an almost exact match.[18] The assigned stereochemistry was subsequently verified by cyclization of the C_7 hydroxyl group on to the $C_{10,11}$ alkene in **22** by an intramolecular oxymercuration using $Hg(OCOCF_3)_2$ in THF, followed by treatment with aqueous KBr (81%).[19] The resulting cis-fused bicyclic mercurial **23** was sufficiently stable to isolate and characterize, and ^1H NMR NOE difference experiments in CD_3CN showed that the methine protons H_7, H_9, and H_{10} were all on the same face. In contrast, the corresponding C_7 epimeric mercurial, prepared in a similar fashion from the minor aldol adduct **20**, did not show these enhancements. This proved that the major aldol isomer had the correct C_7 stereochemistry for the target macrolides. Finally, protection of the hydroxyl group in **22** as the TBS ether (^{t}BuMe$_2$SiOTf, 2,6-lutidine, CH_2Cl_2, -78 °C; 93%) then gave the fully protected C_1–C_{15} segment **8** of swinholide A and scytophycin C. Additionally, the aldehyde **19** was oxidized with sodium chlorite[20] (NaH_2PO_4, Me_2C=CHMe, ^{t}BuOH) to the corresponding *E* unsaturated acid which, after esterification with CH_2N_2 and TBS protection, gave **9**, a fully protected C_1–C_{13} segment of misakinolide A.

In summary, we have achieved a short and highly diastereoselective synthesis (8 steps, 87% overall ds) of two related racemic intermediates for the cytotoxic macrolides **1**–**5**. Key steps are (i) the construction of the dihydropyrone **12** using our recently developed boron aldol–cyclization sequence,[7] (ii) the highly diastereoselective, carbon Ferrier rearrangement of **13** to give the aldehyde **16** directly, followed by (iii) a novel, vinylogous Mukaiyama aldol reaction with the silyl dienol ether **18** selectively giving the enal **19**, with stereocontrol at C_7 arising from a *nonchelation* pathway. Studies towards their asymmetric synthesis, using chiral boron reagents in step (i),[7] and further elaboration into swinholide A, misakinolide A, and scytophycin C are underway.

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Registry No. **1**, 95927-67-6; **3**, 105694-30-2; **4**, 105304-96-9; **8**, 140902-85-8; **9**, 140902-87-0; **10**, 4643-20-3; **11**, 140902-76-7; **12**, 140902-77-8; **13**, 140902-79-0; **13** (alcohol), 140902-78-9; **14**, 140902-81-4; **15**, 140902-82-5; **16**, 140902-80-3; **18**, 98670-68-9; **19**, 140902-83-6; **20**, 141041-72-7; **22**, 140902-84-7; 7-epi-**22**, 141042-59-3; **23**, 140902-86-9; 7-epi-**23**, 141041-73-8; $PhCH_2O(CH_2)_2CHO$, 19790-60-4; TBSOCH=CH_2, 66031-93-4; TBSOC(OMe)=CH_2, 77086-38-5; trimethyl phosphonoacetate, 5927-18-4; swinholide A, 95927-67-6; swinholide C, 105694-30-2; misakinolide A, 105304-96-9.

Supplementary Material Available: Experimental procedures and characterization data for all new compounds (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(18) For the major isomer **22**, the ^{13}C chemical shifts in $CDCl_3$ agreed within ±1.1 ppm, while the ^1H NMR chemical shifts and multiplicities gave a close fit. In contrast, the C_7 epimer showed significant differences, particularly in the ^{13}C NMR spectrum, e.g., the carbon resonances for C_7 and C_9 differed by ca. 5 ppm relative to those in the monomeric seco acid (methyl ester) of swinholide A.[2c]

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Asymmetric Aza-Diels–Alder Reaction Mediated by Chiral Boron Reagent

Kouji Hattori and Hisashi Yamamoto*

Department of Applied Chemistry, Nagoya University, Chikusa, Nagoya 464-01, Japan

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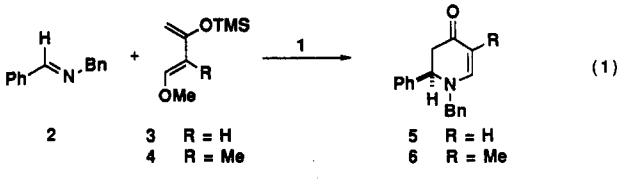
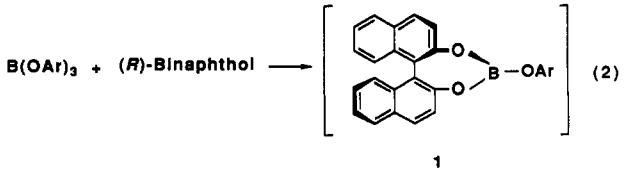
Summary: An asymmetric aza-Diels–Alder reaction of an imines mediated by an in situ generated chiral boron complex is described. The method is successful with several aldimines and affords products of up to 90% ee.

The development of chiral Lewis acid catalysts for carbon–carbon bond forming reactions is one of the most challenging and formidable goals in organic synthesis.[1] Unfortunately, however, the catalytic asymmetric reaction with *imine*, which can open up a wide variety of possibilities for the synthesis of natural products of the alkaloid family,[2] has never been developed to a useful level. In this paper, we wish to describe an asymmetric aza-Diels–Alder reaction[3] of an imine (eq 1) mediated by an in situ generated chiral boron complex of type **1**.[4] The method is successful with several aldimines and affords products of high enantiomeric purity.



2 **3** R = H, **4** R = Me **5** R = H, **6** R = Me (1)



1 (2)

The chiral boron complex was conveniently prepared in situ simply by mixing a 1:1 molar ratio of optically active binaphthol and triphenyl borate[5] in CH_2Cl_2 at ambient

(1) Review: (a) Morrison, J. D. *Asymmetric Synthesis*; Academic Press: New York, 1984; Vol. 3B. (b) Bosnich, B. *Asymmetric Catalysis*; Martinus Nijhoff: Dordrecht, 1986. (c) Narasaka, K. *Synthesis* **1991**, *1*. For recent efforts from our laboratories, see: Furuta, K.; Mouri, M.; Yamamoto, H. *Synlett* **1991**, *561* and references cited therein.

(2) Review: Boger, D. L.; Weinreb, S. M. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic Press, New York, 1987. For more recent work, see: Comins, D. L.; Goehring, R. R.; Joseph, S. P.; O'Connor, S. *J. Org. Chem.* **1990**, *55*, 2574 and references cited therein.

(3) Reports on diastereoselective Diels–Alder reaction of chiral imines. (a) Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768. (b) Midland, M. M.; McLoughlin, J. I. *Tetrahedron Lett.* **1988**, *29*, 4653. (c) Pfrengle, W.; Kunz, H. *J. Org. Chem.* **1989**, *54*, 4261. (d) Waldmann, H.; Braun, M.; Dräger, M. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1468. (e) Midland, M. M.; Koops, R. W. *J. Org. Chem.* **1992**, *57*, 1158.

(4) Although **1** is clearly the most probable structure, we cannot exclude other possible structures for the active species. For a similar borane catalyst in recent literature, see: (a) Kelly, T. R.; Whiting, A.; Chandrakumar, N. S. *J. Am. Chem. Soc.*, **1986**, *108*, 3510. (b) Gross, U.-M.; Bartels, M.; Kaufmann, D. *J. Organomet. Chem.* **1988**, *344*, 277. (c) Kaufmann, D.; Boese, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 545.

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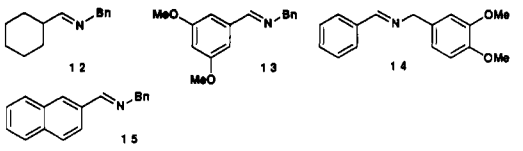
Table I. Asymmetric Aza-Diels–Alder Reaction[a]

entry	imine[b]	diene	catalyst Ar of $B(OAr)_3$	yield[c] (%)	% ee[d]
1	2	3	phenyl	75	82
2			phenyl[e]	70	85
3			2-tolyl	76	84
4			3,5-xylyl	75	86
5			3,5-xylyl[f]	82	86
6		4	phenyl	72	81
7			3,5-xylyl	66	87
8	7	3	phenyl	71	90
9			phenyl[f]	68	90
10	12	3	phenyl	45	76
11			3,5-xylyl	49	72
12		4	phenyl	35	78
13			2-tolyl	31	81
14	13	3	phenyl	89	74
15	14	3	phenyl	73	85
16	15	3	phenyl	83	84

[a] Unless otherwise specified, reactions were carried out in dichloromethane using 1 equiv of the catalyst derived from (*R*)-binaphthol and 1.2 equiv of the diene at −78 °C for 5 h. [b] Structures **12–15** are given below. [c] Yield of products after isolation by column chromatography. [d] The % ee was determined by HPLC using a Chiracel OD or AD column. [e] The reaction was carried out at −100 °C for 5 h. [f] (*S*)-Binaphthol was used.



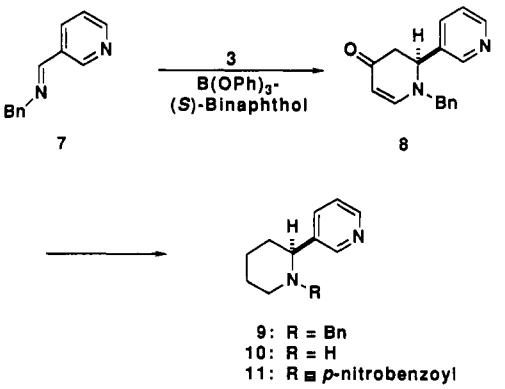
12 13 14

15

temperature for 1 h. The aza-Diels–Alder reaction of an aldimine with Danishefsky diene was promoted by this catalyst solution in the presence of 4-Å molecular sieves at −78 °C for several hours.[6] The product's enantiomer ratio was determined by HPLC and the absolute configuration was ascertained after converting it to the known 2(*R*)-phenylpiperidine.[7] Some examples are listed in Table I.

The new chiral boron reagent disclosed herein offers the following advantages. (1) Both chiral binaphthol and triphenyl borate are commercially available, and the catalyst can be easily generated. Furthermore, no difficult isolation procedure is required and recovery of binaphthol is quantitative. (2) Either the *R* or *S* form of the products may be synthesized since the required reagents are readily accessible in both enantiomeric forms (entries 4,5 and 8,9). (3) The choice of solvent is crucial for high optical yields; for example, the reaction of entry 1 was found to be much more efficient in methylene chloride than either tetrahydrofuran or propionitrile (~20% ee). (4) The use of structurally more bulky aryloxy reagent only slightly improved the optical yield.

Scheme I



The practicability of the new method is illustrated by the synthesis of (−)-anabasine, an alkaloid derived from nicotinic acid (Scheme I).[8] A mixture of 3-pyridylaldimine 7 and diene 3 was treated at −78 °C with the chiral boron catalyst derived from (*S*)-binaphthol to obtain dihydropyridone 8 in 68% yield and 90% ee. Purification by trituration of the resulting solid with ether provided adduct 8, mp 92 °C, which was essentially optically pure by HPLC analysis. Reduction of adduct 8 with L-selectride at −78 °C quantitatively afforded the conjugate reduction product, which was converted to the corresponding anabasine derivative in 68% overall yield from 8 by tosylhydrazone formation followed by sodium cyanoborohydride reduction. Removal of the benzyl group by hydrogenolysis over palladium catalyst gave (−)-anabasine in 72% yield: $[\alpha]_D^{24}$ −79.2° (*c* 0.5, methanol). The absolute configuration was confirmed by its transformation to *p*-nitrobenzoate 11. $[\alpha]_D^{24}$ −130.4° (*c* 0.4, methanol) (lit. $[\alpha]_D^{15}$ −130.0° (*c* 3.0, methanol)).[8]

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Supplementary Material Available: Experimental procedures and spectral data for all compounds (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(5) Purchased from Wako Pure Chemical Industries Ltd. and Tokyo Kasei Co. Ltd.

(6) A typical experimental procedure is exemplified by entry 1. To a suspension of powdered 4-Å molecular sieves (1.0 g) in CH_2Cl_2 (10 mL) were added (*R*)-binaphthol (100 mg) and $B(OPh)_3$ (101 mg) at room temperature under argon. After being stirred for 1 h, the mixture was cooled to 0 °C, and then a solution of imine **2** (68 mg) in CH_2Cl_2 (1 mL) was added. After being stirred for 10 min at the same temperature, the mixture was cooled to −78 °C, and a solution of diene **3** (0.084 mL) in CH_2Cl_2 (1 mL) was added dropwise. After being stirred for 5 h, the solution was washed with water and saturated $NaHCO_3$ and then dried over $MgSO_4$. Evaporation of solvent and purification by column chromatography on silica gel (1:2 hexane/AcOEt) gave dehydropiperidinone **5** as a colorless liquid (69 mg, 75%): $[\alpha]_D^{24}$ −4.7° (*c* 1, $CHCl_3$). The product was transformed into 2(*R*)-phenylpiperidine by treatment with L-Selectride followed by Wolff–Kishner reduction and removal of the protecting group by hydrogenolysis over palladium.

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