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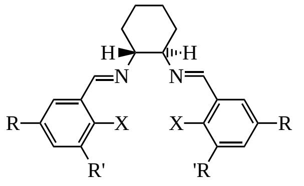
[10] Crystal structure analysis: The data were collected at 293(2) K on a Bruker SMART-CCD diffractometer (graphite-monochromated $\mathrm{Mo_{K\alpha}}$-radiation: $\lambda = 0.71073$ Å). The structures were solved by direct methods (SHELXTL Version 5.10) and refined by full-matrix least-squares on F^2. All non-hydrogen atoms were refined anisotropically. Crystal data for $C_{20}H_{18}N_4CoP_2V_2O_{12}$ (**1**): Crystal dimensions $0.170 \times 0.070 \times 0.070$ mm, monoclinic, space group *C*2/c (no. 15), $a = 25.1399(15)$, $b = 8.1532(5)$, $c = 15.6510(10)$ Å, $\beta = 127.0030(10)^\circ$, $V = 2561.9(3)$ Å^3. $Z = 4$, $\rho_{\mathrm{calcd}} = 1.890\ \mathrm{g\,cm^{-3}}$, $\mu(\mathrm{Mo_{K\alpha}}) = 1.552\ \mathrm{mm^{-1}}$. Of the 6086 reflections measured ($2.60 \leq \theta \leq 23.24^\circ$), 1832 symmetry-independent reflections were used to solve the structure. Based on all these data and 223 refined parameters, $R1 = 0.0349$ (all data), $wR2 = 0.0824$, and goodness-of-fit on F^2 is 1.039. Crystal data for $C_{20}H_{18}N_4NiP_2V_2O_{12}$ (**2**): Crystal dimensions $0.160 \times 0.080 \times 0.050$ mm, monoclinic, space group *C*2/c (no. 15), $a = 25.025(3)$, $b = 8.1660(12)$, $c = 15.610(2)$ Å, $\beta = 127.477(3)^\circ$, $V = 2531.5(6)$ Å^3. $Z = 4$, $\rho_{\mathrm{calcd}} = 1.913\ \mathrm{g\,cm^{-3}}$, $\mu(\mathrm{Mo_{K\alpha}}) = 1.659\ \mathrm{mm^{-1}}$. Of the 6008 reflections measured ($2.05 \leq \theta \leq 23.27^\circ$), 1822 symmetry-independent reflections were used to solve the structure. Based on all these data and 223 refined parameters, $R1 = 0.0385$ (all data), $wR2 = 0.0876$, and goodness-of-fit on F^2 is 1.089. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-137922 (**1**) and CCDC-137923 (**2**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

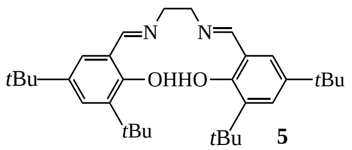
Salen as a Chiral Activator: *anti* versus *syn* Switchable Diastereoselection in the Enantioselective Addition of Crotyl Bromide to Aromatic Aldehydes**

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

Diastereoselective addition of organometallic reagents is widely used in preparative organic synthesis.[1] The stereochemical outcome of the reaction derives from the ability of the metal to behave as a Lewis acid and therefore to control the addition "via" a cyclic or acyclic transition state. Stereogenic allyl chromium reagents normally add to carbonyl compounds to furnish the corresponding homoallylic alcohols with a high level of *anti* diastereoselection "via" a cyclic Zimmermann–Traxler-type transition state.[2] Moreover, when the above-mentioned nucleophilic addition is performed with a catalytic redox cycle ([Cr] 7 mol%, Mn, Me_3SiCl), the same level of diastereoselection is observed.[3] Herein we report that by changing the amount of the salen ligand (**1**)[4] employed (salen = (*R*,*R*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine) it is possible to switch the simple diastereoselection from *anti* to *syn* in the catalytic addition of chiral organochromium reagents to aromatic aldehydes. Recently, we described the first enantioselective version of the Nozaki–Hiyama reaction performed in the presence of a catalytic amount of a [Cr(salen)] complex.[5]



1: X = OH, R = *t*Bu, R' = *t*Bu;
2: X = OMe, R = *t*Bu, R' = *t*Bu;
3: X = OH, R = *t*Bu, R' = H;
4: X = OH, R = *t*Bu, R' = Br;



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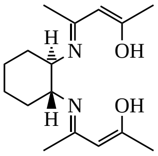

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Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

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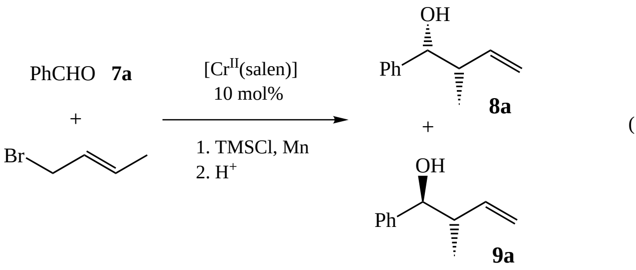


(1)

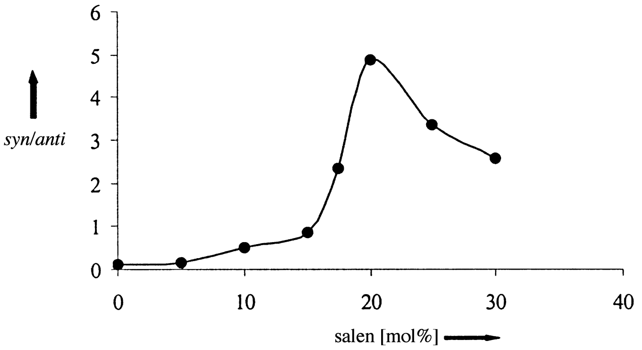


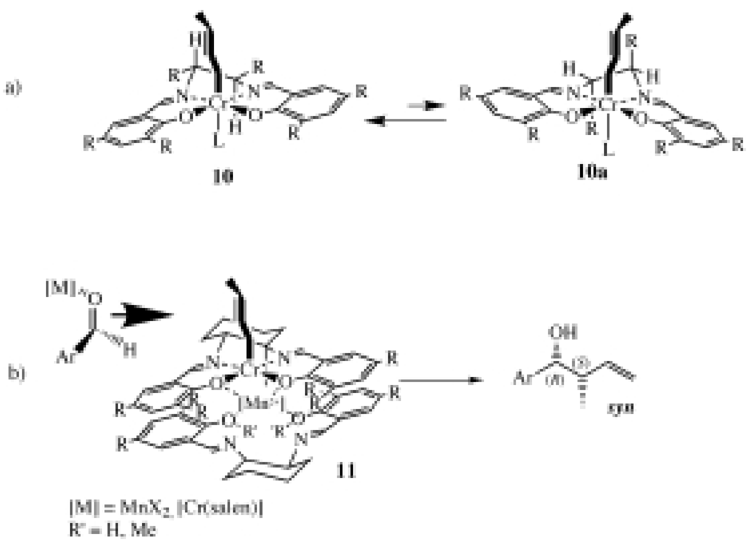
Figure 1. Influence of the amount of salen on the diastereoselectivity of the chromium-catalyzed addition of crotyl bromide to PhCHO.

Table 1. Different additives used for modifying the simple diastreoselection in the addition of crotyl bromide to the PhCHO.[a]

Entry	Additive (10 mol%)	Yield [%][b]	**8a**:**9a**[c]	*ee* of **8a** [%][d]	*ee* of **9a** [%][d]
1	**1**	56	83:17	89(1*R*,2*S*)	36(1*S*,2*S*)
2	**2**	40	76:24	88(1*R*,2*S*)	30(1*S*,2*S*)
3	**3**	41	81:19	77(1*R*,2*S*)	22(1*S*,2*S*)
4	**4**	29	56:44	73(1*R*,2*S*)	12(1*S*,2*S*)
5	**5**	20	31:69	48(1*R*,2*S*)	3(1*S*,2*S*)
6	**6**	46	49:51	80(1*R*,2*S*)	11(1*S*,2*S*)
7	DMF	30	59:41	82(1*R*,2*S*)	10(1*S*,2*S*)
8	DMPU	39	53:47	82(1*R*,2*S*)	10(1*S*,2*S*)
9	Ph_3PO	35	62:38	68(1*R*,2*S*)	20(1*S*,2*S*)
10	Ph_3P[e]	39	52:48	90(1*R*,2*S*)	10(1*S*,2*S*)
11	4-PPNO	17	38:62	80(1*R*,2*S*)	0

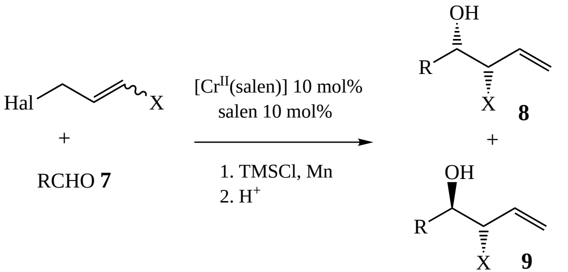
[a] All the reactions were carried out in anhydrous CH_3CN at room temperature. [b] Yield of isolated product after desilylation (HCl/THF) and flash chromatography. The by-product derived from the pinacol coupling was observed. [c] The ratio between **8a** and **9a** was determined by GC analysis of the crude reaction mixture and ^1H NMR analysis after chromatographic purification. [d] Determined by chiral GC analysis of the corresponding *O*-methyl ether. See the Supporting Information for details. The absolute configurations of **8a** and **9a** were assigned by ^1H NMR analysis of the (*R*)-Mosher's esters derivatives (300 MHz, C_6D_6, δ OMe: (1*R*,2*S*) = 3.32, (1*S*,2*R*) = 3.39, (1*R*,2*R*) = 3.22, (1*S*,2*S*) = 3.43); see reference [9]. [e] The reaction was performed employing anhydrous $CrCl_2$ as the chromium source.

Optimal reaction conditions require the preparation of the [Cr^{II}(salen)] catalyst in CH_3CN and the successive oxidative addition of an organohalide. The "in situ" generated organometallic complex was employed in 10 mol% in the presence of Mn and TMSCl to catalyze the addition of allyl chloride to the aldehydes. No reaction was observed when the same protocol was performed with benzaldehyde and (*E*)-crotyl chloride. However, with the more reactive crotyl bromide,[6] we isolated the desired homoallylic alcohol in a satisfactory yield (50%), but with a low degree of distereoselectivity [Eq. 1; *anti*:*syn* = 67:33, **9a** = 5% *ee*, **8a** = 78% *ee*]. After a considerable number of trials, we discovered that the amount of salen used was crucial. In fact, good levels of diastereoselectivity and enantioselectivity were obtained with the addition of crotyl bromide to the benzaldehyde by using an excess of the chiral ligand. The simple diastereoselection strictly depends on the amount of salen ligand (Figure 1). The highest diastereoselection (*syn*:*anti* = 83:17) was recorded when a 2:1 salen:chromium salt ratio was utilized (see Supporting Information). Moreover, under these conditions we isolated the *syn* product with excellent enantiomeric excess ($ee_{syn} = 89\%$, $ee_{anti} = 36\%$, Table 1, entry 1). We suggest that the *syn* diastereoselectivity observed can be explained by the formation of an acyclic transition state in which the aldehyde is coordinated by the manganese salts or by a [Cr(salen)] complex. The latter possibility is in accordance with studies by Jacobsen et al., in which it was proven that both [Cr(salen)] and [Co(salen)] catalysts promote asymmetric processes by cooperative mechanisms.[7] Catalytic amounts of coordinating agents,[8] such as DMF, 1,3-dimethylhexahydro-2-pyrimidone (DMPU), 4-(3-phenylpropyl)pyridine *N*-oxide (4-PPNO), phosphorous ligands (Ph_3PO, Ph_3P), and the Schiff bases **4**–**6** structurally correlated to salen, did not afford the same results either in terms of yield or stereoselection (Table 1, entries 4–11).[9] It is important to note that while the simple diastereoselection appears to be strongly correlated to the nature of the additive used, the facial diastereoselection is less affected. This observation is clear evidence of the presence of two competitive mechanisms for the allylation reaction. The singleness of the salen points to the chiral ligand playing a sort of chiral supramolecular recognition.[10] This effect does not appear to be determined by hydrogen-bonding interactions, because the (*R*,*R*)-*N*,*N'*-bis(3,5-di-*tert*-butyl-methoxy-salicylidene)-1,2-cyclohexanediamine (**2**) gives a result similar to **1** (Table 1, entry 2). Probably, a specific noncovalent binding of the chiral organochromium species with another molecule of salen affords this peculiar behavior. At the present time we can only speculate about the probable structure of such an adduct. However, we propose that a previously reported "head to tail" alignment[7a] between the [Cr(III)crotyl(salen)] species and a different molecule of the ligand coordinated with Mn salts could be involved (Scheme 1b). Such a stacking interaction could shift the conformational equilibrium[11] between the speculated nonplanar diastereomeric conformers **10** and **10a** (Scheme 1a). We further suggest that salen preferentially binds to conformer **10** and that the aggregate **11** is responsible for the increase in the stereoselectivity of the process.[12] Moreover, it is noteworthy that this protocol represents the first *syn*-diastereoselective catalytic addition of stereogenic organohalides to aldehydes with chiral organochromium reagents [Eq. (2)]. In fact, the optimized reaction conditions were successfully used with a range of variously substituted



Scheme 1. a) Equilibrium mixture of the stepped conformational crotyl(salen)-Cr(III) isomers. b) Plausible approach of an aldehyde to the chiral organochromium complex giving the observed diastereoisomer.

aromatic aldehydes.[13] All the results obtained using the $[Cr^{II}(salen)]$ complex (10 mol%) as the catalyst are summarized in Table 2. Excellent enantiomeric excess values for the *syn* isomers (62–90%) and a good level of diastereoselection (*syn*:*anti* 75:25) were recorded.



(2)

7b: R = p-MeC$_6$H$_4$; **7c**: R = p-FC$_6$H$_4$; **7d**: R = p-ClC$_6$H$_4$; **7e**: R = p-BrC$_6$H$_4$; **7f**: R = m-BrC$_6$H$_4$; **7g**: R = p-MeOC$_6$H$_4$; **7h**: R = p-PhC$_6$H$_4$;

In summary, we have shown that high enantio- and diastereoselectivities can be obtained with the [Cr(salen)]-catalyzed addition of stereogenic organohalides to aromatic aldehydes. What is amazing, is the key role played by the amount of chiral ligand in the stereochemical control of the process. In fact, by employing a 10 mol% excess of the Schiff base, complete inversion of the simple diastereoselection *anti* →*syn* was observed. Further studies will be directed at the exploitation of such supramolecolar devices in other [M(salen)]-promoted reactions.

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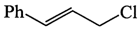
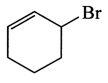
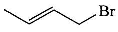
Table 2. Results of the diastereo- and enantioselective addition of organohalides to aromatic aldehydes using chiral [Cr(salen)] catalyst [Eq. (2)].[a]

RCHO	R′X	Yield [%][b]	Product (*syn*:*anti*)[c]	*ee* of *syn* [%][d]	*ee* of *anti* [%][d]
7a		72[e]	75:25[g]	86[g]	26[g]
7a		25[e,f]	75:25[g]	62[g]	25[g]
7b		48	74:26	85(1*R*,2*S*)	26(1*S*,2*S*)
7c	“”	53	74:26	90(1*R*,2*S*)	27(1*S*,2*S*)
7d	“”	46	61:39	82(1*R*,2*S*)	24(1*S*,2*S*)
7e	“”	43	72:28	82(1*R*,2*S*)	28(1*S*,2*S*)
7f	“”	49	66:34	70[h]	43[h]
7g	“”	52	60:40	58(1*R*,2*S*)	15(1*S*,2*S*)
7h	“”	47	71:29[e]	84(1*R*,2*S*)	16(1*S*,2*S*)

[a] Performing the reaction in the presence of $CrCl_3$ as the catalyst (10 mol%), we obtained the *anti* homoallylic alcohols as the major isomer; see Supporting Information. [b] Isolated yield after desilylation (HCl/THF) and flash chromatography. By-products derived from the pinacol coupling reaction were detected by GC analysis. [c] Determined by GC analysis of the crude reaction mixture and ^{1}H NMR analysis after chromatographic purification. [d] Determined by chiral GC analysis of the corresponding *O*-methyl ether. See the Supporting Information for details. The absolute configurations of **8** and **9** were assigned by analogy to the chiral GC analysis of the **8a**/**9a** mixture. [e] Isolated yield after desilylation (Bu_4NF/THF) and flash chromatography. [f] The low yield obtained was derived from the high instability of the chiral organochromium intermediate. In fact, a large amount of bicyclohexyl-2,2′-diene (coupling product) was detected from the MS-GC analysis. [g] Determined by chiral HPLC analysis (Chiralcel OD column). [h] Determined by ^{1}H NMR analysis of the (*S*)-(+)-*O*-acetyl-mandelic ester. See the Supporting Information for details.

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[6] Commercially available crotyl bromide (85% tech.) was used.

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[11] It is well accepted that oxo(salen)manganese(V) and azide(salen)-chromium(III) complexes exist in an equilibrium mixture of two enantio- or diastereomeric conformers: Y. N. Ito, T. Katsuki, *Bull. Chem. Soc. Jpn.* **1999**, *72*, 603–619, and references therein. On the basis of the similar stepped structures of the oxo(salen)chromium complexes reported, we assumed that an analogous conformational equilibrium could involve the crotyl(salen)chromium(III) adduct **10**, see: E. G. Samsel, K. Srinivasan, J. K. Kochi, *J. Am. Chem. Soc.* **1985**, *107*, 7606–7617; K. B. Hansen, J. L. Leighton, E. N. Jacobsen, *J. Am. Chem. Soc.* **1996**, *118*, 10924–10925.

[12] For studies concerning the influence of additives on the geometry and reactivity of [Mn(salen)] and [Cr(salen)] complexes, see: a) T. Hashihayata, T. Punniyamurthy, R. Irie, T. Katsuki, M. Akita, Y. Moro-oka, *Tetrahedron* **1999**, *55*, 14599–14610; b) K. M. Ryan, C. Bousquet, D. G. Gilheany, *Tetrahedron Lett.* **1999**, *40*, 3613–3616; c) A. M. Daly, C. T. Dalton, M. F. Renehan, D. G. Gilheany, *Tetrahedron Lett.* **1999**, *40*, 3617–3620.

[13] The amount of salen employed with enolizable aliphatic aldehydes does not significantly influence the diastereoselectivity of the reaction (salen 20 mol%, crotyl bromide): *n*-octylaldehyde *anti*:*syn* 71:29 (ee_{anti} = N.D., ee_{syn} = 85%), cyclohexylcarbaldehyde *anti*:*syn* 85:15 (ee_{anti} = 0%, ee_{syn} = 70%), hydrocinnamaldehyde *anti*:*syn* 79:21 (ee_{anti} = 63%, ee_{syn} = 87%).

A Designed β-Hairpin Containing a Natural Hydrophobic Cluster[**]

Juan F. Espinosa and Samuel H. Gellman[*]

β-Sheets are a very common substructure in folded proteins,[1] and intermolecular sheet-type interactions play a crucial role in protein–protein recognition[2] and in pathological protein aggregation.[3] Therefore, understanding the balance of noncovalent forces that controls β-sheet formation is a goal of fundamental importance. Recently it has become possible to probe the origins of antiparallel β-sheet stability with short, designed peptides that fold autonomously in aqueous solution.[4] These model systems complement the more traditional approach of examining β-sheets that are embedded within a particular tertiary fold;[5] short peptides allow one to explore small increments of β-sheet in the absence of a specific structural context. Here, we describe a peptide in which a cluster of hydrophobic sidechains from the protein GB1 has been grafted onto a designed sequence. Thermodynamic analysis of folding provides insight on the origins of β-sheet stability.

The "β-hairpin" architectural motif, comprised of two antiparallel strands and a short connecting loop, is essential for creation of short peptides that display antiparallel β-sheet folding in water.[4] β-Hairpins are common in proteins,[6] but natural β-hairpin sequences seldom fold in water when extracted from their native protein context.[4] An exception is a 16-residue segment of the protein GB1, **1**, which displays partial population of a native-like β-hairpin conformation.[7] Peptide **1** differs from other autonomously folding β-hairpins in the unusually large six-residue loop (Asp-Asp-Ala-Thr-Lys-Thr) that connects the two strand segments; other autonomously folding β-hairpins contain loops of two to four residues.[4, 8] Interstrand interactions within the folded conformation of **1** are limited to residues near the termini.[7] Clustering among the hydrophobic sidechains of Trp 3, Tyr 5, Phe 12, and Val 14 presumably provides a drive for β-hairpin folding, which overcomes the entropic cost of ordering the loop segment.

Gly-Ile-Trp-Thr-Tyr-Asp-Asp-Ala-Thr-Lys-Thr-Phe-Thr-Val-Thr-Glu

1

In order to elucidate the contribution of interstrand sidechain interactions to β-sheet stability, we incorporated the residues of the GB1 cluster into a 12-residue sequence, **2**,[9] that was expected to adopt a more highly defined β-hairpin conformation than does **1**. The arrangement of the Trp, Tyr, Phe, and Val residues in **2** allows native-like sidechain juxtapositions if the peptide folds to a β-hairpin conformation with a tight two-residue loop; the D-Pro–Gly segment strongly promotes this type of β-hairpin.[8e, 8g, 10] Our design hypothesis was that the mutually reinforcing effects of the D-Pro–Gly loop and the GB1 cluster in **2** would produce a β-hairpin conformation well-defined over most residues and, therefore, suitable for thermodynamic analysis. Diastereomer **3**, with D-Pro replaced by L-Pro, was expected to serve as a negative control, since L-Pro-Gly discourages formation of tight β-hairpin conformations.[8, 10]

Arg-Trp-Gln-Tyr-Val-Xxx-Gly-Lys-Phe-Thr-Val-Gln-NH_2

2, Xxx = D-Pro
3, Xxx = L-Pro

Peptide **2** displays numerous NOE interactions between residues that are not adjacent in sequence, and all of these nonadjacent effects are consistent with the β-hairpin conformation shown in Figure 1. The subset of interstrand NOE interactions involving backbone protons (NH and H_α; Figure 1 a, b) verifies antiparallel β-sheet formation at the backbone level. Sidechain–sidechain NOE data (Figure 1 c) reveal the anticipated clustering among the GB1 sidechains. No interactions between nonadjacent residues were observed for L-Pro diastereomer **3**, which demonstrates that changing the proline configuration constitutes an "on/off" switch for β-hairpin formation in aqueous solution. The solution structure of **2** was calculated with the program DYANA,[11] using 37 NOE measurements (including all effects between nonadjacent residues) as distance restraints. Among the 20 best structures, the root mean square deviation (RMSD) was 0.58 ± 0.16 Å for the backbone atoms and 1.25 ± 0.22 Å for all heavy atoms, over residues 2–11 (terminal residues 1 and 12 were highly disordered). These results demonstrate that the

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