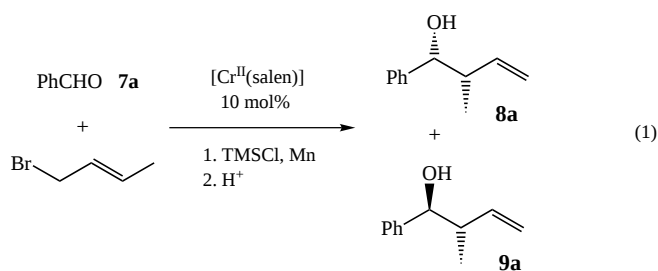


Optimal reaction conditions require the preparation of the $[\text{Cr}^{\text{II}}(\text{salen})]$ catalyst in CH_3CN and the successive oxidative addition of an organohalide. The “in situ” generated organometallic complex was employed in 10 mol % in the presence of Mn and TMSCl to catalyze the addition 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 diastereoselectivity [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

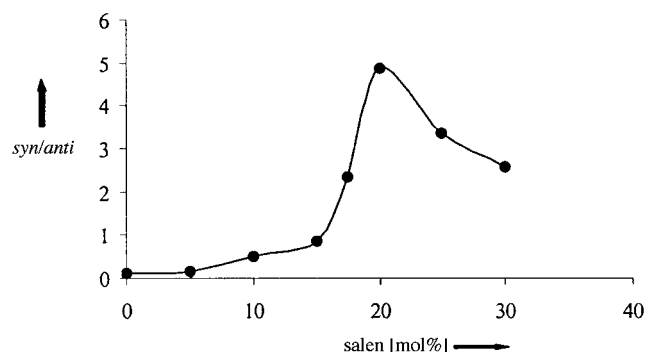


Figure 1. Influence of the amount of salen on the diastereoselectivity of the chromium-catalyzed addition of crotyl bromide to PhCHO.

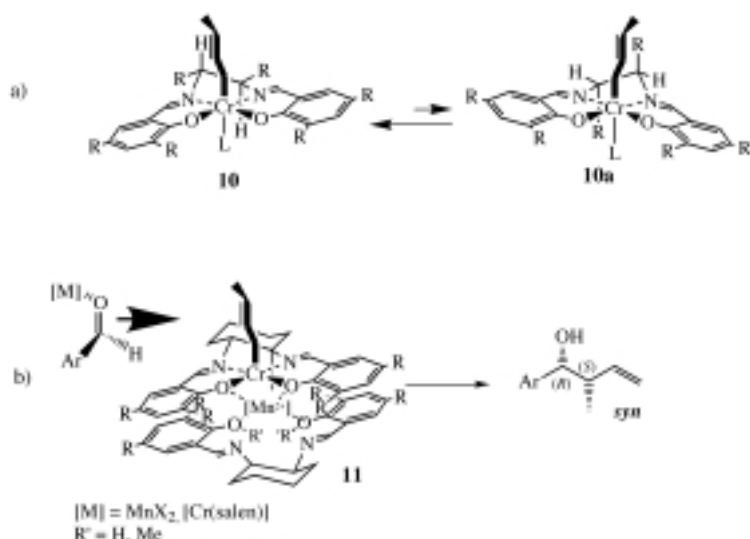
highest diastereoselection (*syn:anti* = 83:17) was recorded when a 2:1 salen:chromium salt ratio was utilized (see Supporting Information). Moreover, under these conditions we isolated the *syn* product with excellent enantiomeric excess (ee_{syn} = 89 %, ee_{anti} = 36 %, Table 1, entry 1). We suggest 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 $[\text{Cr}(\text{salen})]$ complex. The latter possibility is in accordance with studies by Jacobsen et al., in which it was proven that both $[\text{Cr}(\text{salen})]$ and $[\text{Co}(\text{salen})]$ catalysts promote asymmetric processes by cooperative mechanisms.^[7] Catalytic amounts of coordinating agents,^[8] such as DMF, 1,3-dimethylhexahy-

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

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

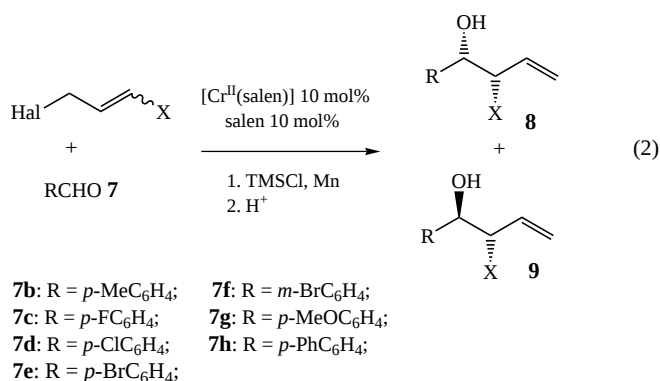
[a] All the reactions were carried out in anhydrous CH_3CN at room temperature. [b] Yield of isolated product after desilylation (HCl/THF) and flash chromatography. The by-product derived from the pinacol coupling was observed. [c] The ratio between **8a** and **9a** was determined by GC analysis of 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.

dro-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 $[\text{Cr}(\text{II})\text{crotyl}(\text{salen})]$ species and a different molecule of the ligand coordinated with Mn salts could be involved (Scheme 1 b). Such a stacking interaction could shift the conformational equilibrium^[11] between the speculated nonplanar diastereomeric conformers **10** and **10a** (Scheme 1 a). 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^{III}(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.



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 supramolecular devices in other [M(salen)]-promoted reactions.

Received: January 12, 2000 [Z14527]

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 (<i>syn:anti</i>) ^[c]	<i>ee</i> of <i>syn</i> [%] ^[d]	<i>ee</i> of <i>anti</i> [%] ^[d]
7a	Ph-CH=CH-Cl	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 <i>R</i> ,2 <i>S</i>)	26(1 <i>S</i> ,2 <i>S</i>)
7c	"	53	74:26	90(1 <i>R</i> ,2 <i>S</i>)	27(1 <i>S</i> ,2 <i>S</i>)
7d	"	46	61:39	82(1 <i>R</i> ,2 <i>S</i>)	24(1 <i>S</i> ,2 <i>S</i>)
7e	"	43	72:28	82(1 <i>R</i> ,2 <i>S</i>)	28(1 <i>S</i> ,2 <i>S</i>)
7f	"	49	66:34	70 ^[h]	43 ^[h]
7g	"	52	60:40	58(1 <i>R</i> ,2 <i>S</i>)	15(1 <i>S</i> ,2 <i>S</i>)
7h	"	47	71:29 ^[e]	84(1 <i>R</i> ,2 <i>S</i>)	16(1 <i>S</i> ,2 <i>S</i>)

[a] Performing the reaction in the presence of CrCl₃ 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 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 **8** and **9** were assigned by analogy to the chiral GC analysis of the **8a/9a** mixture. [e] Isolated yield after desilylation (Bu₄NF/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 ¹H NMR analysis of the (*S*)-(+)-*O*-acetyl-mandelic ester. See the Supporting Information for details.

- [4] For the use of chiral [M(salen)] complexes in asymmetric catalysis, see: L. Canali, D. C. Sherrington, *Chem. Soc. Rev.* **1998**, 28, 85–94, and references therein.
- [5] M. Bandini, P. G. Cozzi, P. Melchiorre, A. Umani-Ronchi, *Angew. Chem.* **1999**, 111, 3558–3561; *Angew. Chem. Int. Ed.* **1999**, 38, 3357–3359.
- [6] Commercially available crotyl bromide (85 % tech.) was used.
- [7] a) R. G. Konsler, J. K. Karl, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, 120, 10780–10781; b) M. H. Wu, K. B. Hansen, E. N. Jacobsen, *Angew. Chem.* **1999**, 111, 2167–2170; *Angew. Chem. Int. Ed.* **1999**, 38, 2012–2014.
- [8] For the role of nonchiral additives and cocatalysts in catalytic asymmetric processes, see: E. M. Vogl, H. Gröger, M. Shibasaki, *Angew. Chem.* **1999**, 111, 1671–1680; *Angew. Chem. Int. Ed.* **1999**, 38, 1570–1577; for other interesting applications concerning the use of chiral activators in asymmetric catalysis, see: K. Mikami, S. Matsukawa, *Tetrahedron: Asymmetry* **1995**, 6, 2571–2574; K. Mikami, S. Matsukawa, *Enantiomer* **1996**, 1, 69–73; K. Mikami, S. Matsukawa, *Nature* **1997**, 385, 613–615.
- [9] D. R. Kelly, *Tetrahedron: Asymmetry* **1999**, 10, 2927–2934.
- [10] J.-M. Lehn, *Angew. Chem.* **1990**, 102, 1347–1362; *Angew. Chem. Int. Ed. Engl.* **1990**, 29, 1304–1319.
- [11] It is well accepted that oxo(salen)manganese(v) and azido(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.

[1] J. Mulzer in *Comprehensive Asymmetric Chemistry, Vol.1* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, **1999**, pp. 35–97.

[2] A. Fürstner, *Chem. Rev.* **1999**, 99, 991–1046, and references therein.

[3] A. Fürstner, N. Shi, *J. Am. Chem. Soc.* **1996**, 118, 12349–12357.

- [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. Renahan, 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

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

1

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 Trp3, Tyr5, Phe12, and Val14 presumably provides a drive for β -hairpin folding, which overcomes the entropic cost of ordering the loop segment.

In order to elucidate the contribution of interstrand side-chain 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,

Arg-Trp-Gln-Tyr-Val-Xxx-Gly-Lys-Phe-Thr-Val-Gln-NH₂

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

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]

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 1a, b) verifies antiparallel β -sheet formation at the backbone level. Sidechain–sidechain NOE data (Figure 1c) 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

[*] Prof. S. H. Gellman, Dr. J. F. Espinosa
Department of Chemistry
University of Wisconsin
1101 University Avenue, Madison, WI 53706 (USA)
Fax: (+1) 608-265-4534
E-mail: gellman@chem.wisc.edu

[**] This research was supported by the National Science Foundation (CHE-9820952). J.F.E. was supported by a fellowship from the Ministerio de Educacion y Cultura (Spain) and the Fulbright Commission. The mass spectrometer was purchased in part with a National Science Foundation grant (CHE-9520868), and the NMR spectrometers were purchased in part with a National Institute Of Health grant (1 S10 RR04981). The CD spectrometer and analytical ultracentrifuge are part of the UW Biophysics Instrumentation Facility (NSF BIR-9512577).