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LEWIS ACID CATALYSIS OF SECOND-GENERATION METALLOSALEN COMPLEXES: AN EXPLANATION FOR STEREOCHEMISTRY OF ASYMMETRIC HETERO DIELS-ALDER REACTION†

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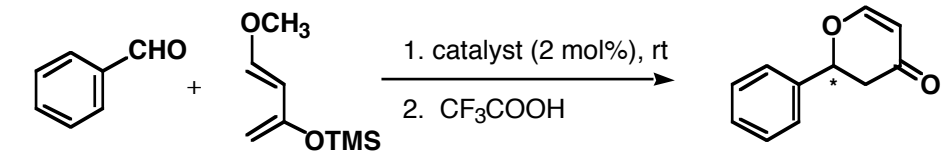
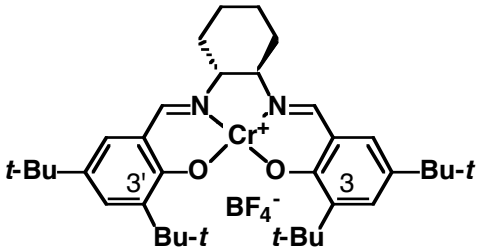
Abstract–Chloro nitrosyl (*R*,*S*)-(salen)ruthenium(II) complex served as a good catalyst for asymmetric hetero Diels-Alder (HDA) reaction of Danishefsky's diene with a wide variety of aldehydes. In contrast with this, (*R*,*R*)-(salen)-chromium(III) and -manganese(III) complexes well catalyze HDA reaction of simple aldehydes, while (*R*,*S*)-(salen)-chromium(III) and -manganese(III) complexes better catalyze HDA reaction of aldehydes bearing a precoordinating group. These features of metallosalen-catalyzed HDA reactions were rationalized by assuming that HDA reaction of aldehydes bearing a precoordinating group would proceed through aldehyde-metallosalen complex which takes *cis*-β-structure.

INTRODUCTION

Recently, optically active metallosalen complexes (hereafter referred to as M-salen complexes) have drawn attention of synthetic chemists for their unique asymmetric catalysis. For example, Mn-, Ru-, and Co-salen complexes catalyze asymmetric oxene or its isoelectronic nitrene and carbene transfer reactions with high enantioselectivity.[1] In addition, they serve as excellent Lewis acid catalysts.[2] In 1995, we found that high valent (salen)manganese complexes served as a Lewis acid catalyst for asymmetric Diels-Alder reaction at -78 °C.[3] In concurrence with this, Co- and Cr-salen complexes were found to be excellent catalysts for Lewis acid-mediated asymmetric reactions by Jacobsen *et al.*[4] Among them, Cr-salen complex (**1**) showed high enantioselectivity up to 93% ee at -30 °C in asymmetric hetero Diels-Alder (HDA) reaction of Danishefsky's diene (1-methoxy-3-trimethylsilyloxy-1,3-butadiene) with aldehydes,[4c] which provides useful building blocks for organic synthesis.[5,6] We, recently, found that second-generation (*R*,*S*)-(ON$^+$)Ru-salen complex (**2**) bearing chiral binaphthyl and ethylenediamine units

† This paper is dedicated to Professor Sho Ito on the occasion of his 77th birthday.





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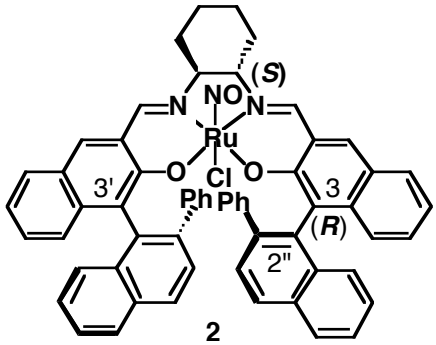

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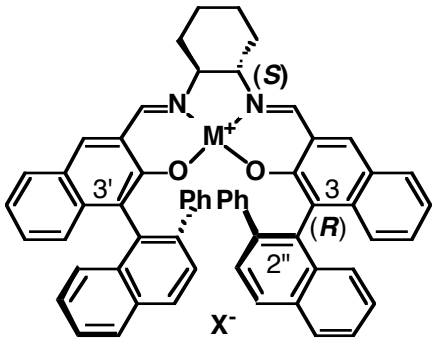
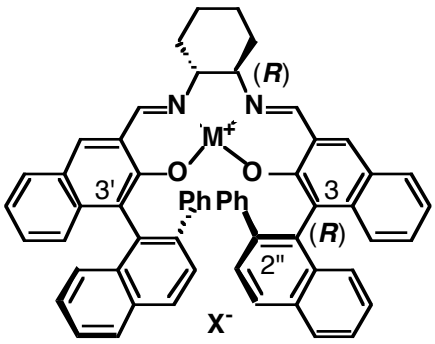
Scheme 1



3: M= Mn, X= PF_6
5: M= Cr, X= BF_4



4: M= Mn, X= PF_6
6: M= Cr, X= BF_4

also served as a catalyst for asymmetric HDA reaction between Danishefsky's diene and benzaldehyde under photo-irradiation.[7] More recently, cationic second-generation Mn-(**3** and **4**) and Cr-salen complexes (**5** and **6**) served as excellent catalysts for asymmetric HDA reaction. To be interested, the reactions of aldehydes bearing a precoordinating functional group such as *o*-methoxybenzaldehyde were efficiently effected by (*R*,*S*)-Mn- (**3**) or (*R*,*S*)-Cr-salen complex (**5**) (96% ee, 0 °C), while the reactions of simple aldehydes such as benzaldehyde and *n*-heptanal by (*R*,*R*)-Mn- (**4**) or (*R*,*R*)-Cr-salen complex (**6**) (benzaldehyde: 93% ee, 0 °C; *n*-heptanal: 97% ee, 0 °C).[8] Some metallosalen complexes bearing a bidentate counter anion have been reported to take *cis*-β-structure.[9] Although the mechanism of asymmetric induction by these second-generation metallosalen complexes was unclear, we assumed that aldehydes bearing a precoordinating group would chelate to the metal ion, forcing salen ligands to take a *cis*-β-structure:[10] in this event, the precoordinating group was considered to be first coordinated to the apical site of the complex and then the aldehyde to be coordinated to the equatorial site giving the adducts described in Figure 1. Differing from this, simple aldehydes were considered to be coordinated to metal ion at the apical site, directing its aryl moiety over a downward naphthalene ring and away from bulky C3(C3')-substituents (Figure 1). To verify this assumption, we examined the stereochemistry

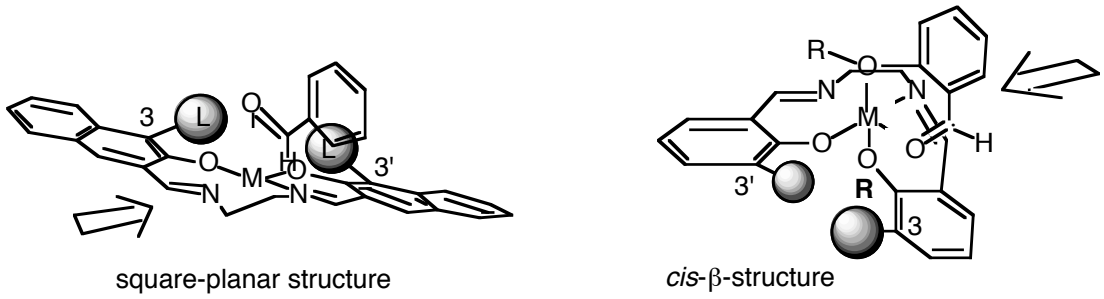


Figure 1

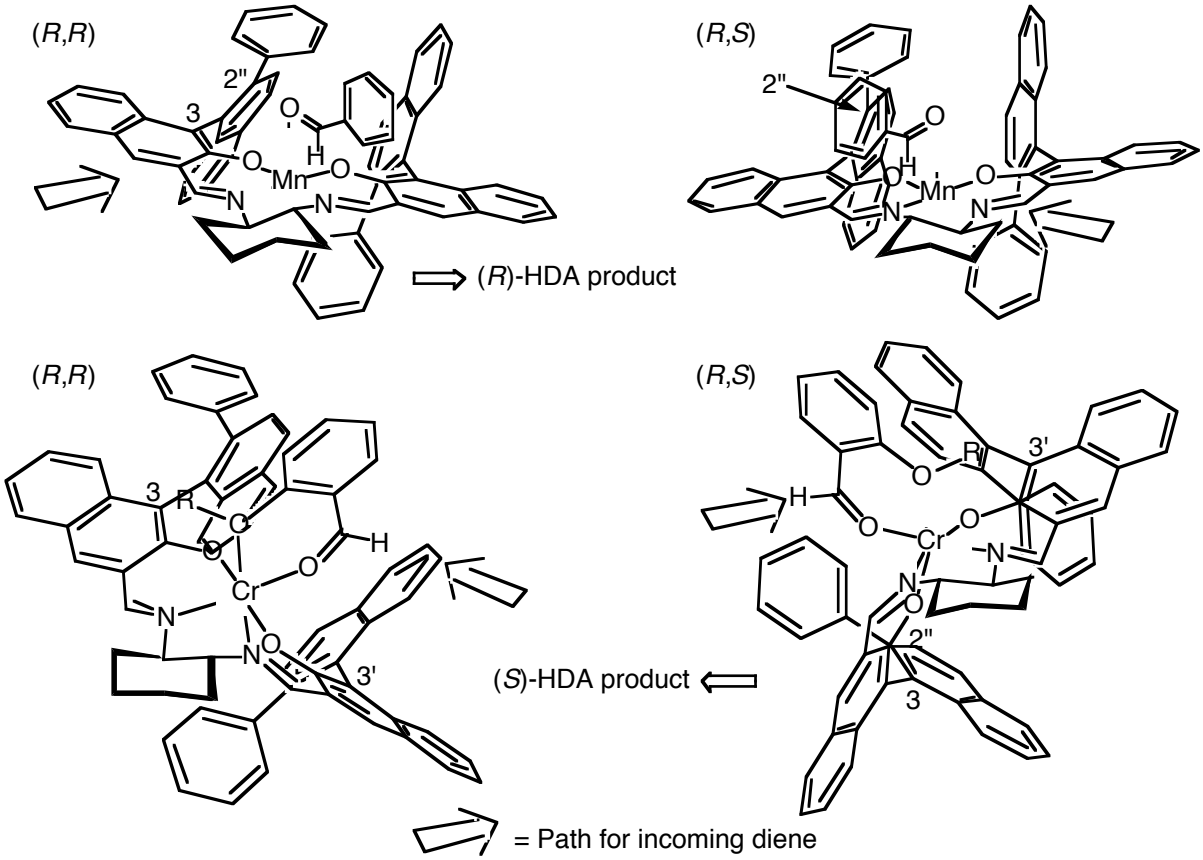
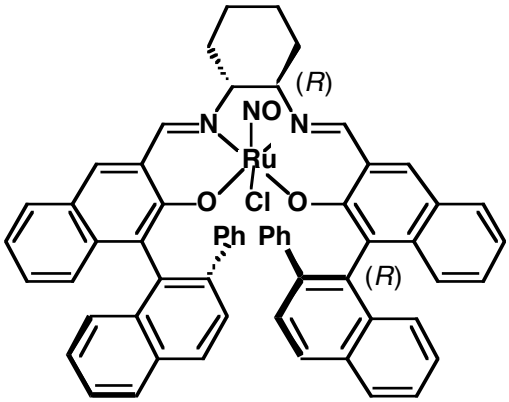


Figure 2

of metallosalen-mediated HDA reaction. The basal salen ligand of (*R*,*R*)-complex has a deeply folded stepped-conformation and the 2"-phenyl group protrudes over the basal salen ligand efficiently regulating the conformation of a ligated simple aldehyde, while (*R*,*S*)-complex has a slightly folded stepped-conformation[11,12] that less efficiently regulated the conformation of the aldehyde as shown in Figure 2. Diene was expected to approach the coordinating aldehyde from the side away from the bulky C3 or C3'-substituent. Thus, the reactions of simple aldehydes with (*R*,*R*)-complex were expected to give HDA products of (*R*)-configuration with higher enantioselectivity. This agreed with the results obtained with Cr- and Mn-salen complexes. On the other hand, aldehydes bearing a precoordinating group chelate with Cr- and Mn-salen complexes forcing them to take *cis*-β-structure as described in Figure 2. The back face

of aldehydes ligated to the (*R*,*S*)-complex of *cis*-β-structure[13] is efficiently blocked by the 3'-substituent, while that ligated to the (*R*,*R*)-complex of *cis*-β-structure is partly screened by the 3-substituent. Thus, (*R*,*S*)-complexes were expected to be the catalysts suitable for the reaction of a chelating substrate and to give HDA products of (*S*)-configuration (Figure 2). Furthermore, the models suggested that, upon diene's approach, the *O*-alkyl group (R in Figure 2) of the chelating *o*-alkoxybenzaldehyde should be directed to the 3'- or 3-substituent side where is sterically congested and, therefore, enantioselectivity might be diminished as the size of the *O*-alkyl group increases.

On the other hand, Ru-salen catalyzed HDA reaction of benzaldehyde was better effected by (*R*,*S*)-complex (**2**) than by the diastereomeric (*R*,*R*)-complex (**7**).[7] This was attributed to the fact that complex (**2**) adopts a unique conformation of doglegged type, in which the left half of the complex was folded down (Figure 3).[14] Thus, a simple aldehyde coordinated to the ruthenium ion protrudes over the downward naphthalene ring and diene approaches it to give the HDA product of (*S*)-configuration.[7] In analogy with Cr- and Mn-salen complexes, the reactions of chelating substrates were also expected to be well effected by (*R*,*S*)-complex (**2**), proceeding through a aldehyde-complex adduct in which the complex adopts a *cis*-β-structure and one of enantiofaces of the coordinated aldehyde is screened by the 3'-substituent, to give (*S*)-HDA-product. However, due to longer bond-length of Ru-O bond as compared with Cr-O and Mn-O bonds, the substrate-complex (**2**) adduct should have a larger space to accept an *O*-alkyl group between the aldehyde and the 3'-substituent than the corresponding substrate-Cr-(or Mn-) salen adduct. Therefore, the reaction of an aldehyde bearing bulky *O*-alkyl group was expected to be



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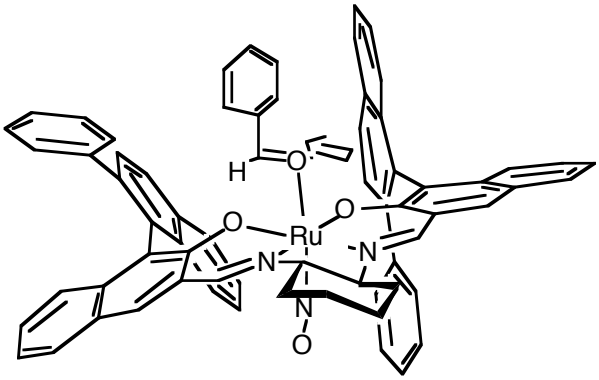
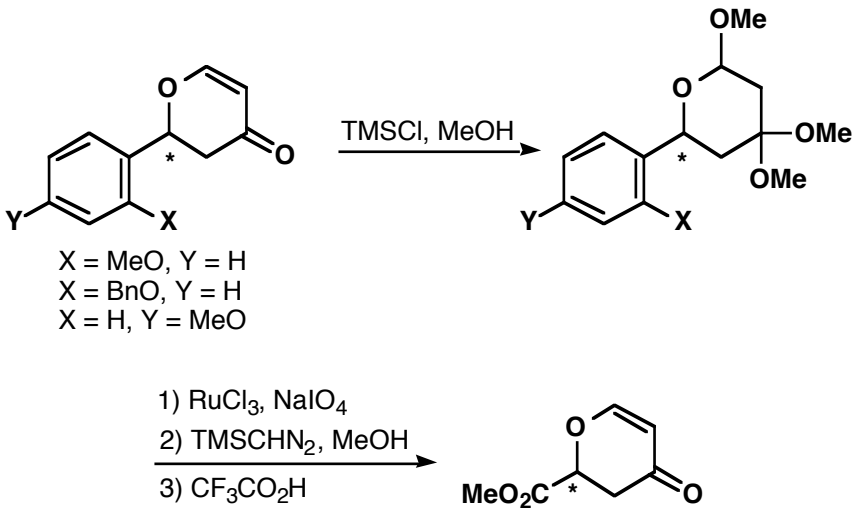


better effected by (*R*,*S*)-complex (**2**) than the corresponding **3** and **5**. Based on these analyses, we carried out the following experiments: i) determination of the configuration of the HDA products derived from *o*- and *p*-methoxy- and *o*-benzyloxybenzaldehydes, and ii) the comparison of stereoselectivity of the reactions of these *o*- and *p*-substituted benzaldehydes with Cr- (**5** and **6**) and Ru-salen (**2** and **7**) complexes.

RESULTS AND DISCUSSION

Absolute configuration of HDA products

Configuration of HDA product of Danishefsky's diene and *o*-methoxybenzaldehyde with (*R*,*S*)-Cr(III)-salen complex (**5**) as the catalyst (Table 1, entry 1) was determined by chemical correlation to the known methyl 2,3-dihydro-4*H*-pyran-4-one-2-carboxylate[6h,15] following the sequence: i) acetalization of enol ether, ii) conversion of the aryl ring to carboxylic acid by treatment with $RuCl_3$ (cat) and $NaIO_4$ (excess) in CCl_4-CH_3CN-H_2O (2:2:3);[16] iii) esterification with $TMSCHN_2$,[17] and iv) CF_3COOH (cat), CH_2Cl_2 (Scheme 2). The specific rotation of the compound thus obtained was compared with the literature value to prove its absolute configuration to be *S*, supporting the assumption that the reaction of a chelating substrates proceeds through a substrate-complex adduct in which the complex adopts a *cis*-β-structure. The configurations of the major enantiomers obtained in the HDA reactions of *o*-benzyloxy- and *p*-methoxybenzaldehydes with Danishefsky's diene catalyzed by complexes (**2**) and (**6**) was also determined to be *S* and *R*, respectively, in the same manner as described above.



HDA reaction of *o*-alkoxybenzaldehyde

HDA reaction of *o*-methoxybenzaldehyde has been efficiently effected by (*R*,*S*)-**5** as the catalyst (Table 1, entry 1).[8] The reaction of non-chelating *p*-methoxybenzaldehyde with the complex (**5**) showed a diminished enantioselectivity (entry 2), while that was well effected by (*R*,*R*)-complex (**6**) (entry 3). The reaction of *o*-benzyloxybenzaldehyde with (*R*,*S*)-**5** as the catalyst was next examined under the same conditions and, as preestimated, its enantioselectivity (90% ee) was found to be inferior to that (96% ee)

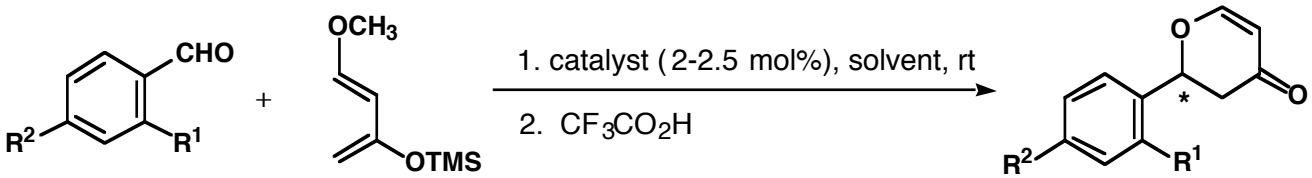


Table 1. Hetero Diels-Alder reaction of benzaldehyde derivatives with Cr- or (ON^+)Ru-salen complexes as the catalysts[a)]

entry	catalyst	R^1	R^2	solvent	temp	time (day)	yield (%)	%ee[b)]	ref
1	**5**	CH_3O	H	CH_2Cl_2	0 °C	1	88	96[c)](*S*)	8
2	"	H	CH_3O	"	"	1	35	70[d)] (*S*)	this work
3	**6**	"	"	"	"	1	86	92 (*R*)	this work
4	**5**	BnO	H	"	"	1	92	90[e)] (*S*)	this work
5	**2**	H	"	TBME	rt	2	40	81[f)] (*S*)	this work
6	**7**	"	"	"	"	"	38	18[f)] (*R*)	this work
7	**2**	CH_3O	"	"	"	2	40	91[c)] (*S*)	this work
8	**7**	"	"	"	"	1	47	6[c)] (*R*)	this work
9	**2**	BnO	H	"	"	1	52	96[e)] (*S*)	this work

a) For Cr(III)-salen catalyzed HDA reaction (entries 1-4), a solution of aldehyde (0.2 mmol), Danishefsky's diene (0.36 mmol), and catalyst (5 μmol) in dichloromethane (0.5 mL) was stirred for 24 h at 0 °C under N_2. Yield was calculated based on the aldehyde used. For (NO^+)Ru-salen catalyzed HDA reaction (entries 5-9), a suspension of aldehyde (0.1 mmol), Danishefsky's diene (0.1 mmol), and catalyst (2 μmol) in TBME (1 mL) was stirred for 48 h at rt under irradiation of light (>400 nm) using halogen lamp as the light source in N_2 atmosphere.
b) Absolute configuration of the major enantiomer was indicated in the parenthesis unless otherwise mentioned.
c) Determined by HPLC analysis using DAICEL CHIRALCEL OD (hexane/*i*-PrOH = 15/1).
d) Determined by HPLC analysis using DAICEL CHIRALCEL AD (hexane/*i*-PrOH = 30/1).
e) Determined by HPLC analysis using DAICEL CHIRALCEL AS (hexane/*i*-PrOH = 9/1).
f) Determined by HPLC analysis using DAICEL CHIRALCEL OD-H (hexane/*i*-PrOH = 9/1).

observed in the reaction of *o*-methoxybenzaldehyde (entry 4). The reactions of *o*-methoxy- and *o*-benzyloxyaldehydes under photo-irradiation were also examined with (ON^+)Ru-salen complexes as catalysts and both the reactions were better effected with (*R*,*S*)-(ON^+)Ru-salen complex (**2**) (entries 7 and 9). Furthermore, the enantioselectivity of the reaction of *o*-benzyloxybenzaldehyde (96% ee) bearing bulky *O*-benzyl group was found to be a superior substrate for this reaction to *o*-methoxybenzaldehyde (91% ee) (*c.f,* entries 7 and 9). Configuration of HDA products derived from benzaldehyde and *o*-substituted benzaldehyde with complex (**2**) was all *S* (entries 5, 7, and 9). All these results obtained are completely consistent with the above-discussion on the mechanism of asymmetric induction for metallosalen-mediated HDA reactions.

In conclusion, we were able to provide strong supports that second-generation metallosalen complexes can adopt *cis*-β-structure when a chelating substrate coexists in the reaction mixture.

EXPERIMENTAL

General procedures

^{1}H NMR spectra were recorded at 400 or 270 MHz on a JEOL GX-400. All signals were expressed as

ppm down field from tetramethylsilane used as an internal standard (δ–value in $CDCl_3$). IR spectra were obtained with a SHIMADZU FTIR–8600 instrument. Optical rotations were measured with a JASCO P–1020 polarimeter. Column chromatography was conducted on silica gel BW–820MH, 70–200 mesh ASTM, available from FUJI SILYSIA CHEMICAL LTD. Preparative thin layer chromatography was performed on 0.5 mm x 20 cm x 20 cm E. Merck silica gel plate (60 F–254). Enantiomeric excesses were determined by HPLC analysis using SHIMADZU LC–10AT–VP equipped with an appropriate optically active column as described in the footnotes of Table 1. Reagents and solvents were used as received unless otherwise mentioned below. Commercially available methanol-free dichloromethane was dried and distilled over calcium hydride before use. *o*-Benzyloxybenzaldehyde (Tokyo Kasei Kogyo Co., Ltd), benzaldehyde, *o*- and *p*-methoxybenzaldehydes (Nacalai Tesque, Inc.), and 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene) (Aldrich) were also purified by distillation prior to use. Chiral (NO^+)Ru(II)-salen complexes (**2** and **7**) and Cr(III)-salen complexes (**5** and **6**) were prepared as described in references 18 and 8, respectively. Reactions were carried out under an atmosphere of nitrogen if necessary. All the products were fully analyzed but only the spectroscopic data are given here for known compounds.

Typical experimental procedure of the asymmetric hetero Diels-Alder reaction with (NO^+)Ru(II)-salen complex (2) as the catalyst. In a 5 mL round-bottomed flask were placed complex (**2**) (2.0 mg, 2.0 μmol) and *t*-butyl methyl ether (1 mL) under nitrogen atmosphere. To this solution were successively added aldehyde (0.1 mmol) and 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (19.5 μL, 0.1 mmol). The mixture was stirred for 2 days at rt under irradiation of light using halogen lamp (100 V, 90 W) equipped with yellow glass filter (>400 nm) and IR filter as the light source. Trifluoroacetic acid (10 μL) was added to the reaction mixture and stirred for another 5 min. To this solution was added several drops of pyridine and the mixture was concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/ethyl acetate = 1/0 to 8/2) to give the corresponding 2-substituted 2,3-dihydro-4*H*-pyran-4-one. The optical purity of the product was determined by HPLC analysis using optically active column (hexane/2-propanol = 9/1, flow rate = 0.5 mL/min) as described in the footnotes of Table 1.

Absolute configuration determination of HDA products. Typical experimental procedure was exemplified by the transformation of 2,3-dihydro-2-(*o*-methoxyphenyl)-4*H*-pyran-4-one from the HDA reaction using Cr(III)-salen complex (**5**) (Table 1, entry 1).[8] To a solution of the pyranone (16 mg, 0.078 mmol, 96% ee) in MeOH (200 μL) was added a catalytic amount of TMSCl at rt. After being stirred at the temperature for 2 h, the mixture was neutralized with Et_3N and concentrated *in vacuo*. The residue was submitted to preparative TLC (silica gel, hexane/ethyl acetate = 2/1) to give 2,4,4-trimethoxy-6-(*o*-methoxyphenyl)tetrahydropyran (15 mg, 68%) as a mixture of the diastereomers (*ca.* 2:1). ^1H NMR (400 MHz) for the major diastereomer: δ 7.56 (dd, *J* = 2.0 and 7.3 Hz, 1H), 7.25 (ddd, *J* = 2.0, 7.3, and 8.3 Hz, 1H), 6.97 (t, *J* = 7.3 Hz, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 4.88 (dd, *J* = 2.4 and 11.2 Hz, 1H), 4.63 (dd, *J* = 2.4 and 9.8 Hz, 1H), 3.84 (s, 3H), 3.52 (s, 3H), 3.30 (s, 3H), 3.23 (s, 3H), 2.34 (ddd, *J* = 2.4, 2.4, and 13.7 Hz, 1H), 2.20 (ddd, *J* = 2.4, 2.4, and 12.7 Hz, 1H), 1.53 (ddd, *J* = 9.8 and 12.7 Hz, 1H), 1.38 (ddd, *J* = 11.2

and 13.7 Hz, 1H). ^{1}H NMR (400 MHz) for the minor diastereomer: δ 7.49 (dd, *J* = 2.0 and 7.3 Hz, 1H), 7.26 (ddd, *J* = 2.0, 7.3, and 8.3 Hz, 1H), 6.99 (t, *J* = 7.3 Hz, 1H), 6.89 (d, *J* = 8.3 Hz, 1H), 5.27 (d, *J* = 14.2 Hz, 1H), 4.99 (d, *J* = 4.9 Hz, 1H), 3.84 (s, 3H), 3.37 (s, 3H), 3.31 (s, 3H), 3.21 (s, 3H), 2.35-2.28 (m, 2H), 1.8 (dd, *J* = 4.9 and 14.2 Hz, 1H), 1.55 (dd, *J* = 11.2 and 14.2 Hz, 1H). The acetal thus obtained (10 mg, 0.035 mmol) was dissolved in a mixed solvent of CCl_4-CH_3CN-H_2O (2:2:3, 700 μL) and to the solution was successively added $NaIO_4$ (100 mg) and a catalytic amount of $RuCl_3$.[16] After being stirred at rt for 4 h, the reaction mixture was extracted with Et_2O (1 mL x 5), dried over Na_2SO_4, and concentrated. The resulting residue was esterified by using $TMSCHN_2$ (excess) and MeOH (1 drop) in Et_2O (200 μL) at rt for <1 min.[17] The mixture was concentrated *in vacuo* followed by treatment with CF_3COOH (cat) in CH_2Cl_2 (200 μL) at rt for 12 h afforded colorless oil (0.28 mg, 5 %). Methyl 2,3-dihydro-4*H*-pyran-4-one-2-carboxylate.[6h,15] $[\alpha]_D^{25}$ +92° (*c* 0.024, $CHCl_3$) [lit.,[15] $[\alpha]_D^{23}$ +100.8° (*c* 1.2, $CHCl_3$) for (*S*)-isomer]. ^{1}H NMR (270 MHz): δ 7.40 (d, *J* = 5.9 Hz, 1H), 5.50 (d, *J* = 5.9 Hz, 1H), 5.04 (t, *J* = 7.9 Hz, 1H), 3.84 (s, 3H), 2.87 (d, *J* = 7.9 Hz, 2H). The ee was determined to be 96% by HPLC analysis using optically active column [DAICEL CHIRALCEL AS, hexane/2-propanol = 3/1, flow rate = 0.5 mL/min, t_R 45.1 min (major) and 59.3 min (minor)].[6h] The absolute configuration was determined to be *S* based on comparison of the measured specific rotation with the literature value.

(*R*)-2,3-Dihydro-2-(*p*-methoxyphenyl)-4*H*-pyran-4-one (Table 1, entry 2). 92% ee. $[\alpha]_D^{25}$ -121° (*c* 0.397, $CHCl_3$). ^{1}H NMR (400 MHz): δ 7.52 (d, *J* = 5.4 Hz, 1H), 7.34 (d, *J* = 8.5 Hz, 2H), 6.94 (d, *J* = 8.5 Hz, 2H), 5.52 (dd, *J* = 1.0 and 5.9 Hz, 1H), 5.38 (dd, *J* = 3.4 and 14.7 Hz, 1H), 3.83 (s, 3H), 2.93 (dd, *J* = 14.7 and 17.1 Hz, 1H), 2.63 (ddd, *J* = 1.0, 3.4 and 17.1 Hz, 1H). IR (KBr): 3071, 3003, 2963, 2936, 2909, 2839, 1676, 1612, 1593, 1516, 1462, 1404, 1306, 1271, 1254, 1231, 1211, 1178, 1036, 988, 932, 835, 797, 575 cm^{-1}. HRFABMS. Calcd for $C_{12}H_{12}O_3$ $[M+H]^+$: 205.0865. Found: 205.0684. The absolute configuration was determined to be *R* in the same manner as described for the 2,3-dihydro-2-(*o*-methoxyphenyl)-4*H*-pyran-4-one (*vide supra*).

(*S*)-2-(*o*-Benzyloxyphenyl)-2,3-dihydro-4*H*-pyran-4-one (Table 1, entry 9). 96% ee. $[\alpha]_D^{25}$ -73.5° (*c* 0.325, $CHCl_3$). ^{1}H NMR (400 MHz): δ 7.46 (d, *J* = 5.9 Hz, 1H), 7.50 (dd., *J* = 1.5 and 7.3 Hz, 1H), 7.39-7.28 (m, 6H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 8.3 Hz, 1H), 5.87 (dd, *J* = 4.4 and 13.7 Hz, 1H), 5.51 (dd, *J* = 1.0 and 5.4 Hz, 1H), 5.14 and 5.11 (ABq, J_{AB} = 12.0 Hz, 2H), 2.84 (dd, *J* = 13.7 and 17.1 Hz, 1H), 2.74 (ddd, *J* = 1.0, 4.4 and 17.1 Hz, 1H). IR (KBr): 3065, 3036, 2920, 2882, 1678, 1601, 1495, 1454, 1404, 1273, 1250, 1225, 1163, 1040, 991, 934, 797, 764, 698 cm^{-1}. HRFABMS. Calcd for $C_{18}H_{16}O_3$ $[M+H]^+$: 281.1178. Found: 281.1173. The absolute configuration was determined to be *S* in the same manner as described for the 2,3-dihydro-2-(*o*-methoxyphenyl)-4*H*-pyran-4-one (*vide supra*).

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