d**	41	77
5	4MeS–C_6H_4CHO-**2e**	46	78
6	*c*C_6H_{11}CHO-**2f**	42	89
7	$PhCH_2CH_2$CHO-**2g**	45	77

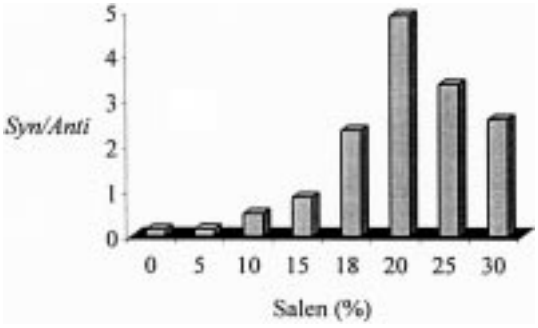
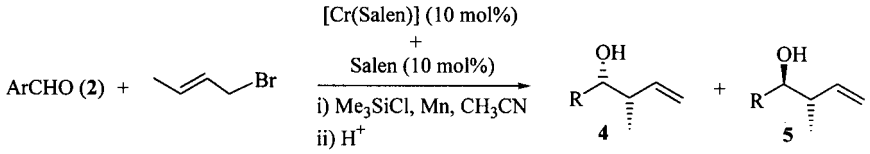


Figure 2. Dependence of the diastereoselection on the total amount of **1** employed in the catalysis. Each reaction was carried out using 10 mol% of chromium salt.

tivity was lower. The motivation to start kinetic and mechanistic studies was determined by some experimental observations. (a) The Me_3SiCl is not essential in the stereodifferentiating step of the reaction. By carrying out the reaction with a stoichiometric amount of chiral [Cr(Salen)allyl] complex[4a] we isolated the desired homoallylic alcohol in good yield and stereoselectivity (yield=56%, ee=80%).[6] (b) Apparently, the MnX_2 salts generated in the catalytic cycle play a crucial role in determining the formation of the catalytically active species. In fact, synthesising the [Cr(Salen)allyl] complex, starting from the Jacobsen's protocol[3c] (i.e. addition of Cr(II) to Salen in THF then changing the solvent to CH_3CN) by adding allyl chloride, no reaction was obtained with benzaldehyde.[7] We previously reported that, in the addition of stereogenic organo halides to carbonyl compounds the diastereoselectivity is greatly affected by the amount of ligand employed (Fig. 2).[4b] As a matter of fact, the addition of crotyl bromide to the benzaldehyde proceeded with a higher diastereoisomeric ratio *syn*:*anti* (83:17)[8] when the reaction was carried out in the presence of a 10 mol% excess of **1**.[9] This modified protocol appeared to be general because good results in terms of enantioselectivity with a variety of aromatic aldehydes were obtained (see Table 2). The unexpected result in this reaction was the *syn* simple diastereoselection observed.[10] In fact, high levels of *anti* stereoselection are usually achieved in the chromium mediated

Table 2. Results of stereoselection in the addition of crotyl bromide to aromatic aldeydes using chiral [Cr(Salen)] catalyst (all the reactions were carried out following the general procedure [see the Experimental])



Entry	ArCHO-**2**	Yield (%)	*Syn*:*Anti* **4**:**5**	Ee of **4** (%)	Ee of **5** (%)
1	PhCHO-**2a**	56	83:17	89	36
2	4Me–C_6H_4CHO-**2b**	48	74:26	85	26
3	4Ph–C_6H_4CHO-**2c**	47	71:29	84	16
4	4F–C_6H_4CHO-**2d**	53	74:26	90	27
5	4Cl–C_6H_4CHO-**2h**	46	61:39	82	24
6	4Br–C_6H_4CHO-**2i**	43	72:28	82	28
7	3Br–C_6H_4CHO-**2j**	49	66: 34	70	43
8	4MeO–C_6H_4CHO-**2k**	52	60: 40	58	15

2. Results and discussion

The addition of allyl chloride to aldehydes promoted by [Cr(Salen)] afforded the corresponding homoallylic alcohols in satisfactory yields with a good level of enantioselection (Table 1). In this process a crucial role of the solvent was detected. In fact, in THF, the reductive pinacol coupling was the main side reaction.† This undesired side process was minimised in CH_3CN. Several additives such as CH_3COCl, $(CH_3CO)_2O$ or different silylating agents ($ClMe_2Si(CH_2)_3CN$, $ClMe_2Si(CH_2)_2SiMe_2Cl$) were screened in order to replace the TMSCl, however they did not afford better conversion and the observed enantioselection of stereogenic allyl halides to aldehydes.[5b] What is the nature of the catalytically active species? Does the reaction work only in the presence of weak Lewis acids (MnX_2, [Cr(Salen)X])? How can we explain the *syn* diastereoselection detected? In order to shed light on these intriguing questions, we performed some mechanistic studies. The addition of crotyl bromide and allyl chloride to the benzaldehyde were chosen as model reactions for such analysis. Firstly, we investigated the dependence of the simple diastereoselection on the catalyst's concentration in the reaction medium. Fig. 3 reports the results obtained varying the catalyst concentration over 5-fold range (from 5.0 mM to 25.0 mM). From a practical standpoint, an aggregation phenomena appears to be involved, in fact, the chromium-**1** catalyst is more diastereoselective at a higher concentration. More direct evidence that aggregates were

† With aliphatic aldehydes, the reduction of the carbonyl substrate took place affording the corresponding primary alcohol.

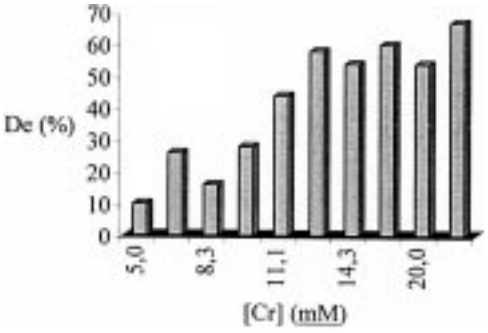


Figure 3. Diastereoselectivity (*syn*:*anti*) vs chromium concentration: evidence of an aggregating nature of the catalytic species.

The triple-shaped curves detected for our catalytic system strongly suggest that an aggregation phenomena is involved in the enantio-differentiating step.[11]

Recently, Jacobsen et al. have shown that the asymmetric ring opening of *meso* epoxides with Me_3SiN_3 catalysed by the [Cr(Salen)] complex displays a second order kinetics dependent on the chromium catalyst. On the basis of this result and as a function of other experimental evidences, it was assumed that in the enantio-descriminating step a cooperative intermolecular bimetallic pathway was operative. To acquire more detailed mechanistic aspects of our reaction, we have performed some kinetics studies. Reaction rates were measured by monitoring the appearance of the silyl-

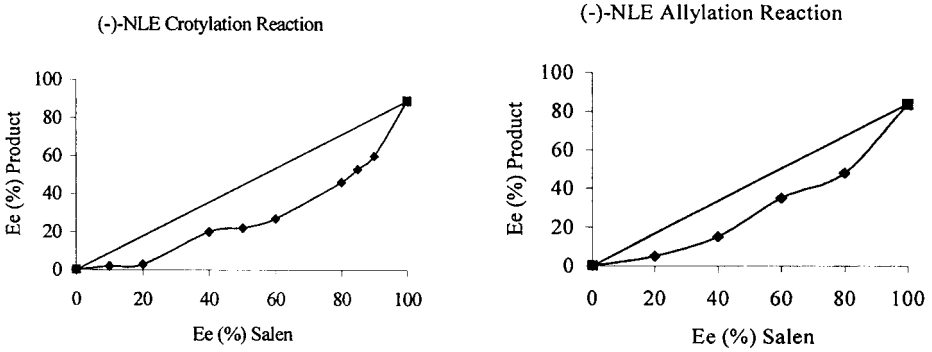


Figure 4. (a) NLE curve of the crotylation reaction. (b) NLE curve of the allylation reaction.

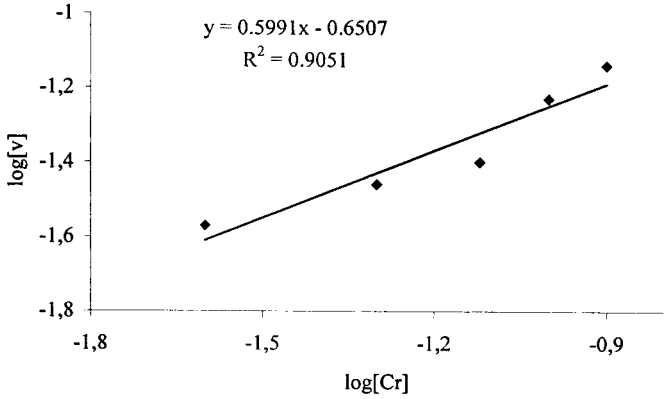


Figure 5. Plotting of log[rate] vs log[Cr]. Determination of the order dependence on total chromium concentration.

involved comes from studies concerning the NLE process.[11] The dependence of the enantiomeric excess (ee) of the product on the optical purity of the catalyst was examined with the addition of crotyl bromide to the benzaldehyde. In the first instance, the simple diastereoselection of the reaction was remarkably insensitive to the ee of the catalyst (dr range 79:21–83:17, see Experimental).[12] The NLE for the ee value of the *syn* isomer is reported in Fig. 4a. In order to verify that this interesting behaviour was not a function of the stereogenic halide used, a similar study was run for the addition of allyl chloride to the benzaldehyde (Fig. 4b). The similarity in shape between the two curves proves that the nature of the organo halide does not significantly influence the NLEs recorded. It is important to point out that these (−)-NLEs are unprecedent for [M(Salen)] mediated reactions. For the [Cr(Salen)] catalysed ring-opening epoxide reaction, distinct asymmetric amplification was observed.[13]

ated homoallylic alcohol in quenched aliquots by capillary GC.[‡] We used an internal standard (anhydrous butyl ether) to measure the reaction rates, following each run from 8% completion to 18–25% conversion. All the monitored reactions showed a rate deceleration over the catalytic turnover probably determined by the sensitivity of the catalytic system to the experimental condition of the kinetic analysis.[§] Varying the chromium concentration ([Cr_{total}]=catalyst concentration) between 5% and 25% and plotting log[rate] vs log[Cr_{total}], the rate order of chromium was found to be approximately 0.5 (Fig. 5).[‖] The half order dependence of

[‡] Note that it was not possible to monitor the disappearance of the benzaldehyde because side reactions were involved.

[§] A typical procedure for the GC kinetics experiment is reported in the Experimental.

[‖] All other components were held at constant concentration.

$$2\,[L_2{}^{*}Cr_2X_2] \rightleftharpoons [L_4{}^{*}Cr_4X_4]$$

Equation 1. The hypothesised equilibrium between the active dimeric and the tetrameric catalytic aggregate.

total chromium concentration suggests that in the rate determining step of the reaction two molecules of the catalyst are involved.[14] On the other hand, the mathematical treatment introduced by Kagan for the NLE analysis of our reaction suggests that a tetrameric species is implicated in such a complicated catalytic system.[11,15] Assuming the equilibrium between dimeric complexes and tetrameric species (Eq. (1)), it is possible to arrive at a mathematical equation for $[L_2{}^{*}Cr_2X_2]$ (catalytically active species) that is proportional to the square root of the $[Cr_{total}]$⇒rate∝$[Cr_{total}]^{0.5}$.[16]

Aggregation phenomena in organometallic chemistry are often determined by the presence of weak Lewis acids in solution and are strictly correlated to the nature of the ligand used. On the other hand, it is well known that oxygen atoms of the metal complexes of the Schiff bases are able to coordinate to metals.[17] The manganese salts produced during the reaction are likely responsible for the formation of aggregated species.[18] In light of these results, we propose that a dimeric [Cr(Salen)] aggregate is involved in the transition state of our reaction. Probably, one molecule of [Cr(Salen)-allyl] and one of [Cr(Salen)X] synergistically work in the stereo-differentiating step of the addition of organo halides to aromatic aldehydes. We believe that the weak Lewis acid centre of the dimeric catalyst ([Cr(Salen)X]) could activate the carbonyl compound in proximity of the chiral allyl nucleophile favouring an acyclic transition state (⇒*syn* diastereoselection). A working model for this catalytic redox cycle is represented in Fig. 6. We have also suggested that the particular *anti*/*syn* dichotomy detected in our reaction can be explained considering a selective complexation of the free Salen ligand with the Mn–[Cr-(Salen)] aggregate, which is capable of modifying steric interactions between the two reaction partners in the transition state.[4b]

The presence of strong Lewis acid can have deleteriuos effects on these reactions. In fact, when $Zn(OTf)_2$ was catalytically employed as an additive (10 mol%), the stereoselection was significantly affected and both the distereo- and enantioselectivity dropped (dr=66:34 (*syn*), ee_{syn}= 71%). Moreover, with other Lewis acids such as $Sc(OTf)_3$ and $BF_3{\cdot}OEt_2$, only racemic products were isolated, probably because the [Cr(Salen)] complex was not stable under such conditions.[19]

3. Conclusion

In this study we have investigated the mechanism of a [Cr(Salen)] mediated asymmetric addition of organo halides to carbonyl compounds. The latent role played by weak Lewis acids (specifically MnX_2 and [Cr(Salen)X]) in controlling the aggregation state and the stereo-efficancy of a dimeric catalytically active species has been discovered. Self assembly and molecolar recognition phenomena are deeply connected to this complicated catalytic reaction. These studies show that bimetallic active catalysts can be realised using the particular properties of the Schiff base ligands. From this perspective, the action of weak Lewis acids present in solution is remarkable and may constitute an important element for designing new catalytic redox reactions mediated by metallo-Salen complexes.

4. Experimental

^{1}H NMR spectra were recorded on Varian 200 MHz or Varian 300 MHz spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (deuterochloroform: δ 7.27 ppm). Data are reported as follows: chemical shifts, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet), coupling constants (Hz). ^{13}C NMR spectra were recorded on a Varian 50 MHz or Varian 75 MHz spectrometers with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (deuterochloroform: δ 77.0 ppm). Mass spectra were performed at an ionizing voltage of 70 eV. Chromatographic purification was done with 240–400 mesh silica gel. Analytical gas chromatography (GC) was performed on a Hewlett-Packard HP 6890 gas chromatograph with a flame ionization detector and split mode capillary injection system, using a

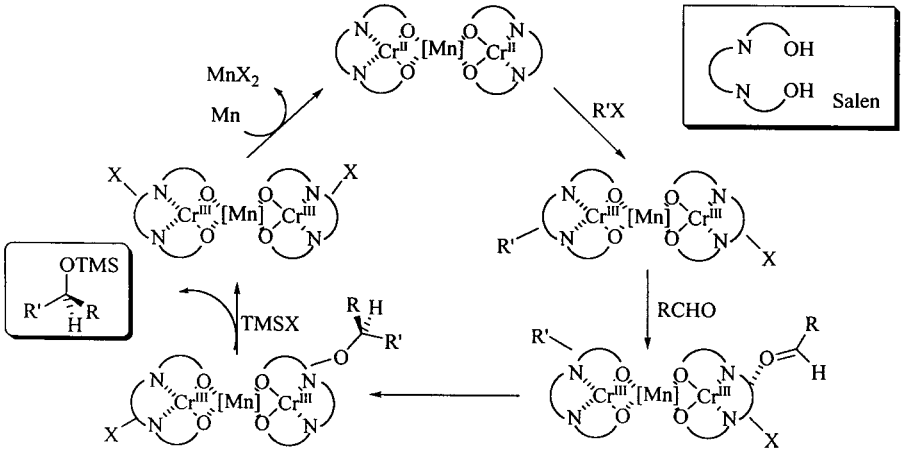


Figure 6. A simplified picture for the proposed catalytic redox cycle. Oligomers that could be in equilibrium with the dimeric catalyst were not shown for clarity.

Crosslinked 5% PH ME Siloxane (30 m) column or a Megadex5 chiral (25 m) column (flow rate 15 mL/min, method: 50°C for 2 min, ramp at the rate of 10°C/min to 250°C for 15 min). Analytical high performance liquid chromatograph (HPLC) was performed on a HP 1090 liquid chromatograph equipped with a variable wavelength UV detector (deuterium lamp 190–600 nm), using a Daicel Chiralcel™ OD column (0.46 cm I.D.×25 cm) (Daicel Inc.). HPLC grade isopropanol and hexane were used as the eluting solvents. Elemental analyses were carried out by using a EACE 1110 CHNOS analyser. All the reactions were carried out under a nitrogen atmosphere in flame-dried glassware using standard inert techniques for introducing reagents and solvents. All the aldehydes were distilled prior to use. All the other commercially obtained reagents were used as received. Anhydrous CH_3CN were purchased from the Fluka Co. Manganese powder (50 mesh) was purchased from Aldrich Co. and used as received. Different batches of 50 mesh manganese give reproducible results.

4.1. Typical procedure for asymmetric allylation reaction of aldehydes using [Salen(Cr)] as catalyst

$CrCl_3$ (8 mg, 0.05 mmol) and Mn (83 mg, 1.5 mmol) were added to anhydrous CH_3CN (2 mL) and the mixture was kept for about 5–8 min, then the reaction mixture was stirred until a green–white precipitate was observed. The ligand **1** (27 mg, 0.05 mmol) was introduced followed by dried triethylamine (14 μL, 0.1 mmol) and the resulting brown solution was stirred at room temperature for 1 h. The solution was treated with allylchloride (58 μL, 0.75 mmol) and the resulting red solution was stirred for 1 h at room temperature. Finally, **2** (0.5 mmol) and Me_3SiCl (95 μL, 0.75 mmol) were added and the mixture was stirred until the complete consumption of the aldehyde. After quenching with a saturated solution of $NaHCO_3$, the reaction mixture was filtered on a celite© bed, and the CH_3CN was evaporated under reduced pressure. The residue was extracted with Et_2O and the organic phases were collected and evaporated under reduced pressure. The oil obtained was dissolved in THF (2 mL) and treated with 0.5 mL of 1N HCl. The mixture was stirred to complete desilylation (checked by TLC). After evaporation of THF, the residue was extracted with Et_2O. The organic phases were collected, dried over Na_2SO_4 and concentrated in vacuo to give a brown residue purified by flash chromatography (silica gel, Cyclohexane/Et_2O).

4.1.1. (*R*)-1-Phenyl-but-3-en-1-ol (3a).[20] Yield 50 mg (67%) (pale yellow oil). Determination of the enantiomeric excess by chiral GC analysis (80°C isoterm, T_r: 28.6 min (*R*), 29.6 min (*S*)) on the trimethylsilyl ether derivative: ee=84%. $[\alpha]_D^{25}$=+56.2 (*c* 0.8, $CHCl_3$). MS (EI, 70 eV): *m/z*51, 77, 79, 107. Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16; O, 10.80. Found: C, 81.02; H, 8.10; O, 10.88.

4.1.2. (*R*)-1-(4-Methyl-phenyl)-but-3-en-1-ol (3b).[20] Yield 54 mg (67%) (pale yellow oil). Determination of the enantiomeric excess by chiral GC analysis (115°C isoterm, T_r: 29.7 min (*R*), 32.4 min (*S*)): ee=78%. $[\alpha]_D^{25}$=+53.0 (*c* 1.0, $CHCl_3$). MS (EI, 70 eV): *m/z* 51, 65, 77, 91, 93, 121. Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70; O, 9.86. Found: C, 81.49; H, 8.64; O, 9.87.

4.1.3. (*R*)-1-(4-Phenyl-phenyl)-but-3-en-1-ol (3c). Yield 61 mg (54%) (white solid). Determination of the enantiomeric excess by chiral GC analysis (100°C for 5 min, ramp at the rate of 2°C/min to 180°C, T_r: 52.5 min (*R*), 53.4 min (*S*): ee=82%. $[\alpha]_D^{25}$=+62.2 (*c* 0.9, $CHCl_3$). MS (EI, 70 eV): *m/z* 51, 77, 115, 156, 183, 207. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62–7.59 (4H, m, Ar*H*), 7.47–7.42 (4H, m, Ar*H*), 7.38–7.35 (1H, m, Ar*H*), 5.92–5.80 (1H, m, C*H*=CH_2), 5.24–5.16 (2H, m, CH=CH_2), 4.85–4.65 (1H, m, C*H*OH), 2.60–2.57 (2H, m, CH_2), 2.05 (1H, d, *J*=3.30 Hz, CHO*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 142.8, 140.8, 140.4, 134.4, 128.7, 127.2, 127.2, 127.1, 127.0, 126.2, 118.5, 73.0, 43.7. IR (nujol): 3378, 3026, 1642, 1461, 1410, 1327, 1159, 1055, 1004, 877 cm^{-1}. Anal. Calcd for $C_{16}H_{16}O$: C, 85.68; H, 7.19; O, 7.13. Found: C, 85.78; H, 7.15; O, 7.07.

4.1.4. (*R*)-1-(4-Fluoro-phenyl)-but-3-en-1-ol (3d). Yield 34 mg (41%) (pale yellow oil). Determination of the enantiomeric excess by chiral GC analysis (110°C isoterm, T_r: 32.0 min (*R*), 34.2 min (*S*)): ee=77%. $[\alpha]_D^{25}$=+52.0 (*c* 1.1, $CHCl_3$). MS (EI, 70 eV): *m/z*51, 78, 97, 125. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (2H, dd, J_1=2.10 Hz, J_2=8.70 Hz, ArH), 7.04 (2H, dd, J_1=6.00 Hz, J_2=8.70 Hz, ArH), 5.82–5.70 (1H, m, C*H*=CH_2), 5.20–5.10 (2H, m, CH=CH_2), 4.73 (1H, t, *J*=6.80 Hz, C*H*OH), 2.58–2.45 (2H, m, CH_2), 2.21 (1H, s, CHO*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 164.6, 139.6, 134.1, 127.5, 118.6, 115.4, 72.6, 43.9. IR (neat): 3377, 3085, 2979, 2932, 1638, 1600, 1507, 1427, 1216, 1162, 1049, 1000, 844 cm^{-1}. Anal. Calcd for $C_{10}H_{11}FO$: C, 72.27; H, 6.67; O, 9.63. Found: C, 72.20; H, 6.62; O, 9.62.

4.1.5. (*R*)-1-(4-Methylsulfanyl-phenyl)-but-3-en-1-ol (3e). Yield 35 mg (46%) (pale yellow oil). Determination of the enantiomeric excess by chiral GC analysis (135°C isoterm, T_r: 44.8 min (*R*), 52.1 min (*S*)): ee=78%. $[\alpha]_D^{25}$=+25.5 (*c* 1.1, $CHCl_3$). MS (EI, 70 eV): *m/z*51, 77, 95, 127, 145, 156, 175. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.35–7.21 (4H, m, Ar*H*), 5.85–5.71 (1H, m, C*H*=CH_2), 5.19–5.10 (2H, m, CH=CH_2), 4.70 (1H, dd, J_1=3.40 Hz, J_2=8.10 Hz, C*H*OH), 2.56–2.44 (2H, m, CH_2), 2.47 (3H, s, S*Me*) 2.20 (1H, s, CHO*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 140.7, 137.3, 134.2, 126.5, 126.3, 118.2, 72.8, 43.5, 15.8. IR (neat): 3383, 3071, 2985, 2913, 1640, 1620, 1427, 1328, 1169, 1123, 1070, 924 cm^{-1}. Anal. Calcd for $C_{11}H_{14}OS$: C, 68.00; H, 7.26; O, 8.23. Found: C, 67.91; H, 7.20; O, 8.23.

4.1.6. (*R*)-1-Cyclohexyl-but-3-en-1-ol (3f).[20] Yield 32 mg (42%) (pale yellow oil). Determination of the enantiomeric excess by chiral GC analysis (95°C isoterm, T_r: 52.9 min (*R*), 54.4 min (*S*): ee=89%. $[\alpha]_D^{25}$=−2.9 (*c* 0.7, $CHCl_3$). MS (EI, 70 eV): *m/z* 51, 65, 91, 117, 135. IR (neat): 3413, 3075, 2935, 2854, 1707, 1641, 1446 cm^{-1}. Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76; O,10.37. Found: C, 77.92; H, 11.69; O, 10.39.

4.1.7. (*S*)-1-Phenyl-hex-5-en-3-ol (3g).[20] Yield 40 mg (45%) (pale yellow oil). Determination of the enantiomeric excess by chiral HPLC (flow rate 0.5 mL/min, 5% *i*-PrOH, 95% hexane, T_r: 16.6 min (*R*), 25.0 min (*S*)): ee=77%. $[\alpha]_D^{25}$=−14.8 (*c* 0.7, $CHCl_3$). MS (EI, 70 eV): *m/z* 51, 65, 91, 117, 135.. Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15; O, 9.08. Found: C, 81.87; H, 9.09; O, 9.04.

4.2. Typical procedure for asymmetric crotylation reaction of aldehydes using [Salen(Cr)] as catalyst

$CrCl_3$ (8 mg, 0.05 mmol) and Mn (83 mg, 1.5 mmol) were added to anhydrous CH_3CN (2 mL) and the mixture was kept for about 5–8 min, then the reaction mixture was stirred until a green–white precipitate was observed. The ligand **1** (55 mg, 0.1 mmol) was added followed by dried triethylamine (14 μL, 0.1 mmol). A formation of a brown colour immediately occurred in the reaction mixture, in which a yellow solid was also observed. The heterogeneous mixture was stirred at room temperature for 1 h and then treated with crotyl bromide (0.75 mmol). Finally, after 1 h aldehyde (**2a–d**,**h–k**, 0.5 mmol) and Me_3SiCl (95 μL, 0.75 mmol) were added and the mixture was stirred until the complete consumption of the aldehyde (16–24 h, checked by GC). After quenching with a saturated solution of $NaHCO_3$ (3 mL), the reaction mixture was filtered on a celite© bed, and the CH_3CN was evaporated under reduced pressure. The residue was extracted with Et_2O (3×2 mL) and the organic phases were collected and evaporated under reduced pressure. The oil obtained was dissolved in THF (2 mL) and treated with 0.5 mL of HCl 1N. The mixture was stirred to complete desilylation (checked by TLC). After evaporation of THF, the residue was extracted with Et_2O. The organic phases were collected, dried over Na_2SO_4 and concentrated in vacuo to give a brown residue purified by flash chromatography (silica gel, Cyclohexane: Et_2O 70:30–80:20).

4.2.1. 2-Methyl-1-phenyl-but-3-en-1-ol (4a). Yield 45 mg (56%) (pale yellow oil). Separation of the diastereoisomers (trimethylsilyl ether derivatives) by GC analysis, T_r: 11.71 (*anti*) and 11.75 (*syn*) min provided the diastereomeric ratio *syn*:*anti* 83:17. Determination of the enantiomeric excesses by chiral GC analysis on the methyl ether derivatives: *syn*(1*R*,2*S*) ee=89%, *anti*(1*S*,2*S*) ee=36%. MS (EI, 70 eV): *m*/*z* 51, 77, 91, 105, 107, 112, 115. ^{1}H NMR (300 MHz, $CDCl_3$) (*syn* isomer): δ 7.45–7.20 (5H, m, Ar*H*), 5.83–5.71 (1H, ddd, J_1=7.80 Hz, J_2=10.35 Hz, J_3=19.05 Hz, C*H*=CH_2), 5.09–5.07 (1H, m, CH=CH_2), 5.05–5.03 (1H, m, CH=CH_2), 4.62 (1H, dd, J_1=5.10 Hz, J_2=3.30 Hz, C*H*OH), 2.66–2.55 (1H, m, C*H*Me), 1.91 (1H, d, *J*=3.60 Hz, CHO*H*), 1.03 (3H, d, *J*=6.84 Hz, CH*Me*); (*anti* isomer): δ 5.24–5.18 (2H, m, CH=CH_2), 4.37 (1H, dd, J_1=8.10 Hz, J_2=2.70 Hz, C*H*OH), 0.88 (3H, d, *J*=6.76 Hz, CH*Me*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 140.3, 128.0, 127.3, 126.5, 116.8, 115.5, 76.3, 44.6, 14.0; (*anti* isomer): δ 140.6, 128.2, 127.6, 126.8, 77.8. Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70; O, 9.86. Found: C, 81.32; H, 8.62; O, 10.06.

4.2.2. 2-Methyl-1-(4-methyl-phenyl)-but-3-en-1-ol (4b). Yield 42 mg (48%) (pale yellow oil). Separation of the diastereoisomers (trimethylsilyl ether derivatives) by GC analysis, T_r: 12.47 (*anti*) and 12.51 (*syn*) min provided the diastereomeric ratio *syn*:*anti* 74:26. Determination of the enantiomeric excesses by chiral GC analysis on the methyl ether derivatives: *syn*(1*R*,2*S*) ee=85%, *anti*(1*S*,2*S*) ee=26%. MS (EI, 70 eV): *m*/*z* 51, 65, 77, 91, 93, 121. ^{1}H NMR (300 MHz, $CDCl_3$) (*syn* isomer): δ 7.29–7.18 (4H, m, Ar*H*), 5.84–5.72 (1H, m, C*H*=CH_2), 5.10–5.08 (1H, m, CH=CH_2), 5.03–5.00 (1H, s, CH=CH_2), 4.58 (1H, d, *J*=5.86 Hz, C*H*OH), 2.61–2.57 (1H, m, C*H*Me), 2.36 (3H, s, *Me*Ar), 1.92 (1H, d, *J*=3.66 Hz, CHO*H*), 1.04 (3H, d, *J*=6.60 Hz, CH*Me*); (*anti* isomer): 4.34 (1H, d, *J*=7.50 Hz, C*H*OH), 2.50 (1H, q, *J*=7.50 Hz, C*H*Me), 0.87 (3H, d, *J*=6.74 Hz, CH*Me*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.8, 140.4, 128.9, 126.4, 115.3, 77.2, 44.5, 21.1, 14.2; (*anti* isomer): δ 128.8, 126.7, 116.6, 46.2, 16.5. Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15; O, 9.08. Found: C, 81.68; H, 9.08; O, 9.24.

4.2.3. 2-Methyl-1-(4-phenyl-phenyl)-but-3-en-1-ol (4c). Yield 56 mg (47%). Separation of the stereoisomers by chiral HPLC (Daicel Chiralcel™ OD column, flow rate 0.5 mL/min, 2% *i*-PrOH, 98% hexane, T_r: 22.8 (1*R*,2*R*), 23.6 (1*S*,2*R*), 24.8 (1*S*,2*S*) and 26.4 (1*R*,2*S*) min) provided the diastereomeric ratio *syn*:*anti* 71:29 and the enantiomeric ratios: *syn*(1*R*,2*S*) ee=84%, *anti*(1*S*,2*S*) ee=16%. ^{1}H NMR (300 MHz, $CDCl_3$) (*syn* isomer): δ 7.61–7.55 (4H, m, Ar*H*), 7.42–7.31 (5H, m, Ar*H*), 5.82 (1H, m, C*H*=CH_2), 5.13 (1H, m, CH=CH_2), 5.09 (1H, s, CH=CH_2), 4.69 (1H, br, C*H*OH), 2.62 (1H, m, C*H*Me), 1.07 (3H, d, *J*=6.90 Hz, CH*Me*); (*anti* isomer): δ 4.20 (1H, d, *J*=8.10 Hz, C*H*OH), 0.93 (3H, d, *J*=6.90 Hz, CH*Me*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 140.8, 140.2, 130.8, 129.0, 128.7, 127.6, 127.0, 126.9, 126.7, 115.6, 77.0, 44.6, 14.0; (*anti* isomer): δ 141.6, 140.6, 116.8, 46.2, 16.5. Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61; O, 6.71. Found: C, 85.52; H, 7.54; O, 6.94.

4.2.4. 1-(4-Fluoro-phenyl)-2-methyl-but-3-en-1-ol (4d). Yield 48 mg (53%) (pale yellow oil). Separation of the diastereoisomers (trimethylsilyl ether derivatives) by GC analysis, T_r: 11.45 (*anti*) and 11.48 (*syn*) min provided the diastereomeric ratio *syn*:*anti* 74:26. Determination of the enantiomeric excesses by chiral GC analysis on the methyl ether derivatives: *syn*(1*R*,2*S*) ee=90%, *anti*(1*S*,2*S*) ee=27%. MS (EI, 70 eV): *m*/*z* 51, 55, 75, 77, 97, 123, 125, 133, 146. ^{1}H NMR (300 MHz, $CDCl_3$) (*syn* isomer): δ 7.30–7.27 (2H, m, Ar*H*), 7.06–7.03 (2H, m, Ar*H*), 5.75–5.58 (1H, m, C*H*=CH_2), 5.15–5.01 (2H, m, CH=CH_2), 4.62 (1H, d, *J*=5.70 Hz, C*H*OH), 2.61–5.49 (1H, m, C*H*Me), 1.01 (3H, d, *J*=6.60 Hz, CH*Me*); (*anti* isomer): δ 4.35 (1H, d, *J*=7.80 Hz, C*H*OH), 0.86 (3H, d, *J*=6.90, CH*Me*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.4 (d, J_{C-F}=63.3 Hz), 139.9, 138.0, 127.9, 115.7, 114.7, 77.1, 44.7, 14.0; (*anti* isomer): δ 163.6 (d, J_{C-F}=63.3 Hz), 140.3, 138.1, 128.3, 117.1, 115.0, 46.5, 16.5. Anal. Calcd for $C_{11}H_{13}FO$: C, 73.31; H, 7.27; O, 8.88. Found: C, 73.41; H, 7.23; O, 8.90.

4.2.5. 1-(4-Chloro-phenyl)-2-methyl-1-but-3-en-1-ol (4h). Yield 45 mg (46%) (pale yellow oil). Separation of the diastereoisomers (trimethylsilyl ether derivatives) by GC analysis, T_r: 13.65 (*anti*) and 13.68 (*syn*) min provided the diastereomeric ratio *syn*:*anti* 61:39. Determination of the enantiomeric excesses by chiral GC analysis on the methyl ether derivatives: *syn*(1*R*,2*S*) ee=82%, *anti*(1*S*,2*S*) ee=24%. MS (EI, 70 eV): *m*/*z* 51, 77, 112, 114, 141, 143. ^{1}H NMR (200 MHz, $CDCl_3$) (*syn* isomer): δ 7.50–7.18 (4H, m, Ar*H*), 5.84–5.69 (1H, m, C*H*=CH_2), 5.23–5.18 (2H, m, CH=CH_2), 4.60 (1H, d, *J*=5.14 Hz, C*H*OH), 2.62–2.51 (1H, pq, *J*=6.60 Hz, C*H*Me), 1.71 (1H, br, CHO*H*), 1.00 (3H, d, *J*=6.88 Hz, CH*Me*); (*anti* isomer): δ 4.35 (1H, d, *J*=7.68 Hz, C*H*OH), 2.44 (1H, pq, *J*=7.00 Hz, C*H*Me), 0.86

(3H, d, J=6.90 Hz, CH*Me*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.0, 139.8, 133.1, 127.8, 127.2, 115.8, 76.5, 44.6, 13.9; (*anti* isomer): δ 140.8, 140.1, 128.3, 128.1, 117.1, 77.0, 46.2, 16.3. Anal. Calcd for $C_{11}H_{13}ClO$: C, 67.18; H, 6.66; O, 8.14. Found: C, 67.28; H, 6.62; O, 8.16.

4.2.6. 1-(4-Bromo-phenyl)-2-methyl-but-3-en-1-ol (4i). Yield 52 mg (43%) (pale yellow oil). Separation of the diastereoisomers (trimethylsilyl ether derivatives) by GC analysis, T_r: 14.68 (*anti*) and 14.75 (*syn*) min provided the diastereomeric ratio *syn*:*anti* 72:28. Determination of the enantiomeric excesses by chiral GC analysis on the methyl ether derivatives: *syn*(1*R*,2*S*) ee=82%, *anti*(1*S*,2*S*) ee=28%. MS (EI, 70 eV): *m*/*z* 51, 77, 79, 157, 159, 185, 187, 240. ^{1}H NMR (200 MHz, $CDCl_3$) (*syn* isomer): δ 7.50–7.46 (2H, m, Ar*H*), 7.27–7.18 (2H, m, Ar*H*), 5.85–5.62 (1H, m, C*H*=CH_2), 5.29–5.05 (2H, m, CH=CH_2), 4.60 (1H, d, J=5.42 Hz, C*H*OH), 2.65–2.49 (1H, m, C*H*Me), 1.92 (1H, d, J=2.44 Hz, CHO*H*), 1.00 (3H, d, J=6.76 Hz, CH*Me*); (*anti* isomer): 4.34 (1H, d, J=7.70 Hz, C*H*OH), 0.87 (3H, d, J=6.80 Hz, CH*Me*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 139.8, 131.1, 128.5, 128.2, 121.1, 116.0, 77.4, 44.6, 13.8; (*anti* isomer): δ 140.1, 131.3, 121.5, 117.3, 46.3, 16.4. Anal. Calcd for $C_{11}H_{13}BrO$: C, 54.79; H, 5.43; O, 6.64. Found: C, 54.68; H, 5.39; O, 6.63.

4.2.7. 1-(3-Bromo-phenyl)-2-methyl-but-3-en-1-ol (4j). Yield 59 mg (49%) (pale yellow oil). Separation of the diastereoisomers (trimethylsilyl ether derivatives) by GC analysis, T_r: 14.32 (*anti*) and 14.35 (*syn*) min provided the diastereomeric ratio *syn*:*anti* 66:34. Determination of the enantiomeric excesses by ^{1}H NMR analysis on the (*S*)-(+)-*O*-acetyl-mandelic ester: *syn*(1*R*,2*S*) ee=70%, *anti*(1*S*,2*S*) ee=43%. MS (EI, 70 eV): *m*/*z* 51, 77, 79, 157, 159, 185, 187, 240, 242. ^{1}H NMR (200 MHz, $CDCl_3$) (*syn* isomer): δ 7.61–7.52 (1H, m, Ar*H*), 7.48–7.40 (1H, m, Ar*H*), 7.26–7.21 (2H, m, Ar*H*), 5.86–5.69 (1H, m, C*H*=CH_2), 5.26–5.04 (2H, m, CH=CH_2), 4.61 (1H, t, J=4.40 Hz, C*H*OH), 2.64–2.51 (1H, m, C*H*Me), 1.98 (1H, d, J=3.66 Hz, CHO*H*), 1.00 (3H, d, J=6.64 Hz, CH*Me*); (*anti* isomer): δ 4.32 (1H, dd, J_1=7.70 Hz, J_2=2.58 Hz, C*H*OH), 0.89 (3H, d, J=6.68 Hz, CH*Me*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 139.8, 130.4, 129.7, 125.5, 125.1, 122.4, 116.0, 76.9, 44.5, 16.4, 13.6; (*anti* isomer): δ 140.0, 130.4, 129.8, 126.2, 124.4, 122.5, 117.3, 46.3, 18.0, 16.4. Anal. Calcd for $C_{11}H_{13}BrO$: C, 54.79; H, 5.43; O, 6.64. Found: C, 54.65; H, 5.38; O, 6.62.

4.2.8. 1-(4-Methoxy-phenyl)-2-methyl-but-3-en-1-ol (4k). Yield 50 mg (52%) (pale yellow oil). Separation of the diastereoisomers (trimethylsilyl ether derivatives) by GC analysis, T_r: 14.25 (*anti*) and 14.28 (*syn*) min provided the diastereomeric ratio *syn*:*anti* 60:40. Determination of the enantiomeric excesses by chiral GC analysis on the methyl ether derivatives: *syn*(1*R*,2*S*) ee=58%, *anti*(1*S*,2*S*) ee=15%. MS (EI, 70 eV): *m*/*z* 55, 66, 77, 91, 109, 137, 159. ^{1}H NMR (200 MHz, $CDCl_3$) (*syn* isomer): δ 7.29–7.22 (2H, m, Ar*H*), 6.91–6.87 (2H, m, Ar*H*), 5.79 (1H, m, C*H*=CH_2), 5.28–5.15 (2H, m, CH=CH_2), 4.55 (1H, dd, J_1=5.66 Hz, J_2= 3.02 Hz, C*H*OH), 3.82 (3H, s, *Me*O), 2.61–2.47 (1H, m, C*H*Me), 1.90 (1H, d, J=3.54 Hz, CHO*H*), 1.03 (3H, d, J= 6.82 Hz, CH*Me*); (*anti* isomer): δ 4.31 (1H, dd, J_1=8.06 Hz, J_2=2.04 Hz, C*H*OH), 2.12 (1H, d, J=2.48 Hz, CHO*H*), 0.85 (3H, d, J=6.80 Hz, CH*Me*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 140.3, 127.9, 127.8, 115.4, 113.5, 73.1, 55.3, 44.7, 14.3; (*anti* isomer): δ 140.9, 127.0, 126.9, 116.7, 113.6, 46.2, 16.6. Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39; O, 16.64. Found: C, 74.97; H, 8.33; O, 16.70.

Influence of the catalyst concentration on the diastereoselectivity of the addition of crotyl bromide to benzaldehyde (all the reactions were carried out at room temperature. Reaction time: 96 h)

$[Cr]_{total}$ (mM)	*syn*:*anti*	De (%)	Ee_{syn} (%)	Ee_{anti} (%)
5.0	55:45	10	76	18
6.3	68:32	26	78	30
8.3	58:42	16	79	23
10.0	64:36	28	82	22
11.1	72:28	44	84	23
12.5	79:21	58	79	24
14.3	77:23	54	82	23
16.7	80:20	60	80	24
20.0	77:23	54	82	28
25.0	83:17	67	89	36

4.2.9. NLE studies. All the reactions were carried out at 25±1°C and the enantioselectivity was monitored after 24 h (conversion 35–55%).

(−)-NLE of the crotylation reaction (Ee_{syn} given in this table are the average of three runs)

Ee (%) (*R*,*R*)-Salen	*syn*:*anti*	Ee (%) *syn* isomer	Ee (%) *anti* isomer
0	79:21	0	0
10	83:17	2	1
20	81:19	3	22
40	86:14	20	2
50	79:21	22	4
60	83:17	27	7
80	80:20	46	16
85	88:12	53	16
90	80:20	60	21
100	83:17	89	36

(−)-NLE of the allylation reaction (Ee_{syn} given in this table are the average of two runs)

Ee (%) (*R*,*R*)-Salen	Ee (%) product
0	0
20	5
40	15
60	35
80	80
100	84

4.2.10. Kinetics studies. A typical GC kinetics experiment was performed as reported for the crotylation reaction. Anhydrous butyl ether (25 μL, 0.25 mmol) was added as internal standard. All reactions were carried out at

25±1°C. A 30 μL aliquot was drawn by syringe every 60 min. Diluted with Et_2O, quenched with $NaHCO_3$ and directly analysed by GC.

Detemination of the order dependence on total chromium

$[Cr_{total}]$ (%)	log[Cr]	log[v]
5	−1.60	−1.57
10	−1.30	−1.46
15	−1.12	−1.40
20	−1.00	−1.23
25	−0.90	−1.14

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6. Me_3SiCl did not affect the stereochemistry of the addition of crotyl bromide to the benzaldehyde, in fact a stoichiometric run gave *syn*:*anti*=86:14 and ee_{syn}=83%.
7. A tentative explanation of such a behaviour is as follows. Probably when the manganese salts are not present during the complexation step, the [Cr(Salen)] complexes are dimeric in solution and the oxidative addition of allyl halides is more difficult.
8. The *anti*/*syn* ratio does not depend on the *E*/*Z* configuration of the starting crotyl halide. In fact, using 3-bromocyclohexene as the precursor of the organo-chromium reagent in the reaction with the benzaldehyde, the *syn* homoallylic alcohol was obtained as the major diastereoisomer: see Ref. 4b.
9. The excess of **1** can be added during the reaction course or just before the complexation step (see Experimental). In all cases, the yields and the enantioselectivities observed with several aldehydes were comparable.
10. The stereoselection appeared function of the aldehydes employed, in fact, with aliphatic substrates the *anti* isomer was the major product. At the present time we have no explanation for such a different behaviour.
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15. The triple-shaped curves detected for the crotylation reaction (Fig. 4a) has been fitted with the simplified mathematical equation of the $(ML)_4$ model (parameters: EE_0^*=64%; g=10; f=34; R^2=0.9953); for more details concerning such a mathematical analysis see: (a) Pitchen P.; Duñach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188–8193. (b) Guillaneux, D.; Zhao, S.-H.; Samuel, O.; Rainford, D.; Kagan, H. B. *J. Am. Chem. Soc.* **1994**, *116*, 9430–9439.
16. In fact, considering Eq. (1): $K_{eq}=[L_4{}^*Cr_4X_4]/[L_2{}^*Cr_2X_2]_2$. Moreover, the total chromium concentration is given by: $[Cr_{total}]=4[L_4{}^*Cr_4X_4]+2[L_2{}^*Cr_2X_2]$. Elaborating and solving

for the $[L_2^*Cr_2X_2]$ in terms of $[Cr_{total}]$ the following equation is obtained $[L_2^*Cr_2X_2] = \frac{1}{4K_{eq}}(\sqrt{1 + 4K_{eq}[Cr_{total}]} - 1)$.[14]

17. Concerning role played by the manganese salts in the reaction course, it is noteworthy to add these points: (1) The [Mn-(Salen)(III)] complexes are not able to promote the allylation reaction. (2) The enantiomeric and diastereoisomeric excess of the homoallylic alcohol do not change during the reaction course and they are not affected by the increasing concentration of the manganese chloride. (3) [Cr(Salen)] complex appear to be stable in the presence of MnX_2. For the stability of the Salen complexes in the presence of metal halides see: Solari, E.; Corazza, F.; Floriani, C.; Chiesi-Villa, A.; Guastini, C. *J. Chem. Soc., Dalton Trans.* **1990**, 1345–1355.
18. For recent reported crystal structures see: (a) Gleizes, A.; Julve, M.; Kuzmina, N.; Alikhanyan, A.; Lloret, F.; Malkerova, I.; Sanz, J. L.; Senocq, F. *Inorg. Chem.* **1998**, *37*, 1169–1174. (b) Carbonaro, L.; Isola, M.; La Pegna, P.; Senatore, L.; Marchetti, F. *Inorg. Chem.* **1999**, *38*, 5519–5525, and references cited therein. (c) Sasaki, M.; Manseki, K.; Horiuchi, H.; Kumagai, M.; Sakamoto, M.; Sakiyama, H.; Nishida, Y.; Sakai, M.; Sadaoka, Y.; Ohba, M.; Okawa, H. *J. Chem. Soc., Dalton Trans.* **2000**, 259–263. (d) Gallo, E.; Solari, E.; Re, N.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *J. Am. Chem. Soc.* **1997**, *119*, 5144–5154; and references cited therein.
19. In fact, the appearance of free Salen ligand during the reaction course was observed.
20. Yamada, K.; Tozawa, T.; Nishida, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2301–2308.