DOI: 10.1002/ejoc.200701223

BINOLate–Magnesium Catalysts for Enantioselective Hetero-Diels–Alder Reaction of Danishefsky's Diene with Aldehydes

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Keywords: Asymmetric catalysis / Hetero-Diels–Alder reactions / Nonlinear effect / Magnesium / Danishefsky's diene / Aldehydes

An efficient catalytic enantioselective hetero-Diels–Alder reaction of Danishefsky's diene with aldehydes using the magnesium binaphthoxide system has been developed, affording a variety of 2-substituted 2,3-dihydro-4*H*-pyran-4-ones in high yields and with excellent *ee* values. The aggregation behavior and nonlinear effect of the catalytic system, as well as the remarkable stereoelectronic effects of ligands on the catalysis, have also been investigated. On the basis of the structure of the isolated reaction intermediate, the stereochemistry of the products, and the information attained from a study of the nonlinear effect, a plausible asymmetric induction model has been proposed.

Introduction

The catalytic asymmetric hetero-Diels–Alder (HDA) reaction of Danishefsky's diene with various aldehydes represents one of the most efficient approaches to optically active 2-substituted 2,3-dihydro-4*H*-pyran-4-ones, a type of six-membered oxo heterocycle with extensive applications in natural or unnatural product synthesis.[1,2] A wide variety of nonracemic catalytic systems, including both chiral Brønsted acids[3,4] and chiral Lewis acids,[5,6] have been developed for this type of reaction, with the latter being the focus of most current research owing to their high reactivity and facile tunability. A handful of chiral Lewis acid complexes of oxophilic metals, such as aluminium, zinc, titanium, and lanthanides, have been successfully developed for this transformation.[6] However, the catalytic behavior of these metal complexes are hardly predictable as both the mechanistic pathways and the stereochemical outcomes of the reactions are found to be strongly dependent on both the identity of the Lewis acid metal ions as well as the stereoelectronic properties of the chiral ligands.[5] From the synthetic point of view, the search for other chiral catalytic systems for use in this important reaction is still highly desirable to extend its practical utility.

In recent years, there has been an increasing interest in the research into the synthetic applications of the highly oxophilic main group Lewis acid magnesium(II) species and their complexes.[7–9] In particular, chiral *N*-ligating magnesium complexes have been successfully applied as Lewis acid catalysts or reagents in a variety of asymmetric transformations,[10] such as cycloaddition reactions,[11] radical reactions,[12] Claisen rearrangement,[13] and others.[14] On the other hand, the synthetic use of chiral magnesium alkoxides or phenoxides as Lewis acid catalysts has been much less explored[15] and to the best of our knowledge no chiral magnesium complex has been reported so far to promote the titled reaction. As part of our ongoing effort to develop novel catalytic systems for asymmetric HDA reactions,[4b,4f,6h–6j,6l,6n,6o,16] herein we report our results on the highly efficient enantioselective HDA reactions of Danishefsky's diene and aldehydes under the catalysis of magnesium complexes with readily available enantiopure BINOL (1,1′-binaphthol) derivatives.[17] Isolation of the reaction intermediate and a study of the nonlinear effect in the catalytic system have also been carried out to shed some light on the mechanism of the catalytic reaction.

Results and Discussion

As a preliminary evaluation of Mg^{II}–BINOLate complexes, we initially tested the model HDA reaction of Danishefsky's diene **1** and benzaldehyde (**2a**) in toluene in the presence of 10 mol-% magnesium methoxide and (*R*)-BINOL (1:1). After 24 h at room temperature, the reaction was quenched with trifluoroacetic acid (TFA) and the mix-

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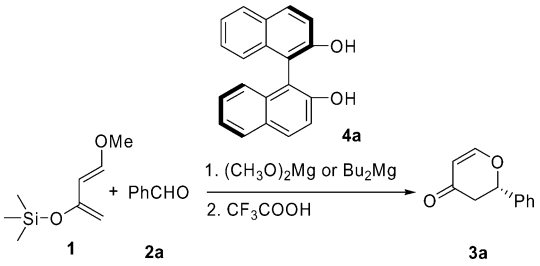
ture was subjected to a simple work-up procedure. As shown in Table 1, although the yield of adduct **3a** was only modest (10%), the enantiomeric excess (*ee*) was rather encouraging (78% in favor of the *S* configuration) (entry 1), which indicates that BINOL is indeed effective for chiral induction in this magnesium-promoted reaction. This observation prompted us to screen other magnesium precursor(s) with a view to enhancing the reactivity. We found that with dibutylmagnesium, a commercially available magnesium reagent that is more active than magnesium methoxide, the yield of **3a** was dramatically improved to 91%, albeit accompanied by a notable deterioration in the product's *ee* (35%, entry 4, Table 1). Consequently, further optimization of the enantioselectivity of the reaction was achieved by tuning the ratio of ligand **4a** and dibutylmagnesium as well as by screening for solvent effects. The results are summarized in Table 1. As is clear from entries 2–10, under otherwise identical conditions, both the reactivity and enantioselectivity of the reaction are strongly influenced by the variation of the **4a**/Bu_2Mg ratios (1:0.8 to 1:1.6). This catalytic behavior suggests that more than one kind of catalytically active species with distinct activities may coexist in the solution and in dynamic equilibria with each other, with the precise nature of the dominating species being dependent on the solution composition. The optimal molar ratio of **4a**/Bu_2Mg in toluene was found to be 1:1.5. Under these conditions the product **3a** was obtained in nearly quantitative yield and 94% *ee* (Table 1, entry 9). With this result in hand, we proceeded to study the effects of solvent under the optimized conditions (entries 11–14, Table 1) and found that the use of coordinating solvents such as THF led to low product yield and very modest *ee* (entry 14, Table 1). Among the solvents examined, toluene turns out to be the best one in terms of both the yield and *ee*.

Table 1. Optimization of the asymmetric HDA reaction of Danishefsky's diene **1** and benzaldehyde (**2a**) by catalysis with BINOLate–magnesium.[a]

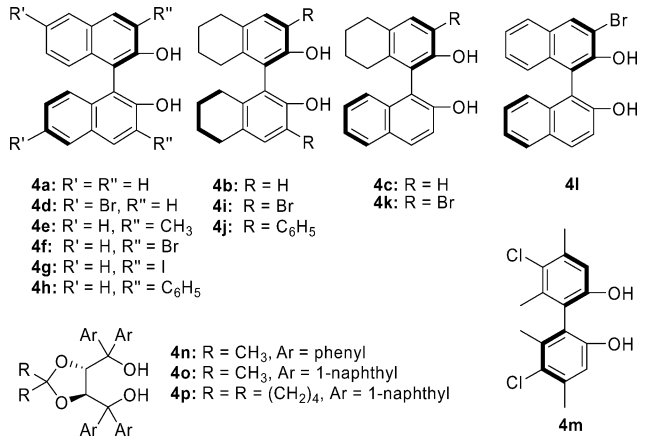


Entry	Solvent	**4a**:$MgBu_2$	% Yield[b]	% *ee*[c]
1	toluene	$(CH_3O)_2Mg$/**4a**[d]	10	78 (*S*)
2	toluene	1:0.8	>99	11 (*S*)
3	toluene	1:0.9	>99	10 (*S*)
4	toluene	1:1.0	91	35 (*S*)
5	toluene	1:1.1	73	65 (*S*)
6	toluene	1:1.2	73	79 (*S*)
7	toluene	1:1.3	94	89 (*S*)
8	toluene	1:1.4	99	93 (*S*)
9	toluene	**1:1.5**	**99**	**94 (*S*)**
10	toluene	1:1.6	69	92 (*S*)
11	diethyl ether	1:1.5	61	85 (*S*)
12	hexane	1:1.5	42	22 (*S*)
13	DCM	1:1.5	99	70 (*S*)
14	THF	1:1.5	33	13 (*S*)

[a] All reactions were performed at room temp. for 24 h in the specified solvent under a catalyst loading of 10 mol-%. [b] Determined by HPLC with biphenyl as an internal standard. [c] The enantiomeric excesses of the products were determined by HPLC on Chiralcel OD column. The configurations of the products were determined to be *S* by comparison of the retention time of HPLC with that of an authentic sample prepared according to the literature.[6h] [d] The catalyst was prepared from **4a** and $(CH_3O)_2Mg$ (2 M in CH_3OH) in a molar ratio of 1:1.2.

These results encouraged us to survey the applicability of other chiral diol ligands to the magnesium-catalyzed model reaction. Accordingly, a series of chiral diol ligands with diverse steric and electronic features, including commercially available or easily prepared (*R*)-BINOL and TADDOL derivatives (**4a**–**l** and **4n**–**p**, respectively, Scheme 1), were treated with 1.5 equiv. of Bu_2Mg and submitted to the catalytic reaction under the aforementioned optimized conditions. The results are summarized in Table 2 and clearly show that the precise structure of the ligand has a profound effect on both the catalytic efficiency and the enantioselectivity of the reaction. The BINOL derivatives generally led to good or excellent yields (with the exception of **4j**, entry 10), albeit with a broad range of *ee* values (entries 1–12), whereas the TADDOL series behaved poorly in terms of both catalytic activity and enantioselectivity (Table 2, entries 14–16). Whereas the modifications made on the binaphthyl unit by partial reduction led to a complicated behavior (**4a** vs. **4b**,**c**, entries 1–3; see also: **4f** vs. **4i** or **4h** vs. **4j**), all kinds of substituent(s) at the 3- or 3,3′-positions of the BINOL ligand backbone (**4d**–**h** and **4l**) had a disadvantageous effect on the enantioselectivity of the reaction as compared to their parent ligand **4a** (entries 1, 4–8, and 12). It is interesting to note that in some cases the sense of product configuration was switched from *S* to *R* (e.g., Table 2, entries 1 and 7), which further confirms that the asymmetric induction capabilities of the BINOL derivatives are highly sensitive to subtle changes in their structures. This ligand screening has shown **4a**–**c** to be superior in terms of both reactivity and enantioselectivity for the magnesium-catalyzed HDA reaction between Danishefsky's diene **1** and benzaldehyde (**2a**), all affording the adduct **3a** in quantitative yields and with more than 94% *ee*.

When (*R*)-BINOL (**4a**) was mixed with dibutylmagnesium in toluene, the solution turned turbid to yield a small amount of a white precipitate which immediately disappeared upon the addition of benzaldehyde giving rise to a yellow homogeneous solution. In order to gain an insight into the relevant process, ^1H NMR experiments were performed on the catalyst system generated in situ in [D_6]benzene at ambient temperature and the spectra are shown in Figure 1. Remarkably, upon the addition of 1.5 equiv. of Bu_2Mg to **4a** in [D_6]benzene, the well-resolved aromatic proton signals of the free ligand **4a** (Figure 1, a) were replaced by a broad bulge at 6.8–8.0 ppm (Figure 1b) which suggests the formation of some aggregated oligomeric or



Scheme 1. Chiral diol ligands examined for the enantioselective hetero-Diels–Alder reactions.

Table 2. Ligand screening for the magnesium-catalyzed enantioselective reaction of Danishefsky's diene **1** and benzaldehyde (**2a**).[a]

Entry	Ligand	% Yield[b]	% *ee*[b]
1	**4a**	99	94 (*S*)
2	**4b**	99	94 (*S*)
3	**4c**	99	97 (*S*)
4	**4d**	99	73 (*S*)
5	**4e**	90	42 (*S*)
6	**4f**	65	0.5 (*R*)
7	**4g**	72	14 (*R*)
8	**4h**	71	11 (*S*)
9	**4i**	94	11 (*R*)
10	**4j**	18	69 (*S*)
11	**4k**	90	11 (*S*)
12	**4l**	99	51 (*S*)
13	**4m**	99	62 (*S*)
14	**4n**	19	12 (*S*)
15	**4o**	17	25 (*S*)
16	**4p**	18	16 (*S*)

[a] All reactions were performed in toluene at room temp. for 24 h with the catalyst (10 mol-% loading) prepared in situ with **4** and Bu_2Mg (molar ratio 1:1.5). [b] See Table 1.

polymeric species in the solution. Catalyst aggregation is often a cumbersome problem for highly oxophilic metals which can lead to deactivation of the catalyst.[5] Aggregation behavior for magnesium complexes has also been documented in the literature.[18] With the present catalyst system, further introduction of an excess amount of benzaldehyde (10 equiv.) to the above mixture resulted in a clear solution and a better resolved spectrum (Figure 1, c), which suggests alleviation of the catalyst aggregation. Presumably the coordination of benzaldehyde to magnesium centers helps to cleave some (or all) of the catalyst aggregates, as was evidenced by the shift of the formyl proton signal from 9.65 ppm in the free aldehyde (Figure 1, d) to 9.41 ppm in the catalyst system. Furthermore, the ^{1}H NMR spectral identification of the isolated primary product (IM) formed by the reaction of **1** with **2a** in the presence of **4a**/Bu_2Mg prior to CF_3COOH treatment suggests that the [4+2] cycloadduct is formed exclusively (see Figure S1 in the Supporting Information) which supports a concerted cycloaddition mechanism for the present reaction.[2f,4f]

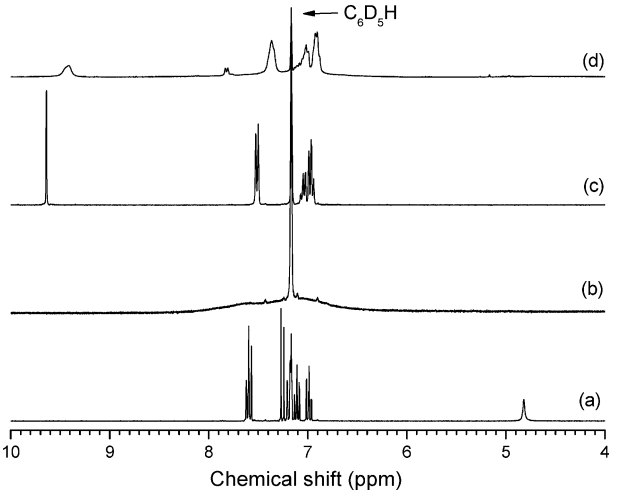


Figure 1. ^{1}H NMR spectra of (a) **4a**, (b) **4a**/Bu_2Mg (1:1.5), (c) PhCHO, and (d) **4a**/Bu_2Mg/PhCHO (1:1.5:10). All the spectra were recorded in C_6D_6 at room temperature with a 300 MHz spectrometer.

The nonlinear effect (NLE) is a powerful tool for detecting the catalyst aggregation that may arise in many asymmetric catalytic reactions.[19] Consequently, the NLE for the present system was investigated by varying the *ee* values of the chiral ligand **4a** while keeping the other reaction conditions the same as above. As shown in Figure 2, a strong positive nonlinear effect was observed which indicates the generation of homo- and heterochiral ligand-bearing magnesium complexes with different activities during the reaction. Although the precise nature and activity of the species involved are still unknown at the present stage, it is tempting to assume that when partially racemic ligand (*R*)-**4a** is employed, both hetero- and homochiral assemblies of magnesium complexes are formed in the catalytic system but, owing to its higher stability and lower reactivity, the heterochiral species is less involved in the reaction, leaving the (*R*)-**4a**-enriched homochiral species free to act as the active catalyst or its precursor, and thus leading to a higher than expected *ee* in the cycloaddition product (positive nonlinear effect).

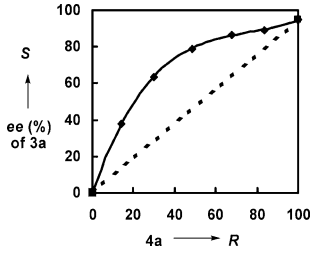
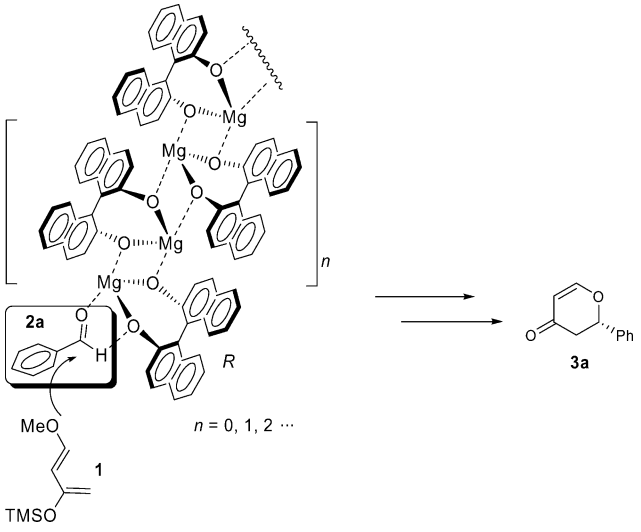


Figure 2. Nonlinear effect for the **4a**/Bu_2Mg-catalyzed asymmetric HDA reaction of Danishefsky's diene **1** and benzaldehyde (**2a**).

Based on the aforementioned aggregation behavior and NLE results, we have tentatively proposed a plausible model (Scheme 2) for the **4a**/Bu_2Mg catalytic system. The active catalyst species is proposed to possess an oligomeric zigzag chain structure comprised of Mg_2O_2 cores from the

BINOL units and magnesium centers.[20] Although the inner magnesium centers are not accessible to the reactants owing to steric congestion, the magnesium sites at the chain ends can activate the aldehyde through interaction with its oxygen. In addition, a hydrogen-bonding interaction between the aldehyde hydrogen and one of the BINOL oxygen atoms[21] might also be helpful in fixing the spatial position of the benzaldehyde molecule. Finally, preferential attack of the diene on the *Si* face of the aldehyde leads to the formation of the cycloadduct with an *S* configuration.



Scheme 2. Schematic representation for chiral induction in the **4a**/Bu_2Mg-catalyzed HDA reaction of Danishefsky's diene **1** and benzaldehyde (**2a**).

The catalyst concentration should be a contributing factor to the degree of aggregation, and lowering the catalyst loading might be beneficial to reduce the aggregation and thus increase the number of available active sites as well as the effective catalyst concentration. Based on this assumption, the reactions catalyzed by the optimal ligands **4a**–**c** were further examined with lower catalyst loadings (Table 3). When the catalyst loading was lowered to 5.0 mol-%, the product *ee* values for all the ligands were improved (up to 99% in the case of **4c**) with only a slight decrease in yield for the **4a**/Bu_2Mg-catalyzed reaction (entry 1). However, further lowering of the catalyst loading to 1 mol-% resulted in considerable losses in both yield and *ee* of the product.

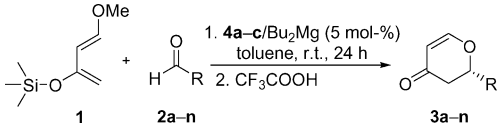
Table 3. Effect of the catalyst loading for the 4**a**–**c**/Bu_2Mg-catalyzed enantioselective hetero-Diels–Alder reaction of **1** and **2a**.[a]

Loading	**4a/Bu_2Mg**		**4b**/Bu_2Mg		**4c/Bu_2Mg**	
[mol-%]	% Yield[b]	% *ee*[b]	% Yield[b]	% *ee*[b]	% Yield[b]	% *ee*[b]
5.0	94	96 (*S*)	99	98 (*S*)	99	99 (*S*)
1.0	68	81 (*S*)	38	75 (*S*)	51	80 (*S*)

[a] All reactions were performed in toluene at room temp. for 24 h with the catalyst prepared in situ with **4** and Bu_2Mg (molar ratio 1:1.5). [b] See Table 1.

With the leading ligand **4a**–**c** and under the optimized conditions, the scope of the present reaction system was then extended to a variety of aldehyde substrates. The results in Table 4 show that all the catalysts are quite effective for the transformations involving a variety of aldehydes with diverse stereoelectronic features. The catalysts comprised of **4b** or **4c** are generally superior to that of **4a**, af-

Table 4. The enantioselective HDA reactions of Danishefshy's diene **1** and aldehydes **2a**–**p** by catalysis with BINOLate–magnesium complexes.



Entry	R	**4a**		**4b**		**4c**	
		% Yield[a]	% *ee*[b,c]	% Yield[a]	% *ee*[b,c]	% Yield[a]	% *ee*[b,c]
1	C_6H_5 (**3a**)	94	96 (*S*)	99	98 (*S*)	99	99 (*S*)
2[d]	3-$MeOC_6H_4$ (**3b**)	91	92	99	96	99	97
3	$C_6H_5CH_2CH_2$ (**3c**)	54	63 (*R*)	92	70 (*R*)	99	80 (*R*)
4	(*E*)-C_6H_5CHCH (**3d**)	61	91 (*S*)	97	96 (*S*)	99	97 (*S*)
5	furan-2-yl (**3e**)	62	82 (*S*)	95	91 (*S*)	99	93 (*S*)
6[d]	3-MeC_6H_4 (**3f**)	99	94	99	96	99	97
7[d]	4-NCC_6H_4 (**3g**)	41	51	74	85	80	85
8[d]	3-BrC_6H_4 (**3h**)	99	83	99	93	99	91
9[d]	3-ClC_6H_4 (**3i**)	99	87	99	94	99	94
10[d]	4-BrC_6H_4 (**3j**)	87	88	99	96	99	95
11[d]	4-ClC_6H_4 (**3k**)	91	81	99	93	99	91
12[d]	2,6-$Cl_2C_6H_3$ (**3l**)	82	88	85	97	91	94
13	2-MeC_6H_4 (**3m**)	77	92 (*S*)	99	94 (*S*)	99	96 (*S*)
14[d]	2-BrC_6H_4 (**3n**)	99	78	99	90	99	88

[a] Yields of the isolated products. [b] Enantiomeric excesses of the products were determined by HPLC on a Chiralcel OD column or Chiralpak AD column. [c] The absolute stereochemistries of the dihydropyranones were assigned by comparison with the optical rotations reported in the literature.[4d,6h,6k,22] [d] The absolute stereochemistry was not determined.

fording the corresponding 2-substituted 2,3-dihydro-4*H*-pyran-4-ones in yields of 74–99% with good-to-excellent *ee* values. As well as the aromatic (entries 1, 2, and 6–14) and heteroaromatic (entry 5) aldehydes, the reactions of the olefinic substrate cinnamaldehyde also proceeded smoothly in high yields and with excellent *ee* values with **4b** or **4c** (entry 4). For the aliphatic substrate 3-phenylpropanal, the corresponding HDA product **3c** was obtained in yields of 54–99% and with 63–80% *ee* (entry 3).

Conclusions

An efficient catalytic enantioselective hetero-Diels–Alder reaction of Danishefsky's diene with aldehydes using the magnesium binaphthoxide system has been developed, affording a variety of 2-substituted 2,3-dihydro-4*H*-pyran-4-ones in high yields and with excellent *ee* values. On the basis of the structure of the isolated reaction intermediate, the stereochemistry of the products, and the information attained by a study of the nonlinear effect, a plausible asymmetric induction model has been proposed. Further research into the details of the mechanism and the application of BINOL–Mg^{II} catalysts in other types of reactions are underway in our laboratory.

Experimental Section

General Considerations: ^{1}H NMR spectra were measured on a Bruker AM300 NMR spectrometer (300 MHz) with $CDCl_3$ or [D_6]DMSO as solvent and recorded in ppm. Chemical shifts are expressed in ppm with TMS as an internal standard (δ = 0 ppm) for ^{1}H NMR spectroscopy. Coupling constants, *J*, are listed in Hertz. Optical rotations were measured on a Perkin–Elmer 341 automatic polarimeter. HPLC analyses were carried out on a JASCO 1580 liquid chromatograph with a JASCO CD-1595 detector and AS-1555 autosampler. Toluene and tetrahydrofuran were distilled from sodium benzophenone ketyl under argon and degassed before use. All reactions were performed under argon. All the chiral diol ligands were purchased from ACROS or prepared by following the literature procedures.[4b,6g,6k,23]

General Procedure for Optimization of Reaction Conditions: A 0.025 M solution of **4a** in the corresponding solvent (0.01 mmol, 0.4 mL) and a calculated amount of a 1 M solution of Bu_2Mg in heptane were added to a 1.5-mL polypropylene microtube. The mixture was kept at room temperature for 0.5 h and then freshly distilled benzaldehyde (10.6 mg, 0.10 mmol) was added. After 10 min at room temperature the reaction mixture was charged with Danishefsky's diene (17.2 mg, 0.1 mmol). The reaction was quenched by introducing five drops of trifluoroacetic acid after 24 h. Biphenyl (10 mg) in toluene, as internal standard, and an aqueous saturated sodium hydrogen carbonate solution (0.5 mL) were added to the quenched mixture. The organic layer was separated and submitted to HPLC analysis to determine the yields and enantiomeric excesses (*ee*). The yields were determined with a JASCO HPLC1500 instrument equipped with an autosampler on an Intersil CN-3 column; eluent: hexane/2-propanol (97:3), flow rate: 0.5 mL/min, UV detection at λ = 254 nm, t_R(biphenyl) = 7.26 min (factor 1.000), t_R(benzaldehyde) = 11.4 min (factor 1.208); t_R(2-phenyl-2,3-dihydro-4*H*-pyran-4-one) = 20.30 min (factor 1.742). The enantiomeric excesses were determined by using the same HPLC analytical system with a Chiralcel OD column; eluent: hexane/2-propanol (90:10), flow rate: 1.0 mL/min, UV detection at λ = 254 nm, retention time: 13.0 min (*S* enantiomer), 15.2 min (*R* enantiomer). The detailed results are summarized in Table 1.

General Procedure for Screening the Chiral Diols Ligands: A 0.025 M toluene solution of **4** (0.01 mmol, 0.4 mL) and a 1 M solution of Bu_2Mg in heptane (0.015 mmol, 15 μL) were added to a 1.5-mL polypropylene microtube. The mixture was kept at room temperature for 0.5 h and then freshly distilled benzaldehyde (10.6 mg, 0.10 mmol) was added. After 10 min at room temperature the reaction mixture was charged with Danishefsky's diene (17.2 mg, 0.10 mmol). The reaction was quenched by introducing five drops of trifluoroacetic acid after 24 h. Biphenyl (10 mg) in toluene, as internal standard, and an aqueous saturated sodium hydrogen carbonate solution (0.5 mL) were added to the quenched mixture. The organic layer was separated and submitted to HPLC analysis to determine the yields and enantiomeric excesses (*ee*). The results are shown in Table 2.

General Procedure for the Enantioselective Hetero-Diels–Alder Reaction of Danishefsky's Diene 1 and Aldehydes 2a–p by Catalysis with 4a–c/$MgBu_2$: A 0.025 M toluene solution of **4a–c** (0.02 mmol, 0.8 mL) and a 1 M solution of Bu_2Mg in heptane (0.03 mmol, 30 μL) were added to a 1.5-mL polypropylene microtube . The mixture was kept at room temperature for 0.5 h and then freshly distilled benzaldehyde (21.2 mg, 0.20 mmol) was added. After 10 min at room temperature the reaction mixture was charged with Danishefsky's diene (34.4 mg, 0.20 mmol). The reaction was quenched by introducing 10 drops of trifluoroacetic acid after 24 h. An aqueous saturated sodium hydrogen carbonate solution (0.8 mL) was added to the quenched mixture. The aqueous layer was extracted with diethyl ether (3 × 15 mL) and the combined organic layers were dried with Na_2SO_4 and concentrated. The crude material was purified by flash chromatography on silica gel with hexanes/ethyl acetate (4:1) as eluent to afford 34.8 mg (99% yield) of 2-phenyl-2,3-dihydro-4*H*-pyran-4-one (**3a**) as a colorless liquid.

Supporting Information (see also the footnote on the first page of this article): ^{1}H NMR spectrum of the primary cycloadduct, spectroscopic data, and HPLC assay parameters for the HDA products **3a**–**n**.

Acknowledgments

Financial support from the National Natural Science Foundation of China (No. 20532050, 20423001), the Chinese Academy of Sciences, the Major Basic Research Development Program of China (Grant No. 2006CB806106), the Science and Technology Commission of Shanghai Municipality, and the Merck Research Laboratories are gratefully acknowledged.

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Received: December 24, 2007
Published Online: ■

