A Highly Enantioselective Hetero-Diels−Alder Reaction of Aldehydes with Danishefsky's Diene Catalyzed by Chiral Titanium(IV) 5,5′,6,6′,7,7′,8,8′-Octahydro-1,1′-bi-2-naphthol Complexes

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The catalytic effect of chiral Lewis acids on the hetero-Diels−Alder reaction between aldehydes and Danishefsky's diene (**1**) has been investigated. A variety of combinations of different ligands and Lewis acids have been examined as catalysts for the hetero-Diels−Alder reaction between benzaldehyde and **1**, and it has been found that the readily accessible Ti(IV)−H_8-BINOL (TiHBOL) complex is a very effective catalyst for the reaction, leading to products with very high enantioselectivity (up to 99% ee) and yield (92%). The hetero-Diels−Alder reaction of other aldehydes with **1** under the catalysis of TiHBOL is a general reaction which proceeds well with very high enantioselectivity and isolated yield for various aldehydes at 0 °C to room temperature. Based on the experimental results, the proposed mechanism of the hetero-Diels−Alder reaction and the dihedral angle effects of ligands are discussed.

Introduction

The development of chiral catalysts for asymmetric synthesis is of tremendous synthetic importance.[1] In this context, catalytic enantioselective carbon−carbon bond-forming reactions have attracted special attention. Particularly notable is the recent development of a number of remarkably effective catalytic processes for the enantioselective Diels−Alders reaction,[2] which is one of the most powerful and versatile methods in organic synthesis. The chiral Lewis acid-catalyzed hetero-Diels−Alder (HDA) reaction is also of particular interest due to its very convenient access to prepare six-membered partly saturated heterocycles, a class of compounds that have found extensive use as starting materials for total synthesis of many natural products and other highly functionalized heterocycles.[3]

Since its description by Danishefsky et al., the hetero-Diels−Alder reaction between general dienophiles and an activated diene such as 1-methoxy-3-(trimethylsilyloxy)butadiene (Danishefsky's diene) has proven to be one of the most reliable transformations for preparing pyranosic synthons.[4] The catalytic asymmetric HDA reaction can be achieved by using Lewis acids, such as Eu(III),[4b,c,d] Rh(II),[5] V(IV),[6] B(III),[7] Al(III),[8] Yb(III),[9] Cr(III),[10] Mn(IV),[10b] Ti(IV),[11] Co(II),[12] or Cu(II)[13] ion, along with chiral ligands containing 3-(heptafluoropropylhydroxymethylene)-

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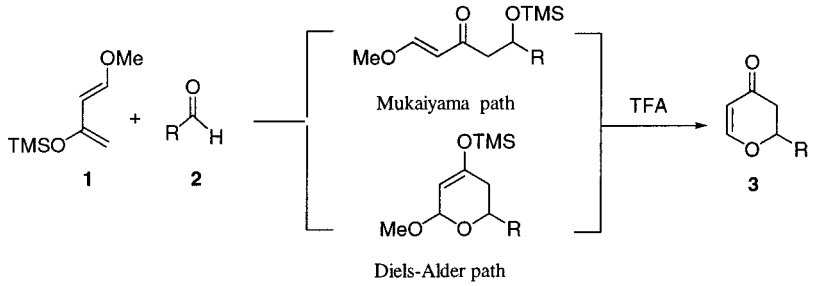
Scheme 1. Two Possible Mechanisms of the Hetero-Diels−Alder Reaction



D-camphorato,[4b,c,d,6] carboxamidate,[5c] *N*-tosyltrytophan,[7a] 3,3′-disubstituted-BINOL,[8a,b,c,d,f] triflylamide,[9a] salen,[10,12a,b] BINOL,[11a,b] bisoxazoline,[5b,9d,11] and BNP[11b,c] ((*R*)-1,1′-binaphthyl-2,2′-diylphosphonate). Other metal-catalyzed HDA reactions using such as Ce(III),[14] Nd(III),[15] and Sm(III)[15] have been reported; however, the catalytic asymmetric process has not been realized by utilizing these metal ions. Among those catalytic asymmetric HDA reactions, the best chiral catalysis (97% yield and 99% ee) is achieved in the asymmetric organoaluminum-catalyzed HDA reaction between **1** and benzaldehyde.[8d] However, there are not good catalysts which could afford the desired product with high enantioselectivity and yield between **1** and extensive aldehydes (Scheme 1). There are two different reaction paths for the formation of the product of the HDA reaction, 2,3-dihydro-2-substituent-4-pyranone, depending on the Lewis acid catalyst used. These paths are classified into two mechanisms formulated as Mukaiyama aldol and concerted [4 + 2] cycloaddition mechanisms. Utilizing boron[5] and titanium[9] catalysts involves a stepwise mechanism involving an initial Mukaiyama aldol addition, followed by cyclization. However, the concerted Diels−Alder pathway has been positively identified in reactions catalyzed by Lewis acids based on zinc,[4a] europium,[4b,c,d] rhodium,[5b] aluminum,[6] chromium,[8] cuprum,[11] and cerium.[12]

Highly enantioselective HDA reactions between less nucleophilic dienes bearing fewer than two oxygen substituents and carbonyl compounds were also achieved by using some chiral Lewis acids, such as Al(III) or Ti(IV)−BINOL, Cu(II)−bisoxazoline, and Cr(III)−Schiff base.[16] Another asymmetric catalytic HDA reaction between vinyl ethers and α,β-unsaturated acyl phosphonate or β,γ-unsaturated α-keto ester has also been realized with high enantioselectivity and chemical yield by utilizing Cu(II)−bisoxazoline catalyst through a concerted [4 + 2] cycloaddition path.[17]

The enantioselective hetero-Diels−Alder reaction has been successfully applied to the synthesis of several natural products,[8c,13a,b,f,18] and recent findings in this area include, for example, development of a new catalyst,[9d] improvement of the old catalytic system in order to obtain high enantioselectivity,[12b] widening substrate generality,[11e] and improvement of reaction economy.[13c,d] Recently, we reported our preliminary studies of the high enantioselective synthesis of optically active dihydropyranone by using chiral titanium(IV) 5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-bi-2-naphthol complexes.[11c] The present paper describes studies of relationships among catalyst structure and activity, substrate generality, mechanism, and limitations.

Results and Discussion

Ligand and Lewis Acid Survey. A variety of different ligands and Lewis acids have been examined as catalysts for the hetero-Diels−Alder reaction of benzaldehyde and Danishefsky's diene. The ligands were prepared according to literature procedures.[19] The catalyst was in situ prepared by stirring a solution of the chiral ligands and $Ti(OiPr)_4$ in toluene in molar ratio of 1.1:1. Without catalyst isolation, adding benzaldehyde to a cooled catalyst solution at 0 °C, followed by dropwise addition of the Danishefsky's diene and treatment with trifluoroacetic acid at the end of reaction, afforded the 2,3-dihydro-2-phenyl-4-pyranone. The enantioselectivity of product was assayed by chiral GC. The absolute configuration of the product was established by compar-

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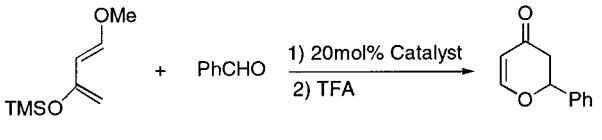
Table 1. Effects of the Catalyst Ligands on the Hetero-Diels−Alder Reaction of Benzaldehyde with Danishefsky's Diene[a]



1 2a 3a

entry	ligand	time (h)	yield (%)[b]	ee (%)[c]	config
1	**4**	30	10	6	*S*
2	**5**	30	9	5	*S*
3	**6**	30	9	5	*S*
4	**7**	48	16	7	*R*
5	**8**	48	21	29	*R*
6	**9**	48	39	49	*R*
7	**10**	48	23	26	*S*
8	**11**	48	13	13	*R*
9	**12**	48	9	29	*R*
10	**13**	48	9	20	*R*
11	**14**	24	0		
12	**15**	24	16	0	
13	**16**	24	42	32	*R*
14	**17**	24	28	4	*R*
15	**18**	24	46	87	*R*
16	**19**	24	60	87	*R*
17	**20**	24	64	95	*R*
18	**21**	24	92	97	*R*

[a] All reactions were carried out at 0 °C in toluene using 20 mol % catalyst. The ratio of $Ti(OiPr)_4$ and ligand is 1:1.1. The substrate concentration was 0.25 M. [b] Isolated yield. [c] The ee value was determined by GC using a chiral column (Cyclodex-β).

ing the optical rotation of the product with that in the literature.[10] This ligand screen revealed that the hetero-Diels−Alder product was formed in highly various yields and enantioselectivities depending on the ligand used. Some representative results are shown in Table 1.

According to the results shown in Table 1, the Ti(IV) complex of (*R*)-H_8-BINOL (**21**) gave the product in high yield with high enantioselectivity. However, Ti(IV) complexes prepared from chiral diols (**4**−**8**) derived from natural tartaric acid and chiral DEA (9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid) were poor enantioselective catalysts (Table 1, entries 1−5). The Ti(IV) complex prepared from (2*R*,4*R*)-dihydroxypentane (**9**) gave moderate enantioselectivity and yield (Table 1, entry 6), while Ti(IV) complexes prepared from the (*cis*,*cis*)-spirol-**10** and (*trans*,*trans*)-spirol-**11** which had a similar five-membered hydroxy coordination group and were more rigid than ligand **9** were not good HDA reaction catalysts (Table 1, entries 7, 8). The Ti(IV) complexes prepared from chiral *N*-methylaminoethanol (**12**), Schiff base (**14**), and monoxazoline (**13**) which were derived from (1*R*,2*S*)-1,2-diphenylaminoethanol did not produce good enantioselectivity either (Table 1, entries 9−11). Ti(IV)(salen) (**15**) complex which had been reported to give very high enantioselectivity in trimethylsilylcyanation of aldehydes[20] had low catalytic activity to give racemic product in 16% isolated yield (Table 1, entry 12) in the HDA reaction, and a new Ti(IV) salen (**16**) complex which had a more bulky group and atropisomeric framework had a little catalytic activity and afforded product in 42% isolated yield with 32% ee (Table 1, entry 13). The (*R*)-BINOL (**19**) and it's derivatives in which certain positions were substituted or hydrogenated such as (*R*)-6,6′-dibromo-BINOL (**18**), (*R*)-2,2′-dimethyl-BINOL (**17**), and (*R*)-H_4-BINOL (**20**) (Table 1, entries 14−18), were also screened. The catalyst derived from (*R*)-BINOL and (*R*)-BINOL derivatives showed a high level of enantioselectivity for the HDA reaction between benzaldehyde and Danishefsky's diene. More significantly, the (*R*)-H_4-BINOL (**20**) or (*R*)-H_8-BINOL (**21**) ligands remarkably enhanced enantioselectivity control and reaction rate, apparently due to the larger steric hindrance of the hydrogen atoms attached to sp^3 carbon atoms in tetralin rings than that of hydrogen atoms on sp^2 carbon atoms in naphthalene rings (Scheme 2). As the steric repulsion between two far-side rings ranges (*R*)-H_8-BINOL > (*R*)-H_4-BINOL > (*R*)-BINOL ≈ (*R*)-6,6′-dibromo-BINOL, the value of the dihedral angle of the axial biaryl groups in the titanium complex was also (*R*)-H_8-BINOL > (*R*)-H_4-BINOL > (*R*)-BINOL ≈ (*R*)-6,6′-dibromo-BINOL (Figure 1). The enantioselectivity and yield showed the same trend. The results indicated that the dihedral angle of the axial biaryl group in BINOL series was very crucial for the high enantiocontrol and yield of the HDA reaction. To our surprise, the titanium complexes of (*R*)-3,3′-dimethyl-BINOL (**17**) produced 2,3-dihydro-2-phenyl-4-pyranone in 28% isolated yield with 4% ee (Table 1, entry 14). This indicated the 3-position substituent on BINOL had little benefit on enantioselectivity of the Ti(IV)-complex-catalyzed HDA reaction. In contrast, the choice of the bulky group in BINOL's 3-position is crucial for the high enantiofacial differentiation of prochiral aldehydes in the asymmetric organoaluminum-catalyzed HDA reaction.[8a,b,d]

Besides Ti(IV)−H_8-BINOL complex, other metal−H_8-BINOL complexes in situ prepared by stirring a solution of (*R*)-H_8-BINOL and corresponding metal alkoxide were also screened in the hetero-Diels−Alder reaction of benzaldehyde with Danishefsky's diene. The results are shown in Table 2. Among the screened Lewis acid complexes, the Al(III)−H_8-BINOL complex provided the product in moderate yield with 9% ee (Table 2, entry 2), and the Ti(IV)−H_8-BINOL complex afforded the product in high enantioselectivity and yield (Table 2, entry 1) and proved to be the optimal catalyst for the HDA reaction of benzaldehyde with Danishefsky's diene.

Solvents Effects. Solubility of the Ti(IV)−H_8-BINOL complex in representative solvents was determined using the standard procedure. The solvent survey revealed a dramatic solvent effect: toluene and benzene were the optimal solvents for the transformation, providing the product of the hetero-Diels−Alder reaction in high yield with high enantioselectivity (Table 3). Toluene and benzene were more favorable than other solvents in the Ti(IV)−H_8-BINOL-catalyzed HDA reaction. In solvents containing a coordinating oxygen or nitrogen atom, such as THF, Et_2O, TBME, and DMF, the reaction afforded the product in high enantioselectivity, but the yield of reaction was low. CH_2Cl_2 was also found to afford the same result as ether-type solvents.

To optimize the reaction conditions for higher enantioselectivity, the effects of the molar ratio of $Ti(OiPr)_4$ to (*R*)-H_8-BINOL on enantioselectivity were examined in detail. When the molar ratio of $Ti(OiPr)_4$ to (*R*)-H_8-BINOL was 1:1.1 or 1:1.5, the optimal enantioselectivity and yield was obtained (Table 4). The enantioselectivity did appreciably vary with the change of molar ratio. When the a molar ratio of $Ti(OiPr)_4$ to (*R*)-H_8-BINOL was 1:2, the worst result was obtained. The other feature in

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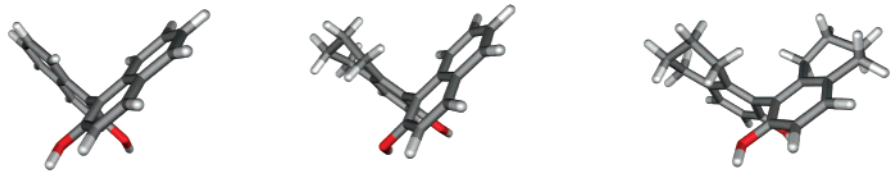
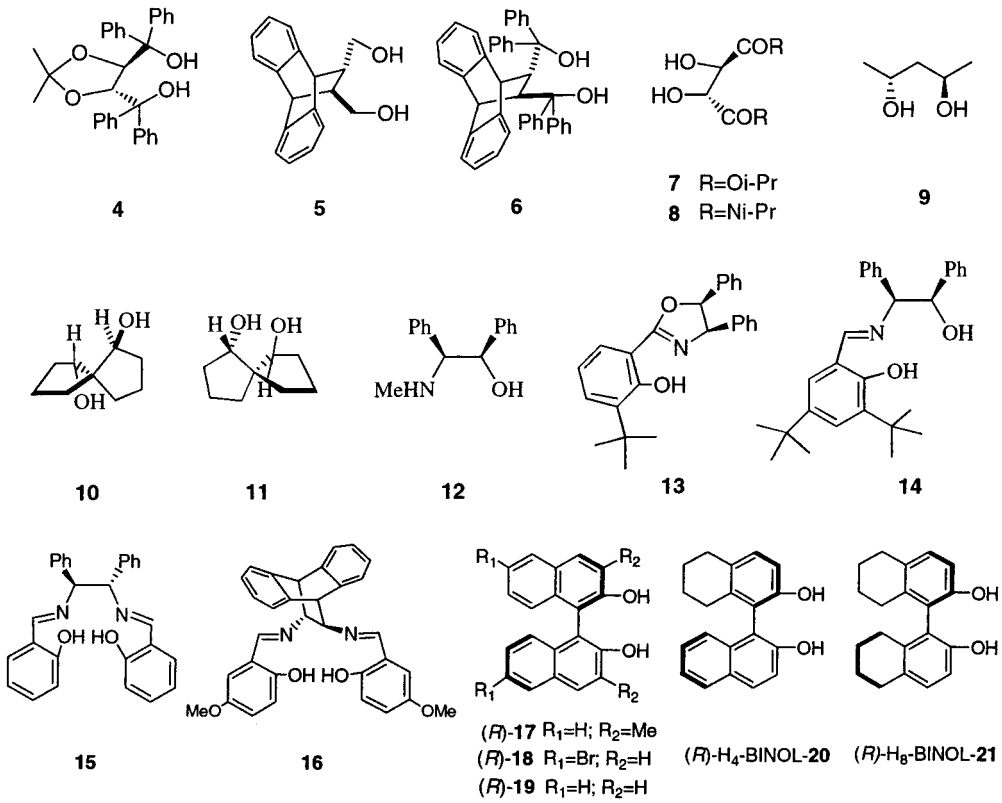


(*R*)-BINOL-**19** (*R*)-H_4-BINOL-**20** (*R*)-H_8-BINOL-**21**

Figure 1. The steric repulsion between the two far-side rings of (*R*)-H_8-BINOL, (*R*)-H_4-BINOL, and (*R*)-BINOL. The 3D structures were constructed and optimized in SYBYL6.7. Tripos force field and Gasteiger−Hückel charges were employed throughout. Black, carbon; red, oxygen; and gray, hydrogen.

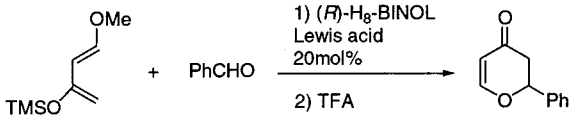
Scheme 2. Ligands Applied to the Hetero-Diels−Alder Reaction of Benzaldehyde with Danishefsky's Diene



the present asymmetric process was the role of 4 Å molecular sieves in obtaining the high enantioselectivity and good yield. In the absence of 4 Å MS, the Ti(IV)−H_8-BINOL catalytic HDA reaction in toluene afforded quite high enantioselectivity (Table 5). However, the isolated yield was lower than the reaction carried out in presence of 4 Å MS. If the Ti(IV)−H_8-BINOL catalysis was carried out at Et_2O, a significant difference in optical yield between the presence and absence of 4 Å MS was observed. So, the addition of molecular sieves in the asymmetric HDA reaction had a beneficial effect of permitting reactions to afford product in high yield with high enantioselectivity.

To obtain the optimal reaction conditions, the effect of the amount of catalyst on the enantioselectivity and yield of the HDA reaction of benzaldehyde with Danishefsky's diene was studied. The amount of catalyst also dramatically influenced the enantioselectivity and yield. The enantiomeric excess increased as the amount of catalyst increased. When the amount of catalyst was 20 mol %, the optimal enantioselectivity (97% ee) and yield (88%) were obtained (Table 6, entry 2). The highest amount of catalyst used was 40 mol % (Table 6, entry 1). There was no difference in enantioselectivity and yield in comparison with 20 mol %. The concentration of substrate and catalyst was found to be an important factor for obtaining high enantioselectivity and yield. The optimal concentration of substrate was 0.25 M at 20 mol % amount of catalyst (Table 7, entry 3). At 1.0 and 0.5 M concentration the HDA reaction of benzaldehyde with Danishefsky's diene afforded the product with a dramatic decrease in enantioselectivity and yield (Table 7, entries 1, 2). If the concentration of substrate and catalyst decreased to 2- and 4-fold low the optimal concentration, the Ti(IV)−H_8-BINOL catalytic HDA reactions proceeded slowly and afforded the product with the almost same high enantioselectivity (Table 7, entries 4, 5) as the 0.25 M concentration. At the higher concentrations, the formation of titanium multinuclear aggregates signifi-

Table 2. Effects of Lewis Acid on the Hetero-Diels−Alder Reaction of Benzaldehyde with Danishefsky's Diene[a]

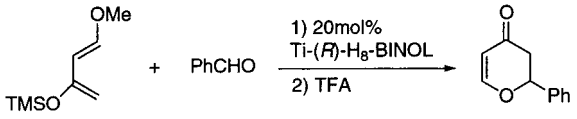


1 2a 3a

entry	metal alkoxide	yield (%)[b]	ee (%)[c,d]
1	$Ti(OiPr)_4$	92	97 (*R*)
2	$Al(OiPr)_3$	45	9 (*S*)
3	$Zr(OEt)_4$	15	8 (*R*)
4	$Sm(OiPr)_3$	0	
5	$Yb(OiPr)_3$	0	
6	$Ce(OiPr)_3$	0	

[a] All reactions were carried out at 0 °C in toluene using 20 mol % catalyst. The ratio of Lewis acid and ligand is 1:1.1. The substrate concentration was 0.25 M. The reaction time was 24 h. [b] Isolated yield. [c] The ee value was determined by GC using a chiral column (Cyclodex-β). [d] Absolute configurations determined by comparison of optical rotations with literature values.

Table 3. Effects of Solvents on the Ti−H_8-BINOL-Catalyzed Hetero-Diels−Alder Reaction of Benzaldehyde with Danishefsky's Diene[a]



1 2a 3a

entry	solvent	yield (%)[b]	ee (%)[c]
1	THF	11	90
2	Et_2O	60	83
3	CH_2Cl_2	23	94
4	DMF	9	95
5	TBME	21	90
6	toluene	88	97
7	benzene	75	95

[a] All reactions were carried out at 0 °C using 20 mol % of Ti−H_8-BINOL catalyst. The ratio of $Ti(OiPr)_4$ and ligand is 1:1.1. The substrate concentration was 0.25 M. The reaction time was 12 h. [b] Isolated yield. [c] The ee value was determined by GC using a chiral column (Cyclodex-β).

Table 4. Effects of the Ratio of $Ti(OiPr)_4$ to Ligand on the Ti−H_8-BINOL-Catalyzed Hetero-Diels−Alder Reaction of Benzaldehyde with Danishefsky's Diene[a]

entry	ratio of $Ti(O^iPr)_4$ to ligand	yield (%)[b]	ee (%)[c]
1	1:2	46	75
2	1:1.5	92	98
3	1:1.1	92	97
4	1:1	73	86
5	1:0.5	38	80

[a] All reactions were carried out at 0 °C in toluene using 20 mol % of Ti−H_8-BINOL catalyst. The substrate concentration was 0.25 M. The reaction time was 24 h. [b] Isolated yield. [c] The ee value was determined by GC using a chiral column (Cyclodex-β).

cantly comprised the catalytic activity,[21] since the active complex is monomeric.

Temperature Profile. An examination of the temperature profile of the Ti(IV)−H_8-BINOL-catalyzed HDA reaction of benzaldehyde with Danishefsky's diene was performed (Table 8). There was a temperature dependence on the yield and enantioselectivity. At slightly higher temperatures, the yield increased without significant impact to selectivity. However, when the reaction was carried out below 0 °C, dihydropyrone was obtained in lower conversion and enantioselectivity. The optimal temperature ranged between 0 °C and 25 °C according to the different aldehydes. At room temperature (23−25 °C), high yield (92%) and enantioselectivity (93% ee) were also obtained (Table 8, entry 1). It should be noted that the enantiomeric excess of 93% was considerably high at 23−25 °C, since most precedent catalytic asymmetric hetero-Diels−Alder reactions required a rather low tem-

Table 5. Effects of 4 Å MS on the Ti−H_8-BINOL-Catalyzed Hetero-Diels−Alder Reaction of Benzaldehyde with Danishefsky's Diene[a]

entry	amount of 4 Å mol sieves, mg	solvent	*T*(°C)/time (h)	yield (%)[b]	ee (%)[c]
1	0	Et_2O	−30/12	14	51
2	120		−30/12	23	94
3	0	toluene	0/24	83	97
4	120		0/24	92	97

[a] All reactions were carried out in toluene using 20 mol % of Ti−H_8-BINOL catalyst. The ratio of $Ti(OiPr)_4$ and ligand is 1:1.1. The substrate concentration was 0.25 M. [b] Isolated yield. [c] The ee value was determined by GC using a chiral column (Cyclodex-β).

Table 6. Effect of the Amount of Catalyst on the Ti−H_8-BINOL-Catalyzed Hetero-Diels−Alder Reaction of Benzaldehyde with Danishefsky's Diene[a]

entry	amount of catalyst (mol %)	yield (%)[b]	ee (%)[c]
1	40	90	98
2	20	88	97
3	15	83	92
4	10	75	73
5	5	62	48

[a] All reactions were carried out at 0 °C in toluene. The ratio of $Ti(OiPr)_4$ and ligand is 1:1.1. The substrate concentration was 0.25 M. The reaction time was 12 h. [b] Isolated yield. [c] The ee value was determined by GC using a chiral column (Cyclodex-β).

Table 7. Effects of Concentration of Substrate on the Ti−H_8-BINOL-Catalyzed Hetero-Diels−Alder Reaction of Benzaldehyde with Danishefsky's Diene[a]

entry	concentration of substrate ($molL^{-1}$)	time (h)	yield (%)[b]	ee (%)[c]
1	1	24	32	73
2	0.5	24	46	82
3	0.25	24	92	97
4	0.125	30	73	93
5	0.0625	30	69	96

[a] All reactions were carried out at 0 °C in toluene using 20 mol % of Ti−H_8-BINOL catalyst. The ratio of $Ti(OiPr)_4$ and ligand is 1:1.1. [b] Isolated yield. [c] The ee value was determined by GC using a chiral column (Cyclodex-β).

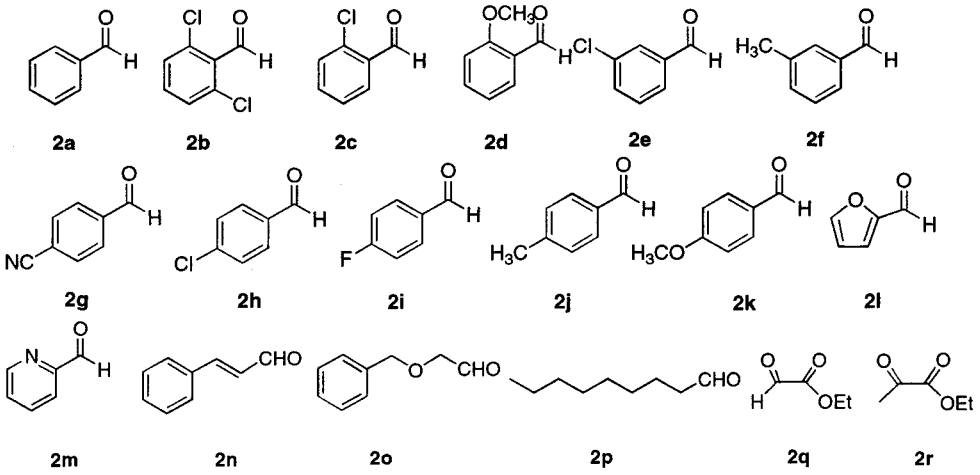
Table 8. Effects of Reaction Temperature on the Ti−H_8-BINOL-Catalyzed Hetero-Diels−Alder Reaction of Benzaldehyde with Danishefsky's Diene[a]

entry	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	23−25	6	92	93
2	12−14	8	92	95
3	0	12	88	97
4	−15	20	78	92
5	−30	29	51	90

[a] All reactions were carried out in toluene using 20 mol % of Ti−H_8-BINOL catalyst. The ratio of $Ti(OiPr)_4$ and ligand is 1:1.1. The substrate concentration was 0.25 M. [b] Isolated yield. [c] The ee value was determined by GC using a chiral column (Cyclodex-β).

(21) (a) Corey, E. J.; Letavic, M. A.; Noe, M. C.; Sarshar, S. *Tetrahedron Lett.* **1994**, *35*, 7553−7556. (b) Terada, M.; Mikami, K.; Nakai, T. *Chem. Commun.* **1990**, 1623−1624. (c) Terada, M.; Mikami, K. *Chem. Commun.* **1994**, 833−834.

Table 9. Asymmetric Hetero-Diels–Alders Reactions of Aldehydes with Danishefsky's Diene[a]



entry	aldehyde	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]	entry	aldehyde	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	**2a**	0	24	92	97[d,f]	10	**2j**	0	24	60	99
2	**2b**	0	24	43	85	11	**2k**	0	24	51	>99
3	**2c**	0	24	71	90	12	**2l**	0	30	78	96[f]
4	**2d**	0	48	55	90[e]	13	**2m**	0	24	55	92[e]
5	**2e**	0	24	81	94	14	**2n**	0	30	80	98[f]
6	**2f**	0	24	81	99	15	**2o**	0	48	39	80
7	**2g**	0	24	64	95	16	**2p**	23–25	72	57	96
8	**2h**	0	24	67	97	17	**2q**	0	24	28	35[e,f]
9	**2i**	0	24	54	98	18	**2r**	0	24	26	47[e]

[a] All reactions were carried out using 20 mol % of catalyst as detail in the experimental procedure. [b] All yields are isolated yields. [c] In all cases ee was determined by HPLC using a chiral column (chiralcel OD), unless otherwise mentioned. [d] Determined by GC using a chiral column (Cyclodex-β). [e] Determined by HPLC using a chiral column (chiralpak AD). [f] Absolute configurations were *R*, which determined by comparison of optical rotations with literature values.[7a,10a,13a]

perature (−78 to −30 °C) to attain a good level of enantioselectivity. Thus, these mild reaction conditions are amenable to large-scale application.

Substrate Generality. Encouraged by the result obtained for the benzaldehyde, we investigated a variety of other aldehydes to probe their behaviors under the current catalytic conditions. As shown in Table 9, aromatic, heteroaromatic, conjugated, and aliphatic aldehydes afforded the corresponding product in moderate to high isolated yield with a considerably high ee. A comparison of the experimental results (Table 9, entries 1−4) revealed the negative effect on enantioselectivity by ortho-substitution on benzaldehyde. The Ti(IV)−H_8-BINOL catalyzed HDA reaction of *o*-chloro- and *o*-methoxybenzaldehyde afforded dihydropyranone of 90% ee, which was lower than the enantioselectivity (94−99% ee) afforded by Ti(IV)−H_8-BINOL-catalyzed HDA reaction of meta- or para-substituted benzaldehyde. Especially, the HDA reaction of 2,6-dichlorobenzaldehyde that had two bulky ortho-substituents on the benzaldehyde afforded an enantiomeric excess of 85%, which was lower than that of the ortho-monosubstituted benzaldehyde. This was probably due to the strong steric hindrance effect of the ortho-substituents, which significantly weakened the coordination of the aldehyde and consequently lowered the enantioselectivity of reaction. In comparison, meta- and para-substituents on the aromatic aldehydes had less effect on the enantioselectivity for the products of dihydropyranone. These results were consistent with the expectation that the electronic effects from the starting materials were less significant than the steric hindrance effect on the enantioselectivity of the reaction. Chan also observed the same effect on asymmetric alkylation of aromatic aldehydes with triethylaluminum.[24a] An analysis of the results from entries 8−11 in Table 9 indicated that the electron-withdrawing, conjugated para-substituent had a negative influence on the enantioselectivity while the electron-donating, conjugated para-substituent had a positive effect. For meta-substituted benzaldehydes, an electron-donating substituent on the phenyl ring was found to increase the enantioselectivity while an electron-withdrawing substituent was found to decrease the enantioselectivity for the desired product. From entries 2−11 in Table 9, we can observe the impact of electronic effects on the yield. The electron-donating, conjugated meta-substituent had a better effect on the yield (81%) of 2,3-dihydro-2-substituent-4-pyranone while the ortho- and para-substituent had less effect (43−71%). We also explored the application of Ti−H_8-BINOL catalyst on the reaction of an activated carbonyl compound with Danishefsky's diene. Under general reaction conditions, low enantioselectivities and yields were obtained (Table 9, entries 17, 18).

To further probe the steric and electronic effects governing the coordination of titanium catalyst and its potential role in controlling the enantioselectivity of

(22) (a) Uemura, T.; Zhang, X.; Matsumura, K.; Sayo, N.; Kumobayashi, H.; Ohta, T.; Nozaki, K.; Takaya, H. *J. Org. Chem.* **1996**, *61*, 5510−5516. (b) Trost, B. M.; Vranken, Van D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327−9343. (c) Trost, B. M.; Breit, B.; Peukert, S.; Zambrano, J.; Ziller, J. W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2386-2388. (d) Hayashi, T.; Ohno, A.; Lu, S.; Matsumoto, Y.; Fukuyo, E.; Yanagi, K. *J. Am. Chem. Soc.* **1994**, *116*, 4221−4226.

(23) Dijkgraff, C.; Rousseau, J. P. G. *Spectrochim. Acta* **1968**, *2*, 1213−1217.

(24) The reaction catalyzed by Ti(IV)−H_8-BINOL: (a) Chan, A. S. C., Zhang, F.; Yip, C. *J. Am. Chem. Soc.* **1997**, *119*, 4080−4081. (b) Zhang, F.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 3651−3655.

Table 10. Effect of Ti Lewis Acid on the Ti−H_8-BINOL-Catalyzed Hetero-Diels−Alder Reaction of Benzaldehyde with Danishefsky's Diene[a]

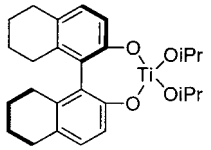
entry	Lewis acid	time (h)	yield (%)[b]	ee (%)[c]
1	$Ti(OiPr)_4$	24	92	97
2	$Ti(OnBu)_4$	40	64	91
3	$Ti(OiPr)_3Cl$	10	85	96
4	$Ti(OiPr)_2Cl_2$	10	75	95

[a] All reactions were carried out at 0 °C in toluene using 20 mol % of Ti−H_8-BINOL catalyst. The ratio of $Ti(OiPr)_4$ and ligand is 1:1.1. The substrate concentration was 0.25 M. [b] Isolated yield. [c] The ee value was determined by GC using a chiral column (Cyclodex-β).

reaction, we chose to perform the HDA reaction of Danishefsky's diene and benzaldehyde catalyzed by the complexes generated from the (*R*)-H_8-BINOL and a titanium-based Lewis acid other than $Ti(OiPr)_4$. Some representative results are given in Table 10. From the available data it would appear that modified steric hindrance caused by the presence of an *n*-butoxy group on the titanium center instead of an isopropoxy group has no apparent effect on the enantioselectivity. When $Ti(OiPr)_2Cl_2$ and $Ti(OiPr)_3Cl$ were used for generating the catalytic complex, which was expected to change the steric effect (a chloride atom is much smaller than an isopropoxy group in term of van de waals radius) and lower the electron density on titanium, considerably high enantioselectivity was also obtained in the HDA reaction of benzaldehyde and Danishefsky's diene. On the basis of the experimental results, it is reasonable to question whether $Ti(OiPr)_2$−(*R*)-H_8-BINOL was the actual catalytically active metal complex, which affords effective enantiocontrol in the transition state of the titanium-catalyzed HDA reaction. To investigate the exact nature of the catalytically active metal complex, a ^{1}H NMR experiment (300 MHz) was carried out at 20 °C in C_6D_6. First, the catalyst was prepared in C_6D_6 as detailed in the experimental procedure. Then the ^{1}H NMR spectrum was recorded. The methyl and methine peak corresponding to the isopropoxy moiety was observed at δ 1.20 and δ 3.91. When a 5-fold amount benzaldehyde was added to the solution of catalyst, there was no apparent change in ^{1}H NMR spectrum in comparison to the previous spectrum. Then, Danishefsky's diene was added to the solution of catalyst and benzaldehyde. After 10 min, the ^{1}H NMR experiments were conducted. The spectra indicated diastereotopic methyl peaks due to the isopropoxy group bound to Ti at δ 1.21 and δ 1.33. The spectral changes strongly suggested that the isopropoxy group bound to Ti transmitted to be bound to the other group. After 1 h, the peak at δ 1.21 disappeared while the peak at δ 1.33 strengthened and became stronger than that in the previous spectrum. That means the real catalytic metal complex was not the $Ti(OiPr)_2$−(*R*)-H_8-BINOL complex **19**, which also can be inferred from the fact that different titanium(IV) reagents have the same enantiocontrol effect (Table 10).

Moreover, the Ti−H_8-BINOL complex **19** and benzaldehyde (5-fold excess) were mixed in the benzene, and the resulting mixture in solution was analyzed by IR spectroscopy. No evidence for any interaction between the complex and benzaldehyde could be detected by comparing the formyl vibration in the former mixture/benzene solution (1706 cm^{-1}) and benzaldehyde-only/benzene solution (1704 cm^{-1}). These results indicate that there was no apparent activation of the formyl group of benzaldehyde by Ti−H_8-BINOL complex **19**, which supports some literature[8a,d] results that also indicated that the real catalyst was a Lewis acid and not the Ti−H_8-BINOL complex **19** (Scheme 3).

Scheme 3. Complex 19



$Ti(OiPr)_2$-(*R*)-H_8-BINOL-**19**

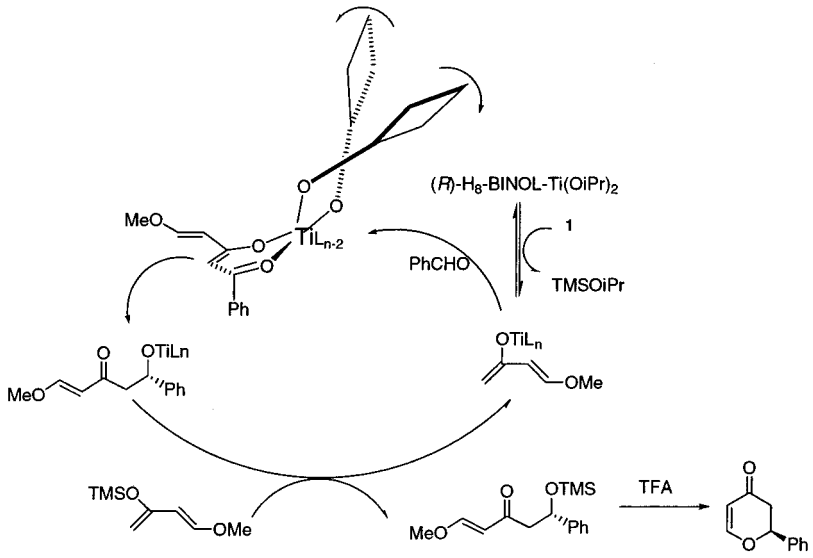
Reaction Mechanism. A reaction mechanism, which agrees with all of the observations discussed above, is proposed (Scheme 4). After the Danishefsky's diene was added to the solution of titanium complex **19**, the active catalytic species was produced. Then, the Mukaiyama aldol[11a] adduct was obtained through a six-membered cyclic transition state which involves the diene linked to the Ti−(*R*)-H_8-BINOL by the C-3 oxygenated substituent and the aldehyde associated to the metal by the carbonyl oxygen. The trimethylsilyl group transferred from Danishefsky's diene substrate to the Mukaiyama aldol adduct to afford an intermediate and the Ti(IV) complex. Upon treatment with trifluoroacetic acid, the intermediates were converted to (*R*)-2,3-dihydro-2-phenyl-4-pyranone.

From the proposed mechanism hypothesis, the transition state has two bicoordination ligands: one is the seven-membered coordination, and the other is the six-membered coordination. In comparison with six-membered or five-membered rings, the seven-membered ring had more flexibility and less rigidity. Since the steric effect of the hydrogen of the far-side ring in H_8-BINOL was more enhanced than the other BINOL-derived ligands, the seven-membered ring formed by H_8-BINOL had more rigidity and a wider dihedral angle of the axial biaryl groups than the other BINOL-derived ligands. These conformational changes made a beneficial chiral pocket effect on the benzaldehyde coordination sites of the H_8-BINOL−Ti complex relative to the other BINOL-derived ligand−Ti complexes. Thus, when different BINOL's derivatives were used, it was observed that the increased dihedral angle resulted in a higher ee in the HDA reaction. These results are consistent with the results of Takaya,[22a] Trost,[22b,c] and Hayashi[22d] regarding asymmetric hydrogenation and hydroxyallylic alkylation.

Conclusion

In conclusion, an efficient catalytic enantioselective hetero-Diels−Alder reaction of Danishefsky's diene and aldehyde utilized H_8-BINOL−Ti complex has been documented. A wide range of aldehydes can be employed, utilizing in situ prepared catalyst, to provide the product in high chemical yields with high enantioselectivities (80−99% ee) under mild conditions. Since the BINOL can be easily prepared in large scale with high enantiomeric excess and H_8-BINOL can be readily derived from BINOL via hydrogenation,[19j] the Ti−H_8-BINOL-catalyzed HDA reaction is expected to have excellent potential for practical applications. Future efforts will be directed toward a new catalyst for the high enantioselective hetero-Diels−Alder reaction of ketones.

Scheme 4. The Proposed Mechanism of the Ti−H_8-BINOL Catalyzed Hetero-Diels−Alder Reaction of Benzaldehyde with Danishefsky's Diene



Experimental Section

General. All reaction were run under argon or nitrogen using oven-dried glassware (at 140 °C for at least 4 h, then stored in the drybox) and magnetic stirring. Molecular sieve powder (4 Å) was purchased from Aldrich and used as received without further activation. Toluene, benzene, THF, Et_2O, and TBME were distilled from a deep-blue solution of sodium−benzophenone ketyl under nitrogen just prior to use. CH_2Cl_2 was distilled from powdered CaH_2 under nitrogen just prior to use. DMF was dried with powdered CaO, distilled at reduced pressure, and stored under nitrogen and over 4 Å molecular sieves. *trans*-1-Methoxy-3-(trimethylsilyloxy)-1,3-butadiene (Danishefsky's diene) was purchased from Lancaster with 95% or 90% purity and used as received without further purification. Aldehyde was distilled and handled under N_2 and stored avoiding light in the refrigerator. $Ti(OiPr)_4$, $Ti(OnBu)_4$, and $TiCl_4$ were purchased from Aldrich and distilled under nitrogen immediately prior to use. TADDOL, (2*R*,4*R*)-pentanediol, diisopropyl D-tartrate, and (*R*)- or (*S*)-1,1′-bi-2-naphthol were purchased from Acros. $Ti(OiPr)_2Cl_2$ and $Ti(OiPr)_3Cl$ were prepared as described in the literature.[23]

(11*R*,12*R*)-9,10-Dihydro-9,10-ethanoanthracene-11,12-dimethanol (**5**),[19a] (11*R*,12*R*)-9,10-dihydro-α,α,α′,α′-tetraphenyl-9,10-ethanoanthracene-11,12-dimethanol (**6**),[19a] *N*,*N*′-diisopropyl-D-tartaramide (**8**),[19b] (1*S*,5*R*,6*S*)-spiro[4.4′]nonane-1,6-diols (**10**),[19c] (1*S*,5*S*,6*S*)-spiro[4.4′]nonane-1,6-diols (**11**),[19d,e] (1*R*,2*S*)-1,2-diphenyl-2-(*N*-methylamino)ethanol (**12**),[19f] (4*S*,5*R*)-4,5-dihydro-4,5-diphenyl-2-(2′-hydroxyl-3′-*tert*-butylphenyl)oxazoline (**13**),[19g] (1*R*,2*S*)-2-(*N*-(3′,5′-di-*tert*-butylsalicylidene)amino)-1,2-diphenyl-1-ethanol (**14**),[19h] (1*S*,2*S*)-*N*,*N*′-bis(2′-hydroxylphenylmethylidene)-1,2-diphenylethylenediimine (**15**),[19i] (*R*)-3,3′-dimethyl-1,1′-bi-2-naphthol (**17**),[19j] (*R*)-6,6′-dibromo-1,1′-bi-2-naphthol (**18**),[19k] and (*R*)-5,6,7,8-tertahydro-1,1′-bi-2-naphthol (**20**)[19l] were prepared according to the literature procedure.

(11*S*,12*S*)-*N*,*N*-Bis-((2′-hydroxy-5′-methoxyphenyl)-methylene)-9,10-dihydro-9,10-ethanoanthracenediimine (16). To a 0.2 M solution of (+)-11(*S*),12(*S*)-diamino-9,10-dihydro-9,10-ethanoanthracene[22b] in absolute ethanol was added 3-methoxy-2-hydroxybenzaldehyde (2.0 equiv). The reaction mixture was stirred at rt for 24 h. Then the solid is collected by filtration to afford **16** in 85% yield as yellow crystalline (recrystallized from EtOH): mp 202−203 °C; $[\alpha]^{27}_D$ +292.3 (c = 1.40, CH_3Cl); ^{1}H NMR (300 MHZ, CD_3Cl)·δ 11.99 (2H, br s), 8.25 (2H, s), 6.67−7.38 (14H, m), 4.31 (2H, s), 3.73 (6H, s), 3.52 (2H, s); ^{13}C NMR (300 MHZ, CD_3Cl): δ 164.1, 154.8, 152.0, 140.2, 139.7, 126.7, 126.6, 125.6, 124.1, 119.7, 118.0, 117.7, 114.6, 76.9, 55.8, 51.5; IR (Nujol) 3045, 3020, 1630, 1590 cm^{-1}. Anal. Calcd for $C_{32}H_{28}N_2O_4$: C 76.17, H 5.59, N 5.50; Found: C 76.14, H 5.75, N 5.56.

(*R*)-2-Phenyl-2,3-dihydro-4*H*-pyran-4-one (3a): General Catalytic HDA Procedure. A mixture of (*R*)-H_8-BINOL (16.2 mg, 0.055 mmol), 1.0 M $Ti(OiPr)_4$ in CH_2Cl_2 (50 μL, 0.05 mmol), and activated powdered 4 Å molecular sieves (120 mg) in toluene (1 mL) was heated at 35 °C for 1 h. The yellow mixture was cooled to rt, and benzaldehyde (26 μL, 0.25 mmol) was added. The mixture was stirred for 10 min and cooled to 0 °C. Danishefsky's diene (60 μL, 0.30 mmol) was added. The mixture was allowed to stir at 0 °C for 24 h and then treated with 5 drops of TFA. After the mixture was stirred at 0 °C for 15 min, saturated $NaHCO_3$ (1.5 mL) was added. The mixture were stirred for 10 min and then filtered through a plug of Celite. The organic layer was separated, and the aqueous layer was extracted with ether (5 × 3 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude residue was purified by flash chromatography (SiO_2, EtOAc:petroleum 1:4, TLC R_f: 0.5) to yield (*R*)-2-phenyl-2,3-dihydro-4*H*-pyran-4-one-**3a** (40 mg, 0.23 mmol, 92% yield) as a clear oil. The isolated material was determined to be in 97% ee by chiral GC analysis (cyclodex-β, 159 °C, 20 min, isothermal, t_R(minor) = 14.43 min, t_S(major) = 14.66 min). $[\alpha]^{27}_D$ −110.83 (c = 0.47, CH_2Cl_2). The absolute stereochemisty was assigned as (−)-*R* based on comparison of the measured rotation with the literature value.[7a,10a]

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Supporting Information Available: The experimental procedure and analytical and spectral data for compound **3b**−**r**, HPLC and GC data for determination of the enantiomeric excess of compound **3a**−**r**, and the ^{1}H NMR, ^{13}C NMR, and IR spectral for compound **16**, **3a**−**r**, and catalyst. This material is available free of charge via the Internet at http://pubs.acs.org.

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