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STUDIES ON THE ASYMMETRIC DIELS-ALDER REACTION OF DIHYDROPYRIDIN-2-ONE WITH SILYLOXYDIENES

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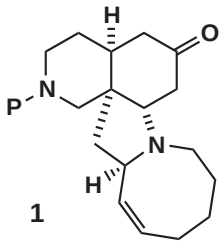
Abstract - The asymmetric Diels-Alder reaction of dihydropyridin-2-one with 2-triethylsilyloxy-1,3-pentadiene was studied in the presence of chiral aluminum reagents. Menthyloxyaluminum dichloride was the most effective catalyst and gave a hexahydroisoquinolin-2-one derivative in 44% ee as an *endo*-product after desilylation.

The formation of carbon-carbon bonds by the Diels-Alder (D-A) reaction is an important transformation in organic synthesis. A variety of natural products have been synthesized using the D-A reaction as a key strategy. Recently, remarkable progress has been made in the asymmetric D-A reaction using chiral Lewis acids,[1] and a catalytic asymmetric version has been well documented.[2]

We have been interested in syntheses of manzamine A and dynemicin A, which are heterocyclic natural products that share a common structural feature of a highly functionalized perhydroisoquinoline core, such as **1** and **2**. To ensure the *cis* relationship of the central ring system, we have demonstrated the utility of the D-A reaction of 3-alkyl-dihydropyridinones (**3**, R=alkyl) and 3-phenylthio-dihydropyridinones (R=SPh), the first of which has been successfully applied to synthesis of the manzamine A core (Scheme 1).[3] Further extension of these D-A reactions with silyloxydienes in which dihydroquinolin-2-one derivatives (**5**) are used as a novel dienophile, has given highly functionalized phenanthridinone derivatives (**6**), which could be a versatile intermediate for dynemicin A core (**2**).[3e] Using a chiral dienophile (**3**), we have successfully obtained optically pure hydroisoquinoline derivative (**4**), which is a key intermediate in the total synthesis of manzamine A.[3i]



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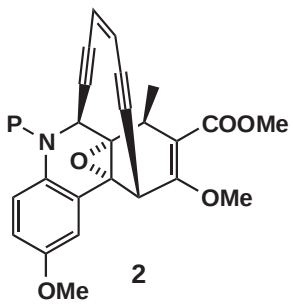
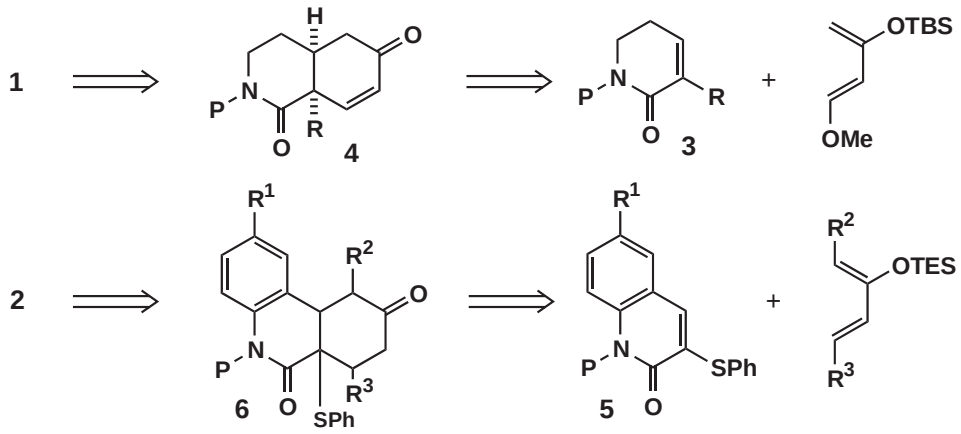


2

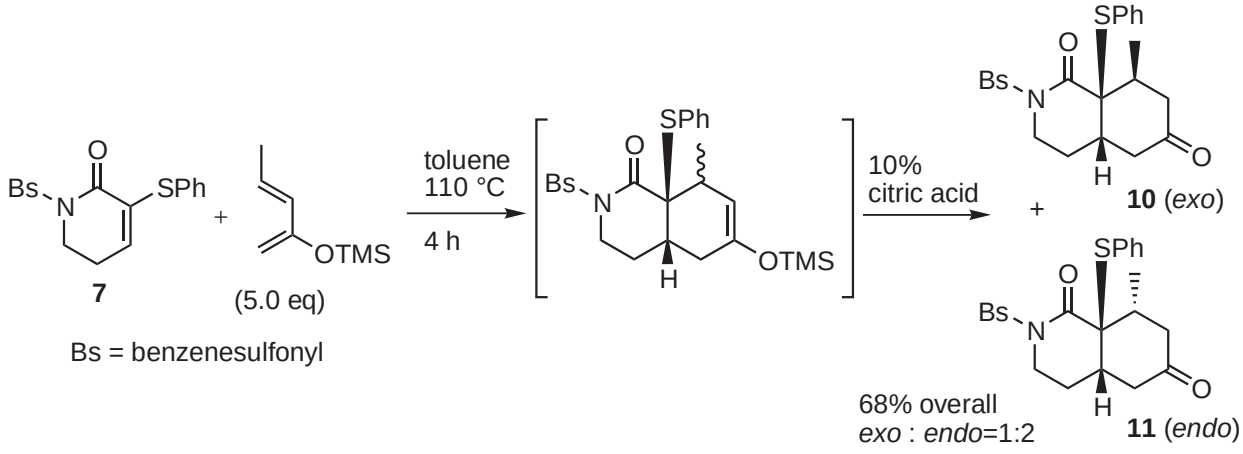
Scheme 1



In this paper, we report the D-A reaction of 3-phenylthiodihydropyridinone (**7**) with (*E*)-2-triethylsilyloxy-1,3-pentadiene (**8**)[3d,3g] using various achiral or chiral Lewis acids, leading to a hexahydroisoquinolin-2-one ring system (**9**).

We have previously examined the effect of the substituent on the nitrogen of dihydropyridinones and found that electron-withdrawing groups such as a benzenesulfonyl group are essential for the successful D-A reaction with silyloxydienes, based on experiments and theoretical calculations.[3c,3e] The D-A reaction of 3-phenylthiodihydropyridinone (**7**) with (*E*)-2-trimethylsilyloxy-1,3-pentadiene was studied under thermal conditions (Scheme 2).

Scheme 2



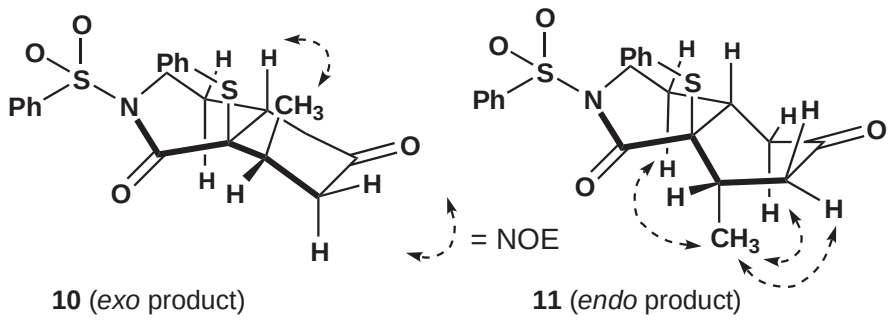


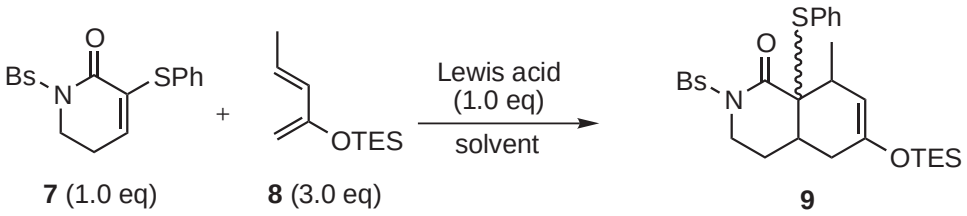
Figure 1. NOE study of 10 and 11.

The D-A adducts were directly converted to a mixture of **10** and **11** in 68% yield by treatment with 10% citric acid. These diastereomeric ketones were separated and the stereochemistry was determined by NMR spectroscopic study. Careful study of the coupling constants in ^{1}H-NMR spectra revealed that both rings in **10** and **11** assumed a boat conformation. Further NOE studies established the stereochemistry of **10** (*exo*-product) and **11** (*endo*-product), as shown in Figure 1.

To develop a chiral version of this D-A reaction, we needed a more stable silyloxydiene, (*E*)-triethylsilyloxy-1,3-pentadiene (**8**),[3g] which was expected to survive under these conditions in the presence of Lewis acid.

Thus, the D-A reaction of the dienophile (**7**) with the diene (**8**) catalyzed by a series of Lewis acids was carried out. The results are summarized in Table 1, which shows that $EtAlCl_2$ was a more effective reagent for this transformation than the other Lewis acids tested. $EtAlCl_2$-promoted cyclization in toluene proceeded regioselectively at -30 ˚C within 30 min to give the expected cycloaddition products (**9**) in almost quantitative yield as a mixture of two diastereomers (entry 2). The use of other catalysts, such as $BF_3 \cdot OEt_2$, $TiCl_2(i\text{PrO})_2$, $Ti(i\text{PrO})_4$, and ZnF_2, and prolonged reaction times promoted substrate decomposition. Other catalysts, such as lanthanide triflates,[4] $Sc(OTf)_3$ and $Yb(OTf)_3$, were tested, but led to decomposition of the diene along with recovery of the dienophile. In contrast to $EtAlCl_2$-catalyzed cycloaddition, no adducts were obtained with methylaluminum dialkoxide, (±)BINOL-Al-Me, while chloroaluminum dialkoxide, (±)BINOL-Al-Cl, gave **9**, but in poor yield.

Table 1. Diels-Alder Reaction of 7 with 8 Using Various Lewis Acids.



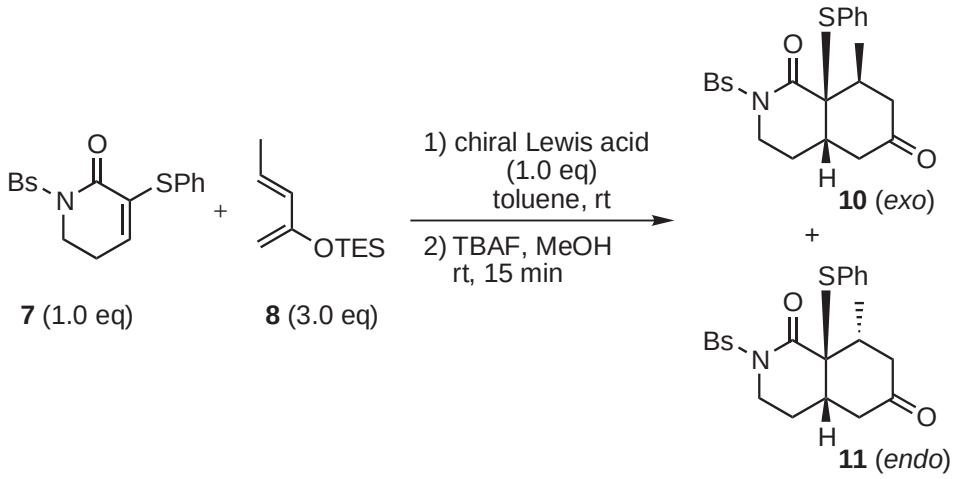
7 (1.0 eq) **8** (3.0 eq) **9**

entry	Lewis acid	solvent	temp.	time (h)	yield (%)
1	$BF_3 \cdot OEt_2$	toluene	rt	24	0
2	$EtAlCl_2$	toluene	-30 °C	0.5	96
3	$TiCl_2(i\text{-PrO})_2$	CH_2Cl_2	rt	34	9
4	$Ti(i\text{-PrO})_4$	CH_2Cl_2	rt	10	0
5	ZnF_2	CH_2Cl_2	rt	18	0
6	$Sc(OTf)_3$	CH_2Cl_2	rt	48	0
7	$Yb(OTf)_3$	CH_2Cl_2	rt	11	4
8	(±)-BINOL-Al-Me	CH_2Cl_2	rt	23	0
9	(±)-BINOL-Al-Cl	CH_2Cl_2	rt	22	8

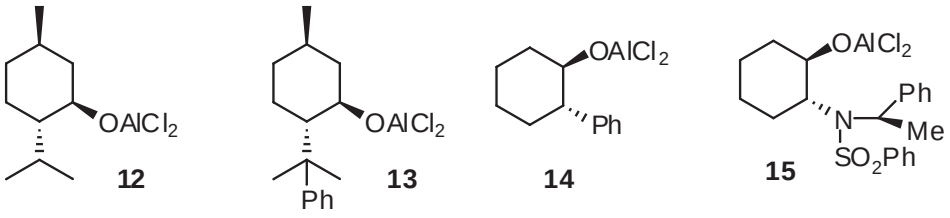
Based on these results, we next focused our attention on the D-A reaction using chiral Lewis acids. Chiral alkoxyaluminum dichlorides, prepared from various chiral alcohols and $EtAlCl_2$, have been reported to be effective chiral catalysts for the enantioselective D-A reaction of cyclopentadiene with typical dienophiles.[2a] Therefore, the D-A reaction of **7** with **8** was carried out under the conditions shown in

Table 2. To a toluene solution of chiral catalyst (**12**), prepared from *l*-menthol and $EtAlCl_2$, were added one equivalent of **7** and three equivalents of **8**. The reaction mixture was stirred for 30 min and then treated with TBAF to give a mixture of *exo* and *endo* cycloadducts (**10** and **11**), respectively, in a ratio of 2.5:1 and 24% yield (entry 1). While these two isomers could be separated by column chromatography, the ratio of **10** and **11** was determined by ^{1}H-NMR spectroscopic analysis, and the optical purity of each enantiomer was determined by HPLC analysis using Chiralpak AS, which showed 44% ee for the *exo* **10** and 39% ee for the *endo* **11**. Prolongation of the reaction time increased the chemical yield up to 71%, but there was no improvement in asymmetric induction (entry 2).

Table 2. Asymmetric Diels-Alder Reaction Using Chiral Alkoxyaluminum Reagents.



entry	chiral Lewis acid	time (h)	yield (%) (2 steps)	*exo* / *endo*	% ee (**10**)	% ee (**11**)
1	**12**	0.5	24	2.5	44	39
2	**12**	3	71	3.0	37	36
3	**13**	6	9	1.6	5	1
4	**14**	5	88	5.3	3	17
5	**15**	24	0	-	-	-



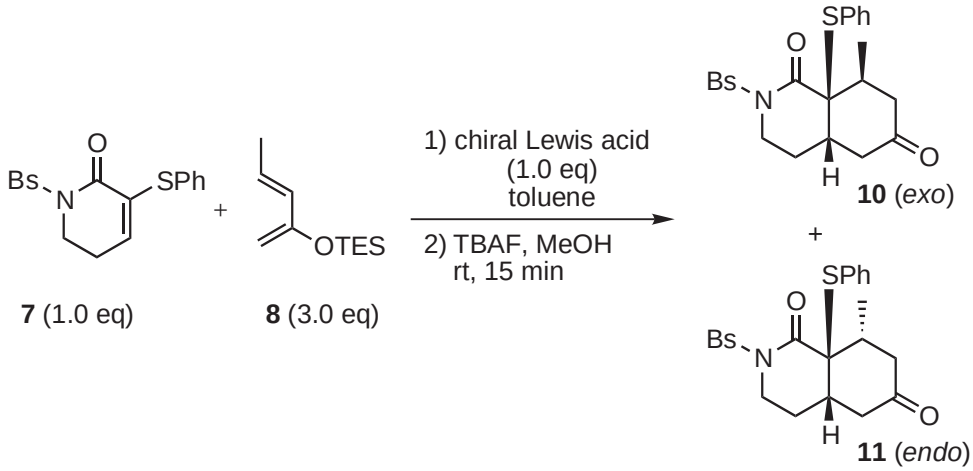
12 **13** **14** **15**

More bulky phenylmenthyloxyaluminum catalyst (**13**) derived from 8-phenylmenthol gave rather poor results (entry 3). However, when the chiral reagent (**14**) was used, the chemical yield increased up to 88%, but with poor selectivity (entry 4). Chiral amino alcohol-derived reagent (**15**)[5] did not catalyze the D-A reaction at all.

We next turned our attention to the D-A reaction with chiral alkylaluminum catalysts such as **16**, **17**, **18**, and **19**, which can be prepared by hydroalumination of α- or β-pinenes, respectively.[6] The results are summarized in Table 3. The D-A reaction of **7** with **8** catalyzed by **16** or **17** proceeded at -30 ˚C, whereas

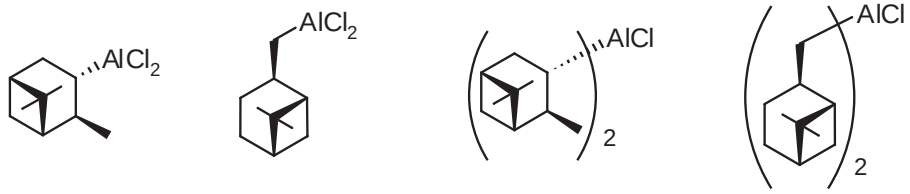
the same reaction using **18** or **19** required a higher temperature, to give the respective adducts in nearly 60% yield. In contrast to our expectation, however, almost no selectivity was observed in any case.

Table 3. Asymmetric Diels-Alder Reaction Using Chiral Alkylaluminum Reagents.



7 (1.0 eq) **8** (3.0 eq)

entry	chiral Lewis acid	temp.	time (h)	yield (%) (2 steps)	*exo* / *endo*	% ee (**10**)	% ee (**11**)
1	**16**	-30 °C	8	60	2.3	2	5
2	**17**	-30 °C	15	59	2.9	1	1
3	**18**	rt	14	61	4.2	1	2
4	**19**	rt	6	67	3.3	0	7



16 **17** **18** **19**

In summary, $EtAlCl_2$ has been shown to be an effective catalyst for the D-A reaction of *N*-benzenesulfonyl-3-phenylthio-5,6-dihydro-2(1*H*)-pyridinone (**7**) and (*E*)–2-triethylsilyloxy-1,3-pentadiene (**8**). An enantioselective D-A reaction of **7** with **8** was developed using the catalyst obtained from *l*-menthol and aluminum dichloride, although the selectivity was still moderate.

EXPERIMENTAL

Diels-Alder reaction of 7 with (*E*)-2-trimethylsilyloxy-1,3-pentadiene.

A mixture of **7** (206 mg, 0.6 mmol) and (*E*)-2-trimethylsilyloxy-1,3-pentadiene (0.6 mL, 3.0 mmol) in toluene (2 mL) was heated to reflux for 4 h. After the mixture was cooled to rt, the solution was diluted with CH_2Cl_2 (40 mL). The solution was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in methanol (5 mL) and treated with 10% citric acid (2 mL) at rt for 10 min. After methanol was removed *in vacuo*, saturated $NaHCO_3$ was added and the product was extracted with CH_2Cl_2 (40 mL). Combined extracts were washed with brine, dried over $MgSO_4$ and concentrated *in*

vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 2:1) to give **10** (59.6 mg, 23%), **11** (114.3 mg, 45%), and recovered **7** (24.7 mg, 12%).

(4a*S,8*S**,8a*S**)-2-benzenesulfonyl-8-methyl-8a-phenylthio-3,4,4a,5,8,8a-hexahydro-2*H*-isoquinoline-1,6-dione (10)**: colorless crystals; mp 201.5-203 °C (AcOEt / *n*-hexane); IR (KBr) 2960, 2930, 1710, 1670, 1550, 1440, 1270, 1170, 1130, 1080, 1060, 750, 680 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.12 (3H, d, J =7.0 Hz), 1.82-1.90 (1H, m), 2.17-2.31 (3H, m), 2.41-2.51 (2H, m), 2.52-2.59 (2H), 4.09-4.13 (2H, m), 6.95 (2H, d, J =7.8 Hz), 7.09 (2H, t, J =7.8 Hz), 7.29 (1H, t, J =7.8 Hz), 7.58 (2H, t, J =7.8 Hz), 7.70 (1H, t, J =7.8 Hz), 8.10 (2H, d, J =7.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 15.36, 23.52, 33.63, 35.09, 43.40, 45.44, 60.46, 128.27, 128.73, 128.88, 129.04, 129.69, 133.78, 136.37, 138.67, 168.42, 207.91; LRMS (EI) m/z: 429 (M^+, 68), 77 (100); HRMS (FAB) m/z calcd for $C_{22}H_{24}NO_4S_2$ (M^++H) 430.1147, found 430.1144.

(4a*S,8*R**,8a*S**)-2-benzenesulfonyl-8-methyl-8a-phenylthio-3,4,4a,5,8,8a-hexahydro-2*H*-isoquinoline-1,6-dione (11)**: colorless crystals; mp 152.5-153.5 °C (AcOEt / *n*-hexane); IR (KBr) 2930, 1705, 1675, 1350, 1165, 1140, 985, 745 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.00 (3H, d, J =7.0 Hz), 1.76-1.86 (1H, m), 2.01-2.07 (1H, m), 2.19 (1H, dd, J = 3.4, 16.0 Hz), 2.26-2.39 (2H, m), 2.47-2.52 (1H, m), 2.81 (1H, dd, J = 7.1, 15.1 Hz), 3.12 (1H, dd, J = 5.8, 16.0 Hz), 3.46 (1H, ddd, J = 3.4, 11.5, 12.7 Hz), 4.30 (1H, dt, J = 4.1, 12.7 Hz), 7.10 (2H, d, J = 8.2 Hz), 7.19 (2H, t, J = 7.7 Hz), 7.36 (1H, t, J = 7.5 Hz), 7.59 (2H, t, J = 7.7 Hz), 7.70 (1H, t, J = 7.4 Hz), 8.09 (2H, d, J = 8.3 Hz); LRMS (EI) m/z 429 (M^+, 62), 320 (100); HRMS (FAB) m/z calcd for $C_{22}H_{24}NO_4S_2$ (M^++H) 430.1147, found 430.1141.

Lewis acid-mediated Diels-Alder reaction of 7 with 8 (Table 1, entry 2).

$EtAlCl_2$ (0.96 M *n*-hexane solution, 1.3 mL, 1.2 mmol) was added to a solution of dienophile (**7**) (406 mg, 1.2 mmol) in toluene (40 mL), and the solution was cooled to -30 °C. Diene (**8**) (700 mg, 3.6 mmol) was then added and the mixture was stirred at the same temperature. After 30 min, disappearance of **7** was checked by TLC analysis, and the reaction mixture was warmed to rt. The reaction was quenched with H_2O (30 mL) and extracted with AcOEt (40 mL x 3). Combined organic layers were washed with brine and dried over $MgSO_4$. Concentration *in vacuo* gave a yellow residue which was purified by column chromatography on silica gel (*n*-hexane/AcOEt = 8 / 1) to give **9** (615 mg, 96%).

2-Benzenesulfonyl-8-methyl-8a-phenylthio-6-triethylsilyloxy-3,4,4a,5,8,8a-hexahydro-2*H*-isoquinolin-1-one (9): a mixture of diastereo isomer, ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.58-0.68 (9H, m), 0.90-1.00 (6H, m), 0.15 (3H, d, J = 7.0 Hz), 1.58-1.68 (1H, m), 1.79 (1H, brd, J = 17.6 Hz), 2.45-2.56 (1H, m), 2.63-2.75 (1H, m), 3.34-3.45 (1H, m), 3.58-3.68 (1H, m), 4.16-4.26 (1H, m), 4.62 (0.8H, brs), 4.78 (0.2H, brs), 6.95-7.05 (3H, m), 7.10 (1H, d, J = 4.4 Hz), 7.26 (1H, tt, J = 1.2, 7.7 Hz), 7.54-7.60 (2H, t, J = 7.8 Hz), 7.65-7.70 (1H, m), 8.07-8.12 (2H, dd, J = 1.3, 8.3 Hz).

Conversion of 9 to 10 and 11.

To a solution of **9** (615 mg, 1.1 mmol) in MeOH (12 mL) was added TBAF (1.5 mL of 1.0 M THF solution, 1.5 mmol), and the mixture was stirred for 15 min at rt. The reaction was quenched with H_2O

(15 mL) and extracted with CH_2Cl_2. Combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification of the yellow residue by silica gel column chromatography on silica gel (15 g, AcOEt/*n*-hexane = 1 : 4) gave **10** and **11** (473 mg, 97%) as colorless solid. The ratio of **10** and **11** was determined, based on the ^{1}H-NMR spectrum of the residue, to be 2.5 by comparing the methyl peaks at δ 1.00 and 1.12 ppm.

Asymmetric Diels-Alder reaction of 7 with 8 using chiral alkoxyaluminum dichloride (Table 2, entry 2).

l-Menthol (157 mg, 1.0 mmol) was dissolved in toluene (15 mL) and the solution was cooled to -78 °C. $EtAlCl_2$ (0.96 M *n*-hexane solution, 1.0 mL, 0.96 mmol) was added to the solution. The mixture was allowed to warm to ambient temperature and stirred for 30 min. A solution of **1** (312 mg, 0.9 mmol) in toluene (18 mL) and **2** (538 mg, 2.7 mmol) were added successively and the mixture was stirred for 3 h at rt. After the work-up described above, the crude residue was dissolved in MeOH (10 mL). TBAF (1 M THF solution, 1.2 mL, 1.2 mmol) was added to the solution and the mixture was stirred for 15 min at rt. The reaction was quenched with H_2O (15 mL) and the product was extracted with CH_2Cl_2 (20 mL x 3). Combined organic layers were washed with brine and dried over $MgSO_4$. Concentration *in vacuo* gave a yellow residue. Column chromatography on silica gel (*n*-hexane/AcOEt = 4:1) gave **10** and **11** (275 mg, 71%, **10**:**11**=3:1). The optical purity of **10** and **11** was determined by HPLC analysis using Chiralpak AS.

10 (*exo*-product): 37% ee [$[\alpha]_D^{23}$ +12.5° (*c* 0.5, $CHCl_3$, for 44% ee); HPLC (Chiralpak AS, *n*-hexane/EtOH = 50/50, flow rate = 1.0 mL/min): t_R = 6.4 min (minor isomer), t_R = 8.3 min (major isomer)].

11 (*endo*-product): 36% ee [HPLC (Chiralpak AS, *n*-hexane/EtOH = 50/50, flow rate = 1.0 mL/min): t_R = 14.5 min (major), t_R = 18.3 min (minor isomer)].

Preparation of chiral alkylaluminum dichloride (18 or 19).

$LiAlH_4$ (9.7 mg, 0.25 mmol) was added to a solution of $AlCl_3$ (100 mg, 0.75 mmol) in Et_2O (0.5 mL) at 0 °C and the mixture was stirred for 15 min under the same conditions. Catalytic amounts of Et_3B (1.0 M *n*-hexane solution, 0.3 mL, 0.3 mmol) and α- or β-pinene (204 mg, 1.5 mmol) were added successively and the mixture was stirred for 2 h at ambient temperature. Et_2O was then removed *in vacuo* and the residue was dissolved in toluene. Freshly prepared chiral alkylaluminum dichloride in toluene (5 mL) was used for the Diels-Alder reaction according to the procedure described above.

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