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Enantioselective glyoxylate-ene reactions catalysed by (salen)chromium(III) complexes

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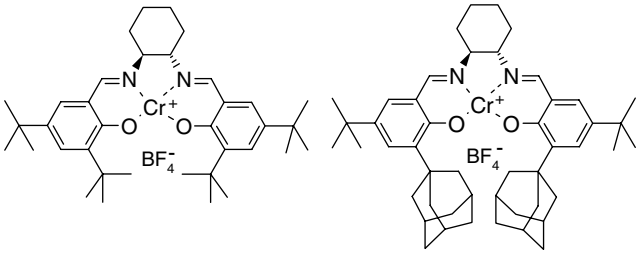
Abstract—An enantioselective carbonyl-ene reaction of alkyl glyoxylates with various 1,1-disubstituted olefins, catalysed by chiral (salen)Cr(III)BF_4 complexes, has been studied. We found that a chromium complex bearing adamantyl substituents at the 3,3′-positions of the salicylidene moiety catalysed the reaction with much greater selectively than the classic Jacobsen-type catalyst. The reaction proceeded effectively under undemanding conditions in the presence of 2 mol % of the catalyst in an acceptable yield and with 59–92% ee.

The carbonyl-ene reaction of glyoxylates with olefins is a method of choice for the construction of α-hydroxy acids containing a double bond at the γ,δ-position, which are important precursors for synthetic chemistry. The enantioselective version of this simple and atom-economic reaction has been intensively investigated since 1989, when Mikami et al. applied BINOL–titanium(IV) complexes as catalysts.[1,2] The literature also describes other chiral catalytic systems utilised for this reaction,[2,3] mainly based on bis-oxazoline (Cu,[4,5] Sc[6]) and bisphosphine (Ni,[7] Pd,[7,8] Pt[9]) ligands. BINOL–Ti(IV)[1] as well as bis-oxazoline–Cu(II) complexes[5] seem to be the most efficient and general catalytic systems for the enantioselective glyoxylate-ene reaction.

Taking into account our previous investigations on asymmetric catalytic hetero-Diels–Alder reactions[10] and allylation of aldehydes,[11] we focused our attention on salen–chromium(III) complexes **1a**.[12] So far, there is no example of the application of C_2-symmetrical Jacobsen complexes to the ene reaction, although Yamada et al.[13] demonstrated that the related chiral β-ketoiminato cobalt(III) efficiently catalysed the ene reaction of phenylglyoxal with 1,1-disubstituted alkenes. Furthermore, chiral Cr(III) tridentate Schiff-base complexes were employed by Jacobsen in the ene-type reactions of 2-methoxy- or 2-TMSO-propene with aromatic and aliphatic aldehydes.[14]

Recently, we have shown that the simple introduction of a bulky group at the 3- and 3′-positions of the salicylidene moiety of salen chromium(III) complexes increased the enantioselectivity of the allylation of aldehydes[15] and hetero-Diels–Alder (HDA) reactions.[16] Introduction of the adamantyl group to give complex **1b** led to excellent selectivity (up to 98% ee), especially in the reaction of alkyl glyoxylates with cyclohexa-1,3-diene.[16] Exploring the range of dienes, we found that, in the case of 2,3-dimethylbuta-1,3-diene, the use of catalyst **1b** did not improve the selectivity of the HDA reaction; instead the chemoselectivity was shifted towards the ene product (Scheme 1). Moreover, the enantiomeric purity of the homoallylic alcohols obtained increased markedly.



1a **1b**

This result prompted us to examine the sterically modified Jacobsen's chromium complexes in the ene reaction.

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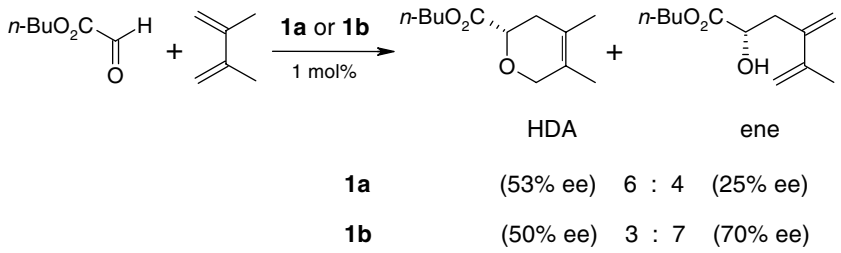
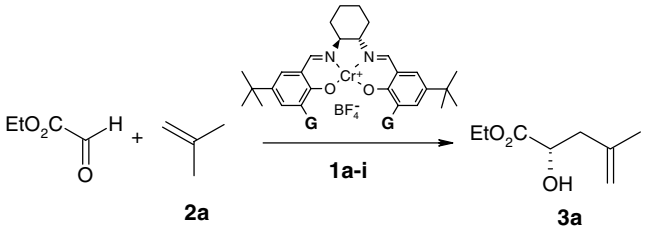


Scheme 1. Chemoselectivity of the (salen)Cr(III)-catalysed reaction of 2,3-dimethylbuta-1,3-diene with glyoxylate.

The (salen)chromium(III)-catalysed reaction of ethyl glyoxylate with isobutylene (**2a**) in toluene was investigated first (Scheme 2). Indeed, increasing the steric hindrance at the 3,3′-positions of the salicylidene moiety of the catalyst exerted a beneficial effect on the enantioselectivity (Table 1). In the series of complexes **1c**–**e** with dialkylphenylmethyl groups, the selectivity increased with the size of the alkyl substituent (entries 2–4). The *ortho* substituents on the aromatic groups (**1i**) further improved the selectivity, in contrast to those in the *para* position (**1f**–**h**) (compare entries 5–7 and 8). The best selectivity was obtained using catalyst **1b** bearing large adamantyl groups (entry 9).

It is worth mentioning that catalyst **1b** not only improved the selectivity of the model reaction from 15% to 79% ee (compared to the classic Jacobsen catalyst), but it is also readily accessible on a multigram scale from inexpensive commercial chemicals via a short, efficient synthesis.[16]

Having the best catalyst in hand, we decided to optimise the reaction conditions. Out of the solvents tested (methylene chloride, toluene, methyl *tert*-butyl ether, THF, acetonitrile and nitromethane), toluene seemed to be the best medium in terms of the enantioselectivity. Further optimisation of the reaction conditions (summarised in Table 2) showed that none of the reaction variables such as temperature, concentration or catalyst loading had a significant influence on the enantioselectivity (Table 2, entries 1–6). Nonetheless, with higher temperature and catalyst loading, better yields were obtained. Finally, the alcohol residue in the glyoxylate was changed, which resulted in a drop in enantioselectivity for more branched groups (Table 2, see entries 1, 7 and 8). It is interesting that extension of the reaction time over 24 h did not improve the yield significantly.



Scheme 2. The trial reaction.

Table 1. Results of the trial reaction as a function of catalyst structure[a]

Entry	Catalyst		Yield (%)	ee[b] (%)
	No.	G		
1	**1a**	*t*-Bu	53	15
2	**1c**	$C(Me)_2Ph$	48	35
3	**1d**	$C(Et)_2Ph$	50	53
4	**1e**	$C(n\text{-}Pr)_2Ph$	36	71
5	**1f**	$C(Me)_2C_6H_4p\text{-}Cl$	51	31
6	**1g**	$C(Me)_2C_6H_4p\text{-}OMe$	52	36
7	**1h**	$C(Me)_2C_6H_4p\text{-}Me$	50	36
8	**1i**	$C(Me)_2C_6H_4o\text{-}Me$	42	48
9	**1b**	Adamantyl	49	79

[a] Reaction conditions: 1 mol % of catalyst **1a**–**i**, 1 mmol of ethyl glyoxylate, 3 mmol of olefin in 1 ml of toluene, rt, 24 h.
[b] Determined by GC on a chiral capillary β-dex 120 column.

The catalytic system proved to be generally applicable for the reaction of 1,1-disubstituted olefins **2a**–**h** under the optimised conditions, leading to the corresponding products of type **3** in moderate to good yields and selectivities, when 2 mol % of **1b** was applied as a catalyst (Table 3).[17] Methyl alkyl disubstituted olefines **2b**–**c** reacted predominantly at the less hindered methyl group, with regioselectivities higher for the more branched substituents (entries 2 and 3). Moreover, the enantioselectivity was higher for more branched substrates (entries 1, 3 and 4), with the best result of 92% ee obtained for 2,3,3-trimethyl-1-butene (**2d**). 2-Arylpropenes **2e**–**f** were slightly less effective substrates in the reaction, leading to products with enantioselectivities around 60% ee (entries 5 and 6). Methylenecyclohexane (**2g**) reacted with a selectivity comparable to α-methylstyrene, whereas the more reactive methylenecyclopentane (**2h**) gave nearly a racemate (entries 7 and 8). Fortunately, the selectivity improved with a decrease in temperature (entry 9).

The absolute configuration of selected products (**3a**, **3g**) was determined by reduction to the corresponding diols and subsequent comparison with a sample of known configuration (Scheme 3). The reference diols were obtained by reduction of the corresponding (2*R*)-bornane-10,2-sultam derivatives, the configuration of which was unambiguously proved via X-ray crystallography.[18] The configuration of the product turned out to be (*S*) whenever the (*S*,*S*)-catalyst was used. The result is in agreement with our earlier observations of the salen-catalysed reactions of glyoxylates[10,11,15,16] and matches the previously presented model of chirality transfer.[10c,11b]

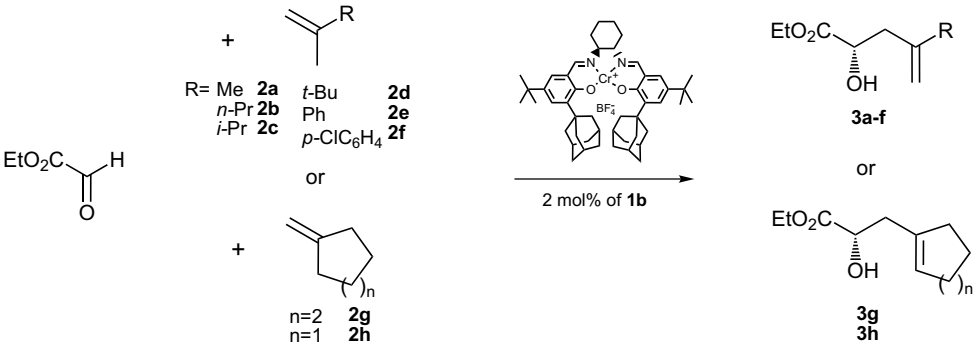
To conclude, we have shown that the sterically modified complex **1b** catalysed the ene reaction of alkyl glyoxylates with good enantioselectivities (up to 92% ee), while

Table 2. Results of the trial reaction under various reaction conditions[a]

Entry	Mol % of **1b**	Concentration of the glyoxylate	T (°C)	Alkyl in the glyoxylate	Yield (%)	ee[b] (%)
1	1	1	20	Et	49	79
2	2	1	20	Et	64	79
3	5	1	20	Et	79	79
4	1	1	4	Et	32	81
5	1	1	−25	Et	7	80
6	1	0.5	20	Et	47	79
7	1	1	20	*n*-Bu	50	76
8	1	1	20	*i*-Pr	45	42

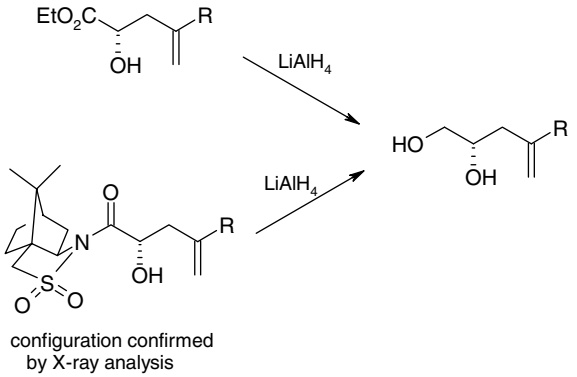
[a] Reaction conditions: **1b** as catalyst, 1 mmol alkyl glyoxylate, 3 mmol of olefin in toluene, 24 h.
[b] Determined by GC on a chiral capillary β-dex 120 column.

Table 3. Reaction of various olefins under optimised conditions[a]



Entry	Olefin R	Yield (%)	Regioselectivity	ee[b] (%)
1	**2a** (Me)	64	—	79
2	**2b** (*n*-Pr)	64	72:28	89 (55)[c]
3	**2c** (*i*-Pr)	65	89:11	84 (62)[c]
4	**2d** (*t*-Bu)	63	—	92
5	**2e** (Ph)	56	—	61[d]
6	**2f** (C_6H_4*p*-Cl)	68	—	59[d]
7	**2g**	69	—	63
8	**2h**	70	—	4
9[e]	**2h**	58	—	30

[a] Reaction conditions: 2 mol % of catalyst **1 b**, 1 mmol ethyl glyoxylate, 1.5 mmol of olefin (3 mmol in the case of **2a**) in 1 ml of toluene, rt, 24 h.
[b] Determined by GC on a chiral capillary β-dex 120 column.
[c] ee of the minor regioisomer given in parentheses.
[d] Determined by HPLC on a Chiracel AS-H column.
[e] The reaction was carried out at −25 °C.



Scheme 3. Determination of the absolute configuration of selected products.

the classic Jacobsen-type catalyst led to nearly racemic mixtures.

Acknowledgements

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