

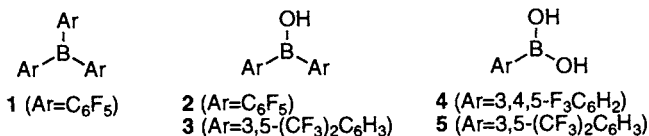
Boron reagents

KAZUAKI ISHIHARA

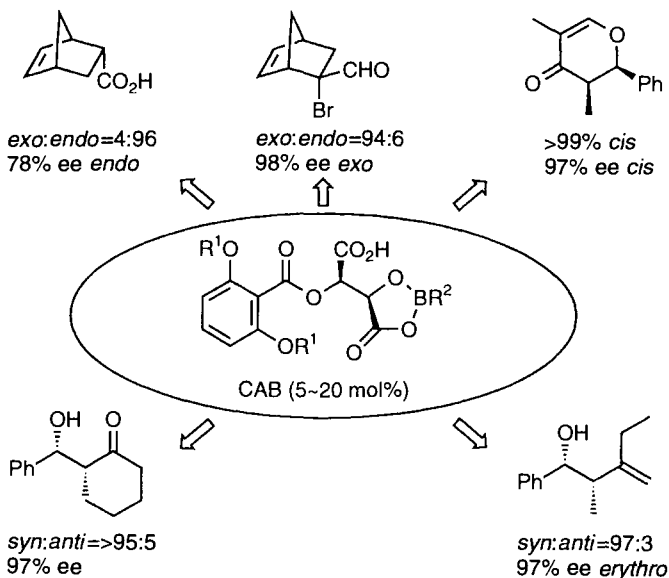
1. Introduction

Arylboron reagents with electron-withdrawing aromatic groups and chiral boron reagents as Lewis acid catalysts are described in this chapter.

The classical boron Lewis acids, BX_3 , RBX_2 and R_2BX ($\text{X} = \text{F}, \text{Cl}, \text{Br}, \text{OTf}$) have become popular tools in organic synthesis. In general, these are used stoichiometrically in organic transformations under anhydrous conditions, since the presence of even a small amount of water causes rapid decomposition or deactivation of the promoters. To obviate some of these inherent problems, we have demonstrated the potential of tris(pentafluorophenyl)boron (**1**), bis(pentafluorophenyl)borinic acid (**2**), bis(3,5-bis(trifluoromethyl)phenyl)borinic acid (**3**), 3,4,5-trifluorophenylboronic acid (**4**), and 3,5-bis(trifluoromethyl)phenylboronic acid (**5**) as a new class of boron catalysts.



Chiral boron catalysts have been widely used as Lewis acids in the asymmetric Diels–Alder, Mukaiyama aldol, Sakurai–Hosomi allylation, and aldol-type reactions of imines. As one successful example, we have achieved highly enantioselective carbo-Diels–Alder, hetero-Diels–Alder, aldol, and allylation reactions using a common chiral (acyloxy)borane (CAB) catalyst as depicted in Scheme 3.1. These carbon–carbon bond formations are very important and useful in asymmetric synthesis.



Scheme 3.1

2. Arylboron reagents with electron-withdrawing aromatic group

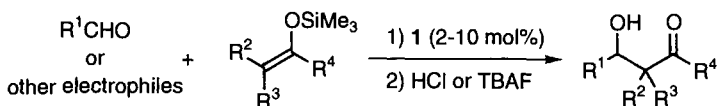
2.1 Tris(pentafluorophenyl)boron as an efficient, air stable, and water-tolerant Lewis acid catalyst

1 is an air stable and water-tolerant Lewis acid catalyst, which is readily prepared as a white solid from boron trichloride by reaction with pentafluorophenyl-lithium.^{1,2} This reagent does not react with pure oxygen.^{1,2} It is very thermally stable, even at 270°C, and soluble in many organic solvents.^{1,2} Although **1** is available when exposed to air (not anhydrous grade), it acts better as a catalyst under anhydrous conditions.

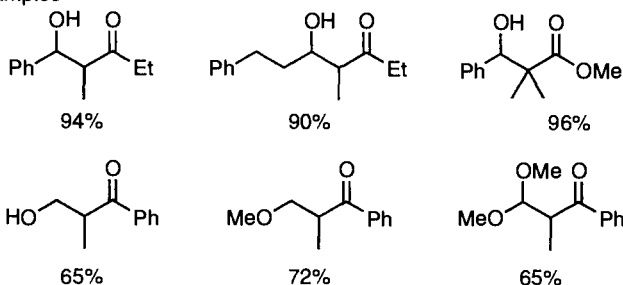
2.1.1 Mukaiyama aldol reactions of silyl enol ethers with aldehydes or other electrophiles^{3,5}

The aldol-type reactions of various silyl enol ethers with aldehydes or other electrophiles proceed smoothly in the presence of 2–10 mol% of **1**. Although the reaction is remarkably promoted by using an anhydrous solution of **1**, the reaction of silyl enol ethers with a commercial aqueous solution of formaldehyde takes place without incident. Silyl enol ethers react with chloromethyl methyl ether or trimethylorthoformate; hydroxymethyl, methoxymethyl, or dimethoxymethyl C1 groups can be introduced at the α -position of the carbonyl group (Scheme 3.2).

3: Boron reagents



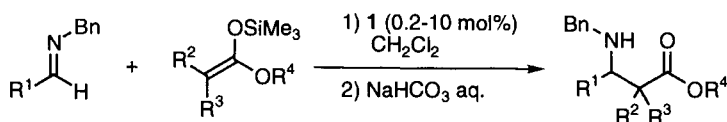
Examples



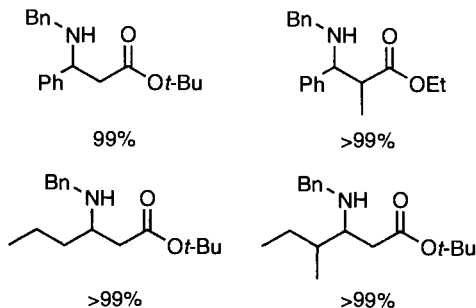
Scheme 3.2

2.1.2 Aldol-type reaction of ketene silyl acetals with *N*-benzylimines^{4,5}

1 (anhydrous grade) is a highly active catalyst for the aldol-type reaction between ketene silyl acetals and *N*-benzylimines because of its stability and comparatively low value of bond energy and affinity toward nitrogen-containing compounds (Scheme 3.3). *N*-Benzylimines are useful substrates because β -benzylamino acid esters produced are readily debenzylated by hydrogenolysis over palladium on carbon. Catalysis is carried out using 0.2–10 mol% catalyst loading in toluene. The condensation proceeds smoothly even with aliphatic enolizable imines derived from primary and secondary aliphatic



Examples



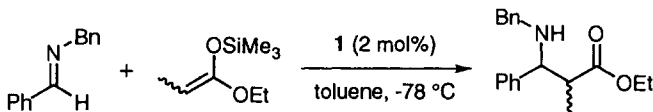
Scheme 3.3

aldehydes, and (*E*)- and (*Z*)-ketene silyl acetals give *anti* and *syn* products as major diastereomers, respectively.

Protocol 1.

Aldol-type reaction of ketene silyl acetals with *N*-benzylimines catalysed by **1**⁵ (Scheme 3.4)

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Scheme 3.4

Equipment

- Two-necked, round-bottomed flask (25 mL)
- Separating funnel (50 mL)
- Magnetic stirrer bar
- Sintered glass filter funnel
- Magnetic stirrer
- Erlenmeyer flasks (50 mL)
- Three-way stopcock
- Column for flash chromatography
- Vacuum/argon source

Materials

- Anhydrous **1** (0.247 M) in toluene,^a 24 μ L, 0.006 mmol
- *N*-Benzylidenebenzylamine (FW 195.3),⁵ 116.8 mg, 0.6 mmol
- 1-Ethoxy-1-(trimethylsiloxy)propene⁵ (FW 174.3), 208.9 mg, 1.2 mmol
- Dry toluene^b
- Silica gel for flash chromatography, Merck 9385

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flammable
flammable toxic
irritant dust

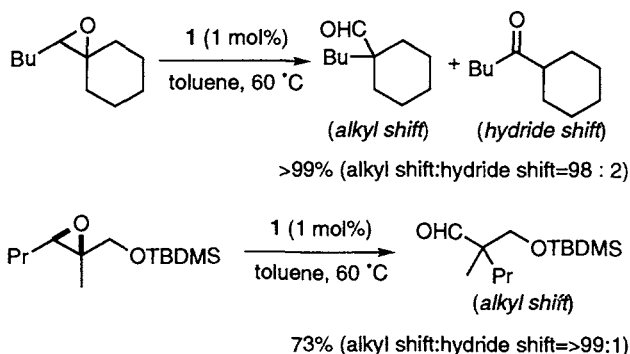
1. Add an anhydrous solution of **1** in toluene dropwise at -78°C to a solution of *N*-benzylidenebenzylamine and 1-ethoxy-1-(trimethylsiloxy)propene (*E/Z* = 85:15) in dry toluene (6 mL).
2. After stirring for 13.5 h at -78°C in a dry ice/methanol bath, warm the reaction mixture to 25°C and stir for another 2 h.
3. After pouring aqueous sodium hydrogencarbonate (0.1 mL) into the resultant solution, dry the mixture over MgSO_4 , filter, and concentrate under vacuum.
4. Purify the crude oil by column chromatography on silica gel (eluant: hexane-ethylacetate, 15:1) to produce ethyl 3-benzylamino-2-methyl-3-phenylpropanoate (178 mg, >99% yield) as a colourless oil. The product is >98% pure by ^1H NMR, IR analysis, and may be characterized further by elemental analysis. *Syn/anti* ratio of the products is 36:64 by ^1H NMR assay.

^a From Tosio-Akuzo Chemical Co. Ltd, Japan; used as received.

^b Distil toluene from calcium hydride under argon.

2.1.3 Stereoselective rearrangement of epoxides⁶

The protic or Lewis acid-promoted rearrangement of epoxides to carbonyl compounds is a well-known synthetic transformation. $\text{BF}_3 \cdot \text{OEt}_2$ appears to be the most widely used Lewis acid for rearrangement. It is often consumed or altered in the course of these reactions, and is thus a reagent rather than a catalyst, although less than an equivalent is effective in some instances. We have found that **1** is a highly efficient catalyst in the rearrangement of epoxides. The rearrangement of trisubstituted epoxides proceeds successfully in the presence of catalytic amounts of **1** (anhydrous grade) *via* a highly selective alkyl shift to give the corresponding aldehydes (Scheme 3.5). The exceptional bulkiness of **1** may be effective in the selective rearrangement of epoxides *via* an alkyl shift.



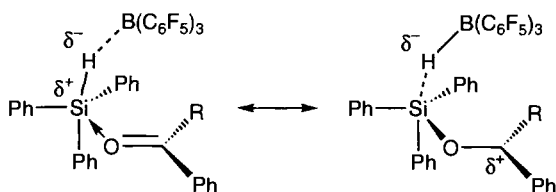
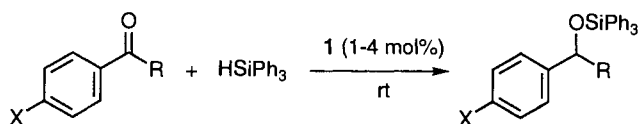
Scheme 3.5

2.1.4 Hydrosilation of aromatic aldehydes, ketones, and esters⁷

Hydrosilation of carbon–oxygen bonds is a mild method for selective reduction of carbonyl functions. Parks and Piers⁷ found that aromatic aldehydes, ketones, and esters are hydrosilylated at room temperature in the presence of 1–4 mol% of **1** and 1 equiv of Ph_3SiH . The reduction takes place by an unusual nucleophilic/electrophilic mechanism: the substrate itself serves to nucleophilically activate the Si–H bond, while hydride transfer is facilitated by **1** (Scheme 3.6).

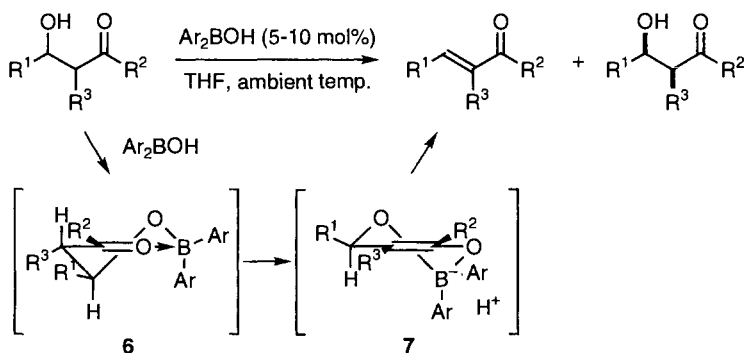
2.2 Diarylborinic acids as efficient catalysts for selective dehydration of aldols⁸

Diarylborinic acids with electron-withdrawing aromatic groups are effective for Mukaiyama aldol condensation.⁸ The catalytic activities of diarylborinic acids **2** and **3** are much higher than those of the corresponding arylboronic acids. Recently, we developed the selective dehydration of β -hydroxy carbonyl compounds catalysed by diarylborinic acids.⁸ The dehydration is strongly promoted in tetrahydrofuran (THF). In most cases, the reaction proceeds smoothly, and

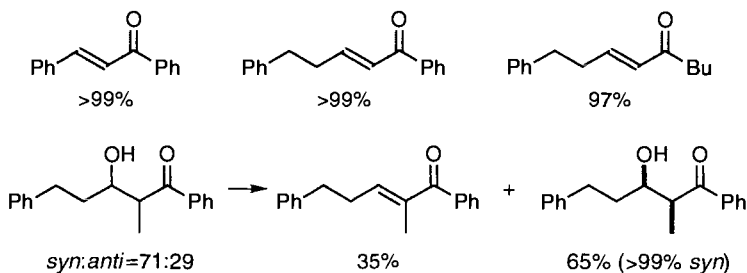


Scheme 3.6

α,β -enones are obtained as *E* isomers in high yields. In the reaction of α -substituted- β -hydroxy carbonyl compounds, α,β -enones are preferentially obtained from *anti*-aldols, and most of the *syn*-aldols are recovered. Thus, the present dehydration is a useful and convenient method for isolating pure *syn*-aldol from *syn*- and *anti*-isomeric mixtures. The transformation to α,β -enones occurs *via* an enolate intermediate **7** derived from the selective deprotonation of a pseudo-axial α -proton perpendicular to the carbonyl face of a cyclic intermediate **6** (Scheme 3.7).



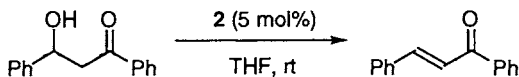
Examples



Scheme 3.7

Protocol 2.**Dehydration of aldols catalysed by 2⁸ (Scheme 3.8)**

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.

**Scheme 3.8****Equipment**

- 3 Round-bottomed flask (5 mL)
- Separating funnel (50 mL)
- Magnetic stirrer bar
- Sintered glass filter funnel
- Magnetic stirrer
- Erlenmeyer flasks (50 mL)
- Pressure-equalized addition funnel (10 mL)
- Column for flash chromatography
- Three-way stopcock
- Vacuum/argon source

Materials

- 2^a (FW 361.9), 3.6 mg, 0.01 mmol
- 1,3-Diphenyl-3-hydroxy-1-propanone (FW 226.3), 45 mg, 0.2 mmol
- Dry THF^b
- Silica gel for flash chromatography, Merck 9385

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irritant
flammable irritant
irritant dust**

1. Add 2 to a solution of 1,3-diphenyl-3-hydroxy-1-propanone in THF (1 mL) and stir the reaction mixture at room temperature for 2 h.
2. Pour the reaction mixture into 1M NaOH aq., and extract with CH₂Cl₂ three times. Dry the combined organic extracts over MgSO₄ filter, and concentrate in vacuum.
3. Purify the crude product by column chromatography on silica gel using a mixture of hexane and ethyl acetate (5/1) as eluent to give chalcone (40 mg, 0.19 mmol, 96%). The product is >98% pure by ¹H NMR, IR analysis, and may be characterized further by elemental analysis.

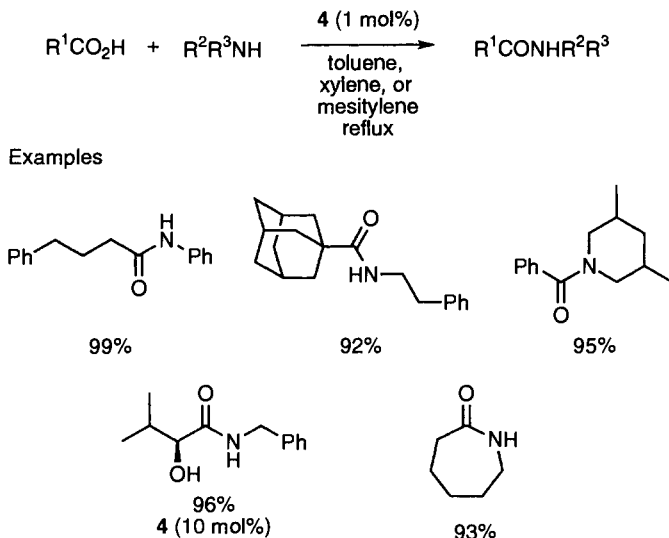
^a2 can be prepared by hydrolysis of the known bis(pentafluorophenyl)boron chloride. Chambers, R. D.; Chivers, T. J. *Chem. Soc.* **1965**, 3933.

^bDistil THF from sodium and benzophenone under argon.

2.3 3,4,5-Trifluorophenylboronic acid as an amidation catalyst⁹

There are several different routes to carboxamides. In most cases, a carboxylic acid is converted into a more reactive intermediate, e.g. acid chloride, which is then allowed to react with an amine. For practical reasons, it is preferable to form the reactive intermediate *in situ*. We have found that arylboronic acids with electron-withdrawing groups **4** and **5** act as highly efficient

catalysts in the amidation between carboxylic acids and amines (Scheme 3.9). The catalytic amidation of optically active aliphatic α -hydroxycarboxylic acids with benzylamine proceeds with no measurable loss of enantiomeric purity.

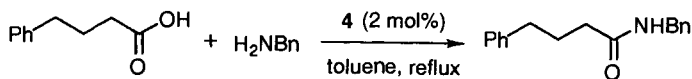


Scheme 3.9

Protocol 3.

Amidation reaction of carboxylic acids and amines catalysed by **4**⁹ (Scheme 3.10)

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Scheme 3.10

Equipment

- Round-bottomed flask (50 mL)
- Separating funnel (50 mL)
- Magnetic stirrer bar
- Sintered glass filter funnel
- Magnetic stirrer
- Erlenmeyer flasks (50 mL)
- Pressure-equalized addition funnel (10 mL)
- Column for flash chromatography
- Three-way stopcock
- Vacuum/argon source
- Reflux condenser
- Oil bath

Materials

- **4**^a (FW 175.9), 8.8 mg, 0.05 mmol
- 4-Phenylbutyric acid (FW 164.2), 821 mg, 5 mmol
- Benzylamine (FW 107.16), 546 μ L, 5 mmol
- Dry toluene^a
- 4-Å molecular sieves ca. 4 g

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irritant
flammable
flammable toxic
pellets

1. Add 4-phenylbutyric acid, benzylamine, and **4** in 25 mL of toluene to a dry, round-bottomed flask fitted with a stirrer bar and a pressure-equalized addition funnel (containing a cotton plug and 4-Å molecular sieves and functioning as a Soxhlet extractor) surmounted by a reflux condenser.
2. Bring the mixture to reflux by the removal of water.
3. After 18 h, cool the resulting mixture to ambient temperature, wash with aqueous ammonium chloride and aqueous sodium hydrogencarbonate successively, and extract the product with ethyl acetate. Dry the combined organic layers over magnesium sulfate. Evaporate the solvent, and purify the residue by column chromatography on silica gel (eluant: hexane–ethyl acetate = 3:1) to give *N*-benzyl-4-phenylbutyramide (1.221 g, 96% yield). The product is >98% pure by ¹H NMR, IR analysis, and may be characterized further by elemental analysis.

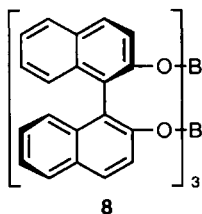
^a Distil toluene from calcium hydride under argon.

3. Chiral boron reagents as Lewis acids

3.1 Catalytic enantioselective carbo-Diels–Alder reactions

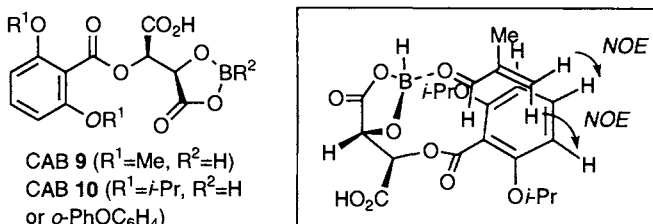
The asymmetric Diels–Alder reaction is now of great interest because of its potential to introduce some asymmetric centres simultaneously during carbon–carbon bond formation.

Kaufmann and Boese¹⁰ developed asymmetric catalyst **8** derived from H₂BBr–SMe₂ and 1,1-binaphthol. The diborate structure with a propeller-like shape has been established by X-ray analysis. The reaction between methacrolein and cyclopentadiene catalysed by **8** gives the cycloadducts with 97% exo selectivity and 90% ee.

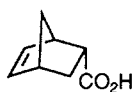


Using another promising approach^{11–16} it was found that an (acyloxy) borane RCO₂BR'₂ behaves as a Lewis acid, and the chiral (acyloxy)borane

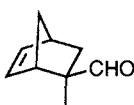
(CAB) **9** is an excellent asymmetric catalyst for the Diels–Alder reaction between cyclopentadiene and acrylic acid¹¹ or methacrolein^{12,13} (Scheme 3.11). The α -substituent on the dienophile increases the enantioselectivity. When there is a β -substitution on the dienophile, the cycloadduct is almost racemic, but for a substrate having substituents at both α - and β -positions, high ee's have been observed. According to NOE studies, the effective shielding of the *si*-face of the co-ordinated α,β -enal arises from π -stacking of the 2,6-di-isopropoxybenzene ring and the co-ordinated aldehyde.



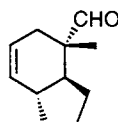
Examples



9 (10 mol%)
exo/endo: 4/96
endo: 78% ee



9 (10 mol%)
exo/endo: 89/11
exo: 96% ee



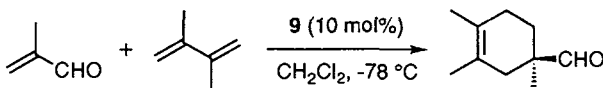
9 (10 mol%)
exo/endo: 4/96
exo: 92% ee

Scheme 3.11

Protocol 4.

Enantioselective Diels–Alder reaction catalysed by CAB **9**¹³ (Scheme 3.12)

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Scheme 3.12

Equipment

- Three-necked round-bottomed flask (100 mL)
- Separating funnel (500 mL)
- Magnetic stirrer bar
- Sintered glass filter funnel
- Magnetic stirrer
- Erlenmeyer flasks (500 mL)
- Pressure-equalized addition funnel (10 mL)
- Column for flash chromatography
- Three-way stopcock
- Vacuum/argon source
- Rubber septum

Materials

- Mono (2,6-dimethoxybenzoyl) tartaric acid¹³ (FW 314.2),
1.57 g, 5 mmol irritant
- Borane–THF (1.40 M)^a, 3.57 mL, 5 mmol flammable liquid, moisture-sensitive
- Methacrolein (FW 70.09)^b, 4.14 mL, 50 mmol flammable liquid, corrosive
- 2,3-Dimethyl-1,3-butadiene (FW 82.15)^c, 8.49 mL, 75 mmol flammable liquid
- Dry dichloromethane^d flammable toxic
- 4-Å molecular sieves ca. 4 g pellets

1. Equip a three-necked round-bottomed flask containing a magnetic stirrer bar with a rubber septum and three-way stopcock with an argon inlet. Repeat flushing with dry argon to displace the air.
2. Charge the flask with mono(2,6-dimethoxybenzoyl) tartaric acid and 50 mL of dry dichloromethane, and cool in an ice bath.
3. Through the septum, with a syringe, add dropwise a borane–THF solution at 0°C over a period of 30 min.
4. Stir the reaction mixture for 15 min at 0°C and then cool to –78°C in a dry ice/methanol bath.
5. Add freshly distilled methacrolein to this solution via a syringe dropwise.
6. After the addition is complete, introduce 2,3-dimethyl-1,3-butadiene to the solution at the same temperature and stir the mixture for 12 h.
7. Pour the cold reaction mixture into 150 mL of ice-cold saturated sodium bicarbonate and extract the product with three 200-mL portions of hexane. Wash the combined organic phase with brine (2 × 200 mL), dry over sodium sulfate, filter, and concentrate at atmospheric pressure. Distil the residue at reduced pressure to afford (1*R*)-1,3,4-trimethyl-3-cyclohexene-1-carboxaldehyde (6.53 g, 86%) as a colourless liquid, b.p. 92–93°C (23 mm). The product is >98% pure by ¹H NMR, IR analysis, and may be characterized further by elemental analysis.^e

^a Titrate borane–THF complex which can be obtained from Tosoh-Akzo Chemical Company, Ltd. in Japan before use. Vigorous evolution of hydrogen is observed during addition of borane–THF solution to the reaction mixture.

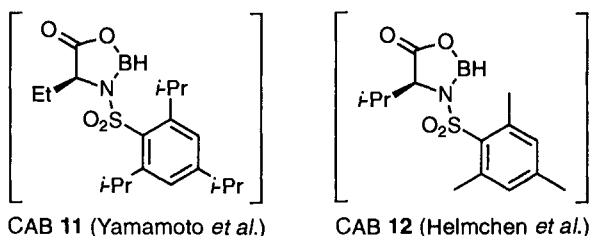
^b Dry methacrolein from Tokyo Kasei Kogyo Company, Ltd with calcium sulfate and distil through a 20-cm Vigreux column under argon prior to use.

^c Distil 2,3-dimethyl-1,3-butadiene, from Tokyo Kasei Kogyo Company Ltd, before use.

^d Distil dichloromethane from calcium hydride under argon.

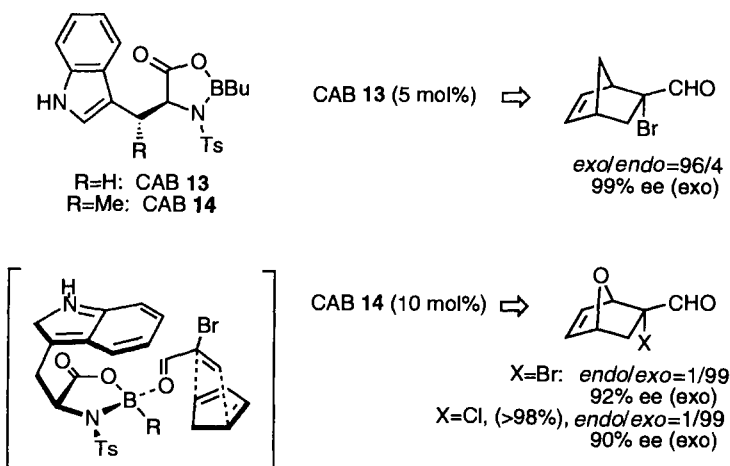
^e The optical purity of this adduct is 95% as determined by 200 MHz ¹H NMR spectroscopy and GC analysis (capillary column PEG, 0.25 mm × 25 m, purchased from Gaskuro Kogyo Company, Ltd in Japan) after conversion into the corresponding chiral acetal as follows. Stir a solution of the adduct, (2*R*,4*R*)-2,4-pentanediol (1.2 equiv, obtained from Wako Pure Chemical Industries), triethyl orthoformate (1.2 equiv.), and *p*-toluenesulfonic acid monohydrate (as a 5 mM solution) in dry benzene at ambient temperature for 3 h. Pour the mixture into saturated sodium bicarbonate and extract the product with ether. Dry the combined organic phases over sodium sulfate and concentrate on a rotary evaporator. Purify the residue by flash column chromatography on silica gel using hexane–ethyl acetate (25:1) as eluant to give the acetal quantitatively.

In 1991, Helmchen *et al.*^{17,19} and our group¹⁸ found that *N*-sulfonyl derivatives of α -amino acid react with diborane, giving complexes formulated as CAB (Scheme 3.13). These CAB complexes catalyse asymmetric cycloadditions between α,β -enals and dienes.



Scheme 3.13

A similar effect was also published by Corey *et al.* on CAB **13**.^{20–24} Especially efficient is the asymmetric catalysis of cycloaddition between 2-bromoacrolein and various dienes (>90–95% ee). The transition-state is believed to be as represented in Scheme 3.14.²¹ Attractive interactions between the indolyl moiety and the π -acidic dienophile protect one face of the dienophile. CAB **14** derived from *N*-tosyl (αS , βR)- β -methyltryptophan catalyses the cycloaddition of 2-bromoacrolein and furan with 92% ee.²⁴

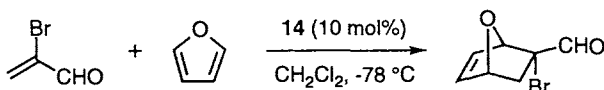


Scheme 3.14

Protocol 5.

Enantioselective Diels–Alder reaction catalysed by CAB 14²⁴
(Scheme 3.15)

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Scheme 3.15

Equipment

- Three-necked round-bottomed flask
- Separating funnel
- Magnetic stirrer bar
- Sintered glass filter funnel
- Magnetic stirrer
- Erlenmeyer flasks
- Column for flash chromatography
- Three-way stopcock
- Soxhlet extractor
- Reflux condenser
- Rubber septum
- Vacuum/nitrogen source

Materials

- *N*-Tosyl ($\alpha S, \beta R$)-methyltryptophan²¹ (FW 358.4), 2.06 g, 5.6 mmol
- Butylboronic acid (FW 101.9), 0.60 g, 6.7 mmol
- 2-Bromoacrolein (FW 135.0)²⁰
- Furan (FW 68.1)
- Dry toluene^a
- Dry THF^b
- Dry dichloromethane^a
- CaH_2
- Sand

irritant
hygroscopic
flammable liquid, corrosive
highly toxic cancer suspect agent
flammable liquid, toxic
flammable liquid, irritant
toxic, irritant
flammable solid, moisture sensitive

1. Add *N*-tosyl ($\alpha S, \beta R$)-methyltryptophan and butylboronic acid in a round-bottomed flask equipped with magnetic stirrer and a Soxhlet extractor with reflux condenser with a rubber stopper at the top, connect to a vacuum manifold and place under nitrogen.
2. A thimble in the extractor contains layers of sand (3 cm, bottom) and CaH_2 (3 cm, top).
3. After the addition of 20 mL of dry THF and 40 mL of dry toluene, heat the mixture at rapid reflux for 20 h using an oil bath heated to $>165^\circ\text{C}$.
4. Quickly disconnect the reaction flask and attach to a vacuum line, and remove the solvent *in vacuo* leaving catalyst **14** as a colourless viscous oil. Store **14** in a tightly sealed flask as a 0.1 M solution in 9:1 toluene–THF.
5. Remove the solvent *in vacuo* and exchange with CH_2Cl_2 toluene or other solvent just prior to the Diels–Alder reaction. THF serves to stabilize toluene solutions of catalyst **14**.

Protocol 5. Continued

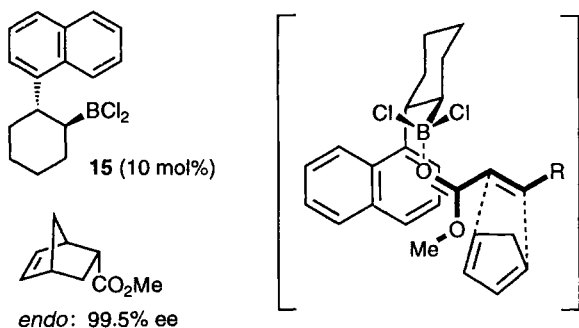
6. The reaction of 5 equiv. of furan with 2-bromoacrolein in the presence of 10 mol% of **14** in dichloromethane at -78°C is complete in 5 h and gives the Diels–Alder adduct in 98% yield and 96:4 enantioselectivity, as determined by 500 MHz analysis of the α -methoxy- α -(trifluoromethyl)phenylacetic ester of the corresponding primary alcohol (from NaBH_4 reduction of the aldehyde). The *N*-tosyl carboxylic acid precursor of **14** is efficiently recovered for reuse in each case.

^a Distil toluene and dichloromethane from calcium hydride under nitrogen.

^b Distil THF from sodium and benzophenone under nitrogen.

Itsuno *et al.* explored the possibility of using polymer-supported chiral Lewis acids in the cycloaddition of methacrolein with cyclopentadiene.^{25–28} Using insoluble polymer-supported CAB, high enantioselectivity (up to 95% ee) has been achieved.²⁸

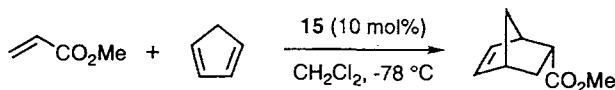
Hawkins *et al.*^{29,30} developed a simple and efficient catalyst for Diels–Alder reaction based on a chiral alkyldichloroborane **15** (Scheme 3.16). They have predicted the approach of the diene on one of the faces of the methyl crotonate because the other face is protected by π – π donor-acceptor interactions on the basis of the crystal structure study of a molecular complex between methyl crotonate and **15**.



Scheme 3.16

Protocol 6.**Enantioselective Diels–Alder reaction catalysed by chiral alkyldichloroborane 15³⁰ (Scheme 3.17)**

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.

**Scheme 3.17****Equipment**

- Schlenk flask (100 mL)
- Separating funnel (100 mL)
- Magnetic stirrer bar
- Sintered glass filter funnel
- Magnetic stirrer
- Erlenmeyer flasks (100 mL)
- Column for flash chromatography
- Vacuum/nitrogen source

Materials

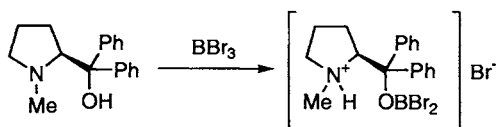
- (1*R*,2*R*)-**15**^{29,30} (FW 291.0), 352.1 mg, 1.21 mmol
- Cyclopentadiene (FW 66.1), 4.66 g, 70.5 mmol
- Methyl acrylate (FW 86.1), 1.21 g, 14.1 mmol
- Dry dichloromethane

moisture sensitive
flammable liquid, toxic
flammable liquid, lachrymator
toxic, irritant

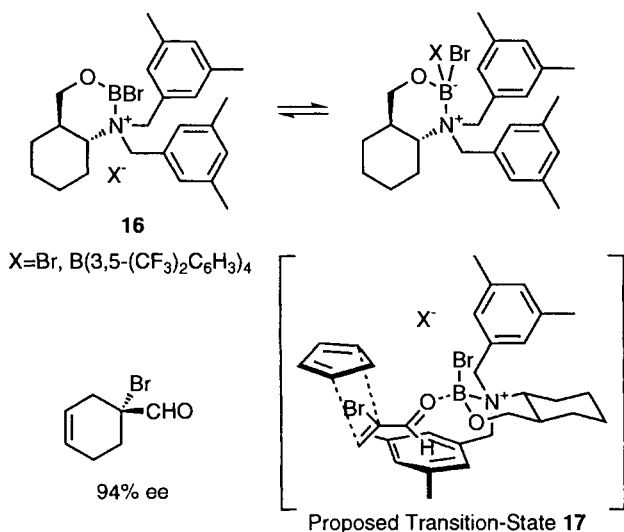
1. Add (1*R*,2*R*)-**15** in a Schlenk flask, cool the flask to -78°C , and add 14 mL of freshly distilled CH₂Cl₂ slowly. Add enough CH₂Cl₂ to establish a solvent to diene ratio of 3:1 (v/v).
2. Then, add cyclopentadiene and methyl acrylate successively.
3. Seal the reaction flask and allow to warm to the reaction temperature.
4. Quench the reaction with 10% NaHCO₃ (aq) and isolate the products (95% yield) by flash chromatography. Determine enantiomeric excess with chiral GC (97% ee).^a

^a Chiral GC analyses are performed with J&W Cyclodex-B β -cyclodextrin column.

Mukaiyama *et al.* have found that prolinol derivatives combined with BBr₃ are good chiral catalysts for some Diels–Alder reactions.^{31,32} For example, methacrolein and cyclopentadiene afford the *exo* adduct (*exo:endo* = >99:1) in 97% ee (20 mol% of catalyst). The chiral catalyst is believed to be the HBr adduct salt of the amino boron derivative (Scheme 3.18).

**Scheme 3.18**

Recently, a new chiral Lewis acid **16** was developed, and its utility was demonstrated in cycloadditions with both reactive and unreactive 1,3-dienes (Scheme 3.19).³³ In the hypothetical transition-state model **17**, one of the *N*-CH₂Ar substituents serves to block attack on the lower face of the *s-trans*-co-ordinated dienophile whereas the other screens another region in space and limits the rotational position of dienophile and *N*-CH₂Ar moieties.

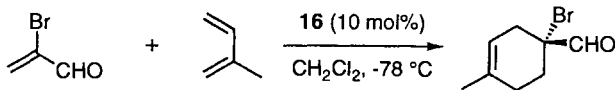


Scheme 3.19

Protocol 7.

Enantioselective Diels–Alder reaction catalysed by chiral cationic Lewis acid **16**³³ (Scheme 3.20)

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Scheme 3.20

Equipment

- Vacuum/argon source

- There is no information about apparatus.³³

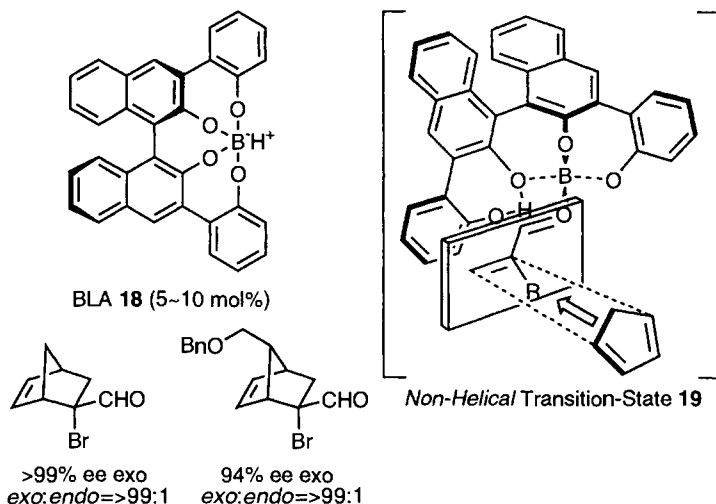
Materials

- The silyl ether of chiral ligand (FW 423.7),³³ 40.3 mg, 0.095 mmol
 - Boron tribromide (FW 250.5), 0.46 M in CH₂Cl₂ 187 μ L, 0.086 mmol
 - Ag⁺B[C₆H₃-3,5-(CF₃)₂]₄⁻ (FW 971.1),^a 83.5 mg, 0.086 mmol
 - 2-Bromoacrolein (FW 135.0), 76 μ L, 0.94 mmol
 - Isoprene (FW 68.1), 500 μ L 5 mmol
 - Dry dichloromethane
- corrosive moisture-sensitive
toxic
flammable liquid, irritant
cancer suspect agent, flammable liquid
toxic, irritant

1. Add a solution of BBr₃ in CH₂Cl₂ to a solution of the silyl ether of chiral ligand in 1 mL of CH₂Cl₂ at -94 °C (hexane-liquid N₂ bath) under dry argon, and after 5 min, replace the cooling bath with dry ice-acetone to bring the temperature to -78 °C.
2. After adding a freshly prepared dry solution of Ag⁺B[C₆H₃-3,5-(CF₃)₂]₄⁻ in 1 mL of CH₂Cl₂, stir the reaction mixture for 20 min at -78 °C and then cool to -94 °C.
3. Add 2-bromoacrolein and isoprene successively (each dropwise), and stir the reaction mixture for 1 h at -94 °C and then quench with 150 μ L of triethylamine.
4. After warming the reaction mixture to room temperature and removing the inorganic salts by filtration, evaporate the solvents, and purify the residue by chromatography on silica gel to give 191 mg (99%) of the isoprene Diels-Alder adduct, [α]_D²³ + 82.2° (c 0.8, CH₂Cl₂) and also recover ligand (28.6 mg, 83%).

^a Prepare the silver salt as follows. Shake an ethereal solution of NAB[C₆H₃-3,5-(CF₃)₂]₄ (Broolhart, M.; Grant, B.; Volpe, A. F., Jr *Organometallics* **1992**, *11*, 3920) with 2 equiv. of aqueous AgNO₃ in a separating funnel for 5 min, and separate the layers. Evaporation of the ether layer affords a quantitative yield of the colourless silver salt which is dissolved in ether to give a clear 0.1 M solution. Store this at -78 °C in a flask wrapped with aluminium foil to exclude light. To prepare the catalyst, concentrate a measured amount of this ethereal solution *in vacuo*, dissolve in dry CH₂Cl₂, and dry over activated molecular sieves 4 Å for 1 h at room temperature (with constant protection from light).

We found that Brønsted acid-assisted chiral Lewis acid (BLA) **18** achieved high selectivity through the double effect of intramolecular hydrogen binding interaction and attractive π - π donor-acceptor interaction in the transition-state (Scheme 3.21).³⁴ Extremely high enantioselectivity (>99-92% ee) and *exo*-selectivity (>99-97% *exo*) are obtained for cycloadditions of α -substituted α,β -enals with dienes. The absolute stereopreference in the reaction can be easily understood in terms of the most favourable transition-state assembly **19**. The co-ordination of a proton of 2-hydroxyphenyl group with an oxygen of the adjacent B-O bond in complex **19** plays an important role in asymmetric induction; this hydrogen binding interaction via Brønsted acid causes Lewis acidity of boron and π -basicity of phenoxy moiety to increase.

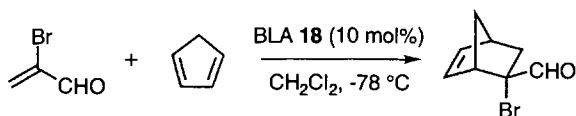


Scheme 3.21

Protocol 8.

Enantioselective Diels–Alder reaction catalysed by chiral BLA **18**³⁴ (Scheme 3.22)

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Scheme 3.22

Equipment

- Round-bottomed flask (10 mL)
- Separating funnel (50 mL)
- Magnetic stirrer bar
- Sintered glass filter funnel
- Magnetic stirrer
- Erlenmeyer flasks (50 mL)
- Column for flash chromatography
- Vacuum/argon source
- Pressure-equalized addition funnel
- Three-way stopcock

Materials

- (*R*)-3,3'-bis(2-hydroxyphenyl)-2,2'-dihydroxy-1,1'-binaphthyl (FW 472.5),³⁴ 23.5 mg, 0.05 mmol
- Trimethyl borate (FW 103.9), 0.1 M in CH₂Cl₂ 0.5 mL, 0.05 mmol
- 2-bromoacrolein (FW 135.0), 80.8 μL, 1 mmol
- Cyclopentadiene (FW 66.1), 332 μL, 4 mmol

white solid, irritant

flammable liquid, moisture-sensitive
flammable liquid, irritant
flammable liquid, toxic

3: Boron reagents

- Dry dichloromethane^a
- Dry THF^b
- 4-Å molecular sieves

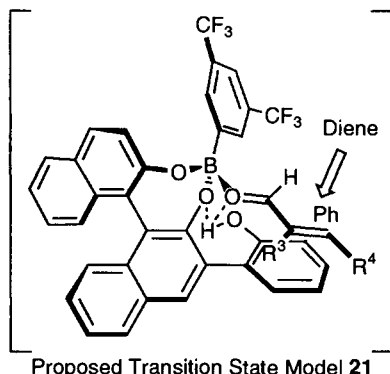
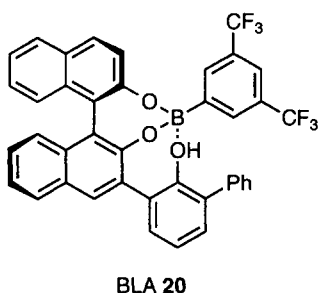
toxic, irritant
flammable irritant
pellets

1. Add (*R*)-3,3'-bis(2-hydroxyphenyl)-2,2'-dihydroxy-1,1'-binaphthyl, trimethyl borate, and 3 mL of dichloromethane in a dry round-bottomed flask fitted with a stirrer bar and a pressure-equalized addition funnel (containing a cotton plug and ca. 4 g of 4-Å molecular sieves (pellets) and functioning as a Soxhlet extractor) surmounted by a reflux condenser.
2. Secure an argon atmosphere, and bring the solution to reflux (bath temperature 50–60 °C).
3. After 2 h, cool the reaction mixture to 25 °C and quickly remove the addition funnel and condenser and replace with a septum.
4. Add dry THF to the white precipitate in dichloromethane at 25 °C, and after 2 h the precipitate is completely dissolved.
5. After cooling a colourless solution of the catalyst (*R*)-**18** to –78 °C, add dropwise 2-bromoacrolein and cyclopentadiene.
6. After 4 h, add 50 mL of H₂O and warm the mixture to 25 °C, dry over MgSO₄, filter, and purify by eluting with hexane/ethyl acetate (10:1) to afford 201 mg of Diels–Alder adduct (1*S*, 2*S*, 4*S*)-bromo aldehyde as a white solid (1.0 mmol, >99% yield, exo:endo = >99:1, >99% ee) and quantitative recovery of pure chiral ligand. Determine enantioselectivity by reduction with NaBH₄, conversion to the Mosher ester, and ¹H NMR and HPLC analysis (Daicel AD).

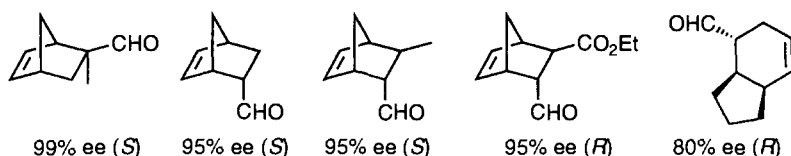
^a Distil dichloromethane from calcium hydride under argon.

^b Distil THF from sodium and benzophenone under argon.

Diels–Alder reactions of α -unsubstituted α,β -enals with BLA **18** as well as most chiral Lewis acids exhibit low enantioselectivity and/or reactivity. We have developed a new type of BLA, **20** which was prepared from a chiral triol and **5** (Scheme 3.23).³⁵ **20** is extremely effective in enantioselective cycloaddition of both α -substituted and α -unsubstituted α,β -enals with various dienes. The Brønsted acid in the BLA clearly accelerates the cycloaddition. The high enantioselectivity and stereochemical results attained in this reaction can be understood in terms of the transition-state model **21**.



Examples

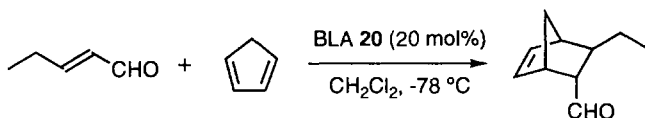


Scheme 3.23

Protocol 9.

Enantioselective Diels–Alder reaction catalysed by BLA 20³⁵
(Scheme 3.24)

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Scheme 3.24

Equipment

- Schlenk flasks (10 mL)
- Separating funnel (50 mL)
- Magnetic stirrer bar
- Sintered glass filter funnel
- Magnetic stirrer
- Erlenmeyer flasks (50 mL)
- Column for flash chromatography
- Vacuum/argon source
- Pressure-equalized addition funnel
- Three-way stopcock
- Oil bath

Materials

- The chiral ligand (FW 454.5),³⁵ 54.5 mg, 0.12 mmol **white solid**
- Monomeric **5** (0.043 M) in CH₂Cl₂-THF-H₂O (20:3:0.054), 23.3 μ L, 0.1 mmol **hygroscopic**
- (*E*)-2-Pentenal (FW 84.12), 42.1 mg, 0.5 mmol **flammable liquid, irritant**
- Cyclopentadiene (FW 66.1), 166 μ L, 2 mmol **flammable liquid, toxic**
- Dry THF^a **flammable irritant**
- Dry dichloromethane^b **toxic, irritant**
- 4-Å molecular sieves **powder**

1. Stir a mixture of the chiral ligand and a solution of monomeric **5** in CH₂Cl₂-THF-H₂O (20:3:0.054) at ambient temperature for 2 h.
2. Transfer the resulting colourless solution into a Schlenk tube containing c. 0.5 mL of anhydrous dichloromethane and MS 4Å (powder, 250 mg, activated by heating at 200°C under vacuum [c. 3 Torr] for 12 h), and use a further c. 0.5 mL of dichloromethane to transfer the residue into the Schlenk.
3. Stir the mixture at ambient temperature for another 12 h.
4. Then, evaporate the solvents and heat the resulting solid to 100°C (oil bath) for 2 h under vacuum (c. 3 Torr) to dry catalyst.
5. After cooling to ambient temperature, purge the flask with argon and add dichloromethane (2 mL).
6. Cool the mixture to -78°C, add dropwise (*E*)-pentenal, and 1 min later add freshly distilled cyclopentadiene slowly along the wall of the flask.
7. After stirring the reaction mixture at -78°C for 72 h, quench the reaction with pyridine (20 μ L, 0.25 mmol), warm to ambient temperature, and filter to remove molecular sieves. Wash the filtrate with ether, dry over MgSO₄, and concentrate to afford the crude products. Purify by silica gel chromatography eluting with pentane-ether to provide the pure Diels-Alder adduct (73% yield, *endo/exo* = 91:9, 98% ee for *endo*-isomer). Determine the *exo/endo* ratio by ¹H NMR analysis (500 MHz): δ 9.38 (d, *J* = 3.3 Hz, 1H, CHO (*endo*)), 9.79 (d, *J* = 2.9 Hz, 1H, CHO (*exo*)). Determine the ee by acetalization with (-)-(2*R*,4*R*)-2,4-pentanediol and GC analysis (90°C, PEG-HT Bonded (25 m \times 0.25 mm)): *t*_R = 29.0 min (major *endo*-isomer), 36.0 min (minor *endo*-isomer), 37.8 min (minor *exo*-isomer), 38.5 min (major *exo*-isomer). The absolute configuration is not established.

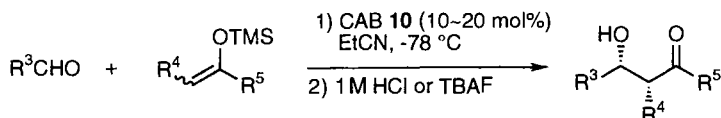
^a Distil YHF from sodium and benzophenone under argon.^b Distil dichloromethane from calcium hydride under argon.

3.2 Catalytic enantioselective aldol and allylation reactions

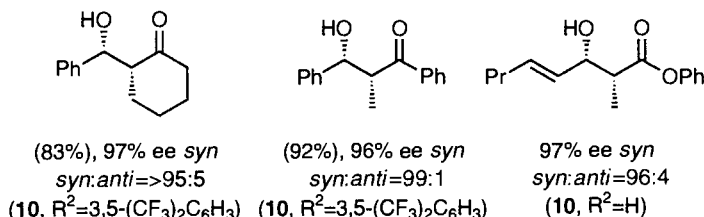
Asymmetric aldol and allylation reactions are now of great interest because of their utility for introduction of asymmetric centres and functional groups.

We have reported that CAB **10**, R² = H, is an excellent catalyst (20 mol%)

for the enantioselective and diastereoselective Mukaiyama condensation of simple enol silyl ethers with various aldehydes.^{36,37} The reaction is accelerated without reducing the enantioselectivity by using 10–20 mol% of **10**, $R^2 = 3,5\text{-(CF}_3)_2\text{C}_6\text{H}_3$. The enantioselectivity is increased without reducing the chemical yield by using 20 mol% of **10**, $R^2 = o\text{-PhOC}_6\text{H}_4$. Another aldol-type reaction of ketene silyl acetals derived from phenyl esters with achiral aldehydes also proceeds smoothly with **10** and can furnish *syn* β -hydroxy esters with high optical purity.^{37,38} Regardless of the stereochemistry of enol silyl ethers, *syn* aldols are highly selectively obtained *via* the acyclic extended transition-state mechanism (Scheme 3.25).



Examples

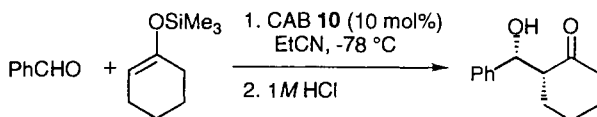


Scheme 3.25

Protocol 10.

Enantioselective Mukaiyama Aldol reaction catalysed by CAB **10**³⁷ (Scheme 3.26)

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Scheme 3.26

Equipment

- Schlenk flask (10 mL)
- Separating funnel (50 mL)
- Magnetic stirrer bar
- Sintered glass filter funnel
- Magnetic stirrer
- Erlenmeyer flasks (50 mL)
- Column for flash chromatography
- Vacuum/argon source
- Three-way stopcock
- Rubber septum

Materials

- Mono(2,6-diisopropoxybenzoyl)tartrac acid¹³
(FW 370.4), 74.1 mg, 0.2 mmol
- **5** (FW 257.9), 51.6 mg, 0.2 mmol
- 1-Trimethylsiloxy-1-cyclohexene (FW 170.3),
204.4 mg, 1.2 mmol
- Benzaldehyde (FW 106.12), 106.1 mg, 1.0 mmol
- Dry propionitrile^a

irritant
hygroscopic

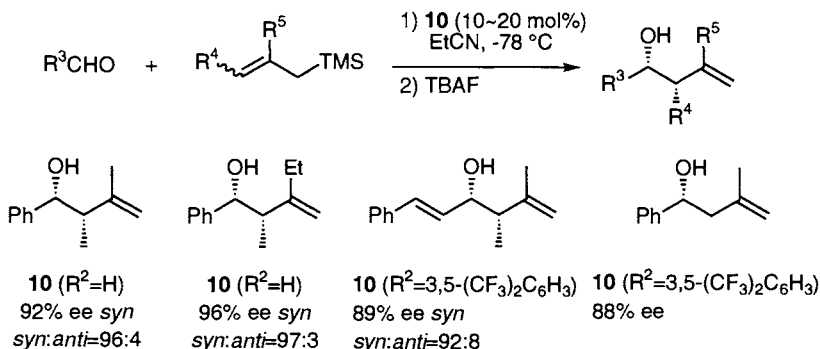
flammable liquid

highly toxic cancer suspect agent
highly toxic flammable liquid

1. Equip a Schlenk flask containing a magnetic stirrer bar with a rubber septum and three-way stopcock with an argon inlet. Repeat flushing with dry argon to displace the air.
2. Add mono(2,6-di-isopropoxybenzoyl)tartrac acid and **5** in the flask, dissolve in 1 mL of dry propionitrile, stir the resulting solution at 25°C for 30 min, and cool the reaction flask to -78°C.
3. Add 1-trimethylsiloxy-1-cyclohexene and benzaldehyde successively and stir the reaction mixture for 12 h at low temperature.
4. Pour this cold solution into water and extract the product with ether repeatedly. Dry the combined ether layers over MgSO₄, concentrate *in vacuo* and treat the residue with 1 M HCl (aq)-THF solution (2 mL, 1/1 in vol.). After usual work-up, purify the crude product by column chromatography on silica gel to give aldol adducts (83% yield, *syn:anti* = >95:5, 97% ee for *syn* diastereomer). The product is >98% pure by ¹H NMR, IR analysis, and may be characterized further by elemental analysis. Determine the *syn/anti* ratio by ¹H NMR analysis (500 MHz), and determine the ee by ¹H NMR analysis of (+)-MTPA ester.

^a Distil propionitrile from calcium hydride under argon.

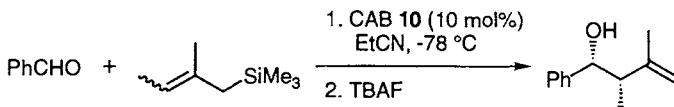
We have found that CAB **10** has a powerful activity for the Sakurai-Hosomi allylation reaction of aldehydes to furnish homoallylic alcohols in excellent enantiomeric excess (Scheme 3.27).³⁹ γ -Alkylated allylsilanes exhibit excellent diastereo- and enantioselectivities affording *syn* homoallylic alcohols of higher optical purity. Regardless of the geometry of starting allylsilanes, the predominant isomer in this reaction has *syn* configuration. The observed preference for relative and absolute configurations for the adducts is predicted on the basis of an extended transition-state model similar to that for the CAB **10** catalysed aldol reaction.³⁶⁻³⁸ The 3,5-bis(trifluoromethyl)phenyl group is the most effective *B*-substituent of **10**.⁴⁰



Scheme 3.27

Protocol 11.**Enantioselective Sakurai–Hosomi allylation reaction catalysed by CAB 10⁴⁰ (Scheme 3.28)**

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Scheme 3.28

Equipment

- Schlenk flasks (10 mL)
- Separating funnel (50 mL)
- Magnetic stirrer bar
- Sintered glass filter funnel
- Magnetic stirrer
- Erlenmeyer flasks (50 mL)
- Column for flash chromatography
- Vacuum/argon source
- Three-way stopcock
- Rubber septum

Materials

- Mono(2,6-diisopropoxybenzoyl)tartrac acid¹³
(FW 370.4) 74.1 mg, 0.2 mmol
- **5** (FW 257.9), 51.6 mg, 0.2 mmol
- 1-(Trimethylsilyl)-2-methyl-2-butene (FW 142.3),
170.8 mg, 1.2 mmol
- Benzaldehyde (FW 106.12), 106.1 mg, 1.0 mmol
- Dry propionitrile^a

irritant
hygroscopic

flammable liquid
highly toxic cancer suspect agent
highly toxic flammable liquid

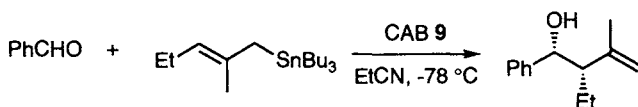
1. Equip a Schlenk flask containing a magnetic stirrer bar with a rubber septum and three-way stopcock with an argon inlet. Repeat flushing with dry argon to displace the air.

3: Boron reagents

2. Add mono(2,6-di-isopropoxybenzoyl) tartaric acid and **5** in the flask, dissolve in 1 mL of dry propionitrile, stir the resulting solution at 25°C for 30 min, and cool the reaction flask to -78°C.
3. Add 1-(trimethylsilyl)-2-methyl-2-butene and benzaldehyde successively and stir the reaction mixture for 12 h at low temperature.
4. Pour this cold solution into brine and extract with ether repeatedly, dry the combined ether layers over MgSO₄, and concentrate *in vacuo*.
5. Treat the residue with tetrabutylammonium fluoride (1.5 mL of 1 M solution in THF, 1.5 mmol) in THF (3 mL).
6. Usual work-up followed by chromatographic separation gives products (82% yield, *syn:anti* = 94.6, 91% ee for *syn* diastereomer). The product is >98% pure by ¹H NMR, IR analysis, and may be characterized further by elemental analysis. Determine the *syn/anti* ratio and the ee by ¹H NMR analysis of (+)-MTPA ester: ¹H NMR δ 5.80 (minor enantiomer of *anti* diastereomer), 5.87 (major enantiomer of *anti* diastereomer), 5.88 (minor enantiomer of *syn* diastereomer), 5.93 (major enantiomer of *syn* diastereomer).

^a Distil propionitrile from calcium hydride under argon.

Marshall *et al.*⁴¹ reported that more reactive allyltin analogues can be used in place of allylsilane nucleophiles in our CAB **9** catalyst system, and that trifluoroacetic anhydride is an efficient promoter (Scheme 3.29).

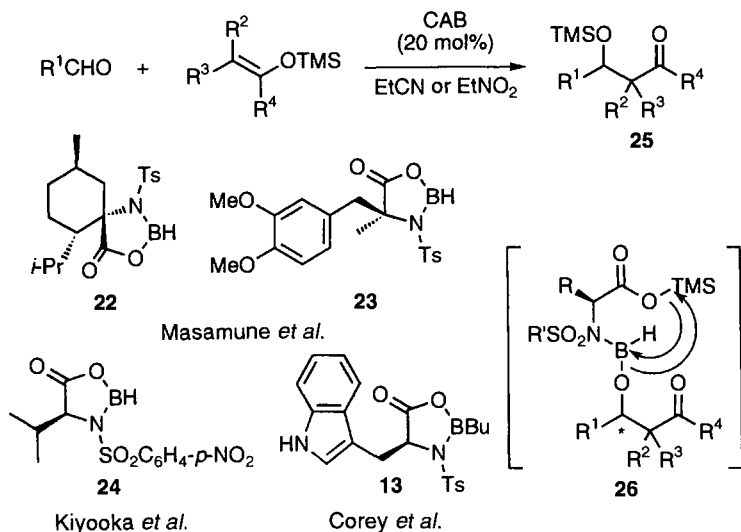


9 (20 mol%) + (CF₃)₂CO (40 mol%) : (88%), *syn:anti*=85:15, 74% ee *syn*
9 (100 mol%) + (CF₃CO)₂O (200 mol%) : (99%), *syn:anti*=90:10, 85% ee *syn*

Scheme 3.29

After the enantioselective aldol reaction using chiral oxaborolidines (another type of CAB) under a stoichiometric condition was reported by Kiyooka *et al.*⁴² Masamune *et al.*,^{43,44} Kiyooka *et al.*,⁴⁵ and Corey *et al.*⁴⁶ independently developed CAB-catalysed-aldol reactions (Scheme 3.30). Masamune *et al.* suggested that the initial aldol adduct must undergo ring closure as indicated by the arrows in **26** to release the final product **25** and to regenerate the catalyst **22** or **23**.^{43,44} In many cases, slow addition of the aldehyde to the reaction mixture has proved beneficial (permitting enough time for **26** to undergo ring closure) in improving the enantioselectivity of the reaction. Kiyooka *et al.*⁴⁵ have reported straightforward improvement of this

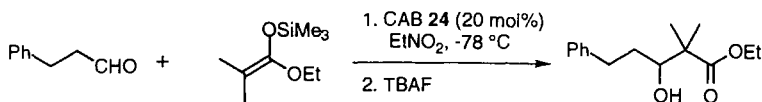
reaction to its catalytic version by employing nitroethane instead of dichloromethane as solvent.



Protocol 12.

Enantioselective Mukaiyama aldol reaction catalysed by CAB 24⁴⁵ (Scheme 3.31)

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Scheme 3.31

Equipment

- Vacuum/argon source

Materials

- The sulfonamide ligand⁴⁰ (FW 302.3), 66.5 mg, 0.22 mmol
- Borane-THF (1.0 M solution in THF), 0.2 mL, 0.2 mmol
- Hydrocinnamaldehyde (FW 134.18), 134.2 mg, 1 mmol
- 1-Ethoxy-2-methyl-1-trimethylsiloxypropene (FW 188.3), 207.2 mg, 1.1 mmol
- Nitroethane

irritant
flammable liquid, moisture-sensitive
irritant

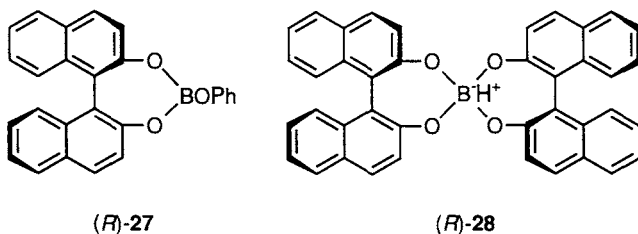
flammable liquid
flammable liquid irritant

1. Add $\text{BH}_3\text{-THF}$ complex in dropwise fashion to a solution of the sulfonamide in nitroethane at 0°C under Ar.
2. Stir the mixture for 0.5 h, allow to warm to room temperature, and stir for another 0.5 h.
3. Add a solution of hydrocinnamaldehyde in THF and a solution of the ketene silyl acetal in THF to the resulting mixture successively at -78°C .
4. Stir the mixture at -78°C for 4 h, whereupon quench the reaction by the introduction of buffer solution (pH 6.8; 5 mL). Extract the mixture with Et_2O (30 mL) twice. After the usual work-up, isolate the pure products of the silylated aldol, the corresponding aldol, and the sulfonamide by silica-gel chromatography. After desilylation with Bu_4NF (a 1.0 M solution in THF), the aldol product is obtained in 97% yield with 95% ee. Determine the ee by HPLC analysis with a chiral Daicel OD column.

Harada *et al.* reported that CAB **14** serves as an excellent catalyst for enantioselective ring-cleavage of 2-substituted 1,3-dioxolanes with silyl enol ethers.^{47–49}

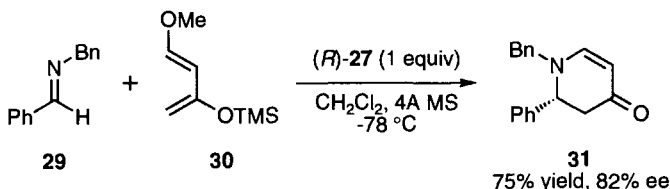
3.3 Asymmetric reactions of imines mediated by chiral boron reagents

Imines are important starting materials for nitrogen-containing compounds such as alkaloids, amino acids, β -lactams, amino sugars, and terpenes. We developed chiral Lewis acids **27** and **28** for asymmetric reactions of imines.



3.3.1 Enantioselective Diels–Alder reaction of imines mediated by chiral boron reagent **27**^{50,51}

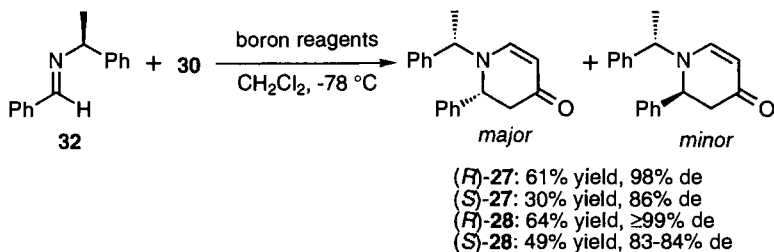
Asymmetric aza Diels–Alder reaction of imines is promoted by an *in situ* generated boron complex **27**. (R)-**27** is prepared *in situ* simply by mixing a 1:1 molar ratio of optically active binaphthol and triphenyl borate in dichloromethane. The aza Diels–Alder reaction of imine **29** with Danishefsky diene **30** is promoted by (R)-**27** at -78°C to give the adduct **31** in 75% yield with 82% ee (Scheme 3.32). The reaction is applicable to aromatic and aliphatic imines and Danishefsky-type dienes.



Scheme 3.32

3.3.2 Double asymmetric induction of Diels–Alder reaction of imines mediated by chiral boron reagents^{50–53}

There have been a number of investigations into reactions exhibiting diastereofacial selectivity with imines containing a chiral auxiliary. We succeeded in the double asymmetric induction of the aza Diels–Alder reaction of chiral imines derived from α -methylbenzylamine mediated by **27**, and thereafter found that new chiral boron reagent **28** is a more efficient promoter than **27**.^{54–56} The X-ray analysis of **28** demonstrates that it exists as a Brønsted acid-assisted chiral Lewis acid (BLA). **28** is prepared by the reaction of B(OMe)₃ (1 equiv) with (*R*)-binaphthol (2 equiv) in dichloromethane at reflux by removing methanol. Almost complete diastereoselectivities are obtained for a variety of imines under an optimum condition with a matching pair (Scheme 3.33).

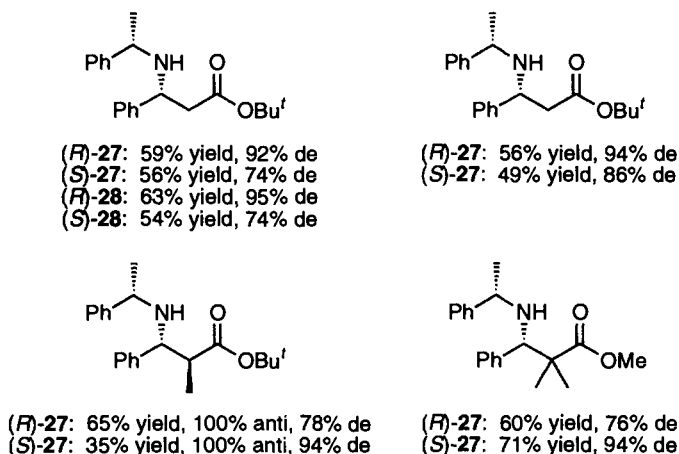


Scheme 3.33

3.3.3 Double asymmetric induction of aldol-type reaction of imines mediated by chiral boron reagents^{52–56}

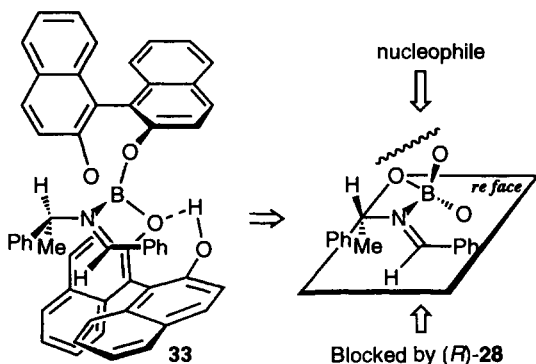
Largely stimulated by the synthesis of β -lactam antibiotics, there have been a great number of investigations into stereochemical aspects of imine condensations. We developed highly stereoselective aldol-type reaction of chiral imines derived from α -methylbenzylamine and aldehydes with ketene silyl acetals in the presence of chiral Lewis acid **27**^{54–56} or BLA **28**.^{52,53} Some examples are listed in Scheme 3.34. The matching and mismatching pairs in double stereo-differentiation depend on the structure of the ketene silyl acetals.

Examples



Scheme 3.34

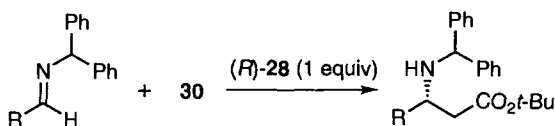
The absolute configuration of the adducts can be understood in terms of a rational model **33** involving an intramolecular hydrogen bonding interaction *via* Brønsted acid (Scheme 3.35).



Scheme 3.35

3.3.4 Enantioselective aldol-type reaction of imines mediated by BLA **28**^{52,53}

We developed the enantioselective synthesis of chiral β -amino acid esters from *achiral* imines and ketene silyl acetals using chiral BLA **28**. The enantioselectivity of the aldol-type reaction is dramatically increased by substituting sterically bulky *N*-substituents. The enantioselective aldol-type reaction of a variety of *N*-benzhydryl imines with **30** by (*R*)-**28** under optimum conditions is

Table 3.1 Enantioselective Aldo-Type Reaction of *N*-Benzhydrylimines

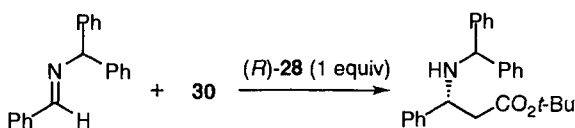
Entry	R	Yield (%)	ee (%)
1	C ₆ H ₅	58	96 (<i>R</i>)
2	<i>p</i> -MeC ₆ H ₄	35	97
3	<i>p</i> -ClC ₆ H ₄	45	98
4	<i>p</i> -AcOC ₆ H ₄	52	98
5	<i>p</i> -2,4-Cl ₂ C ₆ H ₃	49	95
6	2-Naphthyl	43	96

summarized in Table 3.1. Excellent enantioselectivity (95% ee or better) has been achieved in the reactions of aromatic aldehyde-derived imines. The removal of *N*-benzhydryl protecting group from β -aryl β -amino acid esters is easily advanced by catalytic hydrogenation (10% Pd/C, H₂, MeOH).

Protocol 13.

Enantioselective aldol-type reaction of imines^{52,53} (Scheme 3.36)

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.

**Scheme 3.36**

Equipment

- Round-bottomed flask (10 mL)
- Separating funnel (50 mL)
- Magnetic stirrer bar
- Sintered glass filter funnel
- Magnetic stirrer
- Erlenmeyer flasks (50 mL)
- Column for flash chromatography
- Vacuum/argon source
- Pressure-equalized addition funnel
- Three-way stopcock

Materials

- (*R*)-(+)-1,1'-Bi-2-naphthol (FW 286.3), 200.4 mg, 0.70 mmol
- Trimethyl borate (FW 103.9), 0.1 M in CH₂Cl₂ 3.5 mL, 0.35 mmol
- 4Å molecular sieves
- *N*-Benzylidenebenzhydrylamine^{52,53} (FW 271.4), 95.0 mg

irritant

flammable liquid, moisture-sensitive
pellets
colourless crystal

3: Boron reagents

- **3 0** (FW 188.3) 131.8 mg, 0.7 mmol
- Dry dichloromethane^a
- Dry toluene^a

flammable
toxic, irritant
flammable liquid, toxic

1. Add (*R*)-binaphthol, trimethyl borate, and dichloromethane in a dry round-bottomed flask fitted with stirrer bar and a pressure-equalized addition funnel (containing a cotton plug and c. 4 g of 4Å molecular sieves and functioning as a Soxhlet extractor) surmounted by a reflux condenser.
2. Secure an argon atmosphere, and bring the solution to reflux (bath temperature 50–60°C).
3. After 2–3 h, cool the reaction mixture to 25°C, quickly remove the solution funnel and condenser and replace with a septum.
4. After adding 2 mL of dichloromethane, 5 mL of toluene, and *N*-benzylidenebenzhydrylamine to the white precipitate of (*R*)-**28** in dichloromethane at 0°C, stir the yellow suspension at 0°C for 10 min.
5. After cooling the suspension to –78°C, add **3 0** dropwise.
6. After stirring for 20 h, wash the solution with water and saturated NaHCO₃ and then dry over MgSO₄. Evaporation of the solvent and purification by column chromatography on silica gel gives *tert*-butyl 3-(benzhydrylamino)-3-phenylpropionate in 58% yield with 96% ee (*R*). The product is >98% pure by ¹H NMR, IR analysis, and may be characterized by elemental analysis. Determine the ee by HPLC analysis with a chiral Daicel OD-H column (hexane: *i*-PrOH = 100:1, 0.5 mL/min): *t*_R = 10.1 min for (*R*)-enantiomer, *t*_R = 12.1 min for (*S*)-enantiomer.

^a Distil dichloromethane and toluene from calcium hydride under argon.

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