High-Pressure Enantioselective Allylation of Aldehydes Catalyzed by (Salen)Chromium(III) Complexes

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Abstract: The enantioselective addition of allyltributyltin to simple aldehydes (**2a–l**), catalyzed by chiral (salen)Cr(III) complexes **1**, has been studied. The reaction proceeds smoothly with low loading (1–2 mol%) of (salen)Cr(III)BF_4 (**1a**) and allyltributyltin under high-pressure conditions (10 kbar) in good yield and ee values in the range of 35–79%.

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

Catalytic enantioselective allylation of aldehydes is one of the most important methods for preparing enantiomerically enriched secondary alcohols, and until now, many efficient methods for carrying out this reaction have been developed,[1] often using allylstannanes.[2] Lewis acids are typically used as chiral catalysts, and the most efficient are BINOL complexes with Ti(IV),[3] and Zr(IV)[4] as well as chiral acyloxy boranes derived from tartaric acid,[5] BINAP/Ag(I),[6] and chiral bisoxazoline ligands with Rh(III).[7] Generally, most of these procedures require high catalyst loading (10–20 mol%), as well as anhydrous, sometimes even oxygen-free, reaction conditions.

In this work, we focused our attention on the application of stable and readily available (salen)metal complexes for allylation of aldehydes. The first application of (salen)metal complexes for enantioselective allylation was reported by Cozzi and Umani–Ronchi[8] in the catalytic Nozaki–Hiyama–Kishi reaction with allylic halides promoted by (salen)chromium complexes.[8,9] Recently, we published a paper dealing with enantioselective allylations of reactive aldehydes such as alkyl glyoxylates, using allyltributyltin, catalyzed by 1–2 mol% of (salen)Cr(III)BF_4 complexes (Figure 1, compound **1a**), leading to 2-hydroxypent-4-enoic acid esters with good yield and enantioselectivities of 60–76%.[10] The (salen)chromium(III) complexes of type **1**, introduced to enantioselective catalysis by Jacobsen,[11] are known to be efficient catalysts for hetero-Diels–Alder reaction,[12] as well as for ring-opening of epoxides by trimethylsilyl azide[11] and for some other reactions.[13] In our research group, we also used these catalysts for the [4+2] cycloaddition of various 1,3-dienes to glyoxylates[14] and *tert*-butyldimethylsilyloxyacetaldehyde.[15] Unfortunately, the (salen)Cr(III)BF_4 complexes, which are weak Lewis acids compared with typical catalysts used for this type of reaction, do not work well at room temperature, under atmospheric pressure, with simple aldehydes and allyltributyltin (Scheme 1, Figure 2), and afford homoallylic alcohols usually with low yield. We succeeded, however, when high-pressure conditions (10 kbar) were applied.[16] Over 20 years ago Yamamoto et al.[17] found that allylic stannanes react with aldehydes at room temperature under high pressure (10 kbar) without any catalyst. This procedure is a mild method for the allylation of aldehydes, which may be useful for preparation of the labile, thermally unstable and acid-sensitive compounds. To our knowledge, this high-pressure methodology has not been used for enantioselective allylation. However, we found in the literature some examples of diastereoselective allylation of chiral aldehydes,[17c,18] e.g. α-amino aldehydes.

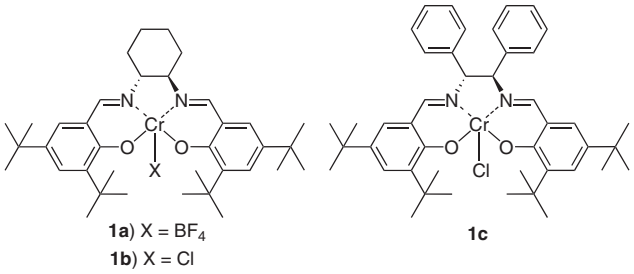
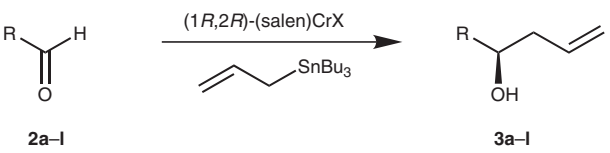


Figure 1 The (salen)chromium(III) complexes used



Scheme 1 Allylation of aldehydes

As a model, we have chosen the reaction of furfural (**2a**) with allyltributyltin[19] in dichloromethane. The reaction was very slow under ambient conditions (Table 1, entry 1) leading, after three days, to the expected product having 56% ee, in ca. 10% yield. In such a situation, we decided to optimize the reaction conditions. Increasing temperature up to 60 °C did not improve the yield satisfactory even when the reaction was carried out without any solvent. Addition of molecular sieves raised the yield up to

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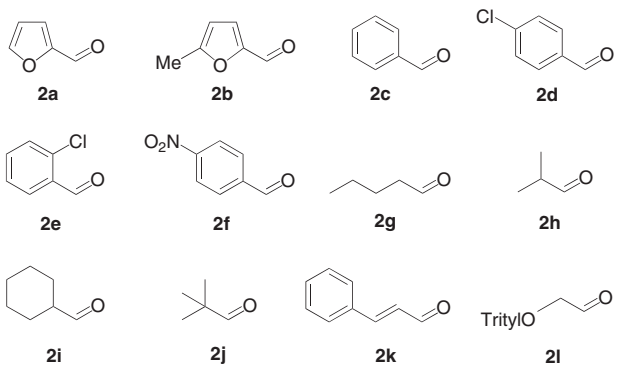
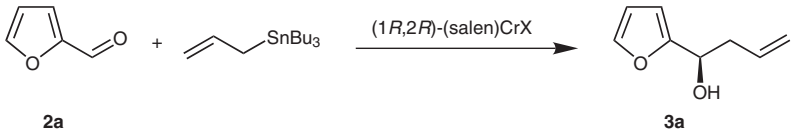


Figure 2 Aldehydes used for allylation

46% but the results were still not satisfactory (entry 2). As already mentioned, we succeeded under high-pressure conditions. High pressure not only accelerated the reaction rate but also increased the enantioselectivity from 56% to 67% (entries 3 and 4); the best results were obtained in those reactions performed at pressures under 10 kbar.[20] Unfortunately, addition of molecular sieves to the reaction mixture under high-pressure conditions lowered the ee (entry 5). Contrary to many known enantioselective procedures, concentration of 2 mol% of catalyst is enough in this method for effective allylation of furfural to afford expected homoallylic alcohols in high yield of ca. 90% (e.g. entry 4). For comparison, we carried out the analogous reaction but without any catalyst, and the yield was much lower (entry 6). This means that the (salen)$CrBF_4$ complexes, which are rather weak Lewis acids, have a strong influence on the rate of investigated reaction under high-pressure conditions.

The next stage of our study was an attempt to optimize the reaction conditions at a pressure of under 10 kbar. We investigated several factors such as loading of the catalyst, solvents, additives, concentration of the aldehyde. Load-

Table 1 Results of the Model Reaction of Furfural (**2a**) with Allyltributyltin[a]



2a **3a**

Entry	Catalyst	Mol% of catalyst	Concentration of **2a** (mol/L)	Pressure (bar)	Solvent	Time (h)	Yield (%)[b]	ee (%)[c]
1	**1a**	2	1.4	1	CH_2Cl_2	72	10	56
2	**1a**	2 + MS 4 Å	1.4	1	CH_2Cl_2	72	46	58
3	**1a**	2	0.5	7000	CH_2Cl_2	24	71	62
4	**1a**	2	0.5	10000	CH_2Cl_2	24	91	67
5	**1a**	2 + MS 4 Å	0.5	10000	CH_2Cl_2	24	95	52
6	**No cat.**	–	0.5	10000	CH_2Cl_2	24	17	0
7	**1a**	5	0.5	10000	CH_2Cl_2	24	94	68
8	**1a**	1	0.5	10000	CH_2Cl_2	24	82	64
9	**1a**	0.5	0.5	10000	CH_2Cl_2	24	69	61
10	**1a**	2	1.0	10000	CH_2Cl_2	24	94	68
11	**1a**	1	1.5	10000	CH_2Cl_2	24	89	67
12	**1a**	2	0.5	10000	$CHCl_3$	24	91	66
13	**1a**	2	0.5	10000	$(CH_2Cl)_2$	24	84	67
14	**1a**	2	0.5	10000	*i*-$PrNO_2$	24	56	71
15	**1b**	2	0.5	10000	CH_2Cl_2	24	67	66
16	**1c**	2	0.5	10000	CH_2Cl_2	24	81	20
17[d]	**1a**	2	0.5	10000	CH_2Cl_2	24	92	60

[a] High-pressure reactions were carried out in a 2 mL Teflon ampoule using 1.1 equiv of allyltributyltin at 20 °C.
[b] Yield was determined by GC.
[c] The ee was determined by GC on capillary chiral β-dex 120 column.
[d] Instead of allyltributyltin, 1.1 equiv of allyltrimethyltin was used.

ing of the catalyst in a range of 5–0.5 mol% has a slight influence on enantioselectivity (compare entries 4 and 7–9). What is very promising in this method, even 0.5 mol% of **1a** gives quite good results (entry 9). Allylation proceeds, without lowering the ee, at higher concentration of the aldehyde (entry 10), even when the 2 mL Teflon ampoule was filled with 3 mmol of **2a**, 1 mol% of **1a**, 1 mL of allyltributyltin and made up with CH_2Cl_2 (entry 11). The possibility of using concentrated reaction mixtures is a great advantage because of limitation of the volume of high-pressure chambers (the average volume is 50 mL). Unfortunately, the reaction does not work well without solvent for furfural **2a** and other aldehydes, which are insoluble in allyltributyltin.

Besides dichloromethane, of the solvents studied, $CHCl_3$, 1,2-dichloroethane, CH_2Cl_2–hexane (1:1), and *i*-$PrNO_2$ also worked well (e.g. entries 12–14). The latter of these solvents gave the highest ee, but the yield was lower.

We have also tested the applicability of two other chromium complexes for this reaction. The commercially available complex **1b**, with a chloride counter-ion, catalyzed the reaction practically with the same enantioselectivity (see entries 4 and 15), but the reaction yield was lower. We have also checked the chromium chloride complex **1c** having another widely used chiral 1,2-diamines, e.g., 1,2-diphenylethylenediamine, but the enantioselectivity was much lower (entry 16). More reactive allyltrimethyltin can also be used instead of allyltributyltin, however, the ee was slightly lower (entry 17).

The next stage of the study was an attempt to show usefulness of the high-pressure method in reaction with other aldehydes. Table 2 summarizes the results obtained for the reactions of a variety of aromatic and aliphatic aldehydes with 1.1 equivalent of allyltributyltin, in the presence of 2 mol% of **1a**. The obtained enantiomeric excesses for aromatic aldehydes **2a–f** range from 55–68% and the yields are 79% and higher. This methodology works well also for aliphatic aldehydes (e.g. **2g–i**), however, sometimes the yields are lower. The lowest ee was obtained for a bulky pivalaldehyde **2j** (entry 10). With good yield and moderate ee (65% and 53%, respectively), the allylation reaction also works for α,β-unsaturated cinnamaldehyde **2k** (entry 11) and the glycolaldehyde derivative **2l** (entry 12).

The enantiomeric excess values were determined by GC employing a capillary chiral β-dex 120 column.[21] In some cases (Table 2, entries 1, 3, 7, 9, 11, and 12), we confirmed the absolute configuration of the obtained homoallylic alcohols via measurement of optical rotation and comparison with the literature data. In all cases when chromium complex (1*R*,2*R*)-**1a** was used, we observed the same direction of asymmetric induction.

In conclusion, we have developed a new and mild method for enantioselective allylation of aldehydes, catalyzed by 1–2 mol% of readily available (salen)$CrBF_4$ (**1a**) affording in good yield homoallylic alcohols having at this stage of our studies moderate to good ee values. The commercially available (salen)CrCl (**1b**) can also be used as an efficient catalyst. According to our knowledge, this is the first example of enantioselective allylation of aldehydes under high-pressure conditions. Even though high-pressure equipment is not common in synthetic laboratories and rather expensive, our approach constitutes a synthetic method of choice having some advantages: requires small amount of readily available stable and recoverable catalyst and can be carried out for concentrated reaction mixtures in reagent grade solvents. What is more, the oxygen-free conditions are not necessary. On the other hand, we show how low active catalyst under normal conditions can be successfully applied for reactions accelerated under high-pressure conditions. Further studies to improve the enantioselectivity, mainly by modification of the structure of catalysts, are underway.

Table 2 Enantioselective Allylation of Aldehydes Catalyzed by (1*R*,2*R*)-**1a**[a]

Entry	Aldehyde[b]	Yield (%)[c]	ee (%)[d]
1	**2a**	89	67 (*R*)
2	**2b**	79	61
3	**2c**	82	55 (*R*)
4	**2d**	81	60
5	**2e**	85	68
6	**2f**	83	68
7	**2g**	52	75 (*S*)
8	**2h**	86	68
9	**2i**	82	79 (*R*)
10	**2j**	70	35
11	**2k**	84	65 (*R*)
12	**2l**	86	53 (*R*)

[a] Conditions: 1 mmol of the aldehyde, 2 mol% of (1*R*,2*R*)-(salen)$CrBF_4$ (**1a**), 1.1 mmol of allylSnBu_3 in CH_2Cl_2 in 2 mL Teflon ampoule; 10 kbar at 20 °C for 24 h.
[b] Structures of aldehydes are shown in Figure 2.
[c] Isolated yield.
[d] The ee was determined by GC on a capillary chiral β-dex 120 column (see ref.[21]).

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(20) **General Procedure for the High-Pressure Allylation:** In a 2 mL Teflon ampoule were placed (salen)$CrBF_4$ (**2a**, usually 13.7mg, 2 mol%), ca. 1 mL of solvent (usually CH_2Cl_2), followed by aldehyde (usually 1 mmol) and allyltributyltin (1.1 equiv). Finally, the ampoule was made up with solvent, closed and placed in a high-pressure vessel, and pressure was slowly increased to 10 kbar at 20 °C. After stabilization of pressure, 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 using hexane–EtOAc. All liquid aldehydes were distilled prior to use.
(21) Enantioselectivity of homoallylic alcohols **3a–l** was determined by GC employing a capillary chiral β-dex 120 column. Alcohols **3c**,**k** were analyzed directly, **3a**,**b**,**d–h**,**j** as their *O*-trimethylsilyl derivatives, **3i** as a trifluoroacetate and **3l** as a isopropylidene derivative of pent-4-ene-1,2-diol.