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Communications

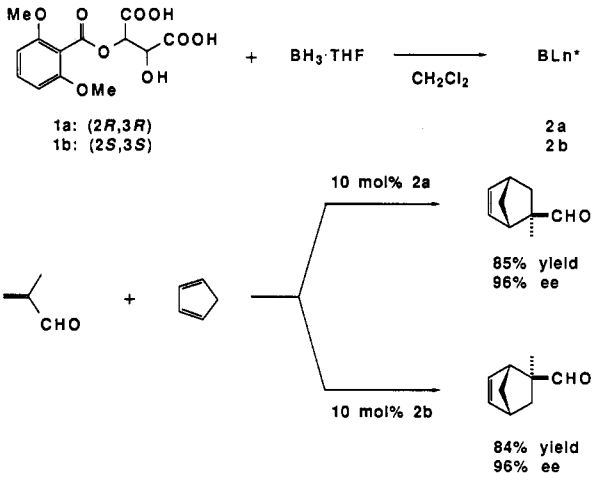
Chiral (Acyloxy)borane (CAB): A Powerful and Practical Catalyst for Asymmetric Diels–Alder Reactions

Summary: Chiral (acyloxy)borane complexes catalyze the Diels–Alder reaction of α,β-unsaturated aldehydes to bring about remarkable induction.

Sir: The Diels–Alder reaction may be the most useful and reliable of known structural transformations in organic synthesis.[1] As shown in Scheme I, we have discovered an efficient catalytic asymmetric Diels–Alder reaction of α,β-unsaturated aldehydes, which is far more selective and practical than any of the previously described methods for this type of asymmetric transformation.[2] The process realizes the excellent introduction of chirality into synthetically important intermediates starting from simple materials induced by only a catalytic amount of chiral source.

In a previous paper, we described the (acyloxy)borane complexes, which are highly effective for the activation of α,β-unsaturated carboxylic acids in the Diels–Alder reaction and also for the introduction of chirality into adducts by a catalytic process in its asymmetric version.[3] In this process, the acid moiety of (acyloxy)borane is activated by the electronegative nature of the trivalent boron atom. Conversely, however, the boron atom of (acyloxy)borane itself should be activated by the electron-withdrawing acyloxy groups. From this point of view, it may be worth considering whether the (acyloxy)borane derivatives have Lewis acidity to catalyze certain reactions as do boron trifluoride or aluminum reagents.[4] Actually, acetoxyborane is known to catalyze the Diels–Alder reaction of naphthoquinone derivatives.[5] We therefore turned to the

Scheme I



(1) For example, see: (a) Desimoni, G.; Tacconi, G.; Barco, A.; Pollini, G. P. *Natural Products Synthesis Through Pericyclic Reactions*; American Chemical Society: Washington, DC, 1983. (b) Carruthers, W. *Some Modern Methods of Organic Synthesis*; Cambridge University Press: Cambridge, 1986.

(2) For the asymmetric Diels–Alder reaction of chiral dienophiles, see: (a) Paquette, L. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1984, Vol. 3. (b) Helmchen, G.; Karge, R.; Weetman, J. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer-Verlag: Berlin, 1986, Vol. 4. (c) Bosnich, B. *Asymmetric Catalysis*; Martinus Nijhoff Publishers: Dordrecht, 1986. (d) Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969. For the catalytic process using chiral Lewis acid: (e) Hashimoto, S.; Komeshima, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1979**, 437. (f) Bednarski, M.; Maring, C.; Danishefsky, S. *Tetrahedron Lett.* **1983**, *24*, 3451. (g) Kelly, T. R.; Whiting, A.; Chandrakumar, N. S. *J. Am. Chem. Soc.* **1986**, *108*, 3510. (h) Narasaka, K.; Inoue, M.; Okada, N. *Chem. Lett.* **1986**, 1109. (i) Maruoka, K.; Sakurai, M.; Fujiwara, J.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 4895. (j) Narasaka, K.; Inoue, M.; Yamada, T. *Chem. Lett.* **1986**, 1967. (k) Bir, G.; Kaufmann, D. *Tetrahedron Lett.* **1987**, *28*, 777. (l) Quimpere, M.; Jankowski, K. *J. Chem. Soc., Chem. Commun.* **1987**, 676. (m) Chapuis, C.; Jarczak, J. *Helv. Chim. Acta* **1987**, *70*, 436. (n) Seebach, D.; Beck, A. K.; Imwinkelried, R.; Roggo, S.; Wonnacott, A. *Helv. Chim. Acta* **1987**, *70*, 954. (o) Takemura, H.; Komeshima, N.; Takahashi, I.; Hashimoto, S.; Ikota, N.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1987**, *28*, 5687. (p) Narasaka, K.; Inoue, M.; Yamada, T.; Sugimori, J.; Iwasawa, N. *Chem. Lett.* **1987**, 2409. (q) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310.

(3) Furuta, K.; Miwa, Y.; Iwanaga, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 6254.

(4) For example, see: Fieser, M.; Fieser, L. F. *Reagents for Organic Synthesis*; John Wiley & Sons: New York, 1967–1986; Vol. 1–12.

(5) (a) Kelly, T. R.; Montury, M. *Tetrahedron Lett.* **1978**, 4311. (b) Russell, R. A.; Collin, G. J.; Sterns, M.; Warrener, R. N. *Tetrahedron Lett.* **1979**, 4229. (c) Kelly, T. R.; Ananthasubramanian, L.; Borah, K.; Gillard, J. W.; Goerner, R. N., Jr.; King, P. F.; Lyding, J. M.; Tsang, W.-G.; Vaya, J. *Tetrahedron* **1984**, *40*, 4569. See also ref 2g.

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Table I. Asymmetric Diels–Alder Reaction of α,β-Unsaturated Aldehydes Catalyzed by Chiral (Acyloxy)borane[a]

dienophile	diene	temp, °C	time, h	yield,[b] %	isomers,[c] endo/exo	ee,[d] %
		−78	6	85	11/89	96[e]
		−78	6	84[f]	10/90	96[g]
		−78	7.5	61		97
		−78	11	38	97/3[h]	93
		−40	10.5	65	98/2[h]	91
		−20	10.5	40	93/7	82
		−78	14.5	90	88/12	84[e]
		−78	10	46	>99/1	80[i]
		−78	10.5	53		84[j]
		−78	10	53	90/10	2[k]
		−78	9.5	91	3/97	90

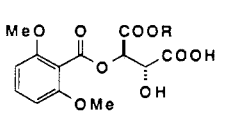
[a] All reactions were carried out on 1–2-mmol scale of dienophiles in the presence of 10 mol % boron catalyst. Unless otherwise specified, **1a** was used as a chiral ligand. [b] Isolated yields. [c] Determined by GLC and ^{1}H NMR analyses. The stereochemical assignments were based on ^{1}H NMR analysis and further confirmed by the transformation of adducts to carboxylic acids followed by iodolactonization. [d] Unless otherwise specified, the ee values were determined by GLC analysis after conversion to the chiral acetals.[7] The figures correspond to the major isomer of the reactions. [e] The absolute configuration was determined to be *R* by the comparison of the sign of optical rotation.[2e] [f] **1b** was used as a chiral ligand. [g] Determined to be *S* configuration based on the optical rotation. [h] Ratio of regioisomers. The major isomer was assigned to the 1,4-adduct based on ^{1}H NMR analysis. [i] Determined to be *R* configuration based on the optical rotation of corresponding alcohol.[8] [j] Determined by ^{1}H NMR analysis (500 MHz) of the chiral acetal. [k] The optical yield of minor exo isomer was determined to be 66%.

possibility of using our chiral (acyloxy)borane (CAB) complex as a Lewis acid catalyst for the introduction of chirality. Here, we disclose that the chiral (acyloxy)borane complex derived from tartaric acid and borane also catalyzes the Diels–Alder reaction of simple achiral α,β-unsaturated aldehydes to bring about remarkable asymmetric induction in a truly catalytic manner.

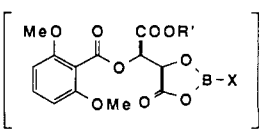
The following experiment is typical: To a stirred suspension of 63 mg (0.2 mmol) of monoacylated tartaric acid **1a**[3] in 2 mL of dichloromethane under Ar was added 0.2 mmol of BH_3·THF (1 M solution in THF) at 0 °C. After 15 min, during which the reaction mixture turned to a clear solution with the evolution of a hydrogen gas, 166 μL of methacrolein (2.0 mmol, 10-fold excess to borane complex) and 488 μL of cyclopentadiene (6.0 mmol) were successively introduced to this catalyst solution at −78 °C, and the mixture was stirred at the same temperature for 3 h. Diels–Alder adduct was isolated after the usual workup in 85% yield (endo/exo = 11/89) and was shown to be 96% ee (major exo isomer) with *R* configuration.[6] Analogously, the use of **1b**, derived from an unnatural form of tartaric acid, as a chiral ligand resulted in the formation of *S* isomer (84% yield; endo/exo = 10/90; 96% ee).

This process is quite general and is applicable to various dienes and aldehydes with high enantioselectivity. Some examples are listed in Table I.

A striking feature of the process can be seen from the table. The α-substituent on the dienophile increases the enantioselectivity (acrolein vs methacrolein), while β-substitution dramatically decreases the selectivity (crotonaldehyde). In case of a substrate having substituents at both α- and β-positions, high enantioselectivity was observed; thus the α-substituent effect overcomes the β. These trends apparently relate to the structure of the transition state of this reaction. From a mechanistic standpoint the actual structures of the chiral boron catalyst and its complex with dienophile are of considerable interest. In a series of investigations using several kinds of tartaric acid derivatives, we found out that the boron atom might form a five-membered ring structure with α-hydroxy acid moiety of tartaric acid, and the remaining carboxyl group might not bond to the boron atom. Thus, in the reaction of **1a** with BH_3·THF, the evolution of only 2.2–2.3 equiv of hydrogen was observed under the present reaction conditions (0 °C, 15 min). Furthermore, the tartaric acid derivative of type A revealed comparable enantioselectivity to **1a**. Work is now in progress to clarify the reaction mechanism.



A: R=Alkyl



R'=H or Alkyl
X =H or Acyloxy

(6) The enantiomeric excess of the Diels–Alder adduct was determined by GLC analysis after conversion to chiral acetal (see ref 7). The exo adduct (aldehyde) also showed a specific rotation ($[\alpha]_D$) of −22.3° (*c* = 4.82, ethanol), which corresponds to 96% optical purity with *R* configuration.[2e]

(7) **Method A** (procedure for nonepimerizable adducts): A mixture of the adduct (10–20 mg), 2(*R*),4(*R*)-(−)-pentanediol (1.5 equiv), triethyl orthoformate (1.1 equiv), and *p*-toluenesulfonic acid monohydrate (1–2 mg) in dry benzene (1 mL) was stirred at room temperature for several hours (TLC check). **Method B** (procedure for epimerizable adducts): A solution of the adduct (10–20 mg) and 2(*R*),4(*R*)-(−)-pentanediol (1.5 equiv) in acetonitrile (1 mL) was stirred at ambient temperature overnight in the presence of pyridinium *p*-toluenesulfonate (4–5 mg).

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The practicability of this new method is one of its more attractive aspects: (1) chiral sources (tartaric acids) are easily obtainable in both enantiomeric forms at low cost, and thus either of the enantiomers can be synthesized with high enantiomeric excess (Scheme I); (2) simple α,β-unsaturated aldehydes can be used without any derivatizations, making further transformation of the adduct easy; (3) only a catalytic amount (10 mol % or less) of chiral Lewis acid is needed; (4) the operation is simple without any complexity in the workup or isolation procedure so that excellent reproducibility is available.

The present enantioselective, catalytic C–C bond forming process is discriminating to a degree barely rivaled by any other stoichiometric process. Further application of the CAB catalyst as chiral Lewis acid to other reactions is now under investigation.

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Kyoji Furuta, Sadahiro Shimizu
Yoshikazu Miwa, Hisashi Yamamoto*
Department of Applied Chemistry
Nagoya University
Nagoya 464-01, Japan
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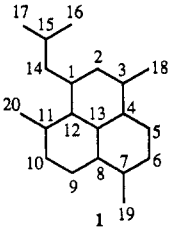
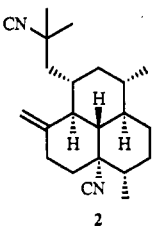
Total Synthesis of (±)-8,15-Diisocyano-11(20)-amphilectene

Summary: With 2-(methoxycarbonyl)-3-methylcyclohexanone and (*E*)-1-(*tert*-butyldimethylsiloxy)-6-iodo-3-(trimethylstannyl)-2-hexene as starting materials, the structurally novel, antimicrobial diterpenoid (±)-8,15-diisocyano-11(20)-amphilectene (**2**) was synthesized in 20 steps.

Sir: The structurally novel and biologically interesting amphilectane family of diterpenoids, which possess the basic carbon skeleton **1**, have been isolated from marine sponges.[1-3] One member of this group of natural products, (−)-8,15-diisocyano-11(20)-amphilectene, was obtained from *Hymeniacidon amphilecta* and was shown by X-ray diffraction analysis to possess the constitution and relative stereochemistry shown in **2**.[1] We report here a stereocontrolled synthesis of (±)-**2**.



1



2

Alkylation (PhMe, reflux, 48 h) of the potassium enolate of 2-(methoxycarbonyl)-3-methylcyclohexanone[4] with (*E*)-1-(*tert*-butyldimethylsiloxy)-6-iodo-3-(trimethylstannyl)-2-hexene[5] provided (70% yield) the keto ester **3**[6] (Scheme I), accompanied by a small amount of O-alkylation product.[7] As expected,[4] the sole C-alkylation product was that derived from approach of the alkylating agent from the side of the enolate anion opposite to the secondary methyl group. Efficient conversion of compound **3** into the diene **4** was accomplished by a one-pot sequence of reactions involving conversion of **3** into the corresponding enol trifluoromethanesulfonate,[8] followed by a Pd(0)-catalyzed intramolecular coupling process.[5,9]

A Diels–Alder reaction of the diene **4** with propenal, followed by equilibration (NaOMe, MeOH) of the resultant mixture of four adducts,[10] provided a mixture of the two aldehydes **5** and **8** in a ratio of ≈3:7, respectively. Clean separation of **5** and **8** by flash chromatography[11] on silica gel afforded the two pure substances in yields of 29 and 58%, respectively. Conversion of **8** into **9** was accomplished efficiently by known methodology, in which reductive displacement of a primary (*p*-tolylsulfonyl)oxy group with lithium triethylborohydride[12] played a key role.

Introduction of a necessary functional group at C-11 (amphilectane numbering) of the intermediate **9** was effected smoothly by an allylic oxidation with CrO_3–3,5-dimethylpyrazole.[13] Reduction of the resultant α,β-unsaturated ketone **10** (mp 53–54 °C) with sodium in ammonia containing 2.3 equiv of Me_3COH[14] produced a single product **11** (mp 79–81 °C) in high yield. Stereochemically, this reduction would be expected to produce the product in which the six-membered rings are trans-fused, and, therefore, the relative configuration of **11** could be assigned with confidence. Treatment of the ketone **11** with a reagent derived from zinc dust, CH_2Br_2, and $TiCl_4$[15] provided the required alkene **12** (mp 45–48 °C).

The correct stereochemistry at C-1 was introduced by epimerization of the axially oriented formyl group in compound **13** (mp 68–70 °C), which was readily derived from **12**. Subjection of the epimeric aldehyde **14** (mp 65–67 °C) to a Wittig–Horner reaction with the potassium salt of trimethyl 2-phosphonopropionate gave, after column chromatography on silica gel, the geometrically isomeric α,β-unsaturated esters **15** (77% yield, mp 106–108 °C) and **16** (19% yield, mp 101–103 °C). Treatment of **15** with sodium benzeneselenoate in refluxing THF–hexamethylphosphoramide (HMPA)[16] (78 h)[17] gave the dicarboxylic

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(5) Piers, E.; Friesen, R. W. *Can. J. Chem.* **1987**, *65*, 1681.
(6) All compounds reported herein exhibited spectra consistent with assigned structures and gave satisfactory molecular mass determinations (high-resolution mass spectrometry). The purity of all compounds was established to be ≥95% by ^1H NMR, TLC, and/or GLC analyses.
(7) Similar alkylations in tetrahydrofuran (THF) or 1,2-dimethoxyethane gave significantly higher amounts of the O-alkylation product.
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(10) On the basis of earlier work[5] on the Diels–Alder reactions of dienes structurally similar to **4**, the structures of the four adducts (relative proportions ≈ 28:2:62:8) could be assigned as **5**, **6**, **7**, and **8**, respectively. As expected,[5] base-catalyzed equilibration converted **6** and **7** into **5** and **8**, respectively.
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(14) Similar reductions with lithium or potassium gave significant amounts of side product(s) and/or gave inconsistent results. Details will be given in a full paper.
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