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# Asymmetric hetero Diels–Alder reaction of Danishefsky's dienes and glyoxylates with chiral bis(oxazolinyl)phenylrhodium(III) aqua complexes, and its mechanistic studies

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Dedicated to Professor Kenji Itoh on the occasion of his 60th birthday.

**Abstract**—Asymmetric hetero Diels–Alder reaction of Danishefsky's dienes with glyoxylates is catalyzed in high enantioselectivity and *cis* (*endo*)-diastereoselectivity by chiral (Phebox)$RhCl_2(H_2O)$ complexes [Phebox=2,6-bis(oxazolinyl)phenyl], via the concerted [4+2] mechanism with perpendicular conformation of two carbonyl moieties of glyoxylates. Dibromide and difluoride complexes were newly synthesized and found to exhibit a slightly higher enantioselectivity of the hetero Diels–Alder products than the parent dichloride complex (Cl: 80% ee, Br: 82% ee, F: 84% ee). 

## 1. Introduction

Recently, many transition–metal complexes have been applied as attractive chiral Lewis acid catalysts for asymmetric reactions, particularly in terms of carbon–carbon bond forming reactions.[1] Comparing with traditional Lewis acids, transition-metal complexes are generally single well-defined species, insensitive to water.[2] Therefore, identification of their active intermediates being Lewis acid–base complexes[3] and consideration of their transition states are easier than those of traditional Lewis acid complexes.

We have already designed a meridional tridentate ligand, 2,6-bis(oxazolinyl)phenyl derivative (abbreviated to Phebox) as a chiral N–C–N type ligand with one central covalent bond to a metal,[4,5] and have demonstrated that Phebox–Rh(III) complexes **1** acted as chiral Lewis acid catalysts for the enantioselective addition of allyltributyltin to aldehydes.[5] In this catalytic allylation, the (Phebox)$RhCl_2$ fragments A, generated by releasing $H_2O$ from (Phebox)$RhCl_2(H_2O)$ complexes **1**, are active Lewis acid catalysts. Furthermore, these air-stable and water-tolerant aqua complexes **1** could be recovered quantitatively from the reaction media.[6] Now we wish to report herein the synthesis of (Phebox)$RhX_2(H_2O)$ complexes (**2**: X=Br, **3**: X=F), the asymmetric hetero Diels–Alder reaction of Danishefsky's dienes[7,8] and glyoxylates catalyzed by the Phebox–Rh(III) complexes **1**–**3**, and its mechanistic studies on the reaction pathway and the transition state assembly (Chart 1).

## 2. Results and discussion

### 2.1. Asymmetric hetero Diels–Alder reaction

We first examined the reaction of trimethylsilyl (TMS)-derived diene **4a** and *n*-butyl glyoxylate **5a** catalyzed by *i*-Pr–Phebox-derived dichloride complex **1a**. However, decomposition of the diene **4a** into 4-methoxy-3-buten-2-one was very fast, and a trace amount of the desired hetero Diels–Alder adduct was obtained (Table 1, entry 1). While the reaction of *tert*-butyldimethylsilyl (TBS)-derived diene **4b** and **5a** proceeded smoothly by a catalytic amount (2 mol%) of the complex (*S*,*S*)-**1a** in toluene at −78°C to give dihydropyrone **6a** in 86% isolated yield after acid treatment (TFA: trifluoroacetic acid) with 26% ee (entry 2). The enantioselectivity was highly dependent on the substituents of both the chiral catalysts and the ester moieties of glyoxylates, and the reaction solvents. The enantioselectivity using Ph–Phebox-derived complex **1b** was decreased to 19% ee, furthermore, Me- and *t*-Bu–Phebox-derived complexes **1c** and **1d** gave almost racemic products (entries 3–5). Whereas, the remarkably high enantiomeric excess (80% ee) of **6a** was determined by HPLC analysis (Daicel CHIRALPAK AD) using Bn–Phebox-derived complex **1e** (entry 6). Although the reaction proceeded smoothly in dichloromethane, the enantiomeric excess of the dihydropyrone **6a** decreased to 36% (entry 7). The enantioselectivity of the reaction with methyl glyoxylate **5b**, which is

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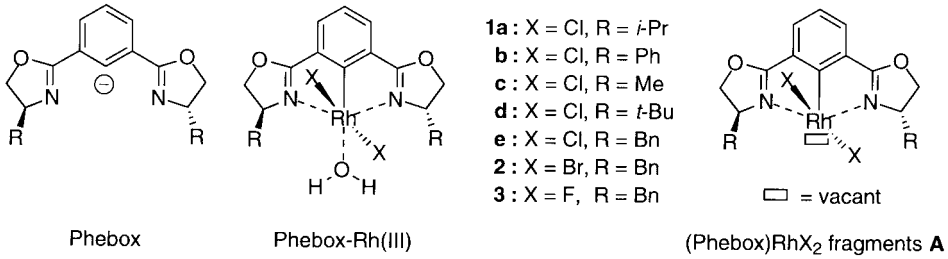



**Chart 1.**

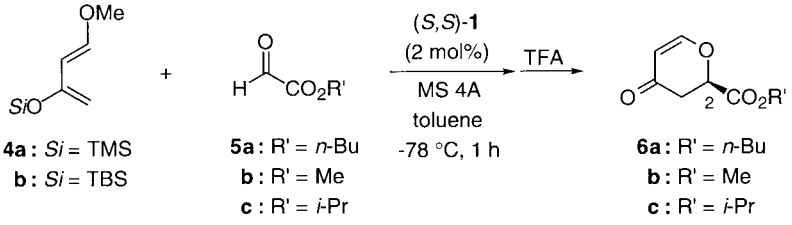
the small ester substituent, fell to 68% ee (entry 8). While the reaction of bulky *iso*-propyl glyoxylate **5c** made the enantiomeric excess of dihydropyrone **6c** slightly increased to 82%, the chemical yield was remarkably decreased to 76% isolated yield (entry 9). The absolute configurations of the dihydropyrones **6a–c** were proved to be 2*R* (*re*-face attack of the diene) by comparisons of the optical rotation with the literature values.[9] This *re*-face attack of the diene **4b** to the aldehyde's C═O planes is the opposite enantioface-selection in the allylation of aldehydes with allyltributyltin catalyzed by (*S*,*S*)-**1**.[5]

Recently, much attention has been focused on the effect of counter ions on catalytic activity and enantioselectivity. Especially, a fluoride counterion shows distinctive electronic, structural and bonding properties.[10] So we next synthesized the dibromide and difluoride complexes (**2** and **3**), and examined the counter ion effect on catalytic activity and enantioselectivity of the present reaction.

Both dibromide and difluoride complexes **2** and **3** were prepared from the dichloride complex **1e**. The reaction of **1e** with carbon tetrabromide in methanol gave the dibromide complex **2** in 91% isolated yield. While **1e** was first reacted with silver acetate, then the corresponding diacetate complex was led to the difluoride complex **3** by treatment with tetrabutylammonium fluoride and hydrofluoroboric acid in dichloromethane (Scheme 1).

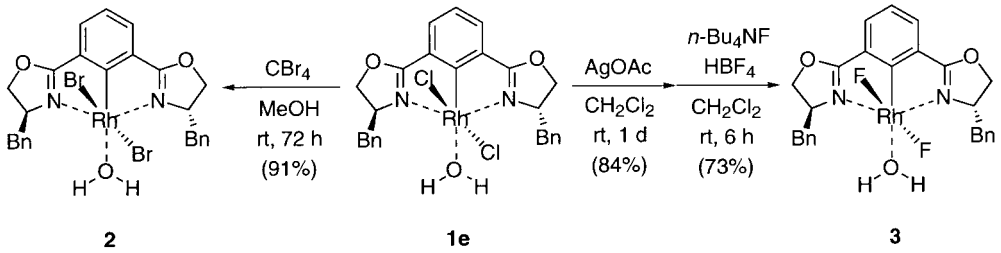
The reaction of diene **4b** and glyoxylate **5a** catalyzed by

**Table 1.** Asymmetric hetero Diels–Alder reaction of Danishefsky's dienes **4** and glyoxylates **5** catalyzed by Phebox–Rh(III) complexes **1** (all reactions were carried out using 0.6 mmol of diene **4**, 0.5 mmol of glyoxylate **5**, and 0.01 mmol of complexes **1** in 2 mL of solvent in the presence of MS 4A (250 mg) at −78°C for 1 h)



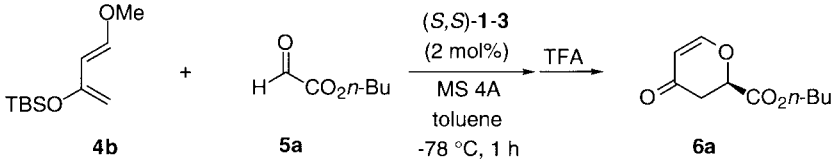

| Entry | Complex | Diene | Glyoxylate | Product | % Yield | % Ee[a] | Abs. config.[b] |
|---|---|---|---|---|---|---|---|
| 1 | **1a** | **4a** | **5a** | **6a** | Trace | – | – |
| 2 | **1a** | **4b** | **5a** | **6a** | 86 | 26 | *R* |
| 3 | **1b** | **4b** | **5a** | **6a** | 87 | 19 | *R* |
| 4 | **1c** | **4b** | **5a** | **6a** | 56 | 5 | *R* |
| 5 | **1d** | **4b** | **5a** | **6a** | 87 | 3 | *S* |
| 6 | **1e** | **4b** | **5a** | **6a** | 90 | 80 | *R* |
| 7[c] | **1e** | **4b** | **5a** | **6a** | 95 | 36 | *R* |
| 8 | **1e** | **4b** | **5b** | **6b** | 93 | 68 | *R* |
| 9 | **1e** | **4b** | **5c** | **6c** | 76 | 82 | *R* |

[a] Determined by HPLC analysis using Daicel CHIRALPAK AD.
[b] Determined by comparison of the $[\alpha]_D$ value with reported data: see Experimental.
[c] In $CH_2Cl_2$.




**Scheme 1.**

**Table 2.** Asymmetric hetero Diels–Alder reaction of Danishefsky's diene **4b** and glyoxylate **5a** catalyzed by (Bn–Phebox)$RhX_2(H_2O)$ complexes **1**–**3** (all reactions were carried out using 0.6 mmol of diene **4b**, 0.5 mmol of glyoxylate **5a**, and 0.01 mmol of complexes **1**–**3** in 2 mL of solvent in the presence of MS 4A (250 mg) at −78°C for 1 h)




4b 5a 6a

| Entry | Complex | % Yield | % Ee[a] | Abs. config.[b] |
|---|---|---|---|---|
| 1 | **1e** (X=Cl) | 90 | 80 | *R* |
| 2 | **2** (X=Br) | 99 | 82 | *R* |
| 3 | **3** (X=F) | 90 | 84 | *R* |

[a] Determined by HPLC analysis using Daicel CHIRALPAK AD.
[b] Determined by comparison of the $[\alpha]_D$ value with reported data: see Experimental.

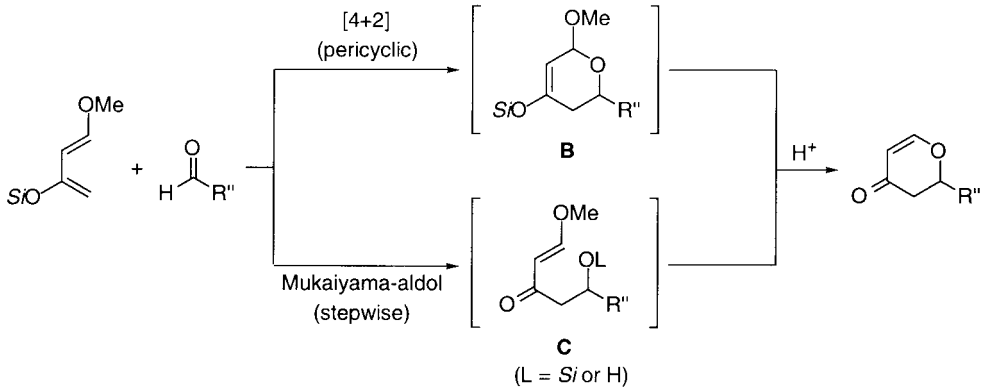
(Bn–Phebox)$RhX_2(H_2O)$ complexes was carried out in a similar manner as above (Table 2). Both dibromo and difluoro complexes **2** and **3** show the high catalytic activity similar to the parent dichloride catalyst **1e**. The optical purity of the dihydropyrone **6a** was slightly increased using the difluoro complex **3** (Cl: 80% ee, Br: 82% ee, F: 84% ee, respectively).

Although these Phebox–Rh(III) complexes **1**–**3** are effective chiral Lewis acid catalysts for the reaction of Danishefsky's diene **4b** with highly reactive glyoxylates **5**, other simple or activated aldehydes or ketones such as benzaldehyde, (benzyloxy)acetaldehyde or ethyl pyruvate can not react with an activated diene **4b** under influence of the complexes **1**–**3**.

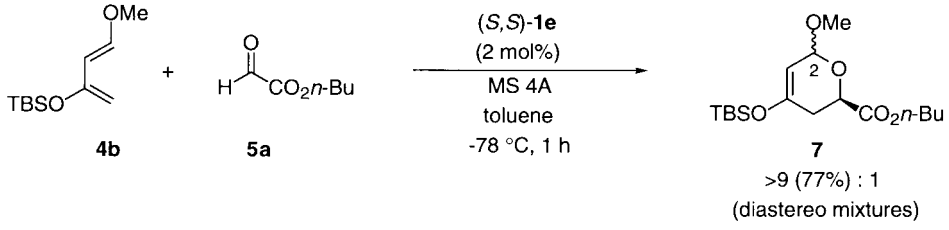
## 2.2. Reaction mechanism

There are two reaction pathways for the Lewis acid-catalyzed (or promoted) reaction of Danishefsky's dienes **4** and aldehydes.[11] One is a concerted [4+2] cycloaddition (pericyclic) mechanism like the classical all-carbon Diels–Alder process. In this case, cycloadduct **B**[12] is directly produced. The other is a stepwise mechanism; a Mukaiyama-aldol reaction leads to intermediates **C** (L=*Si* or H),[13] followed by cyclization (Scheme 2). Danishefsky et al. concluded that the reactions with stronger Lewis acids such as $BF_3$ occur via a stepwise mechanism, whereas $ZnCl_2$ or lanthanides-catalyzed reactions are concerted.[11b] So, we next checked the intermediate of the present Phebox–Rh(III) catalyzed reaction.

The $^1H$ NMR spectrum of the crude product, obtained by the reaction of diene **4b** and glyoxylate **5a** using 2 mol% of complex **1e** in toluene at −78°C for 1 h, revealed no acyclic (Mukaiyama-aldol) intermediates **8**. The signals of the cycloadduct **7**[12b] appeared exclusively with >9:1 diastereo mixtures at an anomeric C-2 position (Scheme 3). The major




**Scheme 2.**




4b 5a

**Scheme 3.**

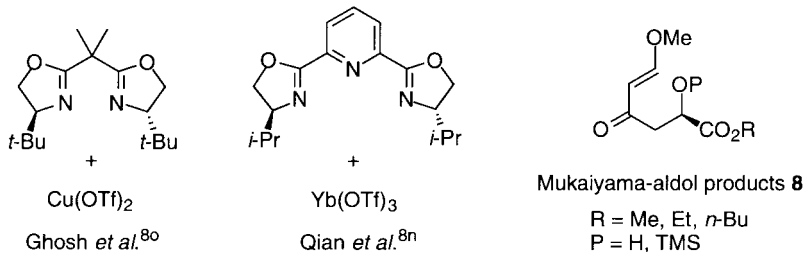



**Chart 2.**

product of **7** could be isolated by silica gel chromatography in 77% yield, and the isolated adduct was readily converted to the dihydropyrone **6a** by treatment with trifluoroacetic acid. These results showed that the present catalytic reaction of Danishefsky's diene **4b** with glyoxylate **5a** proceeds via the concerted [4+2] cycloaddition pathway, in contrast to the stepwise (Mukaiyama-aldol) mechanism catalyzed by bis(oxazoline)-$Cu(OTf)_2$[8o] or bis(oxazolinyl)pyridine-$Yb(OTf)_3$[8n] system (Chart 2).

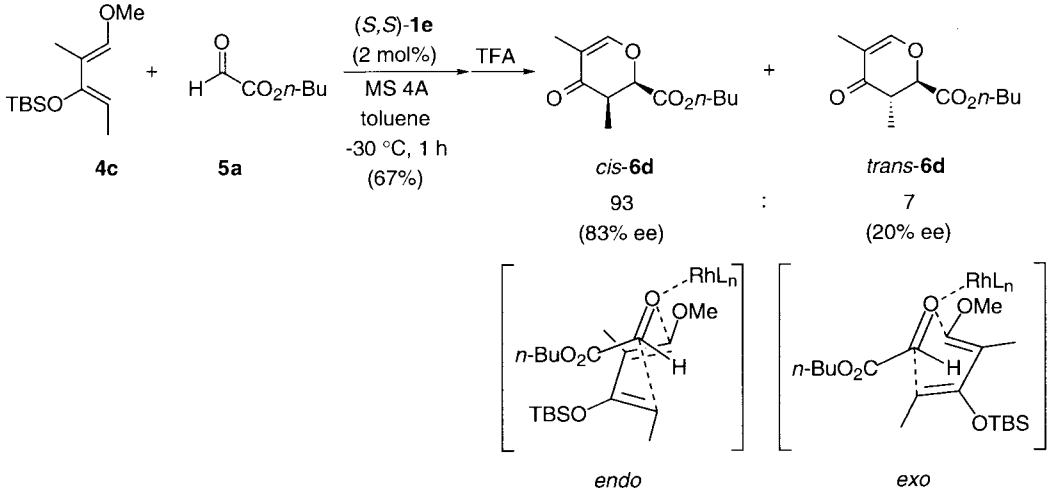
### 2.3. Transition state assembly

In order to clarify the direction of diene-approach to glyoxylates **5** bound to the (Phebox)$RhX_2$ fragments, including the *endo* or *exo* orientation and the C=O enantioface, we first examined the diastereoselectivity of this catalytic system using 2,4-dimethyl diene **4c** and *n*-butyl glyoxylate **5a**. Reactivity of the 2,4-disubstituted diene **4c** was relatively lower than that of **4b**, although the reaction temperature rising −30°C resulted in 67% yield of **6d** with *cis*/*trans* ratio of 93:7 (Scheme 4). This *cis*-selectivity and Diels–Alder mechanism imply that the reaction with Phebox–Rh(III) complexes proceeds via *endo*-transition state; *endo*-orientation of the ester group of glyoxylate relative to the diene. The *cis* (*endo*)-**6d** indicated 83% ee by chiral HPLC analysis (Daicel CHIRALPAK AD), but the enantioselectivity of *trans* (*exo*)-isomer was only 20%.

A transition state that accounts for the observed *re*-face selectivity of the glyoxylate's C=O plane is explained by the perpendicular conformation of two carbonyl moieties of glyoxylates **5**. If both the carbonyl groups of **5** are the parallel conformation (Fig. 1, **D**), the dienes **4** approach the carbonyl *si*-face like allylation of aldehydes with allyltin reagents (Fig. 1, **F**).[5b] The molecular orbital calculation of the protonated methyl glyoxylate **5b** using the PM3 method in WinMOPAC Ver. 2[14] resulted in only the perpendicular conformation obtained (Fig. 1, **E**). In such a case, the steric repulsion between the ester moiety of glyoxylates **5** and one substituent on the oxazoline rings exists (Fig. 1, **G**). When the C=O plane of glyoxylates bound to the rhodium atom is shifted to the Cl–Rh–Cl plane for avoiding the steric repulsion (Fig. 1, **G′**), one of the substituents on the oxazoline rings plays the crucial role of shielding *re*-face of the C=O plane from attack of the dienes **4**. This perpendicular structure is consistent with the substituent effect of the ester moieties on the enantioselectivity of the products **6**. The bulky ester moiety increases the steric repulsion toward the benzyl group on the Phebox ligand, so the conformation of **G′** is more favored than that of **G**.

## 3. Conclusion

It has been shown that the (Phebox)$RhCl_2(H_2O)$ complexes are efficient chiral Lewis acid catalysts for the reaction of Danishefsky's dienes with glyoxylate. We have newly synthesized the (Phebox)$RhX_2(H_2O)$ complexes (X=Br, F), and found that these dibromo and difluoro catalysts are found to exhibit a slightly higher enantioselectivity than the parent dichloride complex. We have also clarified that the present reaction proceeds via the concerted [4+2]




**Scheme 4.**

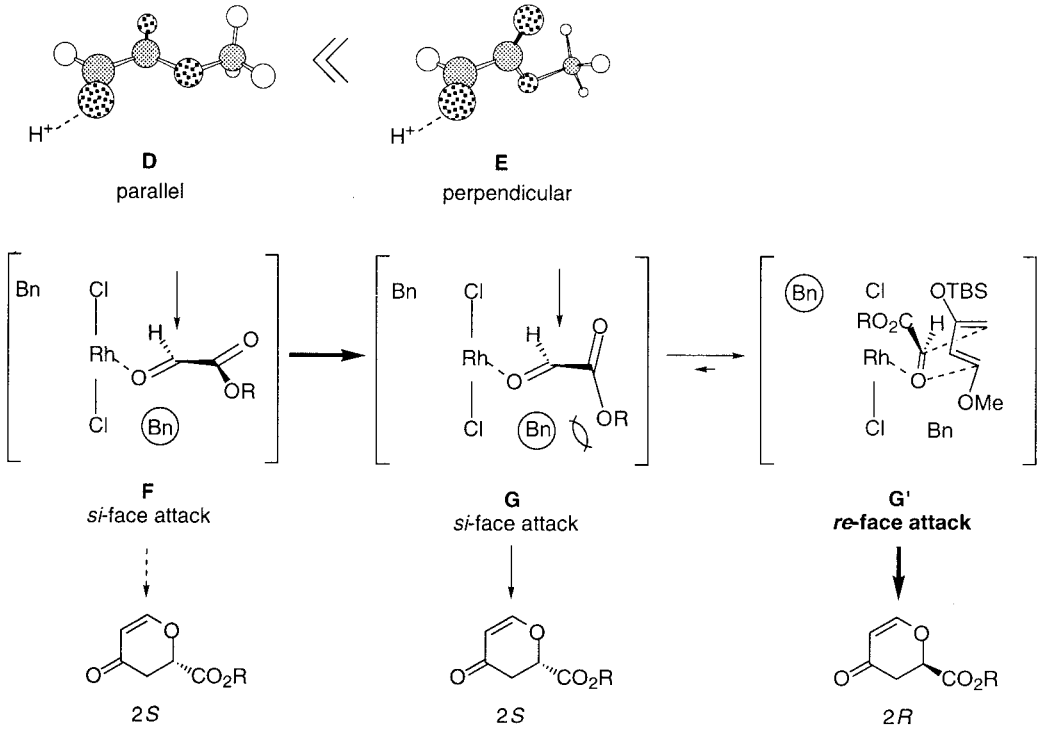



**Figure 1.**

mechanism with the perpendicular conformation of the both carbonyl moieties of glyoxylates **G′**.

## 4. Experimental

### 4.1. General methods

Anhydrous toluene and dichloromethane were purchased from Kanto Chemical Co. 4Å Molecular Sieves (activated powder) and silver acetate were purchased from Aldrich Chemical Co. Hydrofluoroboric acid ($HBF_4$) was purchased from Kishida Chemical Co. Carbon tetrabromide and tetrabutylammonium fluoride (TBAF) were purchased from Tokyo Chemical Industry Co. $^1H$ and $^{13}C$ NMR spectra were measured on Varian Mercury 300 (300 MHz) and Inova 400 (400 MHz) spectrometers. Chemical shifts for $^1H$ NMR were described in parts per million downfield from tetramethylsilane as an internal standard ($\delta$=0) in $CDCl_3$, unless otherwise noted. Chemical shifts for $^{13}C$ NMR were expressed in parts per million in $CDCl_3$ as an internal standard ($\delta$=77.1), unless otherwise noted. IR spectra were measured on a JASCO FT/IR-230 spectrometer. High-performance liquid chromatography (HPLC) analyses were performed on a JASCO PU-980 HPLC pump, UV-975 and 980 UV/VIS detector, and CO-966 column thermostat (at 25°C) using Daicel CHIRALPAK AD or AS columns. Optical rotations were measured on a JASCO DIP-140 polarimeter. Column chromatography was performed with silica gel (Merck, Art 7734). Elemental analyses were performed on a Yanaco CHN corder MT-6. Analytical thin-layer chromatography (TLC) was performed on glass plates and aluminum sheets precoated with silica gel (Merck, Kieselgel 60 $F_{254}$, layer thickness 0.25 and 0.2 mm, respectively). Visualization was accomplished by UV light (254 nm), anisaldehyde, and phosphomolybdic acid. All reactions were carried out under a nitrogen or argon atmosphere. (Phebox)$RhCl_2(H_2O)$ complexes **1** were prepared by our method.[5] Danishefsky's dienes **4** were prepared by the literature method.[15] Glyoxylates **5** were prepared by the literature method.[16]

**4.1.1. (Bn–Phebox)$RhBr_2(H_2O)$ (2).** To a stirred solution of (Bn–Phebox)$RhCl_2(H_2O)$ (**1e**) (317.0 mg, 0.54 mmol) in methanol (50 mL) was added carbon tetrabromide (1.79 g, 5.40 mmol) at room temperature under argon atmosphere. After stirring for 72 h, the reaction mixture was concentrated under reduced pressure. Purification by silica gel chromatography (hexane/ethyl acetate=3:1) gave (Bn–Phebox)$RhBr_2(H_2O)$ (2) in 91% yield (333.1 mg, 0.49 mmol); pale yellow solid. Mp. >300°C. IR (KBr) $\nu$ 3437, 2924, 1618, 1487, 1330, 1149, 970, 737, 704 $cm^{-1}$. $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 2.36 (bs, 2H), 2.81 (dd, $J$= 14.2, 9.8 Hz, 2H), 3.65 (dd, $J$=14.2, 3.9 Hz, 2H), 4.51–4.76 (m, 6H), 7.23–7.36 (m, 11H), 7.63 (d, $J$=7.3 Hz, 2H). $^{13}C$ NMR (67.8 MHz, $CDCl_3$) $\delta$ 40.2, 63.5, 75.1, 122.9, 126.6, 128.0, 129.0, 131.4, 136.8, 171.4 ($J_{Rh-C}$=2.9 Hz), 180.8 ($J_{Rh-C}$=25.4 Hz). Anal. $C_{26}H_{25}N_2O_3Br_2Rh$: Found C 46.10, H 3.47, N 4.13%; Calcd C 46.18, H 3.73, N 4.14%.

**4.1.2. (Bn–Phebox)$Rh(OAc)_2(H_2O)$.** To a stirred solution of (Bn–Phebox)$RhCl_2(H_2O)$ (**1e**) (84.2 mg, 0.143 mmol) in dichloromethane (8 mL) was added silver acetate (95.7 mg, 0.573 mmol) at room temperature under argon atmosphere. After stirring for 1 day, the reaction mixture was filtered through a pad of Celite, then concentrated under reduced pressure. Purification by silica gel chromatography (dichloromethane/ethyl acetate=3:1) gave (Bn–Phebox)-$Rh(OAc)_2(H_2O)$ in 84% yield (76.5 mg, 0.121 mmol); pale yellow solid. Mp. 115–117°C (decomp). IR (KBr) $\nu$ 3343,

2926, 1616, 1486, 1397, 1327, 1148, 969, 740, 703 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 1.75 (s, 6H), 2.63 (dd, $J$=13.9, 9.7 Hz, 2H), 3.70 (dd, $J$=13.9, 3.0 Hz, 2H), 4.52–4.68 (m, 6H), 6.45 (bs, 2H), 7.22–7.32 (m, 11H), 7.62 (d, $J$=7.7 Hz, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 23.9, 40.0, 64.1, 75.4, 123.3, 126.9, 127.9, 128.9, 129.4, 131.9, 137.0, 172.4 ($J_{Rh-C}$=4.2 Hz), 182.7, 189.1 ($J_{Rh-C}$=24.3 Hz).

**4.1.3. (Bn–Phebox)$RhF_2(H_2O)$ (3).** To a stirred solution of (Bn–Phebox)$Rh(OAc)_2(H_2O)$ (159.7 mg, 0.25 mmol) and 70% TBAF in water (1.87 g, 5.0 mmol) in dichloromethane (10 mL) was added 42% $HBF_4$ solution (443 mL, 2.5 mmol) at room temperature under argon atmosphere. After stirring for 6 h, the organic layer was separated and concentrated under reduced pressure. Purification by silica gel chromatography (dichloromethane/ethyl acetate=20:1) gave (Bn–Phebox)$RhF_2(H_2O)$ (**3**) in 73% yield (109.2 mg, 0.18 mmol); pale yellow solid. Mp. 177–180°C (decomp). IR (KBr) $\nu$ 3430, 2924, 1618, 1592, 1487, 1399, 1149, 969, 736, 704 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 2,69 (bs, 2H), 2.81 (dd, $J$=14.0, 10.0 Hz, 2H), 3.67 (dd, $J$=14.0, 4.0 Hz, 2H), 4.52–4.76 (m, 6H), 7.19–7.37 (m, 11H), 7.61 (d, $J$=7.6 Hz, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 40.6, 63.7, 75.6, 123.3, 127.0, 128.4, 129.0, 129.2, 131.5, 137.0, 171.4 ($J_{Rh-C}$=3.4 Hz), 179.5 ($J_{Rh-C}$=22.3 Hz). Anal. $C_{26}H_{25}N_2O_3F_2Rh\cdot(CH_2Cl_2)_2$: Found C 46.75, H 3.80, N 3.88%; Calcd C 46.43, H 4.04, N 3.87%.

### 4.2. General procedure for the hetero Diels–Alder reaction of Danishefsky's dienes 4 and glyoxylates 5 catalyzed by Phebox–Rh(III) complexes 1–3

**4.2.1. Butyl 3,4-dihydro-4-oxo-2*H*-pyran-2-carboxylate (6a).** To a suspension of MS 4A (250 mg) in toluene (2 mL) was added (*S*,*S*)-(Bn–Phebox)$RhCl_2(H_2O)$ complex **1e** (0.01 mmol) and freshly distilled *n*-butyl glyoxylate **5a** (65 mg, 0.5 mmol) at room temperature. The solution was cooled down to −78°C, then 1-methoxy-3-[(*t*-butyldimethylsilyl)oxy]-1,3-butadiene **4b** (129 mg, 0.6 mmol) was added. After the mixture was stirred for 1 h at −78°C, trifluoroacetic acid (45 μL, 0.59 mmol) was added. Then the reaction mixture was warmed to room temperature and quenched by the addition of saturated aqueous $NaHCO_3$ (1 mL). The solution was filtered through a pad of Celite and Florisil, and the filtrate was extracted three times with ether (totally 10 mL). The combined organic layer was washed with brine (5 mL), dried over $MgSO_4$ and evaporated under reduced pressure. Purification by silica gel chromatography (hexane/ethyl acetate=2:1) gave butyl 3,4-dihydro-4-oxo-2*H*-pyran-2-carboxylate **6a** in 90% yield. $[\alpha]_D^{24}$=−38.6° (*c* 1.00, $CHCl_3$; 80% ee, 2*R*); lit.[8l] $[\alpha]_D^{21}$+45.3° (*c* 1.00, $CHCl_3$; 45% ee, 2*S*). IR (neat) $\nu$ 2966, 1756, 1684, 1601, 1404, 1278, 1210, 1040 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.94 (t, $J$=7.2 Hz, 3H), 1.39 (tq, $J$=6.0, 7.2 Hz, 2H), 1.66 (tt, $J$=6.8, 6.0 Hz, 2H), 2.86 (d, $J$=7.7 Hz, 2H), 4.23 (t, $J$=6.8 Hz, 2H), 5.02 (t, $J$=7.7 Hz, 1H), 5.48 (d, $J$=6.2 Hz, 1H), 7.40 (d, $J$=6.2 Hz, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 13.7, 19.1, 30.5, 38.4, 66.2, 76.2, 108.1, 161.9, 168.1, 189.6. Anal. $C_{10}H_{14}O_4$: Found C 60.71, H 7.15%; Calcd C 60.59, H 7.12%.

The ee was determined by HPLC analysis (Daicel CHIRALPAK AD, UV detector 254 nm, hexane/*i*-PrOH=9:1, flow rate 1 mL/min) $t_R$=12.2 min (2*R*), 16.4 min (2*S*), or (Daicel CHIRALPAK AS, UV detector 254 nm, hexane/*i*-PrOH=3:1, flow rate 1 mL/min) $t_R$=13.2 min (2*S*), 15.2 min (2*R*).

**4.2.2. 2,3-Dihydro-2-carbomethoxy-4*H*-pyran-4-one (6b).** $[\alpha]_D^{24}$=−30.8° (*c* 0.65, $CHCl_3$; 68% ee, 2*R*); lit.[8i] $[\alpha]_D^{21}$+122.8° (*c* 0.60, $CHCl_3$; 94% ee, 2*S*). IR (neat) $\nu$ 2962, 1756, 1682, 1601, 1441, 1406, 1280, 1220, 1042, 886, 804 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 2.86 (d, $J$=8.0 Hz, 2H), 3.80 (s, 3H), 5.04 (t, $J$=8.0 Hz, 1H), 5.48 (d, $J$=6.0 Hz, 1H), 7.39 (d, $J$=6.0 Hz, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 38.4, 53.1, 76.1, 108.1, 161.8, 168.5, 189.4. Anal. $C_7H_8O_4$: Found C 53.70, H 5.30%; Calcd C 53.85, H 5.16%.

The ee was determined by HPLC analysis (Daicel CHIRALPAK AD, UV detector 254 nm, hexane/*i*-PrOH=9:1, flow rate 1 mL/min) $t_R$=17.2 min (2*R*), 36.4 min (2*S*), or (Daicel CHIRALPAK AS, UV detector 254 nm, hexane/*i*-PrOH=3:1, flow rate 1 mL/min) $t_R$=19.5 min (2*S*), 25.2 min (2*R*).

**4.2.3. 2,3-Dihydro-2-carboisopropoxy-4*H*-pyran-4-one (6c).** $[\alpha]_D^{24}$=−119.0° (*c* 0.45, $CHCl_3$; 82% ee, 2*R*); lit.[8i] $[\alpha]_D^{21}$+44.2° (*c* 1.20, $CHCl_3$; 46% ee, 2*S*). IR (neat) $\nu$ 2986, 1746, 1682, 1601, 1406, 1280, 1220, 1106 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 1.28 (d, $J$=6.4 Hz, 3H), 1.29 (d, $J$=6.4 Hz, 3H), 2.84 (d, $J$=7.8 Hz, 2H), 4.98 (t, $J$=7.8 Hz, 1H), 5.14 (sept, $J$=6.4 Hz, 1H), 5.47 (d, $J$=6.0 Hz, 1H), 7.39 (d, $J$=6.0 Hz, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 21.72, 21.74, 38.4, 70.3, 76.3, 108.0, 161.9, 167.6, 189.6. Anal. $C_9H_{12}O_4$: Found C 58.71, H 6.55%; Calcd C 58.69, H 6.57%.

The ee was determined by HPLC analysis (Daicel CHIRALPAK AD, UV detector 254 nm, hexane/*i*-PrOH=9:1, flow rate 1 mL/min) $t_R$=13.5 min (2*R*), 26.2 min (2*S*).

**4.2.4. 2,3-Dihydro-2-carbobutoxy-3,5-dimethyl-4*H*-pyran-4-one. *cis*-6d.** $[\alpha]_D^{24}$=−62.7° (*c* 1.00, $CHCl_3$), (83% ee, 2*R*,3*R*). IR (neat) $\nu$ 2966, 1760, 1676, 1624, 1462, 1386, 1309, 1174, 1013, 754 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.93 (t, $J$=7.4 Hz, 3H), 1.10 (d, $J$=7.6 Hz, 3H), 1.38 (tq, $J$=7.9, 7.4 Hz, 2H), 1.59~1.71 (m, 2H), 1.67 (d, $J$=1.1 Hz, 3H), 2.23 (qd, $J$=7.6, 3.7 Hz, 1H), 4.16–4.31 (m, 2H), 4.90 (d, $J$=3.7 Hz, 1H), 7.24 (q, $J$=1.1 Hz). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 10.4, 10.9, 13.5, 19.0, 30.5, 41.9, 65.7, 79.6, 113.4, 157.3, 167.7, 195.3. Anal. $C_{12}H_{18}O_4$: Found C 63.67, H 7.90%; Calcd C 63.70, H 8.02%.

The ee was determined by HPLC analysis (Daicel CHIRALPAK AD, UV detector 254 nm, hexane/*i*-PrOH=9:1, flow rate 0.5 mL/min) $t_R$=16.0 min (2*R*,3*R*), 19.6 min (2*S*,3*S*).

**4.2.5. *trans*-6d.** IR (neat) $\nu$ 2966, 1752, 1676, 1628, 1460, 1390, 1311, 1166, 1021, 754 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.93 (t, $J$=7.4 Hz, 3H), 1.22 (d, $J$=7.2 Hz, 3H), 1.36 (tq, $J$=7.5, 7.4 Hz, 2H), 1.58–1.69 (m, 2H), 1.66 (d, $J$=1.2 Hz, 3H), 2.87 (qd, $J$=8.4,, 7.2 Hz, 1H), 4.20 (ddd, $J$=8.4, 6.7, 1.7 Hz, 2H), 4.62 (d, $J$=8.4 Hz, 1H), 7.21

(q, $J$=1.2 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 10.5, 12.7, 13.5, 19.0, 30.4, 41.5, 65.9, 82.0, 113.5, 157.3, 168.6, 193.6. Anal. $C_{12}H_{18}O_4$: Found C 63.80, H 7.96%; Calcd C 63.70, H 8.02%.

The ee was determined by HPLC analysis (Daicel CHIRALPAK AD, UV Detector 254 nm, hexane/*i*-PrOH= 9:1, Flow Rate 0.5 mL/min) $t_R$=15.1 min (2*R*,3*S*), 25.4 min (2*S*,3*R*).

**4.2.6. Isolation of the hetero Diels–Alder adduct (7) of Danishefsky's diene 4b with *n*-butyl glyoxylate 5a.** To a suspension of MS 4A (250 mg) in toluene (2 mL) was added (Bn–Phebox)$RhCl_2(H_2O)$ complex **1e** (0.01 mmol) and freshly distilled *n*-butyl glyoxylate **5a** (65 mg, 0.5 mmol) at room temperature. The solution was cooled down to −78°C, then 1-methoxy-3-[(*t*-butyldimethylsilyl)oxy]-1,3-butadiene **4b** (129 mg, 0.6 mmol) was added. After stirring for 1 h at −78°C, the reaction was quenched by the addition of triethylamine (2 mL). The resultant mixture was filtered through a pad of Celite and Florisil, then the filtrate was concentrated under reduced pressure to give crude cycloadduct **7** (>9:1 diastereo mixture). Purification by silica gel chromatography (hexane in 1% $Et_3N$/ethyl acetate=2:1) gave pure major-**7** in 77% yield. IR (neat) $\nu$ 2958, 2868, 1741, 1677, 1468, 1375, 1259, 1211, 1134, 1060, 840 782 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.18 (s, 6H), 0.92 (s, 9H), 0.94 (t, $J$=7.8 Hz, 3H), 1.40 (m, 2H), 1.66 (m, 2H), 2.30 (dd, $J$=16.8, 5.1 Hz, 1H), 2.48 (dd, $J$=16.8, 7.0 Hz, 1H), 3.46 (s, 3H), 4.1–4.2 (m, 2H), 4.36 (dd, $J$=7.0, 5.1 Hz, 1H), 4.80 (d, $J$=1.8 Hz, 1H), 5.14 (d, $J$=1.8 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ −4.3, −4.2, 13.9, 18.2, 19.3, 25.8, 30.8, 31.4, 55.4, 65.3, 70.1, 98.9, 102.7, 152.0, 170.9. Anal. $C_{17}H_{32}O_5Si$: Found C 59.18, H 9.35%; Calcd C 59.27, H 9.36%.

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