A Sterically Modified (Salen)Chromium(III) Complex – An Efficient Catalyst for High-Pressure Asymmetric Allylation of Aldehydes

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Abstract: A novel (salen)chromium(III) catalyst with a modified salen ligand was synthesised in a simple way starting from readily available precursors. High-pressure allylation reaction of aromatic and aliphatic aldehydes with allyltributyltin upon application of 1 mol% of a modified (salen)chromium(III) complex provides homoallylic alcohols in good yield and with high enantioselectivity (up to 92%). The catalyst reveals higher enantioselectivity than the classic Jacobsen's complex.

Key words: aldehydes, allylstannane, asymmetric catalysis, high-pressure technique, homoallylic alcohols, salen(chromium) complexes

Chiral metallosalen complexes are very attractive catalyst candidates and have been shown to catalyse a large number of reactions.[1] Among them are tetradentate chromium complexes of type **1a**, introduced by Jacobsen.[2] These complexes are well known as efficient catalysts for hetero- and homo-Diels–Alder reactions,[3] ring-opening of epoxides with trimethylsilyl azide,[2,4] epoxidation of alkenes,[5] alkylation of tributyltin enolates[6] as well as for allylation in the catalytic Nozaki–Hiyama–Kishi reaction with allylic halides[7] and for certain other reactions.[1,8]

In this communication, we focus our attention on the application of modified chromium complexes in the asymmetric synthesis of homoallylic alcohols via allylation of simple aldehydes (Scheme 1). The optically active homoallylic alcohols are very useful chiral building-blocks in organic synthesis. Until now, many efficient methods for carrying out allylation have been developed,[9] often using allylstannanes in the presence of chiral Lewis acids as catalysts. The most efficient catalysts are BINOL complexes with Ti(IV),[10] and Zr(IV)[11] as well as BINAP/Ag(I)[12] and chiral acyloxy boranes derived from tartaric acid.[13] Generally, most of these procedures require large amounts (10–20 mol%) of catalyst, as well as anhydrous, sometimes even oxygen-free, reaction conditions.

Recently, we published a communication concerning enantioselective allylation of aldehydes with allyltributyltin under high-pressure conditions catalysed by the classic Jacobsen's (salen)chromium(III) complex (**1a**; Figure 1).[14] The complex afforded good yields; however, the enantioselectivities obtained were rather moderate, usually in the range of 55–79%. Complex **1a** works well under ambient conditions only for highly reactive aldehydes such as glyoxylates[15] and is ineffective as a catalyst for simple aromatic and aliphatic aldehydes due to its relatively low Lewis acidity. The solution to this problem is the application of a high-pressure technique, a well-known methodology in organic synthesis,[16] but asymmetric synthesis under high pressure is practically restricted to diastereoselective methods. The high-pressure technique was used for the allylation of aldehydes with allylic stannanes at room temperature without any catalyst over 20 years ago by Yamamoto et al.,[17] and, contrary to the catalytic version reported by us,[14] the non-catalysed reaction proceeds via a six-membered-ring transition state and is much slower.

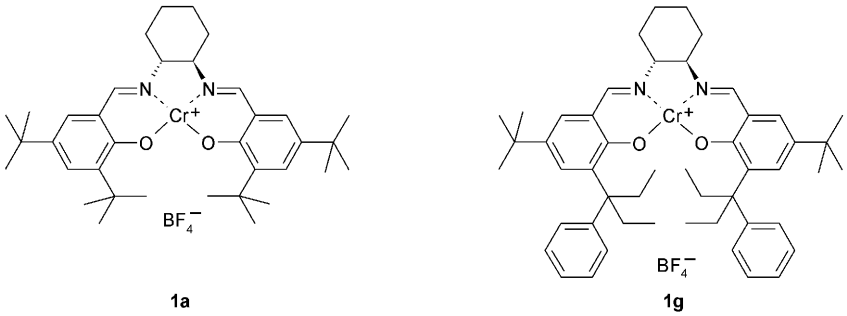

Figure 1 The classic Jacobsen's catalyst **1a** and the improved, modified complex **1g**

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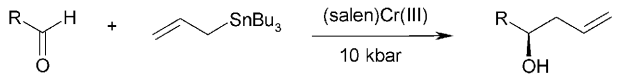


2a R = 2-Furyl **2d** R = *p*-$O_2NC_6H_4$
2b R = Ph **2e** R = Cyclohexyl
2c R = *p*-ClC_6H_4 **2f** R = PhCH=CH

3a–f

Scheme 1 Allylation of aldehydes

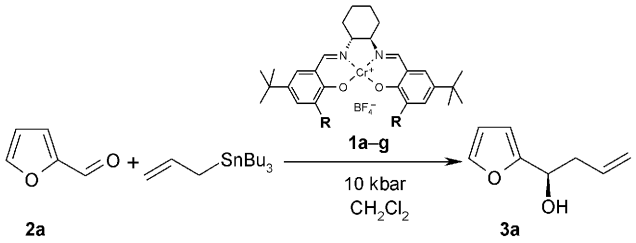
In continuation of our previous studies[14] we attempted to optimise this catalytic system via modification of the salen ligand. Application of known chiral C_2-diamines other than 1,2-diaminocyclohexane lowered the enantioselectivity. Also simple modifications to the substituents on the salicylidene moiety usually resulted in lowering (for a substituent smaller than *t*-Bu at the 3-position) or keeping (*t*-Bu at the 3-position) the enantioselectivity level. Therefore, we decided to modify the salen structure by introducing a more sterically demanding substituent at the 3-position. Modification of the salicylidene moiety at this position was widely investigated by Katsuki at al.[18,19] They synthesised a catalyst bearing additional elements of chirality at the 3-position e.g. 1-phenylprop-1-yl substituent,[18] which has similar steric properties to those introduced by us (e.g. in catalysts **1d** and **1g**). The best results they achieved were with so-called second generation catalysts bearing binaphthyl units with axial chirality,[19] however, synthesis of this type of ligand is difficult and expensive.

At the beginning of our work, we applied a ligand having a 1-methylcyclohex-1-yl substituent at the 3-position. The resulting complex **1b** displayed a lower enantioselectivity (Table 1, entry 2) compared to the classic catalyst (Table 1, entry 1). These results are analogous to the results reported by Jacobsen for the epoxidation of olefins with manganese complexes.[20]

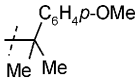
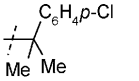
When the cyclohexyl moiety was retained and methyl was replaced with phenyl (catalyst **1c**), we observed some improvement in the enantioselectivity (increased to 76%; Table 1, entry 3). A better induction was achieved when cyclohexyl was replaced with isopropyl and the phenyl substituent was retained (catalyst **1d**; Table 1, entry 4). In the case of the model reaction with furfural, the induction observed was slightly above 80% ee, whereas the classic catalyst gave 67% ee under analogous reaction conditions. This known ligand was employed for the synthesis of the manganese complex and used for the olefin epoxidation reaction, where it gave a slightly increased (by about 10%) asymmetric induction compared to the classic system.[21]

As one can see from the examples, the presence of the cyclohexyl substituent decreases the enantioselectivity compared to the catalysts having the isopropyl substituent (Table 1, cf. entries 2 and 3 vs. 1 and 4). The change of the electronic properties of the phenyl group resulting from adding an electron-donor group (e.g., methoxy) has practically no influence on the asymmetric induction (Table 1, entry 5), whereas the presence of a chlorine atom at this

Table 1 Results of High-Pressure Allylation of Furfural (**2a**) with Allyltributyltin Catalysed by Various (salen)$CrBF_4$ Complexes[a]



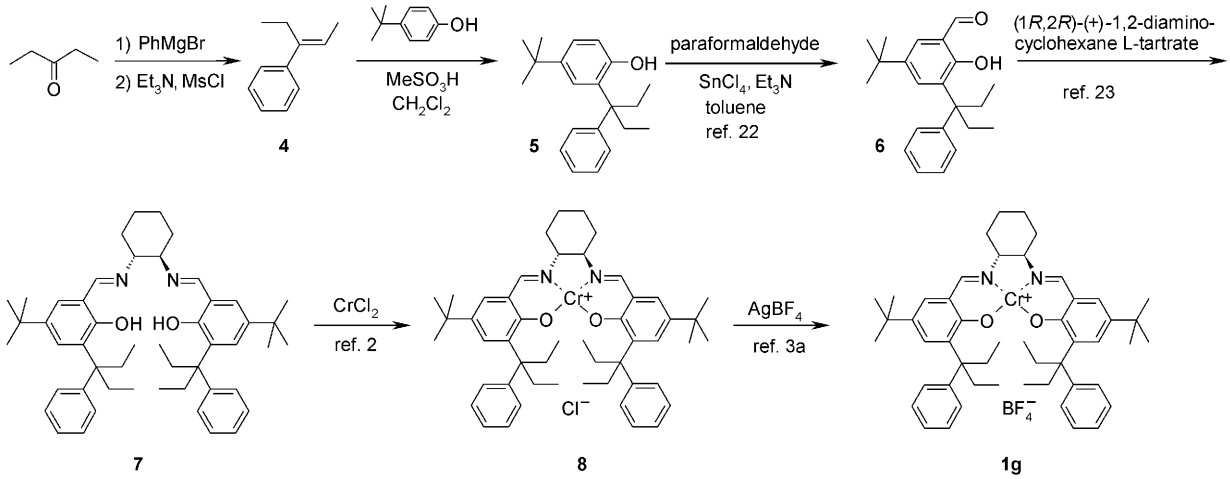
2a **3a**

Entry	Catalyst	R	Yield (%)[b]	ee (%)[c]
1	**1a**	*t*-Bu	91	67
2	**1b**		81	57
3	**1c**		82	76
4	**1d**		87	81
5	**1e**		89	82
6	**1f**		82	72
7	**1g**		86	91

[a] The reactions were carried out in a 2-mL Teflon ampoule using furfural (**2a**; 1 mmol), (salen)chromium complex (2 mol%), allyl$SnBu_3$ (1.1 mmol), CH_2Cl_2, 10 kbar, 20 °C, 24 h.
[b] The yield was determined by GC.
[c] The ee was determined by GC on a capillary chiral β-dex 120 column.

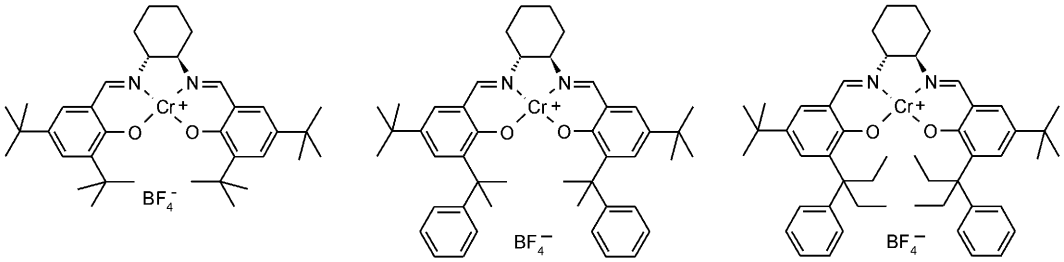
position decreases the enantioselectivity slightly (Table 1, entry 6). Until now, the best results (ee >90%) were observed for catalyst **1g** bearing the 3-(3-phenylpentyl) group at the 3-position, a sterically demanding substituent (Table 1, entry 7); the synthesis of **1g** is shown in Scheme 2.

The advantage of catalyst **1g** is that phenol **5**, aldehyde **6** and ligand **7** are readily accessible from inexpensive materials, are easily isolated and purified. Phenol **5** was obtained from olefin **4** (readily available from 3-pentanone and bromobenzene) and 4-*tert*-butylphenol in the presence of $MeSO_3H$; **5** was isolated in 25% yield by crystallisation from ethanol (this reaction was not optimised). Formylation[22] to aldehyde **6** and synthesis of ligand **7**[23,24] proceed in good yields, 70% and 80%, respectively, after crystallisation. Solid chromium complexes **8**[25] and **1g** were synthesised according to known procedures by Jacobsen.[2,3a]



Scheme 2 Synthesis of the catalyst **1g**.[2,3a,22,23]

Table 2 Asymmetric Allylation of Aldehydes Catalysed by the Complexes (1*R*,2*R*)-**1a**, (1*R*,2*R*)-**1d** and (1*R*,2*R*)-**1g**[a]



Catalyst			**1a** (2 mol%)		**1d** (2 mol%)		**1g** (1 mol%)	
Entry	Aldehyde		Yield (%)[b]	ee (%)[c]	Yield (%)[b]	ee (%)[c]	Yield (%)[b]	ee (%)[c]
1	**2a**	R = 2-Furyl	89	67 (*R*)	85	81 (*R*)	84	90 (*R*)
2	**2b**	R = Ph	82	55 (*R*)	87	67 (*R*)	89	86 (*R*)
3	**2c**	R = *p*-ClC_6H_4	81	60	80	77	90	87
4	**2d**	R = *p*-$NO_2C_6H_4$	83	68	90	80	92	83
5	**2e**	R = Cyclohexy	82	79 (*R*)	90	84 (*R*)	90	92 (*R*)
6	**2f**	R = PhCH=CH	84	65 (*R*)	94	85 (*R*)	92	92 (*R*)

[a] Reaction conditions: aldehyde (1 mmol), (1*R*,2*R*)-chromium complex (1 or 2 mol%), allyl$SnBu_3$ (1.1 mmol) in CH_2Cl_2; 2 mL Teflon ampoule, 10 kbar at 20 °C for 24 h.[26]
[b] Isolated yield.
[c] The ee was determined by GC on a capillary chiral β-dex 120 column.[27]

Encouraged by the results of the reaction with furfural, we applied this reaction to a range of aldehydes (Table 2). The type of catalyst used had no significant influence on the yield; the yields are good, usually above 80%. With regard to the ee values, they rise in the following order: **1a** (55–79% ee), **1d** (67–85% ee), and **1g** (above 80% ee, up to 92% ee, even if only 1 mol% of the catalyst is present). Quite a wide range of aldehydes were used; the reaction is effective for aromatic aldehydes **2a**–**d**, simple aliphatic aldehyde **2e**, as well as α,β-unsaturated aldehyde **2f**.

Summing up, we have synthesised a novel salen ligand and found its chromium complex to be a highly selective catalyst for the allylation of aldehydes under high pressure. It resulted in good yields (80%) and asymmetric inductions (up to 92% ee). Its significant advantage is a relatively simple synthesis and effectiveness at low concentrations (ca. 1 mol%) with no need for anhydrous solvents or an inert atmosphere.

Future work will focus on the application of this catalytic system to other reactions as well as on further attempts at modification of the substituents at the 3-position of the salicylidene moiety, aimed at further improving the enantioselectivity.

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(24) Analytical data for the modified salen ligand (1*R*,2*R*)-**7**: mp 89–93 °C; $[\alpha]_D^{29}$ –329.5 (*c* 1.0, $CHCl_3$); IR (KBr): 2963, 2875, 1628, 1597, 1445, 1263, 699 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 13.13 (s, OH, 2 H), 8.00 (s, CHN, 2 H), 7.45 (d, *J* = 1.8 Hz, 2 H), 7.25–7.09 (m, 10 H), 6.92 (d, *J* = 1.8 Hz, 2 H), 3.13–2.99 (m, 2 H), 2.50–2.25 (m, 4 H), 2.12–1.94 (m, 4 H), 1.86–1.69 (m, 4 H), 1.66–1.44 (m, 2 H), 1.30 (s, 18 H), 0.60 (t, *J* = 7.2 Hz, 6 H), 0.53 (t, *J* = 7.2 Hz, 6 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.5 (2 × CHN), 157.5 (2 × C), 148.5 (2 × C), 139.2 (2 × C), 133.1 (2 × C), 129.2 (2 × CH), 127.2 (4 × CH), 127.0 (4 × CH), 125.8 (2 × CH), 124.7 (2 × CH), 117.5 (2 × C), 72.3 (2 × CH), 49.0 (2 × C), 34.0 (2 × C), 32.9 (2 × CH_2), 31.5 (6 × CH_3), 28.0 (2 × CH_2), 27.1 (2 × CH_2), 24.3 (2 × CH_2), 8.7 (4 × CH_3); Anal. Calcd for $C_{50}H_{66}N_2O_2$: C, 82.60; H, 9.15; N, 3.85. Found: C, 82.55; H, 9.23; N, 3.83; HRMS: $[M + Na]^+$ calcd for $C_{50}H_{66}N_2O_2Na$: 749.5022, found: 749.5021.
(25) Analytical data for the complex (1*R*,2*R*)-**8**: $[\alpha]_D^{29}$ –1420 (*c* 0.01, $CHCl_3$); IR (KBr): 3429, 2961, 2873, 1622, 1533, 1437, 1258, 700, 546 cm^{-1}; HRMS: $[M - Cl]^+$ calcd for $C_{50}H_{64}N_2O_2Cr$: 776.4373, found: 776.4392.
(26) **General Procedure for High-Pressure Allylation:** In a 2-mL Teflon ampoule were placed catalyst **1g** (8.7 mg, 1 mol%), CH_2Cl_2 (ca. 1 mL), followed by aldehyde (1 mmol) and allyltributyltin (1.1–1.2 equiv). Finally, the ampoule was filled with CH_2Cl_2, closed and placed in a high-pressure vessel, and the pressure was slowly increased to 10 kbar at 20 °C. After the pressure had stabilized, the reaction mixture was kept under these conditions for 24 h. After decompression, the reaction mixture was diluted with wet Et_2O and dried over $MgSO_4$. After evaporation of solvents, the residue was chromatographed on a silica gel column (hexane–EtOAc).
(27) The enantioselectivity of homoallylic alcohols **3a**–**f** was determined by GC employing a capillary chiral β-dex 120 column. Alcohol **3f** was analyzed directly, **3a**, **3c** and **3d** as their *O*-trimethylsilyl derivatives, **3b** as an acetate and **3e** as a trifluoroacetate.