Development of an Unusually Highly Enantioselective Hetero-Diels–Alder Reaction of Benzaldehyde with Activated Dienes Catalyzed by Hypercoordinating Chiral Aluminum Complexes

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Abstract: The effect of Lewis acid catalysis of the hetero-Diels–Alder reaction between benzaldehyde and activated dienes (e.g. the Danishefsky's diene) has been investigated. In the present work we decided to study a series of chiral aluminum complexes as potential catalysts for the hetero-Diels–Alder reaction in order to gain a better understanding of the effect on the chiral induction of varying the steric and electronic environment of the metal ion. The results of this study prompted us to conclude that steric effects in the ligand coordination sphere and hypercoordination are strongly contributing factors to the optical yield of the reaction. Optimization of the reaction culminated in the synthesis of the hetero-Diels–Alder product in 99.4% *ee* and 97% yield of the isolated product. Based on the experimental results the mechanism for the hetero-Diels–Alder reaction is discussed and it is postulated that hypercoordination to the chiral aluminum Lewis acid center is of importance for the reaction.

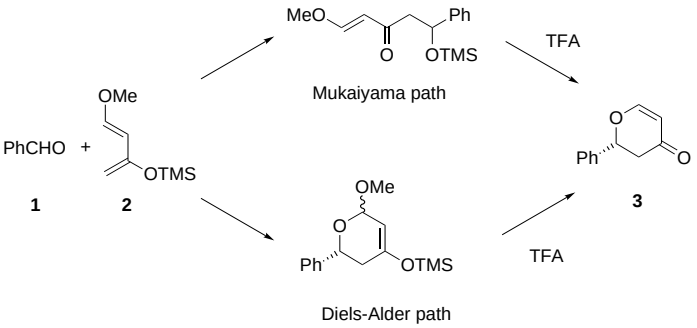
Keywords: aluminum · asymmetric catalysis · hypercoordination · hetero-Diels–Alder reactions · reaction mechanisms

Introduction

The hetero-Diels–Alder (HDA) reaction[1] provides a very convenient synthesis of six-membered partly saturated heterocycles, a class of compounds that has found extensive use as starting materials for total synthesis of many natural products and other highly functionalized heterocycles.[2] Heterocyclic synthesis by using Diels–Alder methodology is particularly useful because of the highly stereoselective nature of the reaction, which often results in the formation of only one isomer, a remarkable selectivity considering the fact that as many as four diastereoisomers can, in principle, be formed in the reaction of a diene with an aldehyde. The HDA reaction can be catalyzed by a number of reagents or under conditions of ultra-high pressure, but the use of Lewis acids for the catalysis has become especially attractive following the development of chiral Lewis acids, which enable a large number of HDA reactions to be performed under very mild conditions with catalyst loadings generally in the 1–10 mol% region.

The reaction between benzaldehyde (**1**) and *trans*-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (Danishefsky's diene) (**2**), has been studied in detail by, for example, Danishefsky et al. who demonstrated that the product of the reaction, 2,3-dihydro-2-phenyl-4(1*H*)pyranone (**3**), can be formed by two different modes of cyclization depending on the Lewis acid catalyst employed.[3] The intermediates of the two pathways were identified, and the two mechanisms formulated as i) a traditional Diels–Alder type cycloaddition reaction and ii) formation of the HDA adduct by a Mukaiyama aldol reaction path (Scheme 1). Upon treatment with trifluoroacetic acid (TFA), both intermediates were converted to the pyranone **3** (Scheme 1).

Subsequent studies of the same reaction under the influence of various Lewis acids in catalytic or stoichiometric amounts have come to the same conclusions, namely that a given Lewis acid will catalyze the reaction by either the cycloaddition or the Mukaiyama pathway.



Scheme 1. Two possible pathways for the reaction of benzaldehyde (**1**) and the Danishefsky's diene **2** to give **3**.

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Although the HDA reaction outlined in Scheme 1 has been under intense scrutiny and has been optimized with great attention to detail, the best optical yield obtained so far is 95% *ee* reported by Yamamoto et al. but with modest chemical yields (55%) in a reaction catalyzed by chiral (acyloxy)boranes.[4] In an earlier publication Corey et al. reported a quantitative reaction catalyzed by a chiral oxazaborolidine,[5a] which was demonstrated to proceed by the Mukaiyama pathway to give the product in 82% *ee*. The Mukaiyama pathway was also identified as the active pathway by Keck et al., who reported that the BINOL-Ti(O-*i*Pr)$_4$ catalyzed reaction proceeded in 83% yield and 75% *ee* (BINOL = 2,2′-dihydroxy-1,1′-binaphthalene).[6] Danishefsky et al. in an early report of chiral induction, described a synthesis[7] of **3** in 18% *ee* in a reaction catalyzed by [Eu(hfc)$_3$] (hfc = 3-(heptafluoropropylhyroxymethylene)-D-camphorate) and this reaction was shown to proceed by the Diels–Alder pathway. More recently Jacobsen et al. presented the results of the reaction catalyzed by a chiral, substituted Cr^{III}(salen) complex (salen = N,N′-bis(salicylidene)ethylenediamine dianion),[8] which gave the product in 98% yield and 65% *ee*, also by a Diels–Alder reaction pathway. Finally, Yamamoto et al. reported the reaction to proceed in 56% *ee* in the presence of a highly sterically hindered substituted BINOL-AlMe$_3$ derived catalyst, but no yield was given, and the intermediate of the reaction was not determined.[9]

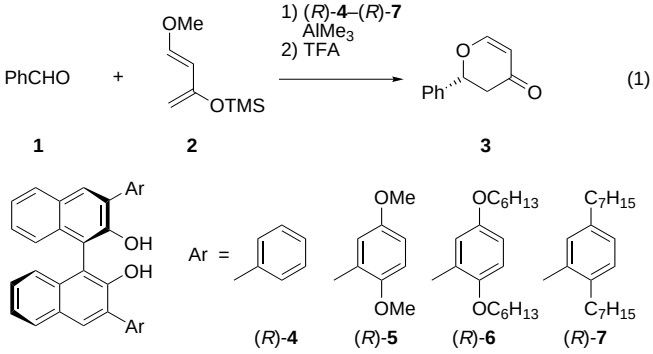
There appears to be a firm correlation between the pathway and the Lewis acid employed. The Mukaiyama pathway has so far only been observed with catalysts based on titanium[6] and boron[5] complexes, while the Diels–Alder pathway has been positively identified in reactions catalyzed by Lewis acids based on europium,[7] chromium,[8] and zinc.[3a] The reaction path in the aluminum-catalyzed reactions has not been established (vide infra).

This paper presents the development of a catalytic system based on hypervalent chiral aluminum complexes which catalyzes the HDA reaction of benzaldehyde (**1**) with Danishefsky's diene **2** giving product **3** (Scheme 1) in more than 99% *ee*. Furthermore, the mechanism of the aluminum-catalyzed HDA reaction is discussed.

Abstract in Danish: *Effekten af Lewis syrer på hetero-Diels–Alder reaktionen af benzaldehyd og aktiverede diener (f.eks. Danishefsky's dien) er blevet undersøgt. Det foreliggende arbejde har sit udgangspunkt i studiet at kirale aluminium komplekser som mulige katalysatorer for hetero-Diels–Alder reaktioner for at undersøge indflydelsen af de steriske og elektroniske forhold omkring metalionen på den kirale induktion. Resultatet af disse undersøgelser godtgør, at både steriske effekter i ligandkoordinationssfæren og hyperkonjugation er meget vigtige faktorer for det optiske udbytte af reaktionen. Optimering af reaktionen kulminerede i syntesen af hetero-Diels–Alder produktet i 99.4% enantiomert overskud og 97% isoleret udbytte. På basis af de eksperimentelle resultater er mekanismen for hetero-Diels–Alder reaktionen diskuteret og det er postuleret at hyperkonjugation fra den kirale ligand til aluminiumionen har stor vigtighed for reaktionen.*

Results and Discussion

Recently, we presented a highly enantioselective version of the inverse-electron demand 1,3-dipolar cycloaddition reaction of nitrones with vinyl ethers, in which the chiral induction was achieved by using a catalyst generated from new substituted BINOLs and AlMe$_3$.[10] Optical yields of >99% *ee* were achieved in these highly selective reactions, and stimulated by these results we decided to screen similar catalyst systems with other monodentate coordinating substrates, which by default have more degrees of freedom in binding to the catalyst, and which therefore rarely are amenable to optical induction to a preparatively useful degree (>90% *ee*).[11] The synthesis of the HDA product **3** from benzaldehyde (**1**) and Danishefsky's diene **2** presented itself as an obvious starting point for this study, mainly because of the large amount of evidence already present in the literature regarding catalytic enantioselective versions of the reaction, which would provide a welcome benchmark for the efficiency. Thus, we performed the HDA reaction on a 0.2 mmol scale by generating the catalyst (20 mol%) from (*R*)-3,3′-bis(2,5-dihexyloxyphenyl)-BINOL (**6**) [Eq. (1)] and AlMe$_3$ in dry CH_2Cl_2 at 0 °C, after which **1** and the diene **2** were added sequentially. Stirring for 3 h followed by quenching with a 1% solution of TFA in CH_2Cl_2 provided the pyranone **3** in 88% yield and 57% *ee* [Eq. (1)]. ^{1}H NMR spectroscopy of the intermediate, isolated from the reaction without the use of TFA, demonstrated that the reaction proceeds by the Diels–Alder pathway (Scheme 1).



Encouraged by this result we chose to optimize the reaction in Equation (1) with respect to solvent, temperature, and Lewis acid catalyst loading to probe the potential of this catalytic system; the results of these experiments are summarized in Table 1. Variation of the solvent revealed a dramatic solvent effect; in toluene the yield of **3** dropped to 68%, but the *ee* raised to 84% compared with the results in CH_2Cl_2 (entries 1 and 2). Ethereal solvents proved even more advantageous; in Et_2O the reaction proceeded to give a 73% yield of **3** with 88% *ee*, but the optimal solvent turned out to be *tert*-butyl methyl ether (TBME), in which the reaction after full conversion gave 74% yield and 92% *ee* on a 0.2 mmol scale (entries 3 and 4). Further optimization with regard to temperature and catalyst loading was carried out, resulting in the finding that a reaction temperature of −38 °C was optimal. Carrying out the reaction at this temperature in

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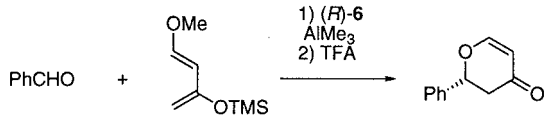
Table 1. Solvent and catalytic effects of (*R*)-**6**-AlMe complexes on the hetero-Diels–Alder reaction of benzaldehyde (**1**) and Danishefsky's diene **2** [Eq. (1)].[a]



1 **2** **3**

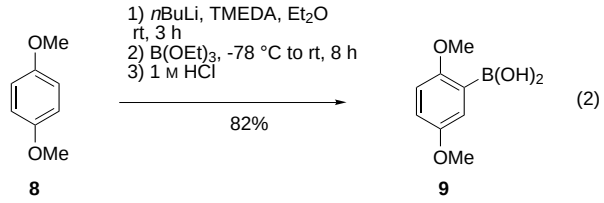
Entry	solvent	*T* [°C]	Catalyst [mol%]	Yield[b] [%]	*ee* [%][c]
1	CH_2Cl_2	0	20	88	57
2	$PhCH_3$	0	10	68	84
3	Et_2O	0	10	73	88
4	*t*BuOMe	0	10	74	92
5	*t*BuOMe	–38	10	97	99.4
6	*t*BuOMe	–38	5	76	93
7	*t*BuOMe	–38	2	13	90

[a] The reactions were performed on a 0.2 mmol scale, employing equimolar amounts of **1** and **2**. For further details see Experimental Section. [b] Yield isolated by column chromatography. [c] The *ee* value was determined by HPLC using a Daicel Chiragel OD column.

TBME with a 10 mol% catalyst loading produced **3** in 97% yield and 99.4% *ee* (entry 5). Lowering of the catalyst loading resulted in markedly more sluggish reactions and lower yield and *ee* (entries 6 and 7). The absolute configuration of **3** using (*R*)-**6**-AlMe as the catalyst has been assigned as *R* on the basis of HPLC data.[4]

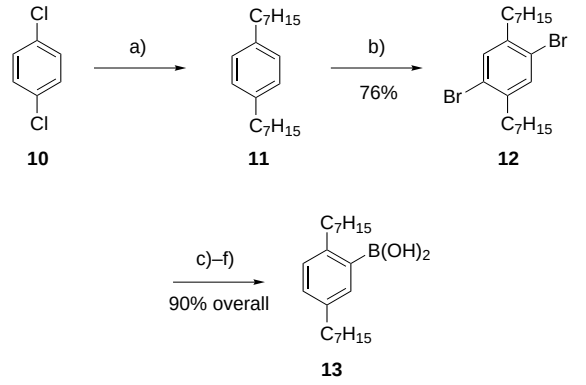
At this point, the question of possible hypercoordination of the ligand ether oxygen atoms to the aluminum metal arose. Hypercoordination has recently been shown to be of importance in Lewis acid catalyzed addition reactions to aldehydes.[12] Thus, we decided to investigate the stereoelectronic factors influencing the course of the reaction by preparing a series of ligands that would allow us to distinguish the steric effects of the ligand side chains from their possible electronic/coordinating role. For this purpose, a series of ligands with varying substituents on the phenyl groups situated close to the active center of the catalyst was prepared (see [Eq. 1]). In the chosen series of four ligands, the BINOL derivative (*R*)-**4** was included to probe the steric effect of a single phenyl substituent on the catalytic activity, whereas the BINOL derivative (*R*)-**5** was prepared to study a ligand with similar coordinating properties to those of (*R*)-**6** but without the high steric bulk of the four hexyloxy side chains of (*R*)-**6**. Finally, BINOL derivative (*R*)-**7** was selected as a ligand with steric requirements very similar to those of (*R*)-**6**, but which eliminated the possibility of coordination of the ether oxygen atoms to the aluminum reactive center. The synthesis of the ligands is described below.

Ligand syntheses: The BINOL derivatives (*R*)-**4**[13] and (*R*)-**6**[14] were already available by literature procedures, while the BINOL derivatives (*R*)-**5** and (*R*)-**7** were prepared according to a synthetic strategy similar to the one developed by Pu et al.[14] The central step in these syntheses is the formation of the bond between the BINOL and the phenyl substituent in a Suzuki coupling reaction. The relevant boronic acids were prepared by site-directed lithiation followed by reaction with the appropriate boron electrophile. In the first example hydroquinone dimethyl ether (**8**) was lithiated in Et_2O using *n*BuLi activated by *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) as the metalating agent. $B(OEt)_3$ was added, and after completion of the reaction the boronic acid ester was hydrolyzed by using 1M HCl to give the boronic acid **9** in 82% yield [Eq. (2)].



8 **9**

The boronic acid **13** required for the synthesis of the BINOL derivative (*R*)-**7** was prepared from 1,4-dichlorobenzene (**10**) in a four-step sequence. Kumada coupling[15] of heptylmagnesium bromide with **10** using [Ni(dppp)Cl_2] (dppp = 1,3-bis(diphenylphosphino)propane) in refluxing Et_2O gave 1,4-diheptylbenzene (**11**),[16] which was dibrominated in a solvent-free reaction catalyzed by I_2 to give 1,4-dibromo-2,5-diheptylbenzene (**12**) in 76% yield, using a modified procedure adopted from Schlüter et al.[17] Selective monolithiation of **12** using *n*BuLi followed by quenching with NH_4Cl at –78 °C produced 1-bromo-2,5-diheptylbenzene (**12b**) in quantitative yield. The crude product was resubjected to halogen–lithium exchange using *n*BuLi (1.2 equiv) in Et_2O, and the resulting monolithio compound was treated with $B(OEt)_3$, and after completion of the reaction and an acidic workup, the boronic acid **13** was isolated in 90% yield (Scheme 2).

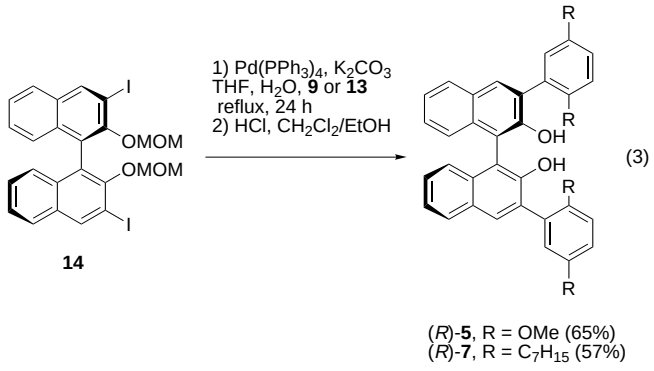


10 **11** **12** **13**

Scheme 2. Conversion of **10** into **13**. a) $C_7H_{15}Br$, [Ni(dppp)Cl_2]; b) Br_2, I_2 (cat.); c) *n*BuLi, Et_2O, room temperature, 1 h; d) NH_4Cl, *n*BuLi, Et_2O, room temperature, 1 h; e) $B(OEt)_3$, –78 °C to room temperature, 8 h; f) 1M HCl.

The boronic acids **9** and **13** were subjected to Suzuki coupling with the known diiodo BINOL derivative **14**[18] in refluxing THF employing a catalytic amount of [Pd(PPh_3)$_4$] and aqueous K_2CO_3 as the base. Subsequently the methoxy methyl (MOM) protecting groups were hydrolyzed by using concentrated HCl in CH_2Cl_2/EtOH to produce the desired

(*R*)-BINOL derivatives **5** and **7** in 65% and 57% yield, respectively [Eq. (3)].

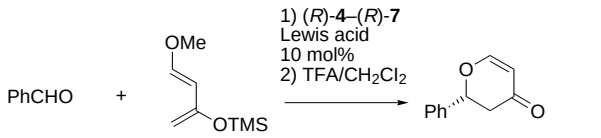


14

(*R*)-**5**, R = OMe (65%)
(*R*)-**7**, R = C_7H_{15} (57%)

Ligand screening: With the new series of ligands in hand, we set out to perform a cross-screening study of combinations of Lewis acids and the ligand series (*R*)-**4**–(R)-**7**. The appropriate ligand (0.02 mmol) was dissolved in TBME, and the chosen Lewis acid was added. The model reaction between benzaldehyde **1** and Danishefsky's diene **2** was performed to give the pyranone **3** in optical yields ranging from 53 to 99.4% *ee* (Table 2). In the second screening the ligand (*R*)-**6** in combination with $AlMe_3$ still gave the best result, whilst the same Lewis acid in combination with the ligands (*R*)-**4**, (*R*)-**5**, and (*R*)-**7** gave 65, 96, and 87% *ee*, respectively (entries 1, 2, 4, and 7). A clear trend thus appears: ligand (*R*)-**4**, which has neither the steric bulk nor the coordinating ether oxygen atoms characteristic of (*R*)-**6**, catalyzes the reaction, but only very modest chemical and optical yields of **3** are obtained. Ligand (*R*)-**5**, substituted with methoxy groups, is nearly as efficient as (*R*)-**6** with an optical yield of 96%, but with a more modest chemical yield. Ligand (*R*)-**7**, which was designed to have similar steric properties to (*R*)-**6**, proved to fall somewhere in between (*R*)-**4** and (*R*)-**6** with 87% *ee*, the enantioselectivity is respectable and significantly better than the results obtained with (*R*)-**4**, but clearly the lack of ether oxygen atoms capable of coordinating to the aluminum center markedly affects the efficiency of the enantioselectivity compared to both (*R*)-**6** and the less sterically demanding compound (*R*)-**5**. These results indicate that hypercoordination to the aluminum center is indeed an important contributing factor.

Table 2. Effects of ligands and Lewis acid on the hetero-Diels–Alder reaction of **1** and Danishefsky's diene **2** in the presence of 10 mol% BINOL-AlR.[a]



1 **2** **3**

Entry	Ligand	Lewis acid	Yield [%][b]	*ee* [%][c]
1	(*R*)-**4**	$AlMe_3$	29	65
2	(*R*)-**5**	$AlMe_3$	56	96
3	(*R*)-**5**	$AlEt_3$	50	82
4	(*R*)-**6**	$AlMe_3$	97	99.4
5	(*R*)-**6**	$AlEt_3$	26	80
6	(*R*)-**6**	Me_2AlCl	53	53
7	(*R*)-**7**	$AlMe_3$	95	87

[a] The reactions were performed on a 0.2 mmol scale at $-38\,^{\circ}C$ for 5 h, by employing equimolar amounts of the diene and dienophile and 10 mol% ligand and Lewis acid, followed by addition of TFA in CH_2Cl_2. For further details see Experimental Section. [b] Yield isolated by column chromatography. [c] The *ee* value was determined by HPLC using a Daicel Chiragel OD column.

To further probe the steric and electronic effects governing the hypercoordination of aluminum and its potential role in controlling the enantioselectivity of the reaction, we chose to perform the HDA reaction of **1** with **2** with catalyst complexes generated from the ligands (*R*)-**5** and (*R*)-**6** in combination with aluminum-based Lewis acids other than $AlMe_3$. In the case of ligand (*R*)-**5**, changing the Lewis acid from $AlMe_3$ to $AlEt_3$ resulted in largely the same chemical yield and a reduction in *ee* from 96% to 82% of **3** (Table 2, entries 2 and 3). Ligand (*R*)-**6** in combination with $AlEt_3$ catalyzed the reaction to give pyranone **3** in 80% *ee* and only 26% yield (entry 5), while the catalyst generated from (*R*)-**6** and $AlClMe_2$ produced **3** in 53% yield and 53% *ee* (entry 6). From the available data it would appear that increased steric hindrance caused by the presence of an ethyl group on the aluminum center instead of a methyl group has a detrimental effect on the ability of the catalyst to coordinate to the metal center through its ether oxygen lone pairs, but the decrease in *ee* values in these reactions might also be explained simply by reduced Lewis acidity of the complex as a result of the stronger electron-donating ethyl substituent. In comparison, the use of $AlClMe_2$ for generating the catalytic complex is not expected to change the steric surroundings of the metal ion to any significant degree (a methyl group is very similar to a chlorine atom in terms of van der Waals radii), but still the substitution of a chlorine for a methyl group markedly decreases the optical yield in the reaction. Probably, the lowered electron density on aluminum in this complex offsets the electronic balance of the hypercoordinated resting catalytic complex by increasing the amount of energy needed to break one of the ether oxygen–aluminum bonds. This increased barrier towards binding of **1** reduces the catalytic efficiency, and this is reflected in the relatively low *ee* value of reactions catalyzed by the complex formed between (*R*)-**6** and $AlClMe_2$.

On the basis of the experimental results it is reasonable to assume that besides the coordination of benzaldehyde, one of the ether oxygen atoms of the chiral ligand is also coordinated to aluminum. This leads to a trigonal-bipyrimidal structure at the aluminum center which can account for the stereochemical outcome of the reaction. On the basis of the absolute configuration of the HDA adduct **3** model calculations show that the preferred geometry for the intermediate is one in which the two oxygen atoms from the BINOL ligand and the methyl substituent are located in the equatorial plane with one of the hypercoordinating ether oxygen atoms of the ligand and the benzaldehyde oxygen atom as the two axial ligands. This intermediate, **15**, is outlined schematically in Figure 1.

The 2,5-dimethoxyphenyl substituent which is not involved in hypercoordination to aluminum is oriented perpendicular

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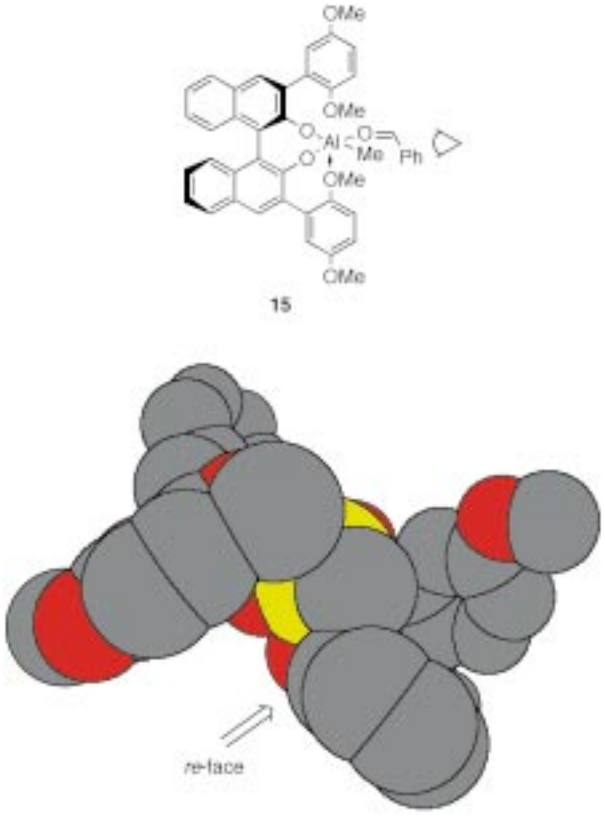

Figure 1. Schematic representation of the intermediate **15** (ChemDraw; color code: carbon: gray; oxygen: red; aluminum: yellow). The *re* face of **15** is available for approach by the diene as indicated by an arrow in the Chem3D model (bottom). The Chem3D model is viewed from the site as shown in **15** in the ChemDraw representation (top).

to the BINOL ligand, while the 2,5-dimethoxyphenyl substituent which hypercoordinates to aluminum is twisted towards the metal. This twisting of the 2,5-dimethoxyphenyl substituent creates a chiral environment because the non-hypercoordinated 2,5-dimethoxyphenyl substituent shields the *si* face of benzaldehyde, while the *re* face is available for approach by the diene as indicated with an arrow in the Chem3D model of **15** in Figure 1. The diene can approach in an *endo* or *exo* fashion and we have found that the former approach is the one taking place.[19] The crucial factor in taking the hypercoodination into account is that the steric enviroment at the aluminum center becomes more sterically crowded increasing the shielding of the carbonyl functionality. With the model for the intermediate presented in **15** one now begins to understand the change in enantioselectivity for the results for the various ligands presented in Table 2; the hexyloxyphenyl- and methoxyphenyl-substituted ligands (*R*)-**6** and (*R*)-**5** are able to hypercoordinate to aluminum thereby increasing the steric crowding at the metal, the heptylphenyl-substituted ligand (*R*)-**7** is also sterically demanding and increases the steric bulk, but the hypercoordinating ability is missing. Finally, the ligand (*R*)-**4** with only phenyl substituents lacks both the hypercoordininating and steric properties and gives the lowest enantioselectivity.

In conclusion we have developed a highly enantioselective hetero-Diels–Alder reaction of benzaldehyde with Danishefsky's diene giving the product in up to 99.4% *ee* and in 97% yield. It is demonstrated that hypercoordination of the chiral ligand to the Lewis acid center is of utmost importance for the reaction.

Experimental Section

General methods: The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 MHz and 75 MHz, respectively, using tetramethylsilane (TMS) or residual solvent as the reference and the deuterated solvent as lock. Chemical shifts are reported in ppm downfield from TMS. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Solvents were dried using standard methods and stored over molecular sieves (4 Å). THF and Et_2O were distilled from sodium benzophenone immediately prior to use. All glass equipment was flame-dried under vacuum before use. Chiral HPLC was performed using a Daicel Chiracel OD column by employing hexane:*i*PrOH 98:2 with UV detection at 247 nm.

Materials: The ligands (*R*)-**4**[13] and (*R*)-**6**[14] were prepared as described in the literature. Benzaldehyde was distilled, kept, and handled under N_2, and stored over 4 Å molecular sieves at 5 °C. TMEDA and $B(OEt)_3$ were distilled immediately before use. $AlMe_3$, $AlEt_3$, and $AlClMe_2$ were purchased as standardized solutions in hexane and handled using Schlenck techniques. *trans*-1-Methoxy-3-(trimethylsilyloxy)-1,3-butadiene (Danischefsky's diene) (**2**) was used as received without further purification.

2,5-Dimethoxybenzeneboronic acid (9): To a solution of 1,4-dimethoxybenzene (**8**) (1.38 g, 10 mmol) in Et_2O (100 mL) at room temperature was slowly added a solution of *n*BuLi (1.6 M in hexane, 7.0 mL, 11.2 mmol) and TMEDA (1.8 mL, 1.39 g, 11.9 mmol) in Et_2O. The solution was stirred for 2.5 h, cooled to −78 °C, and $B(OEt)_3$ (5.5 mL, 4.68 g, 32.0 mmol) was added over a period of 15 min. The solution was allowed to warm up to room temperature, stirred for an additional 3 h, cooled to 0 °C, and 1M HCl (50 mL) was added carefully. The layer was separated and the organic phase was washed with 1M HCl (100 mL), brine (2 × 100 mL), and dried over $MgSO_4$. Column chromatography (SiO_2, EtOAc/hexane 1:5) gave **9** (1.50 g, 82%) as a white solid. M.p. 94–97 °C; ^{1}H NMR: $\delta = 3.80$ (s, 3H; OCH_3), 3.88 (s, 3H; OCH_3), 5.83 (s, 2H; OH), 6.86 (d, $^3J(H,H) = 9.0$ Hz, 1H; arom), 6.98 (dd, $^3J(H,H) = 9.3$ Hz, $^4J(H,H) = 3.3$. Hz, 1H; arom), 7.37 (d, $^4J(H,H) = 3.3$ Hz, 1H; arom); ^{13}C NMR: $\delta = 55.7$, 56.0, 111.2, 118.6, 120.6, 153.8, 158.8; MS (EI): *m/z* (%): 182 ([M^+], 90); $C_8H_{11}BO_4 \cdot 1/8\,H_2O$ (181.98): calcd C 52.16, H 6.15; found C 52.26, H 6.03.

1,4-Dibromo-2-5-diheptylbenzene (12): A 50 mL round-bottomed flask wrapped with foil was charged with 1,4-diheptylbenzene (**11**)[16] (6.75 g, 24.6 mmol) and I_2 (0.06 g, 0.2 mmol), and cooled to 0 °C. To this solution was added bromine (2.58 mL, 8.05 g, 50.4 mmol) over a period of 30 min and the solution was stirred overnight. To the resulting solid was added 20% aqueous NaOH (25 mL), and the mixture was heated until all of the compound had dissolved. After the mixture had been cooled to room temperature, the resulting white compound was filtered and dried. Recrystallization from EtOH gave **12** as white needles (8.10 g, 76%). M.p. 31–33 °C; ^{1}H NMR: $\delta = 0.85$–0.95 (m, 6H; CH_3), 1.2–1.4 (m, 16H; alkyl), 1.5–1.6 (m, 4H; CH_2), 2.69 (t, $^3J(H,H) = 7.7$ Hz, 4H; OCH_2), 7.35 (S, 2H; arom); ^{13}C NMR: $\delta = 14.1$, 22.7, 29.1, 29.3, 29.9, 31.8, 35.6, 123.1, 133.7, 141.3; MS (EI): *m/z* (%): 432 ([M^+], 72); $C_{20}H_{32}Br_2$ (432.28): calcd C 55.57, H 7.46; found C 55.80, H 7.47.

1-Bromo-2,5-diheptylbenzene (12b): To a ice-cooled solution of 1,4-dibromo-2,5-diheptylbenzene (**12**) (4.02 g, 9.3 mmol) in Et_2O (30 mL) was dropwise added a solution of *n*BuLi in hexane (1.5 M, 6.5 mL, 9.8 mmol). After complete addition the solution was stirred for 1.5 h and quenched with saturated aqueous NH_4Cl (3 mL). The solution was transferred to a separation funnel and washed with H_2O (50 mL), brine (50 mL), dried over $MgSO_4$, and evaporated to give compound **13** (3.3 g, 100%) as a clear oil, which was used for the next reaction without further purification; ^{1}H NMR: $\delta = 0.8$–0.9 (m, 6H; CH_3), 1.2–1.4 (m, 16H; alkyl), 1.5–1.65 (m, 4H; CH_2), 2.53 (t, $^3J(H,H) = 7.7$ Hz, 2H; OCH_2), 2.67 (t, $^3J(H,H) = 7.9$ Hz, 2H; OCH_2), 7.02 (dd, $^3J(H,H) = 7.8$ Hz, $^4J(H,H) = 1.8$. Hz, 1H; arom), 7.10 (d, $^3J(H,H) = 7.6$ Hz, 1H; arom), 7.34 (d, $^4J(H,H) = 1.6$ Hz, 1H; arom); ^{13}C NMR: $\delta = 14.1$ (2C), 22.7 (2C), 29.1, 29.2, 29.4, 30.1 (2C), 31.3, 31.8, 31.8, 35.1, 35.8, 124.2, 127.4, 129.9, 132.4, 139.1, 142.3; MS (EI): *m/z* (%): 354 ([M^+], 49).

2,5-Diheptylbenzeneboronic acid (13): To a ice-cooled solution of 1-bromo-2,5-diheptylbenzene **(12b)** (3.25 g, 9.2 mmol) in Et_2O (75 mL) was dropwise added a solution of *n*BuLi in hexane (1.5 M, 6.8 mL, 10.2 mmol). The solution was stirred for 1.5 h, cooled to $-78\,^{\circ}C$ and $B(OEt)_3$ (5.5 mL, 4.68 g, 32.0 mmol) was added over a period of 15 min. The solution was allowed to warm up to room temperature, stirred for an additional 3 h, cooled to $0\,^{\circ}C$, and 1 M HCl (75 mL) was added carefully. The layer was separated and the organic phase was washed with 1 M HCl (75 mL), brine (2×50 mL), and dried over $MgSO_4$. Column chromatography (SiO_2, EtOAc/hexane 1:5) gave **13** as a white semicrystalline solid (2.63 g, 90 %). M.p. 92 – 93 °C (softens at 80 °C); ^1H NMR: $\delta = 0.8 - 0.9$ (m, 6H; CH_3), 1.15 – 1.4 (m, 16H; alkyl), 1.5 – 1.65 (m, 4H; CH_2), 2.63 (t, $^3J(H,H) = 7.7$ Hz, 2H; OCH_2), 3.18 (t, $^3J(H,H) = 7.9$ Hz, 2H; OCH_2), 7.20 (d, $^3J(H,H) = 8.1$ Hz, 1H; arom), 7.28 (dd, $^3J(H,H) = 7.6$ Hz, $^4J(H,H) = 1.7$. Hz, 1H; arom), 8.05 (d, $^4J(H,H) = 1.8$ Hz, 1H; arom); ^{13}C NMR: $\delta = 14.1$, 14.1, 22.7, 22.7, 29.2, 29.3, 29.4, 29.6, 301, 31.7, 31.9, 33.3, 35.2, 35.6, 128.6, 129.7, 132.1, 137.3, 139.4, 148.5; $C_{20}H_{35}BO_2$ (318.31): calcd C 75.47, H 11.08; found C 75.43, H 11.22.

(*R*)-3,3′-Bis(2,5-dimethoxyphenyl)-2,2′-dihydroxy-1,1′-dinaphthyl [(*R*)-5]: In a 50 mL two-necked flask equipped with a condenser were placed (*R*)-**14**[18] (0.51 g, 0.8 mmol), 2,5-dimethoxybenzene boronic acid **9** (0.45 g, 2.4 mmol), and $[Pd(PPh_3)_4]$ (0.05 g, 0.04 mmol), and the flask was evacuated and filled with N_2 three times. THF (15 mL, degassed) and a degassed aqueous solution of K_2CO_3 (2M, 5 mL) were added sequentially. The reaction mixture was heated at reflux for 24 h under N_2, cooled to room temperature, quenched with brine, and diluted with Et_2O (50 mL). The organic phase was washed with 1 M HCl (50 mL) and brine (2×50 mL), and dried over $MgSO_4$. The solvent was removed to give the MOM-protected BINOL as a yellow oil. The crude product was dissolved in CH_2Cl_2 (10 mL) and EtOH (20 mL) and refluxed under N_2 for 18 h in the presence of concentrated HCl (1 mL). The reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (50 mL), and the organic phase was washed with H_2O (50 mL), brine (50 mL), and dried over $MgSO_4$. After concentration the residue was purified by column chromatography (SiO_2, EtOAc:Hexane 1:9) to give (*R*)-**5** as a pale yellow solid (0.29 g, 64 %). M.p. 129 °C (softens at 120 °C); $[\alpha]_D^{25} = +81.3$ ($c = 1.0$ in $CHCl_3$); ^1H NMR: $\delta =$ 3.80 (s, 6H; OCH_3), 3.85 (s, 6H; OCH_3), 6.03 (s, 2H; OH), 6.9 – 7.0 (m, 4H; arom), 7.12 (s br., 2H; arom), 7.3 – 7.4 (m, 6H; arom), 7.92 (d, $^3J(H,H) =$ 7.8 Hz, 2H; arom), 7.97 (s, 2H; arom); ^{13}C NMR δ 55.9, 56.9, 112.9, 114.3, 115.4, 117.7, 123.8, 124.9, 126.7, 128.3, 128.6, 129.3, 131.2, 133.5, 150.4, 150.8, 154.2; MS (PDMS): *m/z* 558.6 ($[M^+]$); $C_{36}H_{30}O_6 \cdot 1/2\,H_2O$ (558.63): calcd C 76.17, H 5.50; found C 75.82, H 5.43.

(*R*)-3,3′-Bis(2,5-diheptylphenyl)-2,2′-dihydroxy-1,1′-dinaphthyl [(*R*)-7]: Prepared similar to (*R*)-**5** by employing (*R*)-**14** (0.91 g, 1.5 mmol), 2,5-diheptylbenzene boronic acid (**13**) (1.38 g, 4.5 mmol), and $[Pd(PPh_3)_4]$ (0.10 g, 0.09 mmol) in THF (30 mL) and 2 M K_2CO_3 (10 mL). After hydrolysis and standard aqueous workup the residue was chromatographed (SiO_2, EtOAc:hexane 1:19) to give (*R*)-**7** as a clear yellow oil (0.56 g, 47 %). $[\alpha]_D^{25} = +49.6$ ($c = 1.0$ in $CHCl_3$); ^1H NMR: $\delta = 0.65 - 0.95$ (m, 6H; CH_3), 1.0 – 1.7 (m, 20H; alkyl), 2.4 – 2.7 (m, 4H; CH_2), 5.0 – 5.1 (m, 2H, OH), 7.11 (2, 2H; arom), 7.15 – 7.45 (m, 10H; arom), 7.87 (s. 2H; arom), 7.91 (d, $^3J(H,H) = 8.4$ Hz, 2H; arom); ^{13}C NMR: $\delta = 14.10$, 14.14, 22.6, 22.7, 29.1, 29.2, 29.5, 29.7, 31.0, 31.5, 31.7, 31.8, 33.2, 35.6, 112.9, 124.0, 124.3, 126.8, 128.3, 128.5, 129.1, 130.5, 130.90, 130.94, 133.3, 133.4, 135.9, 139.2, 140.7; MS (PDMS): *m/z* 831.3 ($[M^+]$); $C_{60}H_{78}O_2 \cdot 2H_2O$ (181.98): calcd C 83.06, H 9.53; found C 83.29, H 9.39.

2,3-Dihydro-2-phenyl-4(1*H*)pyranone (3): General catalytic HDA procedure (Table 1, entry 5): (*R*)-3,3′-Bis(2,5-dihexyloxy)-2,2′-binaphthol (**6**) (18 mg, 0.02 mmol) was dissolved in dry TBME (1.0 mL) in a Schlenck tube under nitrogen, and a solution of 2.0 M $AlMe_3$ in hexane (10 μL, 0.02 mmol) was added, and the resulting yellow reaction mixture was stirred at room temperature for 1 h. The reaction was cooled to $-38\,^{\circ}C$ on a solid CO_2/1,2-dichloroethane cooling bath, and benzaldehyde **1** (20 μL, 0.2 mmol) was added, causing the reaction to undergo a color change to orange. Danishefsky's diene **2** (43 μL, 0.2 mmol) was added in one portion, and the reaction was stirred for three hours at $-38\,^{\circ}C$, after which it was allowed to warm up to room temperature with stirring. The reaction was quenched by the addition of a 1 % solution of TFA in CH_2Cl_2 (2 mL), and then the mixture was stirred for 1 h at room temperature, and filtered through a plug of silica by eluting with Et_2O. Evaporation of the filtrate followed by flash chromatography of the resulting residue (SiO_2, EtOAc:hexane 2:3) gave the product as a yellowish oil, yield 33 mg (97 %); 99.4 % *ee*. HPLC (Daicel OD, hexane/*i*PrOH 98:2, flow rate 0.5 mL min^{-1}, UV detection at 247 nm) $t_r = 11.6$ min (minor, *S* enantiomer), $t_r = 12.9$ min (major, *R* enantiomer).

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[19] In order to determine the approach of the diene to the aldehyde, the reaction of benzaldehyde with dimethyl Danishefsky's diene (2,4-dimethyl-1-methoxy-3-(trimethylsiloxy)-1,3-butadiene) in the presence of 10 mol % (*R*)-**6** and $AlMe_3$ was carried out. The product (2*R*,3*R*)-2,3-dihydro-3,5-dimethyl-2-phenyl-4(1*H*)pyranone was isolated in very high *endo* selectivity (*endo*:*exo* 98:2).

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