Asymmetric Hetero Diels–Alder Reaction Catalyzed by Chromium Complexes of Heterogeneously Hybridized Salen/Salan Ligands

Satomi Eno, Hiromichi Egami, Tatsuya Uchida, and Tsutomu Katsuki*
Department of Chemistry, Faculty of Science, Graduate School, Kyushu University, 33 Hakozaki, Higashi-ku, Fukuoka 812-8581

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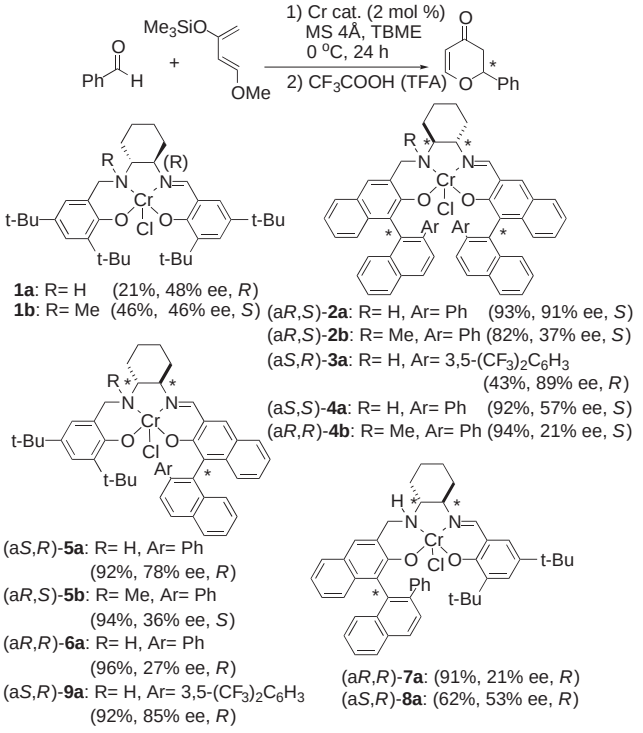
Various heterogeneously or homogeneously hybridized salen/salan ligands were synthesized, and study of hetero Diels–Alder reactions using their chromium complexes as catalysts revealed that a well-designed heterogeneously hybridized ligand serves as a chiral auxiliary as efficiently as the homogeneously hybridized ligand and its chromium complex has high catalytic activity.

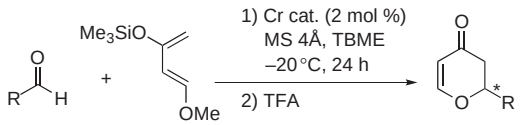
Metal(salen) complexes have been widely used as catalysts in asymmetric syntheses.[1] On the other hand, catalysis by metal(salalen) complexes, one imino bond-reduced derivative of salen complexes (salalen = salen/salan hybrid), has not been explored until recently. However, seminal studies on asymmetric epoxidation[2] and hydrophosphonylation[3] with salalen complexes disclosed their unique catalytic properties distinct from those of metal(salen) complexes.[4] These properties are likely to be related to their unique structure:[2] i) a chiral metal-coordinating nitrogen atom, ii) a flat, rigid salen and a flexible salan units, and iii) a cis-β configuration. Moreover, we recently found that Ru(salalen)$(CO)_2$ complexes consisting of different salen and salan units differ in ligand conformation and asymmetric catalysis.[5] From these results, we inferred that the roles of the salan and the salen units in asymmetric catalysis should be different and that compact but efficient metal(salalen) complexes might be constructed by a combination of achiral salan and chiral salen units or vice versa. Thus, we were intrigued by catalysis by the heterogeneously hybridized salalen complexes. In the course of our study, Berkessel et al. reported asymmetric epoxidation with both types of Ti(salalen) complexes as the catalyst.[6] However, despite the possibilities for heterogeneous-type catalysts, they have not achieved success.[5,6] In this paper, we describe a highly enantioselective hetero Diels–Alder (HDA) reaction[7,8] using a heterogeneous-type Cr(salalen) complex **9a** as the catalyst.

Cr^{III}(salalen) complexes **1**–**9** were prepared by modifying Jacobsen's method for synthesizing Cr^{III}(salen) complexes.[9,10] We first examined the HDA reaction between benzaldehyde and Danishefsky diene at 0 °C in *t*-butyl methyl ether (Scheme 1).[10,11] Complexes **1a** and **1b** exhibited similar modest catalytic activity and enantioselectivity, although their asymmetric induction was opposite from each other. On the other hand, (a*R*,*S*)-N-H complex **2a** induced better asymmetry than (a*R*,*S*)-N-Me **2b**, although their asymmetric induction was identical. The reaction with (a*S*,*R*)-**3a** was of significantly low yield, though the enantioselectivity was high. (a*S*,*S*)-**4a** was a less efficient catalyst than (a*R*,*S*)-**2a** in terms of asymmetric induction. An N-H complex **5a** that carried the binaphthyl group only at the salen unit also showed good enantioselectivity of 78% ee. Again, the N-Me complex **5b** was less efficient. (a*R*,*R*)-**6a** induced only modest asymmetry. Complexes **7a** and **8a** that have



Scheme 1. Asymmetric HDA reaction using homogeneous or heterogeneous Cr(salalen) complexes as catalysts. The values in parentheses are the isolated yield, % ee, and configuration of each product.

the binaphthyl group at the salan unit were inferior catalysts. It is noteworthy that **9a**, possessing a slightly modified naphthyl group, showed better enantioselectivity than the parent **5a**, without reducing its catalytic activity. These results suggested that the presence of a (a*R*,*S*)- or (a*S*,*R*)-salen unit and a secondary amine in the salan unit is essential for high asymmetric induction, while the bulkiness and the stereochemistry of the salan unit induce a secondary effect. Considering these two requirements, we focused our efforts on the catalysis of **2a** and **9a** as typical homo- and heterogeneous-type catalysts. At



R= Ph, **2a**: 60%, 93% ee, *S* R= Ph(CH$_2$)$_2$, **2a**: 38%, 94% ee, *R*
R= Ph, **9a**: 70%, 89% ee, *R* R= Ph(CH$_2$)$_2$, **9a**: 67%, 94% ee, *S*
R= Ph, **2a**: 11%, 94% ee, *S* (in toluene)
R= Ph, **9a**: 95%, 91% ee, *R* (in toluene)

Scheme 2. Asymmetric HDA reaction with **2a** and **9a** as catalysts.

Table 1. Asymmetric HDA reaction of various aldehydes with complex **9a**[a]

Entry	Aldehyde	Yield/%[b]	ee/%	Config.
1	2-$C_{10}H_7CHO$	96	93[c]	—
2	(*E*)-PhCH=CHCHO	80	95	R[d]
3	3-Furaldehyde	68	93	—
4	2-Furaldehyde	67	85	R[d]
5	*o*-$MeOC_6H_4CHO$	92	83	
6	$PhCH_2CH_2CHO$	90	97	S[e]
7	*n*-$C_6H_{13}CHO$	70	95	—
8	*c*-$C_6H_{11}CHO$	20	93	R[d]

[a]The reaction was carried out on a 0.1 mmol scale. [b]Isolated yields. [c]Determined by chiral HPLC analysis. [d]Determined by comparison of the optical rotation (ref 8a). [e]Determined by comparison of the optical rotation (ref 15).

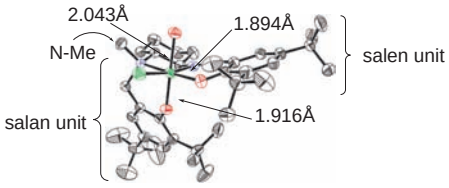


Figure 1. X-ray structure of complex **1b**.

lowered temperature (−20 °C), enantioselectivity increased (Scheme 2). Under the same conditions, the reactions of 3-phenylpropanal with **2a** and **9a** showed the same high enantioselectivity. We next examined solvent effect in the reaction of benzaldehyde and obtained high enantioselectivity (**2a**: 94% ee, **9a**: 91% ee) in toluene, though the reaction with **2a** was significantly slower.[12]

Since **9a** showed comparable asymmetric induction and higher catalytic activity than **2a**, the scope of the reactions with **9a** was examined under optimized conditions (Table 1).[13,14] The reactions of 2-naphth-, (*E*)-cinnam-, and 3-furaldehydes proceeded smoothly with high enantioselectivity (Entries 1–3). However, reactions of aldehydes carrying a precoordinating group showed somewhat reduced enantioselectivity (Entries 4 and 5). The reactions of aliphatic aldehydes were all highly enantioselective (Entries 6–8), while that of an α-branched aldehyde was slow (Entry 8).

Although no single crystals of N-H Cr(salalen) complexes were obtained, we obtained a single crystal of complex **1b**. Its X-ray analysis gave valuable information for understanding the catalytic performance of Cr(salalen) complexes (Figure 1).[16] The salalen ligand adopted a cis-β structure, and the chloro and the aqua ligands occupied the equatorial and the axial positions, respectively. The weakly bound aqua ligand that should be replaced with aldehyde is close to the C3-substituent of the salen unit and is synclinal to the Me–N bond. It is noteworthy that the aqua ligand is trans to the salan unit which plays only an ancillary role in the asymmetric induction.[14]

In conclusion, we were able to reveal that a well-designed heterogeneously hybridized Cr(salalen) complex serves as a catalyst for an asymmetric HDA reaction as efficiently as the homogeneously hybridized ones. The present results will open an avenue to the construction of compact but efficient metal(salalen) complexes.

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10 The salalen ligands were treated at 0 °C with 1.1 equiv of $CrCl_2$ followed by air, according to the reported procedure for the synthesis of Cr(salen) complexes: L. E. Martinez, J. L. Leighton, D. H. Carsten, E. N. Jacobsen, *J. Am. Chem. Soc.* **1995**, *117*, 5897. The N-Me **1b**, **2b**,**4b**, and **5b** and the N-H Cr(salalen) complexes **1a** and **9a** were prepared in good yields, while the complexes **2a**–**8a** were partly reduced to the corresponding Cr(salan) complexes by $CrCl_2$. Thus, **2a**–**8a** were prepared in situ by mixing $CrCl_2$ and the corresponding ligand in a ratio of 1:3; however, it was impossible to separate the complex and the excess ligand and the complexes were used as mixtures.
11 The reaction was carried out with a molar ratio (aldehyde:diene: catalyst = 1:1.8:0.02) on a 0.2 mmol scale. Ee was determined by HPLC analysis (DAICEL CHILALCEL OD-H, hexane/*i*-PrOH = 9:1). Configuration of the product was determined by comparison of the optical rotations (ref 8a).
12 The reactions in solvents such as ether, acetonitrile, and ethyl acetate proceeded with high enantioselectivity, while those in alcohols, THF, and DMF were sluggish.
13 Typical experimental procedure: To a suspension of **9a** (2 μmol) and MS 4 Å (30 mg) in toluene (0.5 mL) were added aldehyde (0.10 mmol) and 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (0.18 mmol) at −20 °C under nitrogen. After stirring for 24 h at that temperature, the mixture was treated with TFA and stirred for another 5 min. The mixture was concentrated, and the residue was chromatographed on silica gel to give the corresponding product. Its ee was determined by chiral HPLC analysis.
14 The reaction of benzaldehyde and 1-methoxy-3-trimethylsilyloxy-1,3-pentadiene (1E,3Z:1E,3E = 3:1) gave the corresponding 5,6-syn product (endo adduct) of 54% ee exclusively in 49% yield.
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