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Improvement of the reactivity and selectivity of the oxo-Diels–Alder reaction by steric modification of the salen–chromium catalyst

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ABSTRACT

Salen–chromium(III) complexes bearing sterically demanding substituents at the 3 and 3′ positions are applied for the oxo-Diels–Alder reaction of various aldehydes with Danishefsky's diene. The readily-accessible complex bearing a bulky 3-phenylpent-3-yl substituent revealed its potential affording the cycloadducts with improved reactivity and excellent selectivities up to 96% ee, being considerably superior to the classic Jacobsen's catalyst.

The oxo-Diels–Alder reaction is a very useful transformation in synthetic organic chemistry.[1] Using simple substrates—aldehydes and butadienes—it enables a straightforward synthesis of a dihydropyran system, an extremely useful building block, bearing up to three stereogenic centers. From the economical and environmental points of view, asymmetric catalysis is a method of choice for the preparation of enantio- and diastereomerically enriched dihydropyrans, as it allows transduction of chiral information from a catalyst molecule to a number of product molecules. Since the pioneering works of Danishefsky and co-workers[2] and Yamamoto and co-workers[3], numerous catalytic systems have been introduced including BINOL,[3a–d,4] bisoxazoline[5] and salen[6] complexes.

A decade ago, Jacobsen applied salen–chromium(III) complexes as efficient catalysts for the reaction of Danishefsky's diene with aldehydes.[6a] Moreover, it was shown that the reaction proceeded via a direct [4+2] cycloaddition, rather than by the Mukaiyama-aldol process. A modification of the classic Jacobsen catalyst by introduction of the binaphthol-derived salicylaldehyde moiety was introduced by Katsuki and co-workers.[6b] Berkessel and Vogl,[6h] on the other hand, proposed a complex based on the rigid *endo,endo*-2,5-diaminonorbornane (DIANANE) backbone. In both cases, the selectivities in reactions of Danishefsky's diene were improved with respect to Jacobsen's catalyst **1a** (Fig. 1).

Recently, both we[7] and others[8] have shown that enlargement of the steric hindrance at position 3 of the salicylidene moiety of the Jacobsen catalyst **1a** has a beneficial effect on the selectivity of cycloadditions and nucleophilic additions to aldehydes. In particular, we have reported that introduction of an adamantyl group to the structure of the chromium catalyst improved the diastereo- and enantioselectivity of the hetero-Diels–Alder reaction of alkyl glyoxylate with cyclohexa-1,3-diene.[7b] Thus, we decided to extend

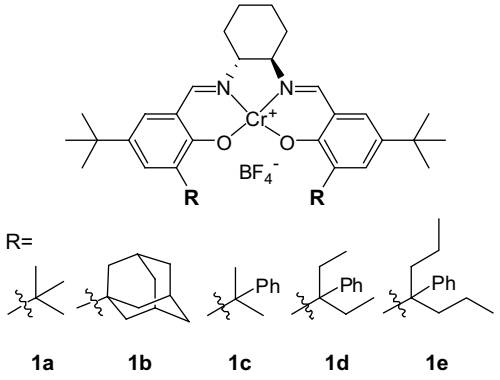

Figure 1. Salen–chromium(III) complexes.

the scope of the procedure to the reaction of Danishefsky's diene with simple aldehydes. Unfortunately, in the model reaction with benzaldehyde, catalyst **1b**, which performed best in the cycloaddition of cyclohexadiene to *n*-butyl glyoxylate, gave very poor results in terms of both yield and enantioselectivity (Table 1, entry 2).

In light of the above observations, we focused our attention on the family of salen complexes **1c–e** bearing dialkylbenzyl substituents at position 3 of the salicylidene moiety (Fig. 1). The catalysts not only gave results comparable to **1b** in cycloadditions of cyclohexa-1,3-diene but also proved their efficiency in the high-pressure addition of allylstannanes to simple nonactivated aldehydes.[7a] In fact, the modified complexes **1c–e** gave stereochemical results superior to the classic system **1a** in the reaction of Danishefsky's diene **2** with benzaldehyde **3a** (Table 1, compare entries 1 and 3–5). It is noteworthy that the modified complex **1d** also produced slightly higher yields. The most sterically hindered complex **1e** produced much lower yields, which is consistent with our previous observations.[7b,7c]

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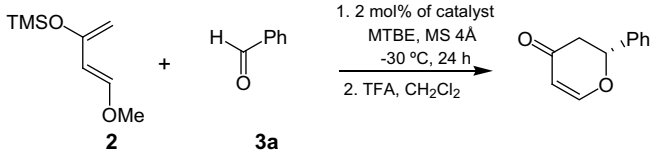
Table 1
Performance of the modified catalysts in the model reaction of benzaldehyde with Danishefsky's diene[a]



Entry	Catalyst	Yield (%)	ee[b] (%)
1	**1a**	84	86
2	**1b**	48	52
3	**1c**	84	93
4	**1d**	92	94
5	**1e**	33	93

[a] The reaction was carried out with 1 mmol of aldehyde, 1 mmol of Danishefsky's diene, 300 mg of 4 Å molecular sieves, and 2 mol % of the catalyst in 200 μl of methyl *t*-butyl ether (MTBE) at −30 °C for 24 h.
[b] Determined by GC on a chiral capillary β-dex 120 column.

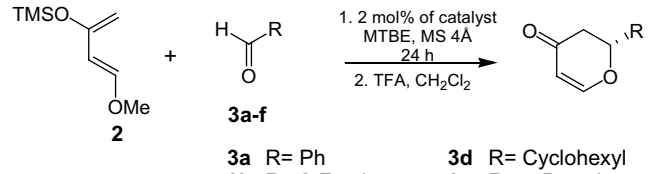
The reaction conditions developed by Jacobsen et al. seemed to be optimal, when **1c** was used instead of **1a**. Neither a change of the solvent nor a change of the concentrations improved the results obtained. However, a decrease in the amount of the catalyst to 1 mol % had a minor influence on the outcome of the reaction. Further reduction of the amount of the catalyst to 0.5 mol %, decreased the yield slightly. The enantiomeric purity of the product obtained was independent of the amount of catalyst.

To show the catalytic efficiency and versatility of the modified catalysts, complex **1d** was compared with the classic catalyst **1a** in the reactions of various aldehydes, viz aromatic **3a–c**, aliphatic **3d–e**, and unsaturated **3f**.[9] In all cases, catalyst **1d** gave results superior to **1a** in terms of both yield and enantioselectivity (Table 2). The best improvement in enantioselectivity was achieved for furfural **3b** and cinnamaldehyde **3f** as substrates (an increase from 73% to 93% ee and from 68% to 89% ee, respectively). As previously mentioned, the reaction can be carried out with as little as 1 mol % of catalyst with the same selectivity and at only a slight cost to the yield (Table 2, entries 2 and 4, yields in parentheses).

Additionally, the complex **1d** gave results comparable to those reported by Katsuki for (salen)Cr(III) catalysts with the salicylaldehyde moiety derived from a chiral binaphthol subunit.[6b] The catalyst **1d** also proved to be superior to the catalyst with an *endo,endo*-2,5-diaminonorbornane backbone (DIANANE) designed by Berkessel,[6h] giving slightly better yields and enantioselectivities with a significantly lower catalyst loading, 1 mol % versus 4 mol %. It is worth mentioning here that our catalyst is easily synthesized from inexpensive materials, compared to the above mentioned complexes.[7a]

In conclusion, we have shown that the readily available sterically-modified catalyst **1d** exerted a higher reactivity and selectivity in the reaction of Danishefsky's diene with aldehydes compared with the classic Jacobsen catalyst.

Table 2
A comparison of the modified catalyst **1d** with the classic **1a** in the reactions of various aldehydes with Danishefsky's diene[a]



3a R= Ph **3d** R= Cyclohexyl
3b R= 2-Furyl **3e** R= *n*-Pentyl
3c R= 2-Thienyl **3f** R= PhCH=CH

Entry	Aldehyde	Temperature (°C)	Catalyst	Yield[b] (%)	ee[c] (%)
1	**3a**	−30	**1a**	84	86
2	**3a**	−30	**1d**	92 (87)	94
3	**3b**	−10	**1a**	87	73
4	**3b**	−10	**1d**	90 (86)	93
5	**3c**	−30	**1a**	79	87
6	**3c**	−30	**1d**	81	95
7	**3d**	−20	**1a**	69	92
8	**3d**	−20	**1d**	72	96
9	**3e**	−40	**1a**	55	86
10	**3e**	−40	**1d**	67	90
11	**3f**	0	**1a**	64	68[d]
12	**3f**	0	**1d**	76	89[d]

[a] The reaction was carried out with 1 mmol of the aldehyde, 1 mmol of Danishefsky's diene, 300 mg of 4 Å molecular sieves, and 2 mol % of the complex **1a** or **1d** in 200 μl of MTBE for 24 h.
[b] Isolated yields. Values in parentheses refer to the reaction carried out with 1 mol % of **1d**
[c] Determined by GC on a chiral capillary β-dex 120 column.
[d] Determined by HPLC on a Chiralpak OD-H column.

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