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Enantioselective allylation of alkyl glyoxylates catalyzed by (salen)chromium(III) complexes

Piotr Kwiatkowski,[a] Wojciech Chaładaj[b] and Janusz Jurczak[a,b,*]

[a]*Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland*
[b]*Department of Chemistry, Warsaw University, Pasteura 1, 02-093 Warsaw, Poland*

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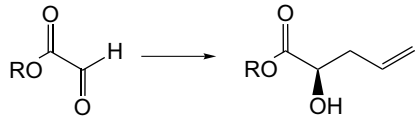
Abstract—The enantioselective addition of allylstannanes and allylsilanes to alkyl glyoxylates of type **1**, catalyzed by chiral (salen)Cr(III) complexes **3**, has been studied. We have found that the reaction proceeded smoothly for low loading (1–2 mol%) of (1*R*,2*R*)-(salen)Cr(III)BF_4 **3a** or (1*R*,2*R*)-(salen)Cr(III)ClO_4 **3c**, and allyltributyltin under simple, undemanding conditions, affording (*R*)-2-hydroxypent-4-enoic acid esters **2** in good yield (61–90%) and enantioselectivity (58–76% ee).

The addition of allylic reagents to aldehydes and ketones leads to homoallylic alcohols, which are very important from the synthetic point of view. Numerous allylic organometallics as well as various Lewis acids are effective in these reactions.[1] Investigation of the enantioselective variant of these reactions was originated in the early 1990s by Yamamoto and co-workers,[2] who used a chiral acyloxy borane catalyst derived from tartaric acid and allyltrimethylsilane. Until now, many efficient methods for enantioselective allylation have been developed, although these methods apply almost exclusively to simple aromatic and aliphatic aldehydes.[3] In general, chiral Lewis acids are used as catalysts. Among the most extensively studied catalysts are BINOL complexes with Ti(IV),[4] as well as BINOL/Zr(IV),[5] BINAP/Ag(I)[6] and chiral bisoxazoline ligands with Zn(II)[7] and Rh(III).[8] Allyltin and allylsilicon derivatives are most frequently used as allylating agents for the reactions catalyzed by chiral Lewis acids. Allyltrichlorosilanes are also employed for enantioselective allylation, and their reactions are catalyzed by chiral Lewis bases, for example, phosphoramide,[9] formamide[10] and *N*-oxides.[11] Another efficient enantioselective allylation is the catalytic Nozaki–Hiyama–Kishi reaction with allylic halides promoted by complexes of chromium(II) with chiral salen[12] and bisoxazoline[13] ligands. Most of these procedures require anhydrous reaction conditions, sometimes even oxygen-free reaction conditions (as in the case of the Nozaki–Hiyama–Kishi reaction).

Our studies concern the allylations of a particular group of active aldehydes, glyoxylates **1** (Scheme 1), which result in 2-hydroxypent-4-enoic acid esters **2**, compounds of significant synthetic interest.[14] Currently, in order to synthesize these compounds and their derivatives in optically pure form, diastereoselective methods using chiral auxiliaries[15,16] are mainly applied. Methods using sultam derivatives of glyoxylic acid have been developed in our research group[16] however no efficient method for the enantioselective allylation of glyoxylates is currently known. This subject was investigated by Mikami and co-workers[17] using a BINOL-titanium complex (10 mol%), but the results obtained for the simple allylation of glyoxylates were poor, both in terms of enantiomeric excess and in terms of yield. In the case



1a R=Bu^n **1c** R=Bu^t **2a-d**
1b R=Pr^i **1d** R= Bn

Scheme 1. Allylation of glyoxylates.

Keywords: Asymmetric catalysis; Allylstannane; Carbonyl-addition reaction; Chromium; Glyoxylate; Homoallylic alcohols; Salen.
* Corresponding author. Tel.: +48-22-6320578; fax: +48-22-6326681; e-mail: jurczak@icho.edu.pl

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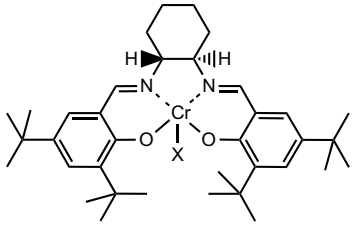
of reactions with allyltrimethylsilane and allyltributyltin, the ee values were 30% and 10%, respectively, and the yields did not exceed 40%. Of interest was the fact that the same catalytic system used for the reaction of simple aliphatic and aromatic aldehydes with allyltributyltin gave much better results (the ee was often above 90%).[4]

We thus decided to search for catalytic systems useful for allylation of glyoxylates **1**. We have chosen the salen complexes of transition metals as candidate chiral Lewis acid catalysts, since they are easy to handle and stable in the presence of moisture and oxygen. The model reaction was the allylation of *n*-butyl glyoxylate (**1a**) with allyltributyltin.[18] Following preliminary screening of chiral salen complexes of type **3** (Fig. 1) of the following metals: Ti(IV), Cr(III), Mn(III), Fe(III), Co(II), Co(III), Ni(II), Ni(III), Cu(II) and Al(III), it turned out that the only enantiomerically efficient catalyst was the (salen)-chromium(III) complex **3a**. Although the remaining complexes did catalyze the allylation, the ee was 10% at best. Activation using the salen-metal complexes was too low to enable efficient reaction of allyltrimethylsilane.

(Salen)chromium(III) complexes of type **3** (Fig. 1) were introduced to enantioselective catalysis by Jacobsen and co-workers,[19] and are known to be efficient catalysts for hetero-Diels–Alder reactions,[20] as well as for ring opening of epoxides by trimethylsilyl azide[19] amongst other reactions.[21] In our research group, we have used these catalysts for [4+2] cycloaddition of various 1,3-dienes to glyoxylates.[22]

As already mentioned, (salen)chromium complexes have been successfully applied to enantioselective allylation reactions using allyl halides, via the Nozaki–Hiyama–Kishi reaction.[12] In this reaction, the active catalytic species is (salen)Cr(II), and the nature of the catalytic cycles is a redox process. In our method, the cationic complex (salen)Cr(III)$^+$ is catalytically active, playing the role of a typical Lewis acid.

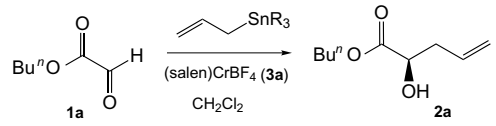
The chromium complex **3a** turned out to be too weak as a Lewis acid to catalyze efficiently the reaction with allyltrimethylsilane. The standard reaction conditions resulted in low yields, below 15%, with enantiomeric excesses of 30–40%. A significant amount of byproduct is observed in this reaction. High pressure (10 kbar) improves the yield slightly (<40%), while the enantioselectivity remains practically the same.



3a X=BF_4, **3b** X=Cl, **3c** X=ClO_4

Figure 1. (Salen)Cr(III)complexes.

Table 1. Results of the reactions of *n*-butyl glyoxylate (**1a**) with various allylating reagents in the presence of (salen)$CrBF_4$ complex (**3a**)[a]



Entry	Allyl reagent	Time (h)	Yield (%)	Ee[b] (%)
1	$Bu^n_3SnAllyl$	3	82	61
2	$Me_3SnAllyl$	3	79	62
3	$Ph_3SnAllyl$	4	70	46
4	$Sn(Allyl)_4$	0.5	82	13

[a] The reactions were carried out using 1 mmol of *n*-butyl glyoxylate (**1a**), 2 mol% of **3a** and 1.2 equiv of $R_3SnAllyl$ (0.3 mmol of $Sn(Allyl)_4$) in 1 mL of CH_2Cl_2 at 20°C.

[b] The enantiomeric excess was determined by GC on a capillary chiral column β-dex 120 (permethyl-β-cyclodextrin).

The use of tin allylating reactants gave much better results (Table 1). Their reactions proceeded at room temperature in good yields. The best results were observed for allyltrialkyltin derivatives, and the enantiomeric excesses exceeded 60% (Table 1, entries 1 and 2).

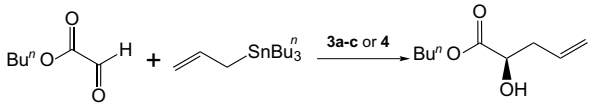
When allyltriphenyltin was used, the enantioselectivity decreased to 46% ee (entry 3). The reaction was most rapid for tetraallyltin, but the enantiomeric excesses obtained were much lower, not exceeding 13% ee (entry 4). Further studies were carried out using only commercially available allyltributyltin.

The next stage of the study was an attempt to improve the enantioselectivity of the reaction of *n*-butyl glyoxylate with allyltributyltin. We investigated several factors such as concentration, temperature, solvent, additives and the counterion of the catalyst (Table 2).

It turned out that when the reaction was conducted in CH_2Cl_2, the presence of 4 Å molecular sieves (entries 1 and 2 in Table 2) and the glyoxylate concentration (entries 1 and 3) had practically no influence on the enantiomeric excess of the product. Moreover, the rate of addition of the allylating agent for the reaction based on 1 mmol scale and the amount of catalyst (2 mol% and more) seemed to have no influence on enantiomeric excess (entries 1 and 4).

To our surprise, lowering the temperature resulted in a drop in enantioselectivity from 61% to 36% ee (entries 4–6). However, the reaction performed in boiling CH_2Cl_2 proceeded much faster, while the drop in enantioselectivity was insignificant (58% ee) (entry 7). When the reactions were conducted in the presence of amines or PPh_3, we observed a slight improvement in enantioselectivity. For example, a small amount of lutidine caused increase in enantiomeric excess from 61% to 68% (see entries 1 and 8, respectively).

Table 2. Results of the enantioselective reaction of *n*-butyl glyoxylate (**1a**) with allyltributyltin catalyzed by chromium(III) complexes **3a**–**c** and **4** under various reaction conditions[a]



1a 2a

Entry	Catalyst	Mol% of the catalyst	Solvent	Concn of **1a** (mol/L)	Temp. (°C)	Time (h)	Yield (%)	Ee[b] (%)
1	**3a**	2	CH_2Cl_2	1	20	3	82	61
2	**3a**+4 Å molecular sieves	2	CH_2Cl_2	1	20	1	82	62
3	**3a**	2	CH_2Cl_2	0.1	20	5	81	61
4	**3a**	5	CH_2Cl_2	1	20	1	80	61
5	**3a**	5	CH_2Cl_2	1	5	24	78	51
6	**3a**	5	CH_2Cl_2	1	$-78 \rightarrow -20$	24	76	36
7	**3a**	5	CH_2Cl_2	1	40	0.25	77	58
8	**3a**+2,6-lutidine (2.5 mol%)	2	CH_2Cl_2	1	20	4	80	68
9	**3a**	2	$MeNO_2$	1	20	3	79	70
10	**3a**+2,6-lutidine (2.5 mol%)	2	$MeNO_2$	1	20	3	80	70
11	**3a**	0.2	$MeNO_2$	2	20	24	61	62
12	**3a**	2	No solvent		$5 \rightarrow 20$	5	90	65
13	**3b**	2	CH_2Cl_2	1	20	3	73	54
14	**3c**	2	CH_2Cl_2	1	20	3	90	65
15	**4**	2	CH_2Cl_2	1	20	3	49	7

[a] The reactions were carried out using 1 mmol of *n*-butyl glyoxylate (**1a**) and 1.2 mmol of allyltributyltin.
[b] The enantiomeric excess was determined by GC on a capillary chiral β-dex 120 column.

Of the solvents investigated, nitromethane appeared to be more efficient than CH_2Cl_2 and raised the enantiomeric excess to 70% (entry 9). The addition of lutidine to the reaction conducted in $MeNO_2$ caused no change (entry 10). It is interesting that the reaction in $MeNO_2$ proceeds in a biphasic system, because allyltributyltin is poorly soluble thereby providing a relatively low and constant concentration of the allylating agent in the reaction medium. The reaction in $MeNO_2$ can be efficiently catalyzed even by minor amounts of the catalyst **3a** (0.2 mol%) accompanied by a decrease in enantioselectivity to 62% ee (entry 11).

A great advantage of this reaction is that it can be successfully performed with no solvent; a slight increase in ee (to 65%) was observed compared to the reaction conducted in CH_2Cl_2 (entries 1 and 12).

We also tested the applicability of other chromium complexes to this reaction. The commercially available (salen)CrCl complex **3b**, which served for the preparation of **3a** and **3c**, catalyzed the reactions less efficiently and decreased the enantioselectivity to 54% (entry 13). The best one, both in respect of yield and enantiomeric excess, turned out to be the perchlorate complex **3c** (entry 14). We have also investigated chromium complexes with diamines other than 1,2-diaminecyclohexane such as 1,2-diphenylethylenediamine and 1,2-di-*tert*-butylethylenediamine, but the enantioselectivities obtained were lower.

In the context of the recent work of Jacobsen concerning the tridentate chromium(III) complex **4** (Fig. 2) and its high efficiency in the hetero-Diels–Alder[23] and the ene

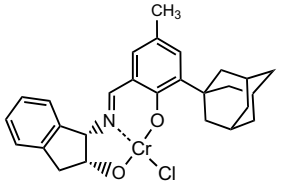


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Figure 2. Tridentate chromium(III) complex.

reactions,[24] we have tested its performance in the allylation reaction. This complex was unsatisfactory, and the enantiomeric excess of product **2a** was not greater than 7% (entry 15).

We have also carried out allylation using other glyoxylates (R = *i*-Pr, *t*-Bu, Bn) (Table 3). With respect to enantioselectivity, the results were similar to those

Table 3. Influence of the alkyl substituent in glyoxylate **1** on the reaction course[a]

Entry	Glyoxylate	Solvent	Yield (%)	Ee (%)
1	**1a** Bu^n	CH_2Cl_2	82	61
2	**1a** Bu^n	$MeNO_2$	79	70
3	**1b** Pr^i	CH_2Cl_2	78	66
4	**1b** Pr^i	$MeNO_2$	74	73
5	**1c** Bu^t	CH_2Cl_2	76	76
6	**1c** Bu^t	$MeNO_2$	65	73
7	**1d** Bn	CH_2Cl_2	84	61

[a] The reactions were carried out using 1 mmol of alkyl glyoxylate (**1a**–**d**), 2 mol% of **3a** and 1.2 mmol of allyltributyltin, in 1 mL of solvent, at 20 °C for 3 h.

obtained for *n*-butyl glyoxylate. In the case of the reactions conducted in CH_2Cl_2, the enantiomeric excess rises slightly (from 61% to 76% ee) along with the increasing bulkiness of the R substituent in the glyoxylate. This effect is not as apparent for the reactions conducted in $MeNO_2$.

In all cases, when the catalysts **3a**–**c** having (1*R*,2*R*) configuration were used, the allylation product had the (*R*) configuration. The absolute configuration of products **2a**–**d** was determined by correlation with 1,2-pentanediol.[16a]

In conclusion, we have developed an efficient, undemanding method for the enantioselective allylation of glyoxylates, which affords products with enantiomeric excesses in the range of 58–76%. The reaction is highly reproducible and not sensitive to external factors such as oxygen or moisture. Moreover, it can be performed on large scale.

According to our knowledge, this reaction is the first example of enantioselective allylation where the salen complex is directly used as a Lewis acid (except for the use of salen in the Nozaki–Hiyama–Kishi reaction). The results seem to be a good starting point to further optimization involving modification of the chiral ligand, especially its 1,2-diamine moiety. Further studies to improve the enantioselectivity of this reaction are underway.

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