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Published on Web 03/08/2003

Chiral Hetero Diels−Alder Products by Enantioselective and Diastereoselective Zirconium Catalysis. Scope, Limitation, Mechanism, and Application to the Concise Synthesis of (+)-Prelactone C and (+)-9-Deoxygoniopypyrone

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Abstract: Catalytic asymmetric hetero Diels−Alder (HDA) reactions using a chiral zirconium complex have been developed. The reactions of aldehydes with Danishefsky's dienes proceeded smoothly to afford the corresponding pyranone derivatives in high yields with high diastereo- and enantioselectivities in the presence of a chiral zirconium complex, which was prepared from zirconium *tert*-butoxide, (*R*)-3,3′-diiodobinaphthol or its derivative, a primary alcohol, and a small amount of water. It is noted that 2,3-*trans*-pyranone derivatives were obtained with remarkably high diastereo- and enantioselectivities in the reaction with 4-methyl Danishefsky's diene. This is the first example of catalytic asymmetric *trans*-selective hetero Diels−Alder reactions of aldehydes. Furthermore, asymmetric HDA reactions with 4-benzyloxy Danishefsky's dienes were conducted to afford 2,3-*cis*-pyranone derivatives in high selectivities. Isolation of an intermediate of this asymmetric hetero Diels−Alder reaction indicated that the reaction proceeded in a stepwise cycloaddition pathway. Finally, these catalytic, asymmetric hetero Diels−Alder reactions were successfully applied to concise syntheses of biologically important natural pyranone derivatives, (+)-Prelactone C and (+)-9-deoxygoniopypyrone.

Introduction

Chiral pyran derivatives are important intermediates for the synthesis of many biologically active compounds. As an approach to these compounds, asymmetric reactions using a catalytic amount of a chiral source are among the most useful and efficient methods. Hetero Diels−Alder (HDA) reactions of aldehydes with Danishefsky's dienes mediated by Lewis acids, which provide 2,3-dihydro-4*H*-pyran-4-one derivatives, are promising tools for the construction of pyran ring systems.[1] In addition, some effective chiral Lewis acid catalysts for HDA reactions have been developed and applied to the total synthesis of natural products recently.[2] However, although high enantioselectivities were observed in some cases, the main products of the HDA reactions are 3-unsubstituted or 2,3-*cis*-disubstituted pyranone derivatives in most cases, and no catalyst system to afford 2,3-*trans*-disubstituted products has been reported.

On the other hand, two mechanistic pathways have been considered for HDA reactions of carbonyl compounds with Danishefsky's diene catalyzed by Lewis acids (Scheme 1). One is a concerted [4 + 2] cycloaddition pathway, and the other is a stepwise cycloaddition pathway (Mukaiyama aldol reaction and cyclization). Danishefsky et al. reported that the reaction of benzaldehyde with 1-methoxy-2-methyl-3-trimethylsiloxy-1,3-pentadiene in the presence of BF_3 as a Lewis acid catalyst proceeded in the stepwise pathway and also that the reaction proceeded in the concerted pathway using $ZnCl_2$ or lanthanides as the Lewis acid catalyst.[3] In the BF_3-catalyzed reactions, the major products obtained had 2,3-*trans* configuration, while the reactions using $ZnCl_2$ gave 2,3-*cis*-products exclusively. In the concerted pathway, a favoured transition state would be *endo*-type cycloaddition to afford a 2,3-*cis*-product, and a 2,3-*trans*-product is scarcely obtained. In HDA reactions using chiral Lewis acid catalysts, reaction pathways were proposed on the basis of the structure of intermediates and the stereochemical outcome of the reactions. Corey et al. isolated a trimethysilylated

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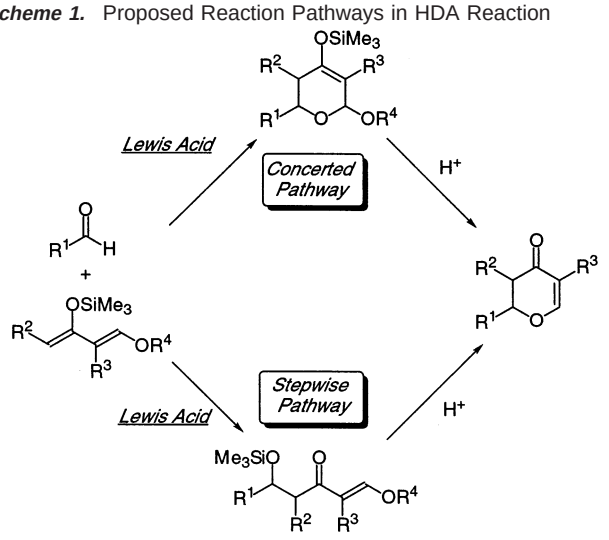
10.1021/ja028186k CCC: $25.00

Scheme 1. Proposed Reaction Pathways in HDA Reaction



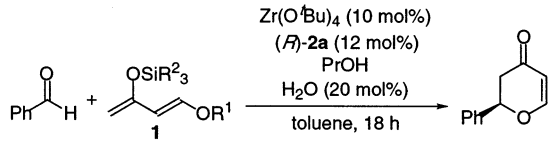
aldol adduct as an intermediate in the HDA reaction catalyzed by a tryptophan-derived oxazaborolidine catalyst.[4] Jacobsen et al. proposed that a chiral salen-Cr complex-catalyzed HDA reaction proceeded via a concerted [4 + 2] cycloaddition pathway inasmuch as a trimethysilylated aldol adduct was not converted to a cyclic product under the reaction conditions.[5,6]

We have shown that several chiral zirconium complexes having 1,1′-bi-2-naphthol (BINOL) moieties are effective catalysts for asymmetric carbon−carbon bond-forming reactions such as Mannich reactions,[7] aza Diels−Alder reactions,[8] Strecker reactions,[9] allylation reactions,[10] Mukaiyama aldol reactions,[11] etc. These reactions proceed in high yields and selectivities, which are strongly dependent on the unique characters of the zirconium catalysts. These catalyst systems would also work well in the HDA reactions to realize high diastereo- and enantioselectivities. Herein, we report full investigations on asymmetric HDA reactions using chiral zirconium catalysts and their applications to the synthesis of biologically important natural pyranone derivatives.[12]

Results and Discussion

Effective activation of aldehydes using a chiral zirconium catalyst has been achieved in Mukaiyama aldol reactions. Therefore, the catalyst that was effective for the aldol reactions might also work well in HDA reactions of aldehydes with Danishefsky's dienes. On the basis of this assumption, we first performed a model HDA reaction of benzaldehyde with 1-methoxy-3-trimethylsiloxy-1,3-butadiene **1a**)[13] using a chiral zirconium catalyst prepared from $Zr(O^tBu)_4$, (*R*)-3,3′-diiodo-1,1′-bi-2-naphthol ((*R*)-3,3′-I_2BINOL), *n*-propanol (PrOH), and water[11b] (Table 1, Chart 1). However, the initial result was rather disappointing, and the corresponding pyranone derivative was obtained in lower yield and selectivity (Table 1, entry 1). The selectivity was improved to 62% ee by increasing the amount of PrOH, albeit the yield was still lower (entry 2). According to the reaction pathway, the product was formed along with elimination of methanol. It was suspected that this methanol might decompose the diene to decrease the yield and that the selectivity might be lowered by interaction of the methanol with the zirconium catalyst. To prevent the production of methanol, we then decided to use 1-*tert*-butoxy-3-trimethylsiloxy-1,3-butadiene (**1b**) instead of **1a**. As expected, the yield and selectivity were improved, and the desired adduct was obtained in 50% yield with 91% ee (entry 3). Furthermore, the yield and selectivity were found to be affected by the amount of PrOH and reaction temperature, and the desired product was obtained in 70% yield with 97% ee when the reaction was carried out using 80 mol % of PrOH at −20 °C (entry 6). We further examined the effects of silicon's substituents of Dan-

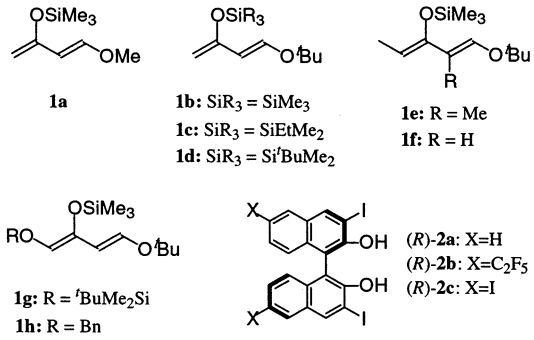
Table 1. Catalytic Asymmetric Hetero Diels−Alder Reactions of Benzaldehyde with Danishefsky's Diene (**1a**−**d**) Using a Chiral Zirconium Catalyst[a]



entry	diene	PrOH (mol %)	temp (°C)	yield (%)[b]	ee (%)
1	**1a**	50	0	39	22
2	**1a**	80	0	35	62
3	**1b**	50	0	50	91
4	**1b**	80	0	65	94
5	**1b**	120	0	44	94
6	**1b**	80	−20	70	97
7	**1b**	80	−45	trace	
8	**1c**	80	−20	80	97
9	**1d**	80	−20	24	89
10[c]	**1c**	80	−20	quant	97

[a] The concentration of the reactions was 0.2 M. After the reactions, the crude products were treated with TFA to afford the desired adducts. [b] Isolated yield. [c] Toluene/^{t}BuOMe (2:1) was used as a solvent.

Chart 1



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(6) Other examples, see: (a) Mujica, M. T.; Afonso, M. M.; Galindo, A.; Palenzuela, J. A. *Tetrahedron* **1996**, *52*, 2167. (b) Ghosh, A. K.; Mathivanan, P.; Cappiello, J.; Krishnan, K. *Tetrahedron: Asymmetry* **1996**, *7*, 2165. (c) Qian, C.; Wang, L. *Tetrahedron Lett.* **2000**, *41*, 2203.
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Table 2. Asymmetric Hetero Diels−Alder Reactions of Aldehydes with the Diene **1c**[a]

entry	aldehyde	solvent	yield (%)[b]	ee (%)
1	PhCHO	toluene	80	97
2	PhCHO	toluene−^{t}BuOMe[c]	quant	97
3	*p*-MeC_6H_4CHO	toluene	63	95
4	*p*-MeC_6H_4CHO	toluene−^{t}BuOMe[c]	95	95
5	*p*-ClC_6H_4CHO	toluene	65	84
6	*p*-ClC_6H_4CHO	toluene−^{t}BuOMe[c]	90	84
7	$PhCH_2CH_2CHO$	toluene	84	90
8	$PhCH_2CH_2CHO$	toluene−^{t}BuOMe[c]	quant	90
9	$CH_3(CH_2)_4CHO$	toluene	69	91
10	$CH_3(CH_2)_4CHO$	toluene−^{t}BuOMe[c]	98	93
11[d]	(*E*)-PhCH=CHCHO	toluene−^{t}BuOMe[c]	97	90

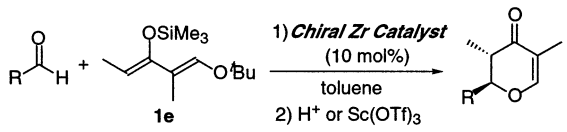
[a] The reactions were performed in the presence of 10 mol % catalyst prepared from $Zr(O^tBu)_4$ (10 mol %), (*R*)-**2a** (12 mol %), PrOH (80 mol %), and H_2O (20 mol %) at −20 °C for 18 h in toluene or toluene/^{t}BuOMe (2:1). The concentration of the reactions was 0.2 M. After the reactions, the crude products were treated with TFA to afford the desired pyranone derivatives. [b] Isolated yield. [c] Toluene/^{t}BuOMe (2:1) was used. [d] $Sc(OTf)_3$ (10 mol %) was used instead of TFA.

ishefsky's dienes and solvents in this HDA reaction. When diene **1c** having an ethyldimethylsilyloxy group was employed, the desired product was obtained in 80% yield with 97% ee (entry 8), although more stable diene **1d** having a *tert*-butyldimethylsilyloxy group did not work well under the conditions (entry 9). Finally, the desired pyranone derivative was obtained quantitatively with 97% ee using a mixed solvent system of toluene/^{t}BuOMe (2:1) (entry 10).[14] It is noted that the lower yield and selectivity obtained in the initial experiment were significantly improved by optimizing several reaction parameters.

We then tested reactions of various aldehydes with diene **1c** in toluene or toluene/^{t}BuOMe (2:1) (Table 2). Aromatic, α,β-unsaturated, and even aliphatic aldehydes reacted with the Danishefsky's diene to afford the desired HDA adducts in good to high yields with high enantioselectivities. It is noted that a high level of stereocontrol has been achieved even in the reactions of aliphatic aldehydes. For the solvents, the toluene/^{t}BuOMe system gave higher yields than toluene in all cases. In these HDA pathways, the reaction was quenched by adding saturated aqueous $NaHCO_3$, and after usual workup, the crude adduct was treated with trifluoroacetic acid (TFA), that accelerated the formation of the pyranone derivative. However, in the reaction of cinnamaldehyde, the desired cyclic product was not obtained in good yield after treatment with TFA, because side reactions occurred. We then investigated other workup conditions and found that treatment with a catalytic amount of scandium triflate ($Sc(OTf)_3$)[15] gave a high yield of the desired product.

Next, the HDA reactions of 4-methyl-substituted Danishefsky's diene were investigated, which includes diastereo- and enantiofacial selectivity issues. 1-*tert*-Butoxy-2-methyl-3-trimethylsiloxy-1,3-pentadiene (**1e**) was selected as a model and was reacted with benzaldehyde using a chiral zirconium catalyst having an (*R*)-3,3′-I_2BINOL moiety under the conditions shown in Table 2 (toluene was used as a solvent). Unexpectedly, the reaction proceeded sluggishly (Table 3, entry 1), and this result

Table 3. Asymmetric Hetero Diels−Alder Reactions of Aldehydes with Diene **1e**[a]



entry	aldehyde	BINOL	yield (%)[b]	*cis*/*trans*	ee (%)[c]
1	PhCHO	**2a**	trace		
2	PhCHO	**2b**	quant	1/12	98
3[d]	PhCHO	**2b**	99	1/24	97
4	*p*-MeC_6H_4CHO	**2b**	93	1/7	90
5[d]	*p*-MeC_6H_4CHO	**2b**	99	1/16	93
6	*p*-ClC_6H_4CHO	**2b**	99	1/9	97
7[d]	*p*-ClC_6H_4CHO	**2b**	99	1/24	98
8[e]	*p*-ClC_6H_4CHO	**2b**	90	1/16	97
9[f,g]	(*E*)-PhCH=CHCHO	**2b**	78	1/7	87
10[g,h]	(*E*)-PhCH=CHCHO	**2b**	96	1/9	90
11[i,j]	$PhCH_2CH_2CHO$	**2b**	23	1/6	79
12[i]	$PhCH_2CH_2CHO$	**2c**	68	1/9	87
13[k]	$PhCH_2CH_2CHO$	**2c**	97	1/9	90
14[i]	$CH_3(CH_2)_4CHO$	**2c**	63	1/10	88
15[k]	$CH_3(CH_2)_4CHO$	**2c**	94	1/10	95

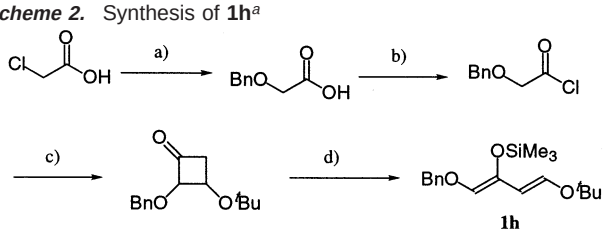
[a] The reactions were performed in the presence of 10 mol % Zr catalyst at −20 °C for 18 h unless otherwise noted. The catalyst was prepared from $Zr(O^tBu)_4$ (10 mol %), (*R*)-**2** (12−15 mol %), PrOH (80 mol %), and H_2O (20 mol %). The concentration of the reactions was 0.2 M. After the reactions, the crude products were treated with TFA to afford the desired adducts. [b] Isolated yield. [c] Trans product. [d] −40 °C, 24 h. [e] The reaction was performed in the presence of 2 mol % Zr catalyst at −40 °C for 168 h. The catalyst was prepared from $Zr(O^tBu)_4$ (2.0 mol %), (*R*)-**2** (2.4 mol %), PrOH (80 mol %), and H_2O (4.0 mol %). The concentration of the reaction was 0.3 M. [f] −10 °C. [g] $Sc(OTf)_3$ (10 mol %) was used instead of TFA. [h] 60 h. [i] The reaction was performed for 48 h using PrOH (120 mol %) in higher concentration (0.5 M). [j] 0 °C. [k] The reaction was performed in toluene/^{t}BuOMe (2:1) for 72 h using PrOH (120 mol %) at −20 °C. The concentration of the reactions was 0.3 M.

clearly showed that 4-substituted diene **1e** was less reactive than 4-unsubstituted dienes **1a**−**d**. We then focused on increasing the Lewis acidity of the zirconium catalyst and introduced electron-withdrawing groups at the 6,6′-positions of BINOL derivatives. (*R*)-3,3′-Diiodo-6,6′-bispentafluoroethyl-1,1′-bi-2-naphthol ((*R*)-3,3′-I_2-6,6′-$(C_2F_5)_2$BINOL, (*R*)-**2b**) was chosen as a chiral ligand, and a chiral zirconium catalyst was prepared from $Zr(O^tBu)_4$, (*R*)-**2b**, PrOH, and water. It was remarkable that in the presence of 10 mol % of this chiral zirconium catalyst, the reaction of benzaldehyde with **1e** proceeded smoothly in toluene at −20 °C to afford the desired HDA adduct quantitatively. Moreover, it was exciting to see that the stereochemistry of the product was 2,3-*trans* and that the enantiomeric excess of the *trans*-adduct was proven to be 98% (Table 3, entry 2). The *trans*-selectivity was further improved when the reaction was carried out at −40 °C (entry 3). We examined reactions of other aldehydes including aromatic, α,β-unsaturated, and aliphatic aldehydes using this new chiral zirconium catalyst. In the cases of aromatic and α,β-unsaturated aldehydes, the reactions proceeded smoothly to give the desired pyranone derivatives in high yields with high *trans*-selectivities, and the enantiomeric excesses of the *trans*-adducts were also high. On the other hand, the yield and selectivities were lower in the reaction of an aliphatic aldehyde (entry 11). They were finally improved when (*R*)-3,3′,6,6′-I_4BINOL ((*R*)-**2c**) was used instead of (*R*)-**2b** and the reaction was conducted in toluene/^{t}BuOMe (2:1) as a solvent, and the desired products were obtained in high yields with high diastereo- and enantioselectivities. It is noted that this is the first example of the catalytic asymmetric

(14) *tert*-Butyl methyl ether was used as an efficient solvent in asymmetric HDA reactions previously. See: Schaus, S. E.; Brånalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403.

(15) (a) Kobayashi, S. *Synlett* **1994**, 689. (b) Kobayashi, S. *Eur. J. Org. Chem.* **1999**, 15. (c) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem. Rev.* **2002**, *102*, 2227.

Scheme 2. Synthesis of **1h**[a]



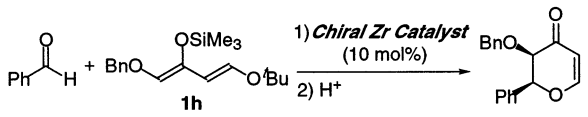
[a] Reaction conditions: (a) Na, BnOH, reflux, 80%; (b) $SOCl_2$, CH_2Cl_2, reflux, 90%; (c) *tert*-butyl vinyl ether, Et_3N, CH_3CN, 80 °C, 76%; (d) LHMDS, Me_3SiCl, THF, 0 °C, 74%.

trans-selective HDA reactions of aldehydes and that a wide variety of aldehydes are applicable to attain high levels of yields and selectivities.

To demonstrate further utility of this reaction, we focused on HDA reactions using more functionalized Danishefsky's dienes. 3-Oxygenated 2-alkyl-2,3-dihydro-4*H*-pyran-4-one derivatives are important synthetic intermediates to afford hexose derivatives.[16] As a new approach to hexose derivatives, a HDA reaction of an aldehyde with Danishefsky's diene having an oxy-substituent at the 4-position has already been developed by Danishefsky et al.[17] However, catalytic asymmetric HDA reactions using this type of diene have not been reported. We decided to investigate HDA reactions of aldehydes with 4-oxygenated Danishefsky's diene using the chiral zirconium catalyst. Initially, the reaction of benzaldehyde with 1-*tert*-butyldimethylsilyloxy-4-*tert*-butoxy-2-trimethylsilyloxy-1,3-butadiene (**1g**) was conducted using the Zr-3,3′,6,6′-I_4BINOL catalyst system. As a result, the reaction proceeded sluggishly, and it was speculated that the bulky substituent at the 4-position prevented the smooth progress of the reaction. Next, we planned to employ 1-benzyloxy-4-*tert*-butoxy-2-trimethylsilyloxy-1,3-butadiene (**1h**) as a diene component. The diene was formerly prepared by oxidation, benzylation, and silylation of Danishefsky's diene **1d**, but the total yield was low.[18] Therefore, we first decided to develop a new method for the preparation of **1h**.[19] A new synthetic route to **1h** is shown in Scheme 2. Benzyloxyacetyl chloride was synthesized according to a standard procedure.[20] The [2 + 2] cycloaddition of benzyloxyacetyl chloride with *tert*-butyl vinyl ether gave the corresponding β-lactone, and the following ring-opening reaction mediated by LHMDS and Me_3SiCl afforded the diene **1h** as a single diastereomer.

We then conducted the HDA reactions of benzaldehyde with diene **1h** using the zirconium catalyts (Table 4). It was unfortunately found that the desired reaction proceeded slowly and that selectivities were not satisfactory in toluene at −20 °C. To improve the reactivity and the selectivities, the reaction conditions were further optimized. First, we examined the effect of the solvents, and it was revealed that toluene/^{t}BuOMe as a mixed solvent was suitable for this reaction. We then examined the amount of PrOH in the catalyst system, and it turned out

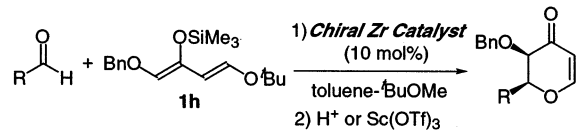
Table 4. Asymmetric Hetero Diels−Alder Reactions of Benzaldehyde with Diene **1h**[a]



entry	PrOH (mol %)	conditions	yield (%)[b]	*cis*/*trans*[c]	ee (%)[d]
1	80	toluene, 28 h	35	4/1	82
2	80	toluene−^{t}BuOMe,[e] 28 h	40	4/1	83
3	120	toluene−^{t}BuOMe,[e] 48 h	58	10/1	96
4	160	toluene−^{t}BuOMe,[e] 48 h	62	24/1	98
5[f]	160	toluene−^{t}BuOMe,[e] 96 h	95	>30/1	97
6[f]	160	toluene, 96 h	71	13/1	93

[a] All reactions were performed in the presence of 10 mol % Zr catalyst at −20 °C. The catalyst was prepared from Zr(O^{t}Bu)$_4$ (10 mol %), (*R*)-**2c** (12 mol %), PrOH, and H_2O (20 mol %). The concentration of the reactions was 0.23 M. After the reactions, the crude products were treated with Sc(OTf)$_3$ (10 mol %) to afford the desired adducts. [b] Isolated yield. [c] *Cis*/*trans* ratio was determined by ^{1}H NMR. [d] *Cis* product. [e] Toluene−^{t}BuOMe (2:1) was used. [f] The concentration of the reaction was 0.5 M, and 1.5 equiv of **1h** was used.

Table 5. Asymmetric Hetero Diels−Alder Reactions of Aldehydes with Diene **1h**[a]



entry	aldehyde	yield (%)[b]	*cis*/*trans*[c]	ee (%)[d]
1	PhCHO	95	>30/1	97
2	*p*-MeC_6H_4CHO	90	19/1	94
3[e]	*p*-ClC_6H_4CHO	quant	>30/1	97
4[e]	*p*-$NO_2C_6H_4CHO$	85	13/1	90
5	(*E*)-PhCH=HCHO	quant	6/1	92
6	$PhCH_2CH_2CHO$	54	12/1	81

[a] All reactions were performed in toluene−^{t}BuOMe (2:1) in the presence of 10 mol % Zr catalyst at −20 °C for 96 h. The catalyst was prepared from Zr(O^{t}Bu)$_4$ (10 mol %), (*R*)-**2c** (12 mol %), PrOH (160 mol %), and H_2O (20 mol %). 1.5 equiv of **1h** was used. The concentration of the reactions was 0.5 M. After the reactions, the crude products were treated with Sc(OTf)$_3$ (10 mol %) to afford the desired adducts. [b] Isolated yield. [c] *Cis*/*trans* ratio was determined by ^{1}H NMR. [d] *Cis* product. [e] The concentration of the reactions was 0.2 M.

that the selectivities were improved to a satisfactory level by increasing the amount of PrOH. Finally, higher concentration of the reaction mixture, a prolonged reaction time, and an excess amount of diene were found to be effective, and the desired product was obtained in high yield with excellent diastereo- and enantioselectivities (entry 5). It should also be noted that the stereochemistry of the obtained adduct was 2,3-*cis*, which was completely reversed from the 2,3-*trans*-selectivity obtained in the reaction with diene **1e** (details of these selectivities are discussed in the following paragraph).

We then tested HDA reactions of other aldehydes with Danishefsky's diene **1h** under the optimized reaction conditions, and the results are summarized in Table 5. Aromatic aldehydes as well as α,β-unsaturated and aliphatic aldehydes reacted with the diene smoothly to afford the desired products in high yields with high *cis*-selectivity, and the enantiomeric excesses of the *cis*-adducts were also high.

To demonstrate the utility of these catalytic asymmetric HDA reactions, we performed the asymmetric synthesis of biologically

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(17) (a) Danishefsky, S. J.; Webb, R. R., II. *J. Org. Chem.* **1984**, *49*, 1955. (b) Danishefsky, S. J.; Maring, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 1269.
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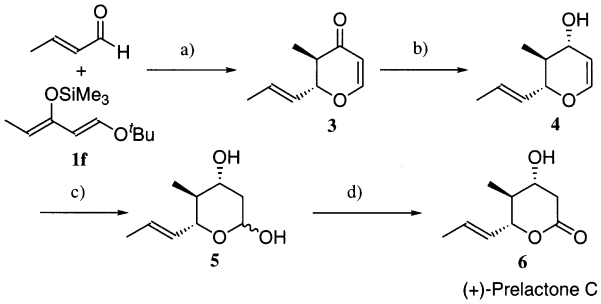
(20) See Experimental Section.

Scheme 3. Synthesis of (+)-Prelactone C[a]

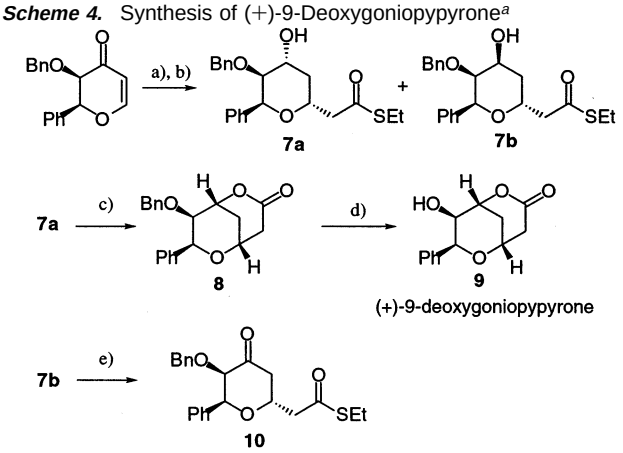


[a] Reaction conditions: (a) $Zr(O^tBu)_4$ (10 mol %), (*S*)-**2c** (15 mol %), PrOH (120 mol %), H_2O (20 mol %), toluene/^{t}BuOMe (2/1), −30 °C, 67 h, 89%, *trans*/*cis* = 6/1, 93% ee; (b) $NaBH_4$-$CeCl_3$, EtOH-CH_2Cl_2, −78 °C, 92%, ds = 96/4; (c) Dowex 50W-X2, LiBr, H_2O, THF, 0 °C, 79%; (d) Ag_2CO_3-Celite, benzene, reflux, 96%.

important natural products. At first, we planned the synthesis of (+)-Prelactone C[21] (Scheme 3), which was isolated from the concanamycin-producing *Streptomyces sp*.[22] (+)-Prelactone C contains a 2,3-*trans*-dialkylpyran ring system, and we chose the asymmetric HDA reaction of crotonaldehyde with 1-*tert*-butoxy-3-trimethylsiloxy-1,3-pentadiene (**1f**) as a key step. The reaction was performed under the optimized conditions using the chiral zirconium catalyst, and the desired adduct (**3**) was obtained in 89% yield with good *trans*-selectivity (*trans*/*cis* = 6/1), and the enantiomeric excess of the *trans*-adduct was 93%. After separation of the diastereomers, the *trans*-pyranone derivative was reduced using sodium borohydride in the presence of cerium chloride to give allylic alcohol **4** in excellent yield and diastereoselectivity (90%, 96/4).[23] The allylic alcohol **4** was then hydrated using acidic resins in the presence of water to produce lactol **5**,[24] which was oxidized selectively using the Fetizon reagent to afford Prelactone C (**6**) in excellent yield.[25] All physical data of **6** were consistent with those of the literature.

Next, we conducted the asymmetric synthesis of (+)-9-deoxygoniopypyrone[26] (Scheme 4), which has cytotoxicity against human tumor cell. As shown in Table 4, the HDA reaction of benzaldehyde with 1-benzyloxy-4-*tert*-butoxy-2-trimethylsilyloxy-1,3-butadiene (**1h**) proceeded in 95% yield with excellent *cis*-selectivity (*cis*/*trans* = >30/1), and the desired *cis*-adduct was obtained with 97% ee. For introduction of a two-carbon unit into the pyran ring in 1,4-addition manner, several kinds of enolates were first employed, but the desired Michael reaction proceeded sluggishly. We then investigated Lewis acid-mediated Mukaiyama−Michael reactions with silicon enolates.[27] After screening several Lewis acids, we found that $Sc(OTf)_3$ was effective in this reaction,[28] and the desired reaction proceeded smoothly to afford the desired Michael adduct as a single diastereomer. The stereochemistry of the product was determined by NOE experiments. Because it was revealed that epimerization at the C5′ position of the product occurred easily under workup conditions, the following reduction of the ketone moiety was carried out without further purification. We then examined several reducing reagents and found that Bu_2SnH_2 was effective in affording the desired alcohol (**7**) in excellent yield, albeit the diastereoselectivity was moderate.[29] Alcohols **7a** and **7b** obtained were separated by silica gel chromatography, and the structure of **7b** was confirmed by X-ray crystal structure analysis.[30] The undesired product **7b** could be converted to the starting ketone **10** without any epimerization using tetrapropylammonium perruthenate (TPAP) oxidation.[31] The alcohol **7a** was readily cyclized in the presence of copper(II) triflate ($Cu(OTf)_2$) to afford the literature known compound **8** in high yield.[32] Deprotection of **8** was achieved according to the literature method, and (+)-9-deoxygoniopypyrone (**9**) was obtained in high yield.[33] All physical data of **9** were consistent with those of the literature.

Scheme 4. Synthesis of (+)-9-Deoxygoniopypyrone[a]



[a] Reaction conditions: (a) $H_2C{=}C(OSiMe_3)SEt$, $Sc(OTf)_3$ (20 mol %), CH_2Cl_2, −78 °C; (b) Bu_2SnH_2, CH_2Cl_2, 0 °C, 88% (two steps, **7a**/**7b** = 63/37); (c) $Cu(OTf)_2$, CH_3CN, 60 °C, 95%; (d) $TiCl_4$, CH_2Cl_2, room temperature, 96%; (e) TPAP (15 mol %), NMO, CH_2Cl_2, room temperature, 93%.

As discussed in the Introduction, favored products in the HDA reactions using chiral Lewis acid catalyst systems were 2,3-*cis*-disubstituted pyranones. On the other hand, in the reactions with 4-methyl Danishefsky's diene using the chiral zirconium complex reported here, remarkable 2,3-*trans*-selectivity was observed. This unique selectivity is not easily explained by the concerted [4 + 2] cycloaddition mechanism, because of the

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(27) (a) Saigo, K.; Osaki, M.; Mukaiyama, T. *Chem. Lett.* **1976**, 163. (b) Lichtenthaler, F. W.; Nishiyama, S.; Weimer, T. *Liebigs Ann. Chem.* **1989**, 1163. (c) Iwasaki, H.; Kume, T.; Yamamoto, Y.; Akiba, K. *Tetrahedron Lett.* **1987**, *28*, 6355. (d) Danishefsky, S. J.; Simoneau, B. *J. Am. Chem. Soc.* **1989**, *111*, 2599.
(28) Kobayashi, S.; Hachiya, I.; Ishitani, H.; Araki, M. *Synlett* **1993**, 472. To the best of our knowledge, this is the first example of the Michael reaction of silicon enolates with pyranone derivatives using a catalytic amount of a Lewis acid.
(29) Clive, D. L.; He, X.; Postema, M. H. D.; Mashimbye, M. J. *Tetrahedron Lett.* **1998**, *39*, 4231.
(30) See Supporting Information.
(31) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, *21*, 1625.
(32) Masamune, S.; Hayase, Y.; Schilling, W.; Chan, W. K.; Bates, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 6756. It is noteworthy that the combination of the *S*-ethyl thioester and a Cu(II) salt gave an excellent yield.
(33) See ref 26b.

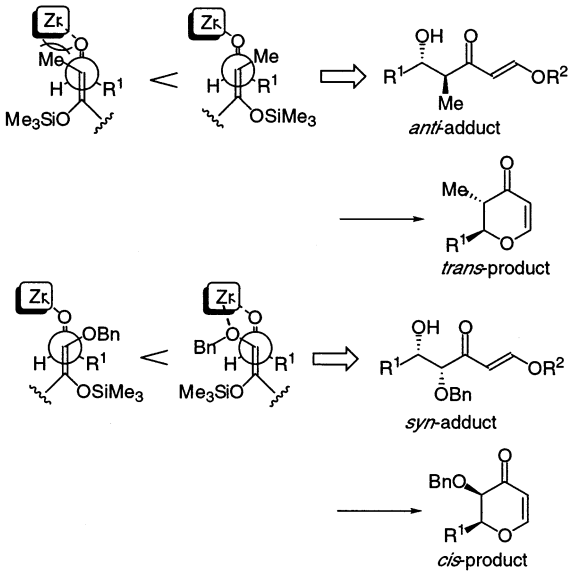
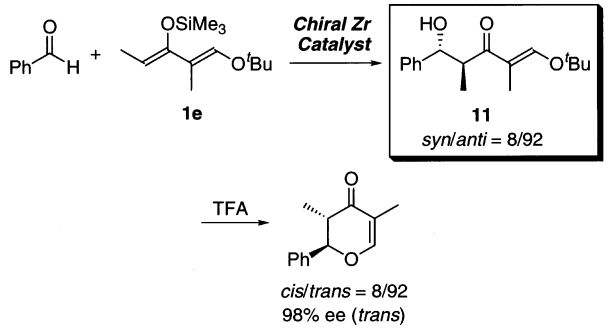


Figure 1. Origin of *trans*- and *cis*-selectivity.

Scheme 5. Isolation of an Intermediate of the HDA Reaction



disadvantage of the *exo*-type transition state. Therefore, we assumed a stepwise mechanism and attempted to isolate an intermediate of the reaction to clarify the reaction mechanism. In almost all HDA reactions using the zirconium catalyst, the reaction mixture was simple, and only one new product was observed by TLC analysis. In the reaction of benzaldehyde with 1-*tert*-butoxy-2-methyl-3-trimethylsiloxy-1,3-pentadiene (**1e**), the product was carefully isolated by deactivated silica gel column chromatography before treatment with TFA. It was revealed that the product isolated was the corresponding *anti*-aldol adduct (**11**) as a hydroxy-free form and that high *anti*-selectivity was observed (*syn*/*anti* = 8/92) as shown in Scheme 5. In addition, the aldol adduct (**11**) easily cyclized quantitatively under acidic conditions to afford the product with high selectivity (*cis*/*trans* = 8/92, 98% ee (*trans*)). These facts, the observed 2,3-*trans*-selectivity and the isolation of the *anti*-aldol intermediate, indicate that the HDA reaction catalyzed by the chiral zirconium complex proceeds via the stepwise (Mukaiyama aldol reaction and cyclization) pathway. Therefore, this unique 2,3-*trans*-selectivity can be explained by the remarkable *anti*-selective Mukaiyama aldol reactions using the chiral zirconium catalyst system, which proceeded with *anti*-preference independent of the *E*- and *Z*-geometry of the silicon enolates.[11] From this point of view, the lower reactivity of diene **1d** would be understood by considering the greater stability of the *tert*-butyldimethylsilyloxy group than that of the trimethylsilyloxy or ethyldimethylsilyloxy group. Moreover, the effect of the *tert*-butoxy group of the dienes on the enantioselectivity could be explained by steric hindrance to prevent the [4 + 2] cycloaddition pathway effectively. On the other hand, remarkable *cis*-selectivity obtained in the reaction with 1-benzyloxy-4-*tert*-butoxy-2-trimethylsilyloxy-1,3-butadiene (**1h**) could also be accounted for by interaction of the benzyloxy group with the zirconium center of the catalyst.[34] In the mechanism of the zirconium-catalyzed *anti*-selective aldol reactions, steric repulsion between the methyl group of the enolate and the zirconium catalyst seemed to be an important factor to explain *anti*-selectivity in an open-chain transition state model.[11b] In the case of the reactions with the diene **1h**, coordination of the oxygen atom of the benzyloxy group would be more favored than the steric repulsion, and the stereochemical outcome results in *cis*-selectivity (Figure 1).[35]

Conclusion

In conclusion, we have developed catalytic asymmetric HDA reactions using chiral zirconium catalysts prepared from Zr(O^{t}Bu)$_4$, 3,3′-I$_2$BINOL derivatives, PrOH, and water, and it was found that the reactions proceeded with remarkable stereoselectivities: high 2,3-*trans*-selectivity of the reactions with 4-methyl Danishefsky's dienes and high 2,3-*cis*-selectivity of the reactions with 4-benzyloxy Danishefsky's dienes. It is noted that a wide variety of aldehydes including aromatic, α,β-unsaturated, and even aliphatic aldehydes were applicable to these reactions, and high yields and selectivities were obtained in all cases. Furthermore, these highly stereoselective reactions were successfully applied to the efficient synthesis of biologically important natural pyranone derivatives, (+)-Prelactone C and (+)-9-deoxygoniopypyrone. Finally, a mechanistic study has revealed that this reaction proceeded via a controlled stepwise cycloaddition pathway.

Acknowledgment. This work was partially supported by CREST and SORST, Japan Science Technology Corporation, and a Grant-in-Aid for Scientific Research from the Japan Society of the Promotion of Sciences.

Supporting Information Available: Experimental section and information on X-ray structure analysis (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(34) A similar intermediate which suggested the stepwise mechanism was also isolated in the reaction of benzaldehyde with **1h**.

(35) Indeed, the aldol reaction using an α-benzyloxy silicon enolate gave the *syn*-aldol adduct. In the presence of the chiral zirconium catalyst prepared from Zr(O^{t}Bu)$_4$ (10 mol %), (*R*)-3,3′,6,6′-I$_4$BINOL (12 mol %), PrOH (80 mol %), and H$_2$O (20 mol %), the aldol reaction of benzaldehyde with (*Z*)-2-benzyloxy-1-phenoxy-1-trimethylsiloxyethene proceeded in toluene-^{t}BuOMe at −20 °C to afford the corresponding *syn*-aldol adduct in high yield with high stereoselectivity (quantitative yield, syn/anti = >30/1, 97% ee (syn)).