

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

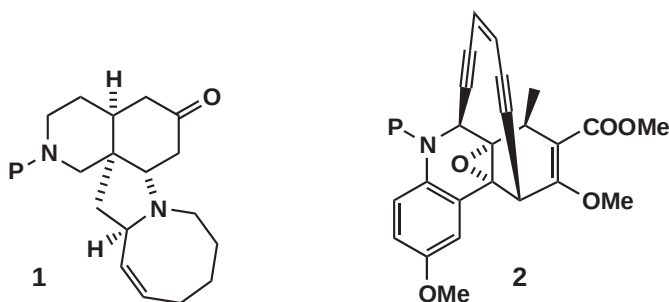
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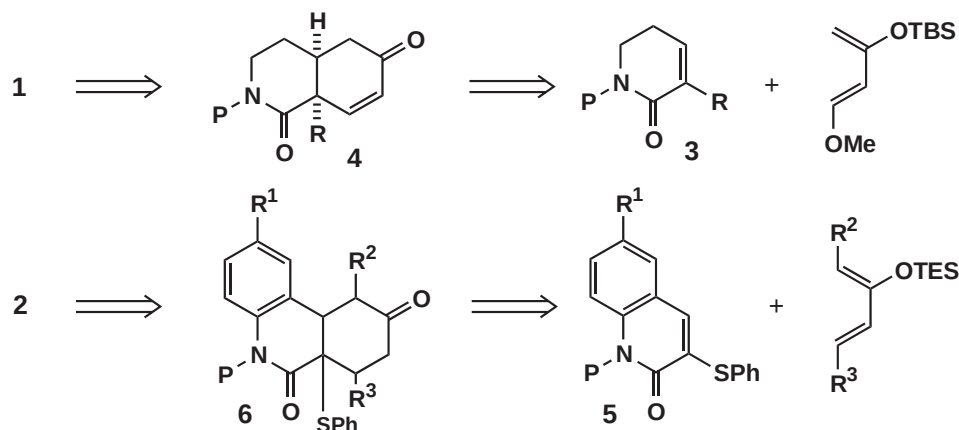
Abstract - The asymmetric Diels-Alder reaction of dihydropyridin-2-one with 2-triethylsilyloxy-1,3-pentadiene was studied in the presence of chiral aluminum reagents. Menthylaluminum dichloride was the most effective catalyst and gave a hexahydroisoquinolin-2-one derivative in 44% ee as an *endo*-product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



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

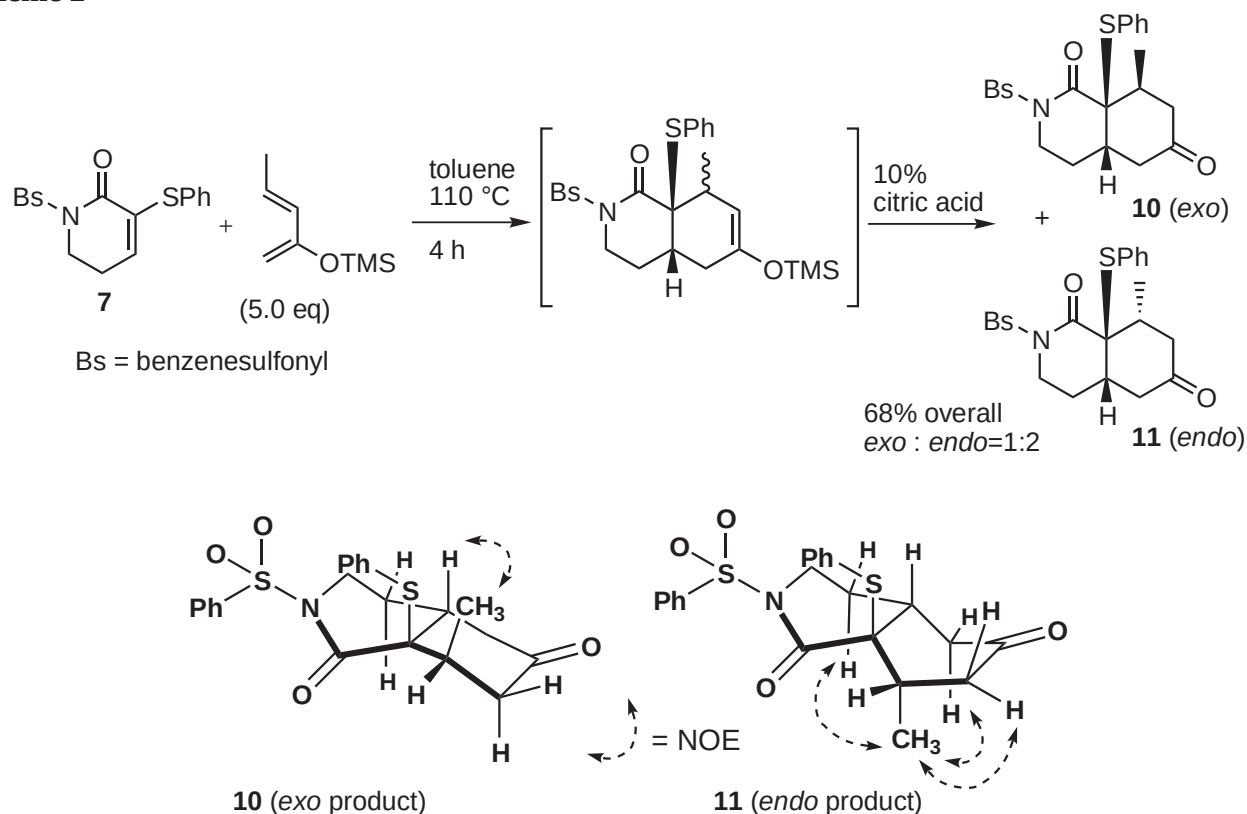


Figure 1. NOE study of **10** and **11**.

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 ^1H -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 $-30\text{ }^\circ\text{C}$ 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 $\text{BF}_3 \cdot \text{OEt}_2$, $\text{TiCl}_2(i\text{PrO})_2$, $\text{Ti}(i\text{PrO})_4$, and ZnF_2 , and prolonged reaction times promoted substrate decomposition. Other catalysts, such as lanthanide triflates,⁴ $\text{Sc}(\text{OTf})_3$ and $\text{Yb}(\text{OTf})_3$, 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, ($\pm$)-BINOL-Al-Me, while chloroaluminum dialkoxide, ($\pm$)-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) $\xrightarrow[\text{solvent}]{\text{Lewis acid (1.0 eq)}}$ 9

entry	Lewis acid	solvent	temp.	time (h)	yield (%)
1	$\text{BF}_3 \cdot \text{OEt}_2$	toluene	rt	24	0
2	EtAlCl_2	toluene	$-30\text{ }^\circ\text{C}$	0.5	96
3	$\text{TiCl}_2(i\text{-PrO})_2$	CH_2Cl_2	rt	34	9
4	$\text{Ti}(i\text{-PrO})_4$	CH_2Cl_2	rt	10	0
5	ZnF_2	CH_2Cl_2	rt	18	0
6	$\text{Sc}(\text{OTf})_3$	CH_2Cl_2	rt	48	0
7	$\text{Yb}(\text{OTf})_3$	CH_2Cl_2	rt	11	4
8	($\pm$)-BINOL-Al-Me	CH_2Cl_2	rt	23	0
9	($\pm$)-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 EtAlCl₂, 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 ¹H-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.

Reaction scheme: 7 (1.0 eq) + 8 (3.0 eq) $\xrightarrow[2) \text{ TBAF, MeOH, rt, 15 min}]{1) \text{ chiral Lewis acid (1.0 eq), toluene, rt}}$ **10** (*exo*) + **11** (*endo*)

entry	chiral Lewis acid	time (h)	yield (%) (2 steps)	<i>exo</i> / <i>endo</i>	% 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	-	-	-

Structures of catalysts: **12** (menthylaluminum dichloride), **13** (1-phenylmenthylaluminum dichloride), **14** (1-phenyl-2-(di-chloroaluminumoxy)cyclohexane), and **15** (1-(2-phenylsulfonylphenylamino)cyclohexylaluminum dichloride).

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.

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

In summary, EtAlCl₂ 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-trimethylsilyloxy-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 CH₂Cl₂ (40 mL). The solution was washed with brine, dried over MgSO₄ 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 NaHCO₃ was added and the product was extracted with CH₂Cl₂ (40 mL). Combined extracts were washed with brine, dried over MgSO₄ 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%).

(4aS*,8S*,8aS*)-2-benzenesulfonyl-8-methyl-8a-phenylthio-3,4,4a,5,8,8a-hexahydro-2H-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; ¹H-NMR (400 MHz, CDCl₃) 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); ¹³C-NMR (100 MHz, CDCl₃) 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 C₂₂H₂₄NO₄S₂ (M⁺+H) 430.1147, found 430.1144.

(4aS*,8R*,8aS*)-2-benzenesulfonyl-8-methyl-8a-phenylthio-3,4,4a,5,8,8a-hexahydro-2H-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; ¹H-NMR (400 MHz, CDCl₃) 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 C₂₂H₂₄NO₄S₂ (M⁺+H) 430.1147, found 430.1141.

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

EtAlCl₂ (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 H₂O (30 mL) and extracted with AcOEt (40 mL x 3). Combined organic layers were washed with brine and dried over MgSO₄. 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-2H-isoquinolin-1-one (9): a mixture of diastereo isomer, ¹H-NMR (400 MHz, CDCl₃) 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 H₂O

(15 mL) and extracted with CH₂Cl₂. Combined organic layers were washed with brine, dried over MgSO₄, 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 ¹H-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. EtAlCl₂ (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 H₂O (15 mL) and the product was extracted with CH₂Cl₂ (20 mL x 3). Combined organic layers were washed with brine and dried over MgSO₄. 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 [[α]_D²³ +12.5° (*c* 0.5, CHCl₃, 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**).

LiAlH₄ (9.7 mg, 0.25 mmol) was added to a solution of AlCl₃ (100 mg, 0.75 mmol) in Et₂O (0.5 mL) at 0 °C and the mixture was stirred for 15 min under the same conditions. Catalytic amounts of Et₃B (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. Et₂O 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.

ACKNOWLEDGMENTS

We thank the Ministry of Education, Culture, Sports, Science and Technology, and the Uehara Memorial Foundation for supporting our research program. We also thank Ms Hara at the Analytical Center, Chiba University, for performing mass spectroscopy.

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