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The synthesis of an enantiopure planar-chiral Lewis acid complex via kinetic resolution and its application in stereoselective additions to imines

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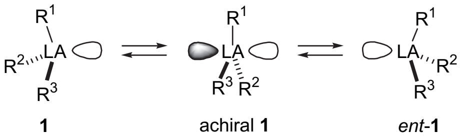
Abstract—This report describes the synthesis and an application of a new planar-chiral Lewis acid based on a 1,2-azaborolyl framework. The enantiopure complex is generated through an intriguing kinetic resolution by a chiral nucleophile. Imines bind in excellent yield to the planar-chiral 1,2-azaborolyl, furnishing crystallographically characterizable adducts that adopt the conformation that had been anticipated on the basis of steric considerations. Nucleophiles add with high stereoselectivity to these complexes, with the predicted sense of asymmetric induction.

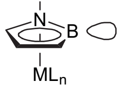
1. Introduction

Chiral Lewis acids have become widely used tools in asymmetric synthesis.[1] For most of the designs that have been described, the Lewis-acidic atom is not stereogenic, although there are a number of noteworthy exceptions to this generalization.[2] Designs in which the Lewis-acidic site is stereogenic may benefit from the close proximity of the asymmetric environment to the site of reaction; on the other hand, the issue of stereochemical lability may arise (e.g., Eq. 1).



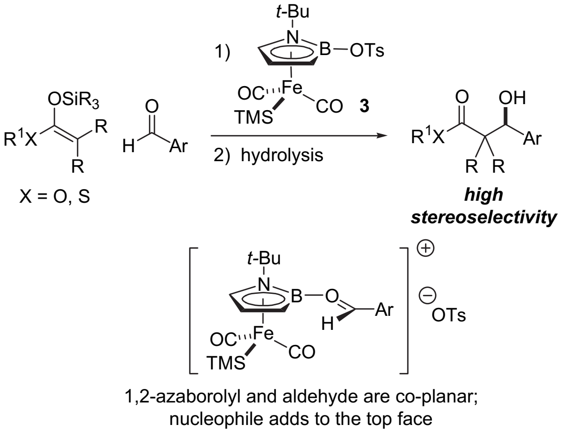
(1)

Several years ago, we initiated a program directed towards the synthesis of planar-chiral Lewis acids (for an illustrative example based on a 1,2-azaborolyl framework, see **2**).[3] This design circumvents the aforementioned complication of configurational lability at the Lewis-acidic site (Eq. 1).



2

As part of an earlier investigation, we described the first application of such planar-chiral Lewis acids in asymmetric synthesis, specifically, Mukaiyama aldol reactions mediated by an (η^5-1,2-azaborolyl)iron complex (Eq. 2).[3b,4–6] In these processes, a π interaction between the Lewis acid and the aldehyde organizes and activates the adduct for a stereoselective nucleophilic addition.



1,2-azaborolyl and aldehyde are co-planar;
nucleophile adds to the top face

(2)

In this report, we add a new dimension to the use of these planar-chiral Lewis acids in asymmetric synthesis. In particular, we demonstrate their effectiveness in mediating stereoselective additions to imines through a substrate–Lewis acid adduct that is conformationally distinct from reactions of aldehydes (Eq. 3 vs Eq. 2).

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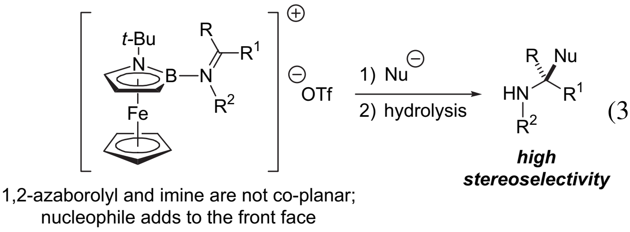
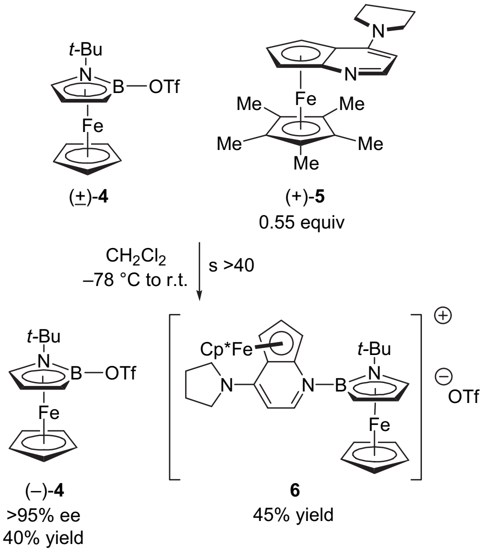


(3)

2. Results and discussion

In our study of the Mukaiyama aldol reaction, we generated enantiopure Lewis acid complex **3** by resolving a precursor via preparative chiral HPLC. In parallel with that investigation, we were exploring the chemistry of 1,2-azaborolyl analogues of ferrocene (e.g., **4** in Eq. 4).[4a] Rather than relying on chromatographic resolution of these adducts, we decided to examine the possibility that they might be separated via kinetic resolution by an enantiopure Lewis base. Specifically, we hypothesized that a planar-chiral DMAP derivative (e.g., **5**[7]) might be effective.



(4)

We were pleased to determine that this strategy is indeed viable. Thus, DMAP derivative (+)-**5** reacts with high selectivity for (+)-**4** to generate complex **6** (selectivity factor >40),[8] thereby allowing unreacted (−)-**4** to be isolated in excellent ee (Eq. 4).[9] The structure of **6** has been confirmed by X-ray crystallography (Fig. 1), which nicely illustrates how the planar chirality of the Lewis acid and the Lewis base impact upon the atropisomer preference of the adduct (FeCp* and *t*-Bu groups avoid each other). To the best of our knowledge, this is the first 1,2-azaborolyl complex that bears a neutral ligand on boron.

In the case of azaborolyl–aldehyde complexes, we had anticipated that a co-planar geometry would be preferred (Eq. 2). On the other hand, we predicted that, for azaborolyl–imine adducts, the co-planar conformation would be destabilized by steric interactions,[10] leading to preferential population of the 'perpendicular' geometry (Eq. 5).

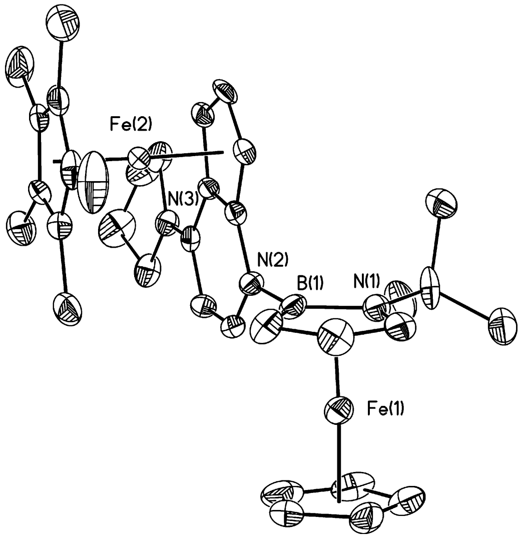
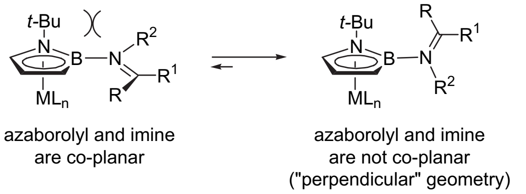


Figure 1. ORTEP illustration, with thermal ellipsoids drawn at the 35% probability level, of complex **6**. For the sake of clarity, the triflate counterion has been omitted.



(5)

Reaction of (−)-**4** with imines furnishes isolable azaborolyl–imine complexes in excellent yield (Eq. 6). An X-ray crystallographic study supports our suggestion that the perpendicular conformation should be preferred (Fig. 2).

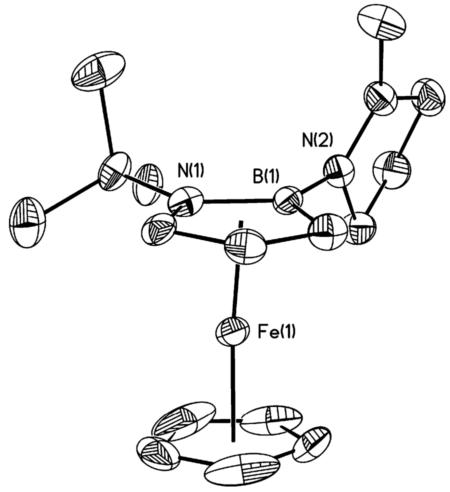
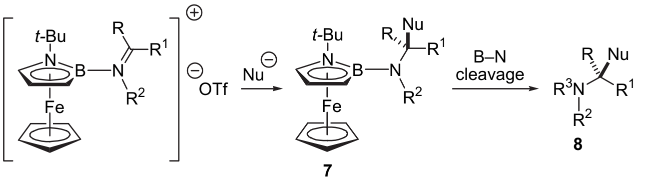
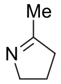
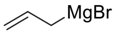
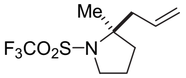
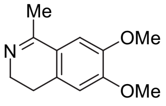
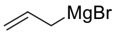
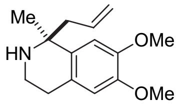
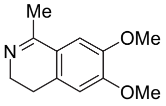
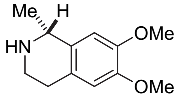


Figure 2. ORTEP illustration, with thermal ellipsoids drawn at the 35% probability level, of an azaborolyl-(2-methyl-1-pyrroline) complex. For the sake of clarity, the triflate counterion has been omitted.

Table 1. Stereoselective additions to planar-chiral azaborolyl–imine complexes

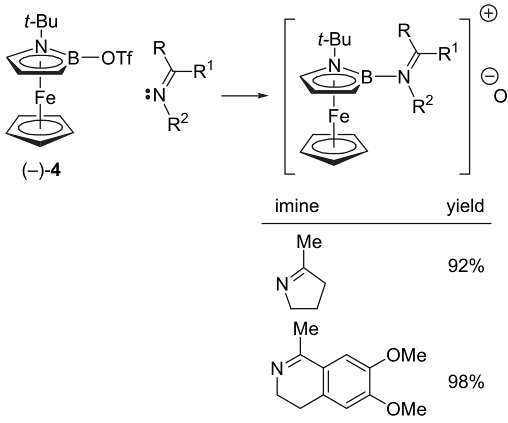


Entry	Imine	Nu	**7** Yield (%); de (%)[a]	**8**	
1			96; >90		94% ee[b]
2			83; 87		86% ee[c]
3		LiBHEt$_3$	69; 86		87% ee[c]

[a] Determined by ^{1}H NMR.

[b] Determined by chiral GC.

[c] Determined by chiral HPLC.



(6)

Just as the co-planar geometry of a planar-chiral azaborolyl–aldehyde complex provides an effective asymmetric environment for stereoselective addition reactions (Eq. 2), we anticipated that the perpendicular orientation of an azaborolyl–imine adduct would also furnish good selectivity, due to blockage of one face by the bulky *tert*-butyl substituent (Fig. 2).[11] Gratifyingly, this expectation has been fulfilled: additions of nucleophiles to azaborolyl–imine complexes do indeed proceed with high levels of stereoinduction (Table 1). For example, reaction with allylmagnesium bromide affords a quaternary stereocenter in good yield and ≥86% ee (entries 1 and 2).[12] Furthermore, addition of LiBHEt$_3$ occurs with high stereoselection to produce 1*R*-(+)-salsolidine,[13] a naturally occurring tetrahydroisoquinoline alkaloid (entry 3). The sense of induction is consistent with our prediction.

In conclusion, we have described a synthesis and an application of a new planar-chiral Lewis acid. The complex is generated in enantiopure form through an intriguing kinetic resolution by a chiral nucleophile. Imines bind in excellent yield to the planar-chiral 1,2-azaborolyl, furnishing crystallographically characterizable adducts that adopt the conformation that had been anticipated on the basis of steric considerations. Nucleophiles add with high stereoselectivity to these complexes, with the predicted sense of asymmetric induction. This study thus adds a new dimension to the use of planar-chiral azaborolyls in asymmetric synthesis, complementing our earlier investigation of additions to aldehydes, which proceed through an orthogonal transition-state geometry, also with good stereoselectivity. Efforts to develop catalyzed transformations are underway.

3. Experimental

All oxygen- and moisture-sensitive manipulations were carried out under an inert atmosphere using either standard Schlenk techniques or a glove box.

1,2-Azaborolyl complex **4**[4a] and DMAP derivative (+)-**5**[14] were prepared according to literature procedures. THF, Et$_2$O, CH$_2$Cl$_2$, and toluene were purified by passage through a neutral alumina column under argon. All other chemicals and solvents were purchased from Aldrich or Strem and used as received.

Silica gel (230–400 mesh; SiliCycle) was heated under vacuum in a 200 °C sand bath for 12 h. Flash chromatography was performed with this pre-treated silica gel under an inert atmosphere.

^{11}B NMR spectra were recorded on a Varian Unity 300 or on a Varian Unity 500 spectrometer at ambient temperature. ^{31}P NMR spectra and ^{19}F NMR spectra were recorded on a Varian Mercury 300 spectrometer with complete proton decoupling at ambient temperature. All chemical shifts are referenced to an external standard: ^{19}F NMR to trifluoroacetic anhydride (δ −78), ^{31}P NMR to 85% H_3PO_4 (δ 0), and ^{11}B NMR to boron trifluoride diethyl etherate (δ 0).

Kinetic resolution of (±)-4 by (+)-5 (Eq. 4). A solution of (+)-**5** (263 mg, 0.699 mmol) in CH_2Cl_2 (7.0 mL) was added dropwise to a −78 °C solution of (±)-**4** (497 mg, 1.27 mmol) in CH_2Cl_2 (45 mL). The reaction mixture was kept at −78 °C for 2 h, and then it was allowed to warm to rt over 7 h. The CH_2Cl_2 was then removed under vacuum until a volume of ~6 mL was reached, at which time pentane (14 mL) was carefully layered on top of the reaction mixture in order to induce crystallization. After 48 h, dark purple crystals of complex **6** had formed, leaving an orange mother liquor. The solid was washed with Et_2O (~20 mL) and dried under vacuum (483 mg, 45%). Crystals suitable for X-ray analysis were grown from a CH_2Cl_2/pentane solution.

Compound 6 (Eq. 4). ^{1}H NMR (500 MHz, CD_2Cl_2): δ 9.08 (d, $^3J_{HH}$=7.0 Hz, 1H), 6.18 (d, $^3J_{HH}$=7.0 Hz, 1H), 5.47 (s, 1H), 4.71 (d, $^3J_{HH}$=4.0 Hz, 1H), 4.46 (s, 5H), 4.16 (d, $^3J_{HH}$=2.5 Hz, 1H), 4.02 (t, $^3J_{HH}$=2.5 Hz, 1H), 3.98–3.78 (m, 3H), 3.74–3.69 (m, 2H), 3.70 (d, $^3J_{HH}$=5.0 Hz, 1H), 2.19–2.31 (m, 4H), 1.70 (s, 15H), 0.88 (s, 9H). Only one diastereomer was detected.

^{13}C NMR (125 MHz, CD_2Cl_2): δ 163.6, 150.3, 107.6, 95.8, 81.2, 77.4, 73.3, 72.4, 70.4, 69.2, 67.0, 66.1, 59.3 (br), 56.3, 52.0, 51.7, 30.7, 26.7, 25.1, 10.1.

^{11}B NMR (160 MHz, CD_2Cl_2): δ 13.9.

FTIR (thin film) 3113, 2978, 2909, 1576, 1551, 1512, 1457, 1411, 1370, 1321, 1273, 1239, 1150, 1031 cm^{-1}.

HRMS (ESI) calcd for $C_{34}H_{45}BN_3Fe_2$ (M^+) 618.2400, found 618.2371.

$[\alpha]_D$ −60 (*c* 0.050, CH_2Cl_2; >95% de).

Mp 135–145 °C (decomposition).

Compound (−)-4 (Eq. 4). The orange mother liquor was filtered through an acrodisc and then concentrated to dryness. This material was purified by column chromatography (pentane → 50% pentane/CH_2Cl_2), which furnished (−)-**4** as an orange oil (199 mg, 40%).

The spectral data for (−)-**4** are identical to those reported for (±)-**4**.[4a]

$[\alpha]_D$ −500 (*c* 0.50, CH_2Cl_2; >95% ee).

General procedure for derivatization to determine the ee of (η^5-1,2-azaborolyl)iron complexes (e.g., 4). In a glove box, a vial was charged with racemic (η^5-1-*tert*-butyl-2-chloro-1,2-azaborolyl)(η^5-cyclopentadienyl)iron[4a] (18.6 mg, 0.0670 mmol), (*S*)-(−)-α-methyl-2-naphthalenemethanol (13.8 mg, 0.0800 mmol), and sodium hydride (4.8 mg, 0.20 mmol). THF (0.6 mL) was added, and the reaction mixture was stirred at rt for 22 h. As the reaction proceeded, the color of the mixture gradually changed from orange to red. At the conclusion of the reaction, pentane was added, and the resulting mixture was filtered through an acrodisc (washed with pentane) and concentrated under vacuum. The desired product was isolated by flash chromatography (pentane → 50% pentane/CH_2Cl_2), which furnished the desired product as a red oil (25.3 mg, 91%). The ^{1}H NMR resonances of the two diastereomers of this 1:1 mixture are well distinguished from one another.

^{1}H NMR (500 MHz, CD_2Cl_2): δ 8.08 (s, 1H), 7.98 (app. t, $^3J_{HH}$=8.5 Hz, 2H), 7.91 (d, $^3J_{HH}$=7.5 Hz, 1H), 7.84–7.80 (m, 5H), 7.56–7.43 (m, 5H), 5.41 (q, $^3J_{HH}$=6.5 Hz, 1H), 5.29 (q, $^3J_{HH}$=6.0 Hz, 1H), 5.13 (s, 1H), 5.08 (s, 1H), 4.19 (s, 5H), 4.07–4.03 (m, 2H), 3.74 (s, 5H), 2.57–2.51 (m, 2H), 1.89 (d, $^3J_{HH}$=6.5 Hz, 3H), 1.59 (d, $^3J_{HH}$=7.0 Hz, 3H), 1.35 (s, 9H), 1.33 (s, 9H).

^{13}C NMR (125 MHz, CD_2Cl_2): δ 144.7, 144.5, 134.0, 133.9, 133.4, 133.1, 128.34, 128.33, 128.32, 128.23, 128.20, 128.1, 126.5, 126.4, 126.0, 125.9, 125.5, 125.1, 124.8, 124.1, 76.0, 75.5, 69.0, 68.9, 68.6, 68.5, 68.4, 68.3, 54.4, 54.3, 41.4 (br, 2C), 30.0, 29.9, 26.0, 25.9.

^{11}B NMR (160 MHz, CD_2Cl_2): δ 17.1.

FTIR (thin film) 3056, 2972, 2927, 1464, 1437, 1424, 1399, 1385, 1366, 1329, 1269, 1238, 1213, 1085 cm^{-1}.

HRMS (EI) calcd for $C_{24}H_{28}BNFeO$ (M^+) 413.1608, found 413.1614.

Determination of the ee of (−)-4 (Eq. 4). The ee was determined through ^{1}H NMR analysis of its (*S*)-(−)-α-methyl-2-naphthalenemethanol derivative, which was prepared according to the general procedure: >95% ee.

^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.83–7.80 (m, 4H), 7.55–7.53 (m, 1H), 7.47–7.42 (m, 2H), 5.41 (q, $^3J_{HH}$=6.5 Hz, 1H), 5.11 (s, 1H), 4.18 (s, 5H), 4.05 (d, $^3J_{HH}$=4.0 Hz, 1H), 2.54 (d, $^3J_{HH}$=4.5 Hz, 1H), 1.87 (d, $^3J_{HH}$=6.5 Hz, 3H), 1.33 (s, 9H).

^{13}C NMR (125 MHz, CD_2Cl_2): δ 144.7, 133.9, 133.1, 128.3, 128.2, 128.1, 126.4, 125.9, 124.8, 124.1, 75.5, 68.9, 68.6, 68.5, 54.4, 41.4 (br), 30.0, 25.9.

^{11}B NMR (96 MHz, CD_2Cl_2): δ 17.1.

FTIR (thin film) 3056, 2973, 1424, 1400, 1386, 1366, 1329, 1268, 1239, 1085 cm^{-1}.

HRMS (EI) calcd for $C_{24}H_{28}BNFeO$ (M^+) 413.1608, found 413.1625.

$[\alpha]_D$ −500 (*c* 0.10, CH_2Cl_2; >95% de).

Recovery of (+)-5 (Ref. 9). In a glove box, a vial was charged with a solution of (−)-**6** (64 mg, 0.083 mmol) in CH_2Cl_2 (0.65 mL). TBAF (1.0 M solution in THF; 92 μL, 0.092 mmol) was added, and then the progress of the reaction was monitored by ^{11}B NMR. Complete conversion was achieved within 3 h, during which time the reaction mixture changed from blue-purple to burgundy (the color of (+)-**5**). The reaction mixture was concentrated under vacuum and then purified by silica gel chromatography (ethyl acetate → ethyl acetate/Et_3N). The first compound to elute was (+)-(η^5-1-*tert*-butyl-2-fluoro-1,2-azaborolyl)(η^5-cyclopentadienyl)iron:[4a] orange solid, 17 mg (78%), $[\alpha]_D$ +160 (*c* 0.31, CH_2Cl_2; >95% ee), mp 47–49 °C. The second, burgundy-colored fraction contained (+)-**5**, which was contaminated with a tetrabutylammonium-containing impurity. Pure (+)-**5** was obtained after aqueous extraction (water/Et_2O) and flash chromatography (ethyl acetate → ethyl acetate/Et_3N) (29.5 mg, 94%).

Determination of the ee of (+)-(η^5-1-*tert*-butyl-2-fluoro-1,2-azaborolyl)(η^5-cyclopentadienyl)iron (Ref. 9). The ee was determined through ^1H NMR analysis of its (*S*)-(−)-α-methyl-2-naphthalenemethanol derivative, which was prepared according to the general procedure: >95% ee.

Eq. 6 (2-methyl-1-pyrroline complex). In a glove box, a vial was charged with a solution of (−)-**4** (40.0 mg, 0.102 mmol) in CH_2Cl_2 (1.2 mL). 2-Methyl-1-pyrroline (15 μL, 0.153 mmol) was added via a syringe. The reaction mixture was allowed to sit at rt for 7 h. Pentane was carefully layered on top of the reaction mixture to induce crystallization. The desired complex crystallized as an orange solid (44.7 mg, 92%). Crystals suitable for X-ray analysis were grown from a CH_2Cl_2/hexanes solution.

^1H NMR (500 MHz, CD_2Cl_2): δ 5.41 (s, 1H), 5.08–5.02 (m, 1H), 4.92–4.87 (m, 1H), 4.61 (d, $^3J_{HH}$=4.0 Hz, 1H), 4.40 (s, 5H), 3.51 (d, $^3J_{HH}$=3.5 Hz, 1H), 3.44–3.39 (m, 2H), 2.56–2.51 (m, 1H), 2.42–2.32 (m, 1H), 2.34 (s, 3H), 1.23 (s, 9H).

^{13}C NMR (125 MHz, CD_2Cl_2): δ 201.8, 73.3, 73.1, 70.6, 67.5, 59.1 (br), 56.4, 42.3, 30.8, 21.1, 20.9.

^{11}B NMR (160 MHz, CD_2Cl_2): δ 10.8.

FTIR (thin film) 3094, 2975, 1641, 1374, 1265, 1224, 1156, 1031 cm^{-1}.

HRMS (ESI) calcd for $C_{17}H_{26}BN_2Fe$ (M^+) 325.1533, found 325.1524.

$[\alpha]_D$ −230 (*c* 0.10, CH_2Cl_2; >95% ee).

Mp 185–187 °C.

Eq. 6 (6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline complex). In a glove box, a vial was charged with a solution of (−)-**4** (50.0 mg, 0.128 mmol) in CD_2Cl_2 (0.9 mL) and then 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline[15] (52.4 mg, 0.255 mmol). The reaction mixture was stirred at rt for 2 h and then at 70 °C for 19 h, after which time ^1H NMR indicated that the reaction was complete. The reaction mixture was cooled to rt, and then Et_2O was carefully layered on top of the reaction mixture in order to induce crystallization. The resulting solid was recrystallized from Et_2O/CH_2Cl_2 (79.6 mg, 103% yield, 95% purity according to ^1H NMR).

^1H NMR (500 MHz, CD_2Cl_2): δ 7.23 (s, 1H), 6.98 (s, 1H), 5.50 (s, 1H), 5.12–5.06 (m, 1H), 4.98–4.90 (m, 1H), 4.65 (d, $^3J_{HH}$=3.5 Hz, 1H), 4.43 (s, 5H), 4.03 (s, 3H), 3.91 (s, 3H), 3.38 (d, $^3J_{HH}$=4.5 Hz, 1H), 3.31–3.26 (m, 2H), 2.58 (s, 3H), 1.30 (s, 9H).

^{13}C NMR (125 MHz, CD_2Cl_2): δ 181.4, 157.9, 149.4, 134.5, 120.4, 112.4, 111.3, 72.9, 72.6, 70.9, 57.8 (br), 57.3, 57.0, 56.5, 55.6, 31.0, 26.7, 24.1.

^{11}B NMR (160 MHz, CD_2Cl_2): δ 14.0.

FTIR (thin film) 3063, 2980, 2943, 2841, 1605, 1550, 1523, 1467, 1430, 1387, 1345, 1265, 1223, 1153, 1068, 1031 cm^{-1}.

HRMS (ESI) calcd for $C_{24}H_{32}BN_2O_2Fe$ (M^+) 447.1901, found 447.1916.

$[\alpha]_D$ −450 (*c* 0.020, CH_2Cl_2; >95% ee).

Mp 120–125 °C (decomposition).

Table 1, entry 1. In a glove box, a vial was charged with a solution of the 2-methyl-1-pyrroline complex (39.3 mg, 0.0829 mmol) in CH_2Cl_2 (2.1 mL). This solution was cooled to −35 °C, and then allylmagnesium bromide (1.0 M solution in Et_2O; 91 μL, 0.091 mmol) was added dropwise. The reaction mixture was allowed to stand at −35 °C, with occasional shaking, for 2 h, and then it was warmed to rt. Pentane was added, the reaction mixture was filtered through an acrodisc, and the filtrate was concentrated under vacuum. The resulting residue was then purified by flash chromatography (pentane/Et_2O/Et_3N), which furnished the desired product as an orange oil (29.0 mg, 96%). ^1H NMR analysis indicated that the de of this mixture was >90%.

^1H NMR (500 MHz, C_6D_6): δ 6.15–6.08 (m, 1H), 5.22–5.14 (m, 2H), 4.82 (s, 1H), 4.13 (s, 5H), 4.10 (d, $^3J_{HH}$=4.0 Hz, 1H), 3.74–3.69 (m, 1H), 3.63–3.58 (m, 1H), 3.19 (d, $^3J_{HH}$=4.0 Hz, 1H), 2.81–2.77 (m, 1H), 2.68–2.64 (m, 1H), 2.09–2.04 (m, 1H), 1.85–1.74 (m, 2H), 1.50–1.44 (m, 1H), 1.18 (s, 3H), 1.10 (s, 9H).

^{13}C NMR (125 MHz, C_6D_6): δ 138.6, 116.6, 71.0, 70.9, 69.0, 63.8, 58.2 (br), 55.3, 54.9, 45.5, 38.7, 30.8, 29.0, 25.3.

^{11}B NMR (160 MHz, C_6D_6): δ 14.3.

FTIR (thin film) 3071, 2960, 2868, 1636, 1431, 1382, 1361, 1210, 1152, 1128, 1106, 1081 cm^{-1}.

HRMS (EI) calcd for $C_{20}H_{31}BN_2Fe$ (M^+) 366.1924, found 366.1933.

$[\alpha]_D$ −510 (*c* 0.10, CH_2Cl_2; >90% de).

Table 1, entry 2. In a glove box, a vial was charged with a solution of the 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline adduct (40.0 mg, 0.0670 mmol) in CH_2Cl_2 (1.6 mL). This solution was cooled to −35 °C, and allylmagnesium bromide (1.0 M solution in Et_2O; 79 μL, 0.079 mmol) was added dropwise. The reaction mixture was allowed to stand at −35 °C, with occasional shaking, for 3 h, and then it was concentrated under vacuum. The resulting residue was purified by silica gel chromatography (pentane/Et_2O/Et_3N). Repurification of this material by flash chromatography (pentane/Et_2O) furnished the desired product as an orange foam (27.1 mg, 83%). ^1H NMR analysis indicated that the de of this mixture was 87%.

^1H NMR (500 MHz, CD_2Cl_2): δ 6.68 (s, 1H), 6.59 (s, 1H), 5.99–5.90 (m, 1H), 5.23 (s, 1H), 5.01–4.94 (m, 2H), 4.24 (d, $^3J_{HH}$=5.0 Hz, 1H), 4.20 (s, 5H), 4.13–4.03 (m, 2H), 3.81 (s, 3H), 3.76 (s, 3H), 3.17 (d, $^3J_{HH}$=5.0 Hz, 1H), 3.11–3.07 (m, 1H), 2.94–2.88 (m, 1H), 2.73–2.69 (m, 2H), 1.29 (app. s, 12H).

^{13}C NMR (125 MHz, CD_2Cl_2): δ 147.4, 146.8, 138.6, 136.9, 128.5, 116.0, 112.0, 111.4, 70.8, 70.1, 69.1, 58.5 (br), 58.5, 56.5, 56.1, 55.4, 48.9, 47.0, 30.8, 30.6, 29.8.

^{11}B NMR (160 MHz, CD_2Cl_2): δ 16.8.

FTIR (thin film) 3070, 2973, 2932, 2908, 2831, 1635, 1610, 1514, 1464, 1362, 1251, 1209, 1189, 1157, 1105 cm^{-1}.

HRMS (EI) calcd for $C_{27}H_{37}BN_2O_2Fe$ (M^+) 488.2292, found 488.2283.

$[\alpha]_D$ −340 (*c* 0.10, CH_2Cl_2; 87% de).

Table 1, entry 3. In a glove box, a vial was charged with a solution of the 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline adduct (18.4 mg, 0.0310 mmol) in CH_2Cl_2 (0.75 mL). This solution was cooled to −35 °C, and lithium triethylborohydride (1.0 M solution in THF; 37 μL, 0.037 mmol) was added dropwise. The reaction mixture was allowed to stand at −35 °C, with occasional shaking, for 2 h, and then it was concentrated under vacuum. The resulting residue was purified by flash chromatography (pentane/Et_2O/Et_3N), which furnished the desired product as an orange oil (9.6 mg, 69%). ^1H NMR analysis indicated that the de of this mixture is 86%.

^1H NMR (500 MHz, CD_2Cl_2): δ 6.63 (s, 1H), 6.60 (s, 1H), 5.19 (s, 1H), 4.33 (q, $^3J_{HH}$=6.0 Hz, 1H), 4.18 (s, 6H), 3.81 (s, 3H), 3.80 (s, 3H), 3.56–3.50 (m, 1H), 3.52–3.31 (m, 1H), 3.11–3.05 (m, 1H), 2.84 (d, $^3J_{HH}$=4.5 Hz, 1H), 2.63–2.58 (m, 1H), 1.49 (d, $^3J_{HH}$=6.5 Hz, 3H), 1.28 (s, 9H).

^{13}C NMR (125 MHz, CD_2Cl_2): δ 147.2, 147.1, 134.8, 127.9, 112.3, 110.4, 70.2, 69.5, 68.6, 56.4 (br), 56.2, 56.0, 55.9, 54.6, 44.9, 30.2, 29.4, 22.9.

^{11}B NMR (160 MHz, CD_2Cl_2): δ 16.7.

FTIR (thin film) 3052, 2963, 2928, 2830, 1610, 1515, 1464, 1393, 1360, 1330, 1246, 1230, 1209, 1118, 1105 cm^{-1}.

HRMS (EI) calcd for $C_{24}H_{33}BN_2O_2Fe$ (M^+) 448.1979, found 448.1996.

$[\alpha]_D$ −480 (*c* 0.10, CH_2Cl_2; 86% de).

General procedure for B–N cleavage (Table 1). In a glove box, TBAF (1.0 M solution in THF; 4 equiv) was added to a solution of compound **7** in THF (0.6 mL). The course of the reaction was followed by ^{11}B NMR. After the starting material had been consumed, the reaction mixture was concentrated under vacuum, and the residue was purified by flash chromatography (CH_2Cl_2/Et_3N).

Table 1, entry 1: B–N cleavage and assay of ee. The general procedure was followed. The 2-allyl-2-methylpyrrolidine was derivatized with trifluoromethanesulfonyl anhydride according to a procedure in lit. 16.

The enantiomeric excess of the sulfonamide was determined to be 94% by GC analysis (Chiraldex β-PH; 20 m×0.25 mm, 105 °C oven temperature, helium as carrier gas; (*S*) isomer (minor) 41.9 min, (*R*) isomer (major) 43.2 min). The configurational assignment (*R*) was made by comparison with the optical rotation reported in the literature: $[\alpha]_D$ +28 (*c* 0.36, CH_2Cl_2); lit.[16] (*R*) enantiomer, $[\alpha]_D$ +29 (*c* 2.0, CH_2Cl_2; 100% ee).

Table 1, entry 2: B–N cleavage and assay of ee. The general procedure was followed.

^1H NMR (500 MHz, CD_2Cl_2): δ 6.65 (s, 1H), 6.53 (s, 1H), 5.71–5.63 (m, 1H), 5.10–5.03 (m, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.08–2.97 (m, 2H), 2.66–2.60 (m, 3H), 2.36–2.31 (m, 1H), 1.34 (s, 3H).

^{13}C NMR (125 MHz, CD_2Cl_2): δ 147.5, 147.4, 135.4, 135.2, 127.7, 118.0, 112.0, 109.7, 56.2, 55.8, 55.0, 47.1, 39.1, 30.4, 29.3.

FTIR (thin film) 3312, 3072, 2931, 2832, 1637, 1610, 1514, 1465, 1401, 1366, 1354, 1325, 1259, 1225, 1153 cm^{-1}.

HRMS (ESI) calcd for $C_{15}H_{22}NO_2$ (M^++H) 248.1645, found 248.1652.

$[\alpha]_D$ −53 (*c* 0.63, THF; 86% ee).

The enantiomeric excess was determined to be 86% by HPLC analysis (Daicel Chiralpak OD; hexane:*i*-PrOH= 97:3, 1.0 mL/min; (*R*) isomer (minor) 13.8 min, (*S*) isomer (major) 15.5 min). The configurational assignment (*S*) was made by comparison with the optical rotation reported in the literature: $[\alpha]_D$ −53 (*c* 0.63, THF); lit.[17] (*R*) enantiomer, $[\alpha]_D$ +48 (*c* 2.1, THF; 76% ee).

Table 1, entry 3: B–N cleavage and assay of ee: (*R*)-salsolidine. The general procedure was followed.

^1H NMR (500 MHz, C_6D_6): δ 6.49 (s, 1H), 6.38 (s, 1H), 3.97 (q, $^3J_{HH}$=7.0 Hz, 1H), 3.44 (s, 3H), 3.42 (s, 3H), 3.07–3.03 (m, 1H), 2.84–2.79 (m, 1H), 2.71–2.65 (m, 1H), 2.50–2.45 (m, 1H), 1.39 (d, $^3J_{HH}$=6.5 Hz, 3H).

The enantiomeric excess was determined to be 87% by HPLC analysis (Daicel Chiralpak OD; hexane:*i*-PrOH= 80:20, 0.5 mL/min; (*S*) isomer (minor) 18.2 min, (*R*) isomer (major) 21.4 min). The configurational assignment (*R*) was made by comparison with the optical rotation reported in the literature: $[\alpha]_D$ +39 (*c* 0.070, EtOH); lit.[18] (*R*) enantiomer, $[\alpha]_D$ +59 (*c* 2, EtOH; 100% ee).

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References and notes

1. For leading references, see: (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; (b) *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley: New York, NY, 2000.
2. For some examples and leading references, see: (a) Gladysz, J. A.; Boone, B. J. *Angew. Chem., Int. Ed.* **1997**, *36*, 551–583; (b) Faller, J. W.; Grimmond, B. J.; D'Alliessi, D. G. *J. Am. Chem. Soc.* **2001**, *123*, 2525–2529.
3. (a) For an overview, see: Fu, G. C. *J. Org. Chem.* **2004**, *69*, 3245–3249; (b) Liu, S.-Y.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 15352–15353; (c) Amendola, M. C.; Stockman, K. E.; Hoic, D. A.; Davis, W. M.; Fu, G. C. *Angew. Chem., Int. Ed.* **1997**, *36*, 267–269; (d) Tweddell, J.; Hoic, D. A.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 8286–8287.
4. For additional investigations of 1,2-azaborolyl chemistry from our laboratory, see: (a) Liu, S.-Y.; Lo, M.-C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 174–176; (b) Liu, S.-Y.; Hills, I. D.; Fu, G. C. *Organometallics* **2002**, *21*, 4323–4325.
5. For leading references to pioneering studies of 1,2-azaborolyl chemistry, see: (a) Schmid, G. *Comprehensive Heterocyclic Chemistry II*; Shinkai, I., Ed.; Elsevier: Oxford, 1996; Vol. 3, Chapter 3.17; (b) Schmid, G. *Comments Inorg. Chem.* **1985**, *4*, 17–32.
6. For a recent report on 1,2-azaborolyl chemistry, see: Fang, X.; Yang, H.; Kampf, J. W.; Holl, M. M. B.; Ashe, A. J., III. *Organometallics* **2006**, *25*, 513–518.
7. For leading references, see: Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542–547.
8. Selectivity factor (*s*)=(rate of fast-reacting enantiomer/rate of slow-reacting enantiomer). For a classic review of kinetic resolutions, see: Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249–330.
9. By reacting **6** with TBAF, enantiopure DMAP derivative (+)-**5** can be recovered in 94% yield (along with the B-fluorinated (η^5-1,2-azaborolyl)iron complex: 78% yield and >95% ee).
10. For a review of *peri* interactions in naphthalene derivatives, see: Balasubramaniyan, V. *Chem. Rev.* **1966**, *66*, 567–641.
11. For leading references to asymmetric additions to imines, see: (a) Vilaivan, T.; Bhanthumnavin, W.; Sritana-Anant, Y. *Curr. Org. Chem.* **2005**, *9*, 1315–1392; (b) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069–1094.
12. For examples of highly enantioselective allylations of ketone-derived benzoylhydrazones with a stoichiometric enantiopure allylsilane reagent, see: Berger, R.; Duff, K.; Leighton, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 5686–5687.
13. For a review of synthetic pathways to salsolidine, see: Kaufman, T. S. *Tetrahedron: Asymmetry* **2004**, *15*, 1203–1237.
14. Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532–11533.
15. This was prepared in analogy to a procedure reported for 6,7-methylenedioxy-3,4-dihydroisoquinoline: Slemon, C. E.; Hellwig, L. C.; Ruder, J.-P.; Hoskins, E. W.; MacLean, D. B. *Can. J. Chem.* **1981**, *59*, 3055–3060.
16. Burgess, L. E.; Meyers, A. I. *J. Am. Chem. Soc.* **1991**, *113*, 9858–9859.
17. Meyers, A. I.; Gonzalez, M. A.; Struzka, V.; Akahane, A.; Guiles, J.; Warmus, J. S. *Tetrahedron Lett.* **1991**, *32*, 5501–5504.
18. Menachery, M. D.; Lavanier, G. L.; Wetherly, M. L.; Guinaudeau, H.; Shamma, M. *J. Nat. Prod.* **1986**, *49*, 745–778.