Sterically Modified Chiral (Salen)Cr(III) Complexes – Efficient Catalysts for the Oxo-Diels–Alder Reaction between Glyoxylates and Cyclohexa-1,3-diene

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Abstract: A group of chiral [(salen)Cr(III)]$^+BF_4^-$ complexes, with enhanced steric hindrance in 3,3′-positions of salicylidene moiety, has been synthesized and applied for the oxo-Diels–Alder reaction of alkyl glyoxylates with cyclohexa-1,3-diene. A readily accessible complex that bears bulky adamanthyl substituents revealed its potential, leading to the cycloadducts with excellent selectivity (up to *endo*/*exo* 99:1, 98% ee), considerably better than the classic Jacobsen catalyst.

Key words: asymmetric catalysis, glyoxylates, hetero-Diels–Alder reaction, salen–chromium complexes

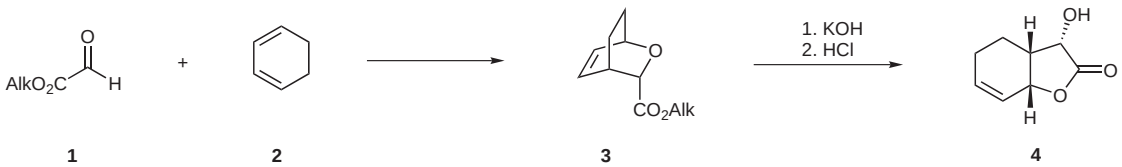
Enantiomerically pure compounds are of steadily growing interest for pharmaceutical, agrochemical or fragrance industry. Asymmetric catalysis opens an economically and environmentally preferable route to homochiral substances. The strategy offers a unique possibility for transferring chiral information from a catalyst to a number of product molecules. Although thousands of catalytic systems have been described, only a few of them prove efficient in a wide variety of reactions. So-called 'privileged' chiral ligands[1] such as BINOL,[2] BINAP,[3] salen[4] or bisoxazoline[5] have been successfully applied in numerous asymmetric transformations including C–C bond formation. The hetero-Diels–Alder (HDA) reaction is of particular interest due to high synthetic potential of its products.[6] Vast majority of HDA reactions are cycloadditions of activated dienes (eg. Danishefsky's diene) to simple aldehydes.[6] Jørgensen was the first to concern the reactions of activated aldehydes with non-activated dienes.[7] Although only a few papers have appeared in the area, high state-of-the-art has been achieved.[8]

Among products of the reaction of glyoxylates **1** with non-activated dienes (e.g. cyclohexa-1,3-diene **2**) of particular interest is the cycloadduct **3** (Scheme 1). It is that useful mainly due to simplicity of conversion to bicyclic crystalline lactone **4**[7,9] (Scheme 1), a versatile chiral building block.[10]

A few years ago, we have published a paper concerning the classic [(salen)Cr(III)]$^+$-catalyzed cycloadditions of non-activated dienes to alkyl glyoxylates; the selectivities that we obtained, however, were usually moderate.[11] Recently, we have shown that increase in steric hindrance in 3,3′-positions of salicylidene moiety of the catalyst exerts beneficial effect on selectivity of [(salen)Cr(III)]$^+$-catalyzed high-pressure addition of allylstannanes to aldehydes.[12] The positive effect of such enhancement of steric hindrance on selectivity has also been observed in other reactions catalyzed by metallosalen complexes.[13]

In this paper, we would like to apply the concept of steric modification of salen complexes to HDA reaction. After preparation of several sterically modified salen complexes of type **5** (Figure 1), we decided to screen their activity using the [4+2] cycloaddition of 1,3-diene **2** to *n*-butyl glyoxylate (**1a**) as a model reaction (Scheme 2).[14] The results are presented in Table 1. The replacing of one among the three methyls in *tert*-butyl groups positioned at 3 and 3′ of classic Jacobsen catalyst **5a** with phenyl resulted in a significant increase in both diastereo- and enantioselectivity (entries 1 and 2). Further development of the steric hindrance by replacing two remaining methyl groups with ethyl (entry 3) or even *n*-propyl (entry 4) caused further improvement in the selectivity of this reaction.

Extension of steric hindrance may also be achieved by enlargement of the aromatic group of the discussed substituent. Indeed, replacement of phenyl with 2-methylphenyl has a beneficial effect on selectivity, contrary to 4-methylphenyl that caused almost no effect (entries 2, 5, 6). Unfortunately, increased steric hindrance lowered the yield



1 2 3 4

Scheme 1

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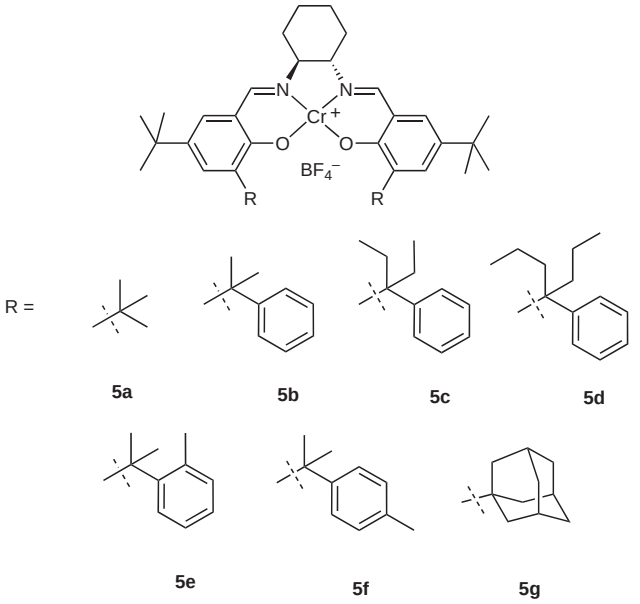


Figure 1 The chromium(III) complexes used

down to 30% for **5d** as a catalyst. Simple introduction of 1-adamanthyl resulted in exceptionally high both endo- and enantioselectivity of a 95:5 ratio and 95% ee, respectively, when as little as 1 mol% of catalyst was used.[15] Noteworthy is the fact, that the complex **5g**[16] is readily available on multigram scale in a short and efficient synthesis from commercial and inexpensive materials.[17,18]

Table 1 Results of the Model Reaction as a Function of Catalyst Structure[a]

Entry	Catalyst	Yield of **3a** (%)	*endo*/*exo*[b]	ee for *endo* (%)[b]
1	**5a**	62	66:34	71
2	**5b**	50	83:17	92
3	**5c**	47	93:7	94
4	**5d**	30	95:5	95
5	**5e**	42	91:9	96
6	**5f**	48	82:18	91
7	**5g**	48	95:5	95

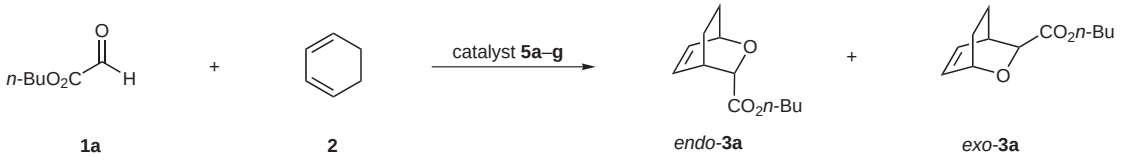
[a] *Conditions*: 1 mol% of the catalyst, *n*-butyl glyoxylate (1 mmol), cyclohexa-1,3-diene (1.5 mmol) in 1 mL of toluene, 20 °C, 24 h.
[b] The *endo*/*exo* ratio and ee were determined by GC on a chiral capillary β-dex 120 column (30 m × 0.25 mm); nitrogen – 100 kPa, oven temp. 150 °C (see ref. 19).

A natural consequence of the above studies was to optimize the reaction conditions (Table 2). Among the investigated solvents (entries 1–5), toluene appeared to be the most efficient in terms of stereoselectivity (*endo*/*exo* 95:5, 95% ee for *endo*). Better yields, though, were obtained when the reaction was carried out in dichloromethane, but the selectivities were significantly lower (entry 2). The Lewis base type solvents, like acetonitrile, seemed to be completely ineffective, probably due to strong coordination to catalyst. Of interest was the fact that the reaction proceeded quite well without any solvent (entry 6), which constitutes a definite advantage of this procedure. The reaction also does not require strictly anhydrous conditions and addition of molecular sieves (the latter usually causes decrease in stereoselectivity).

Lowering the temperature caused only an insignificant improvement in stereoselectivity, at a cost of decrease of yield – slight when temperature was decreased to 4 °C or even marked for –25 °C (entries 7 and 8). Increase in the amount of diene used enhanced the yield, but slightly hampered both diastereo- and enantioselectivity (entries 9 and 10). On the other hand, dilution of the reaction mixture had no effect on selectivity, but lowered the yield markedly (entry 11). Finally, we examined the effect of catalyst loading on the reaction performance (entries 12–14). Augmentation of the amount of catalyst used exerted a beneficial effect not only on the yield but also on the selectivity. When the reaction was run with 5 mol% of catalyst **5g**, the product was isolated in 83% yield as an almost pure *endo*-adduct (*endo*/*exo* 99:1) having 98% enantiomeric purity (entry 13). However, decrease in catalyst loading to 0.5 mol% diminished both yield and selectivity (entry 14).

Having the optimal parameters in hand, we decided to perform the [4+2] cycloaddition of cyclohexa-1,3-diene (**2**) with various alkyl glyoxylates of type **1** (Table 3).[19] The reactions were carried out at room temperature in toluene with 2 mol% of complex **5g** as a catalyst, which seemed to be the best balance between catalyst loading and reaction results. For primary (*n*-Bu and Et, entries 1 and 2) as well as for secondary (*i*-Pr, entry 3) alkyl groups the results were very similar. In the case of the bulky alkyl groups (*t*-Bu, entry 4), both yield and selectivities were lower.

Prompted by excellent results of the model reaction catalyzed by **5g** we decided to investigate the possibility of using other dienes, e.g. 2,3-dimethylbuta-1,3-diene. Unfortunately, the obtained results were much worse than those for classic Jacobsen catalyst **5a**.



Scheme 2 The model reaction

Table 2 Dependence of the Results of the Model Reaction on Various Reaction Conditions[a]

Entry	Concn of **5g** (mol%)	Diene **2** (equiv)	Concn of **1a** (mol/L)	Solvent	Temp (°C)	Yield of **3a** (%)	*endo*/*exo*[b]	ee for *endo* (%)[b]
1	1	1.5	1	Toluene	20	48	95:5	95
2	1	1.5	1	CH_2Cl_2	20	63	82:8	78
3	1	1.5	1	*i*-$PrNO_2$	20	24	76:24	67
4	1	1.5	1	MTBE	20	46	91:9	94
5	1	1.5	1	MeCN	20	4	54:46	7
6	1	1.5	1	No solvent	20	62	90:10	91
7	1	1.5	1	Toluene	4	44	96:4	96
8	1	1.5	1	Toluene	–25	9	96:4	96
9	1	3	1	Toluene	20	50	92:8	93
10	1	6	1	Toluene	20	57	91:9	93
11	1	1.5	0.25	Toluene	20	22	95:5	95
12	2	1.5	1	Toluene	20	68	97:3	97
13	5	1.5	1	Ttoluene	20	83	99:1	98
14	0.5	1.5	1	Toluene	20	31	84:16	88

[a] Reaction time: 24 h.
[b] The *endo*/*exo* ratio and ee were determined by GC on a chiral capillary β-dex 120 column (see ref. 19).

Table 3 Reactions of Various Alkyl Glyoxylates under Optimized Conditions[a]

Entry	Glyoxylate (Alk)	Yield (%)	*endo*/*exo*[b]	ee for *endo* (%)[b]
1	**1a** (*n*-Bu)	68	97:3	97
2	**1b** (Et)	69	94:6	95
3	**1c** (*i*-Pr)	66	94:6	94
4	**1d** (*t*-Bu)	51	73:27	83

[a] *Conditions*: 2 mol% of catalyst **5g**, alkyl glyoxylate (1 mmol), cyclohexa-1,3-diene (1.5 mmol) in 1 mL of toluene, 20 °C, 24 h.
[b] The *endo*/*exo* ratio and ee were determined by GC on a chiral capillary β-dex 120 column (see ref. 19).

The absolute configuration of major *endo*-**3a**–**d** products were determined by their correlation with bicyclic lactone **4** (Scheme 1).[7a,b] In all cases, when (1*S*,2*S*)-salen complexes **5a**–**g** were applied for the reaction of **1** with **2**, cycloadduct (1*R*,3*S*,4*S*)-*endo*-**3**, corresponding to the levorotatory lactone **4**, was obtained.[7a,b]

It was consistent with our previous observations of various metallosalen-catalyzed reactions of aldehydes.[11,12,20] The results also supported the recently presented model of chirality transfer in metallosalen-catalyzed cycloadditions and additions to aldehydes.[20]

Concluding, we have shown that extension of steric properties of the Jacobsen catalyst has beneficial effects on diastereo- and enantioselectivity of the HDA reaction of **1** with **2**. Employing of readily available catalyst **5g** opened a simple and economic route to the cycloadduct **3** of particular interest in synthesis.

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(14) **General Procedure for Cycloaddition of Cyclohexa-1,3-diene to Alkyl Glyoxylates.**
To a solution of catalyst **5a**–**g** (0.5–5 mol%) and alkyl glyoxylate (1 mmol, freshly distilled from P_2O_5) in toluene (1 mL) cyclohexa-1,3-diene (150 μL, 1.5 mmol) was added, and the solution was stirred for 24 h at r.t. Afterwards the reaction mixture was subjected to chromatography (hexanes–EtOAc, 9:1).

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(16) **Analytical Data for Salen Ligand Precursor of 5g.**
Mp 247–248 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.23 (s, 18 H), 1.15–1.35 (m, 2 H), 1.40–1.50 (m, 2 H), 1.65–2.00 (m, 10 H), 2.04–2.09 (m, 6 H), 2.13–2.18 (m, 12 H), 3.26–3,34 (m, 2 H), 6.96 (d, *J* = 2.2 Hz, 2 H), 7.24 (d, *J* = 2.2 Hz, 2 H), 8.29 (s, 2 H), 13.64 (s, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.4, 29.2, 31.4, 33.3, 34.1, 37.2, 37.2, 40.4, 72.4, 117.9, 126.0, 126.7, 136.6, 139.9, 158.2, 166.0. $[\alpha]_D^{25}$ +325.7 (*c* 0.58, $CHCl_3$). IR (KBr): 2950, 2905, 2850, 1625, 1598 cm^{-1}. Anal. Calcd for $C_{48}H_{66}N_2O_2$: C, 82.00; H, 9.46; N 3.98. Found: C, 82.06; H, 9.39, N, 3.82. Catalyst **5g**: HRMS: *m/z* calcd for $C_{48}H_{64}N_2O_2Cr$ $[M - BF_4]^+$: 752.4367; found: 752.4392.

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(19) **Analytical Data for Cycloadducts 3.**
Compound **3a** (ref. 11): GC (column β-dex 120, i.d. 30 m × 0.25 mm, carrier gas – nitrogen 100 kPa, oven temp. 150 °C): $t_{R1[exo\text{-}\mathbf{3a}]}$ = 29.9, $t_{R2[exo\text{-}\mathbf{3a}]}$ = 30.7, $t_{R[(3S)\text{-}endo\text{-}\mathbf{3a}]}$ = 33.1, $t_{R[(3R)\text{-}endo\text{-}\mathbf{3a}]}$ = 34.1 min.
Compound **3b** (ref. 7a,b and 8a): GC (column β-dex 120, i.d. 30 m × 0.25 mm, carrier gas – nitrogen 100 kPa, oven temp. 140 °C): $t_{R1[exo\text{-}\mathbf{3b}]}$ = 18.8, $t_{R2[exo\text{-}\mathbf{3b}]}$ = 19.5, $t_{R[(3S)\text{-}endo\text{-}\mathbf{3b}]}$ = 21.2, $t_{R[(3R)\text{-}endo\text{-}\mathbf{3b}]}$ = 21.8 min.
Compound **3c**: GC (column β-dex 120, i.d. 30 m × 0.25 mm, carrier gas – nitrogen 100 kPa, oven temp. 140 °C): $t_{R1[exo\text{-}\mathbf{3c}]}$ = 19.8, $t_{R2[exo\text{-}\mathbf{3c}]}$ = 20.5, $t_{R[(3S)\text{-}endo\text{-}\mathbf{3c}]}$ = 21.7, $t_{R[(3R)\text{-}endo\text{-}\mathbf{3c}]}$ = 22.6 min. ^{1}H NMR for *endo*-**3c** (500 MHz, $CDCl_3$): δ = 1.21 (d, *J* = 1.8 Hz, 3 H), 1.22 (d, *J* = 1.8 Hz, 3 H), 1.26–1.42 (m, 2 H), 1.71–1.77 (m, 1 H), 2.03–2.10 (m, 1 H), 3.06–3.10 (m, 1 H), 4.26 (d, *J* = 1.8 Hz, 1 H), 4.56–4.59 (m, 1 H), 5.01 (dq, *J* = 1.8, 1.8 Hz, 1 H), 6.23–6.28 (m, 1 H), 6.51–6.55 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.9, 21.7, 25.7, 33.2, 66.4, 68.0, 74.2, 130.4, 134.7, 171.7.
Compound **3d**: GC (column β-dex 120, i.d. 30 m × 0.25 mm, carrier gas – nitrogen 100 kPa, oven temp. 150 °C): $t_{R1[exo\text{-}\mathbf{3d}]}$ = 15.5, $t_{R2[exo\text{-}\mathbf{3d}]}$ = 15.9, $t_{R[(3S)\text{-}endo\text{-}\mathbf{3d}]}$ = 16.2, $t_{R[(3R)\text{-}endo\text{-}\mathbf{3d}]}$ = 16.7 min. ^{1}H NMR for *endo*-**3d** (500 MHz, $CDCl_3$): δ = 1.18–1.28 (m, 1 H), 1.29 (s, 9 H), 1.81–1.87 (m, 1 H), 1.93–2.02 (m, 1 H), 2.16–2.24 (m, 1 H), 2.46–2.53 (m, 1 H), 4.51 (d, *J* = 7.3 Hz, 1 H), 4.59–4.63 (m, 1 H), 5.89–5.94 (m, 1 H), 6.18–6.23 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.1, 23.4, 27.9, 39.7, 70.7, 71.5, 75.5, 122.2, 136.0, 175.4.

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