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# Synthesis and Resolution of Planar-Chiral Derivatives of 4-(Dimethylamino)pyridine

Ryan P. Wurz,[a] Elaine C. Lee,[a] J. Craig Ruble,[a] and Gregory C. Fu[a,*]

[a] Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, USA
Fax: (+1)-617-324-3611; e-mail: gcf@mit.edu

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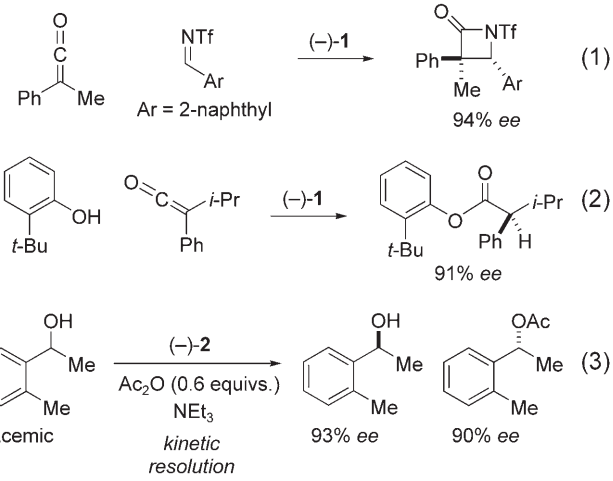
**Abstract:** A safer and more efficient method for the synthesis of planar-chiral 4-(dimethylamino)pyridine (DMAP) derivatives has been developed. Racemic mixtures of the complexes can be resolved *via* classical resolution with commercially available tartaric acids.

**Keywords:** asymmetric catalysis; asymmetric synthesis; heterocycles; homogeneous catalysis

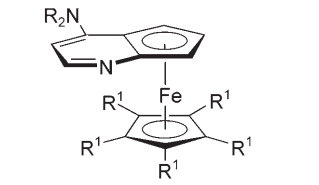
## Introduction

During the past decade, we have established that planar-chiral derivatives of 4-(dimethylamino)pyridine (DMAP) and 4-(pyrrolidino)pyridine (PPY) serve as effective enantioselective catalysts for a wide variety of transformations [e.g., Eqs. (1–3)].[1,2] To build these complexes, we adopted the modular approach illustrated in Scheme 1, which involves a one-pot assembly from $FeCl_2$, a cyclopentadienyllithium, and a heterocycle.

Our initial route to the bicyclic DMAP derivatives (X–H) required six steps from commercially available 2,3-cyclopentenopyridine and proceeded in ~5% overall yield. The racemic planar-chiral DMAP derivatives **1** and **2** were then synthesized as in Scheme 1, and they were resolved *via* HPLC on a chiral stationary phase.[3] However, it was later determined that an intermediate in the original preparation, 4-nitro-2,3-cyclopentenopyridine *N*-oxide,[4] can decompose violently at >100 °C. As a consequence, we developed an alternative nine-step synthesis of the bicyclic pyridines that began with adipoyl chloride.[5] Because access to catalysts **1** and **2** was impeded by the length of the route and the reliance upon HPLC to separate the enantiomers, we sought an improved process. In this report, we describe: 1) streamlined, "low-tech" preparations of the heterocyclic frameworks (X–H), and 2) classical resolutions of the racemic iron complexes.




**Scheme 1.**

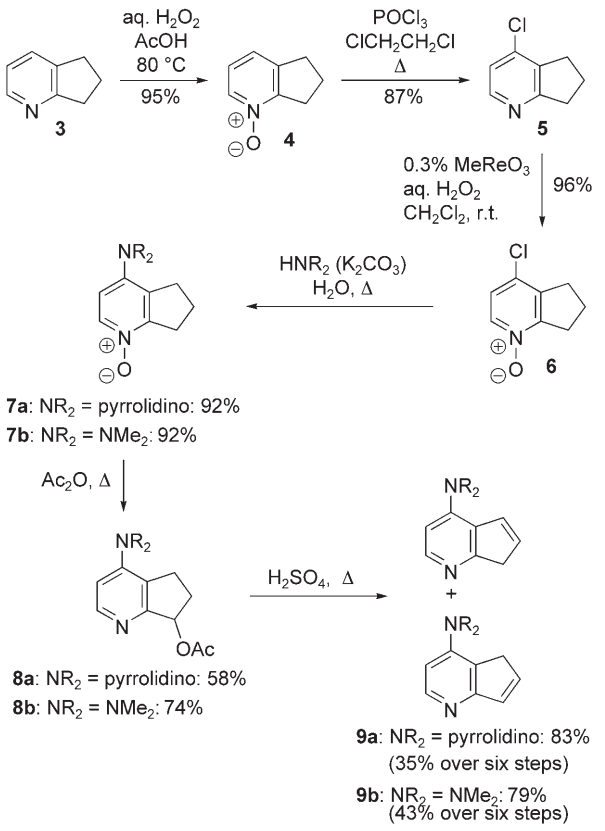


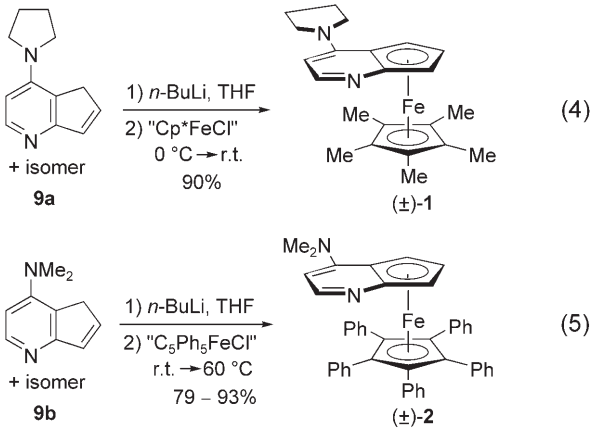
## Results and Discussion

Our new route (Scheme 2) commences with a two-step procedure that effects 4-chlorination of the pyridine ring of 2,3-cyclopentenopyridine.[6] Thus, treatment of **3** with $H_2O_2$/AcOH[7] and then $POCl_3$ furnishes target compound **5** in good overall yield (83% for two steps). The selective chlorination of **4** in the *para* position is noteworthy, since reactions of pyridine *N*-oxides with $POCl_3$ are typically not highly *para* selective.[8] Next, the pyridine nitrogen of **5** is oxidized in almost quantitative yield ($H_2O_2$ and catalytic $MeReO_3$;[9] 96%), thereby setting the stage for amination of the 4 position and oxidation of the fused five-membered ring. This three-step sequence has been conducted on a large scale (>100 g) without chromatographic purification of any intermediate.[10]

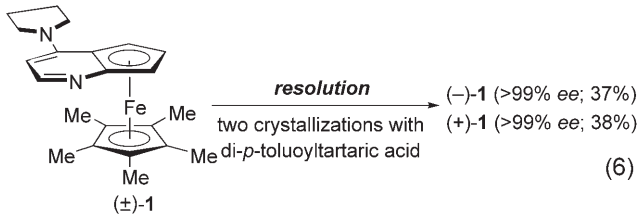
Pyridine *N*-oxide **6** is well-suited for the synthesis of a variety of derivatives *via* substitution of the halide. For our purposes, we need to effect displacement of the chloride with pyrrolidine and dimethylamine, which can be accomplished simply by heating **6** in the presence of aqueous base (92% yield).[11] Treatment of the resulting 4-aminopyridines (**7**) with $Ac_2O$ furnishes the desired acetates (**8**), which undergo elimination under acidic conditions to afford the target bicyclic pyridines as mixtures of olefin isomers (**9**).[12] The relative simplicity and low cost of the reagents that are used in this synthetic sequence are noteworthy (Scheme 2). The heterocycles (**9**) can then be complexed to iron in good yield [Eqs. (4) and (5)].

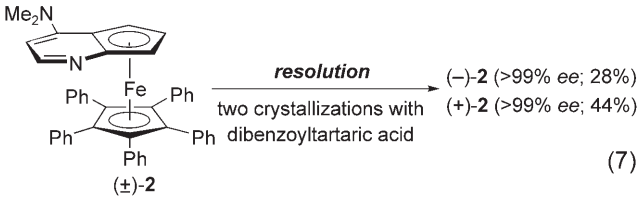



**Scheme 2.**




As indicated above, for our early studies we obtained enantiopure **1** and **2** from the racemic catalysts *via* preparative HPLC on a chiral stationary phase. In order to provide wider access to these complexes, we have now developed classical resolutions with tartaric acid derivatives that furnish the catalysts in >99% *ee*. In the case of **1**, di-*p*-toluoyltartaric acid is the resolving agent of choice [Eq. (6)], whereas, for **2**, dibenzoyltartaric acid has proved to be the most efficient [Eq. (7)].




## Conclusions

We have developed a new route to enantiopure planar-chiral DMAP derivatives that addresses several drawbacks associated with earlier approaches. Specifically, a potentially hazardous intermediate is avoided, improved yields are obtained, and preparative chiral HPLC is unnecessary.

## Experimental Section

### General Remarks

Unless otherwise specified, reactions were performed in the air with no precautions to exclude moisture. Analytical HPLC analyses were carried out on an Agilent Technologies 1100 Series instrument with Daicel Chiralpak® or Regis columns in hexanes/2-propanol or hexanes/$CH_2Cl_2$ mixtures; data are reported as follows: column type, eluent, flow rate, and retention time ($t_r$). Low-resolution mass spectrometric measurements were performed on an Agilent Technologies LC/MSC SL Multimode (ES/APCI) instrument using a Zorbax Eclipse (Agilent) XDB-C18 column (5 μm particle size, 4.6×150 mm).

### Materials

2,3-Cyclopentenopyridine (6,7-dihydro-5*H*-cyclopenta[*b*]pyridine) [Kinbester Co., Limited (China); >98%[13]] was used as received. $FeCl_2$ (Strem) was ground with a mortar and pestle in a glovebox, prior to use. Other reagents and solvents were obtained from Strem or Aldrich and used as received.

### 2,3-Cyclopentenopyridine *N*-Oxide (6,7-Dihydro-5*H*-cyclopenta[*b*]pyridine 1-Oxide; 4)[7]

Glacial acetic acid (500 mL) was added over ~2 min (to control the exotherm) to a 2-liter flask that contained 2,3-cyclopentenopyridine (100 g, 0.84 mol). Then, an aqueous solution of $H_2O_2$ (30%; 90 mL, 0.87 mol) was added, and the flask was fitted with a reflux condenser capped with a septum and a needle (vent). The reaction mixture was heated to 80 °C behind a blast shield (as a precaution; no accidents have occurred). After stirring at 80 °C for 6 h, the solution was treated with additional aqueous $H_2O_2$ (90 mL, 0.87 mol) and stirred for 18 h at 80 °C. Then, the reaction mixture was allowed to cool to room temperature, and the acetic/peracetic acid was removed on a rotary evaporator. The resulting pale-yellow residue was cooled in an ice bath and then carefully treated with aqueous $K_2CO_3$ (100 g in 250 mL of distilled water) until the solution reached pH ~10. The mixture was then extracted with $CHCl_3$ (4× 250 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated on a rotary evaporator. The product crystallized as a white solid, which was rinsed with methyl *tert*-butyl ether (2×200 mL). The washings were concentrated on a rotary evaporator, which led to the precipitation of additional *N*-oxide **4**. This precipitated solid was washed with methyl *tert*-butyl ether (3×30 mL) and then combined with the initial batch of product. Compound **4** was dried under vacuum overnight to afford a free-flowing, white crystalline solid; yield: 108 g (95%); mp 121–123 °C; $^1$H NMR (400 MHz, $CDCl_3$): δ=8.04 (d, $J$=6.2, 0.8 Hz, 1H), 7.13 (d, $J$=6.2 Hz, 1H), 7.05–7.11 (m, 1H), 3.17 (t, $J$=7.7 Hz, 2H), 3.02 (t, $J$=7.7 Hz, 2H), 2.14–2.22 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ=153.3, 142.4, 137.4, 124.0, 122.7, 31.7, 29.7, 22.2; IR (film): $\nu$=3391, 2957, 1602, 1441, 1260, 1063, 1011, 800 cm$^{-1}$; LR-MS (ES/APCI): calcd. for $C_8H_9NO$ [M+Na$^+$]: 158.2, found: 158.1.

### 4-Chloro-6,7-dihydro-1,5-pyrindane (4-Chloro-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine; 5)

Under argon, $POCl_3$ (234 g, 142 mL, 1.52 mol) was added slowly (dropwise over 30 min) to a 0 °C solution of 2,3-cyclopentenopyridine *N*-oxide (**4**; 103 g, 0.76 mol) in anhydrous 1,2-dichloroethane (500 mL) in a 2-L flask that was placed in an ice bath. The reaction mixture, which turned orange-brown, was stirred for 1 h at room temperature (***note:*** this procedure should be adhered to, in order to avoid a substantial exotherm). The reaction vessel was then fitted with a condenser and slowly heated to reflux for 2 h. Next, the reaction mixture was allowed to cool to room temperature, and the solvent and the excess $POCl_3$ were removed on a rotary evaporator, leading to a viscous brown oil. The flask was placed in an ice bath, and small pieces of ice were cautiously added (~50 g; ***note:*** if too much ice is added initially, then a substantial exotherm will result). The mixture was then treated with a solution of 6 N NaOH (~500 mL) *via* a dropping funnel (ice was added, in order to keep the reaction at ~5 °C) until pH 7. The mixture was transferred to a separatory funnel and extracted with diethyl ether (6× 350 mL), and the combined extracts were dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator, affording a dark-orange oil; yield: 102 g (87%).

This material was judged to be 94% pure by $^1$H NMR spectroscopy, and it was used in the next step without further purification. $R_f$=0.17 (20% EtOAc:hexanes); $^1$H NMR (400 MHz, $CDCl_3$): δ=8.24 (d, $J$=5.5 Hz, 1H), 7.07 (d, $J$=5.4 Hz, 1H), 3.10 (t, $J$=7.8 Hz, 2H), 3.01 (t, $J$=7.6 Hz, 2H), 2.12–2.20 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ=167.1, 148.4, 140.5, 135.6, 121.2, 34.9, 29.8, 21.9; IR (film): $\nu$=2959, 1583, 1558, 1458, 1390, 903, 817 cm$^{-1}$; LR-MS (ES/APCI): calcd. for $C_8H_8ClN$ [M+H$^+$]: 154.6; found: 154.1.

### 4-Chloro-6,7-dihydro-1,5-pyrindane *N*-Oxide (4-Chloro-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine 1-Oxide; 6)

$MeReO_3$ (500 mg, 2.01 mmol, 0.31 mol%) was added to a solution of 4-chloro-6,7-dihydro-1,5-pyrindane (**5**; 100 g, 0.65 mol) in $CH_2Cl_2$ (200 mL) in a 2-L round-bottomed flask. To this stirred solution was added an aqueous solution of $H_2O_2$ (30%; 130 mL, 1.26 mol; in one portion). The flask was then capped with a septum and a needle (vent), and the mixture was allowed to stir at room temperature for 25 h (the reaction mixture turned orange, and then bright yellow as the reaction progressed). Next, the excess $H_2O_2$ was quenched by the addition of small portions of activated $MnO_2$ powder (10–20 mg), which resulted in the rapid evolution of $O_2$. After the effervescence had subsided (~30 min), the dark-green reaction mixture was treated with brine (200 mL) and extracted with $CH_2Cl_2$ (4×200 mL). The combined organic extracts were dried over $MgSO_4$ and filtered through a pad of celite. Removal of the solvent on a rotary evaporator resulted in the formation of olive-green crystals, which were dried under vacuum overnight; yield: 106 g (96%).

The product was judged to be 92% pure by $^1$H NMR spectroscopy, and it was used in the next step without further purification; mp 110–113 °C; $R_f$=0.16 (acetone); $^1$H NMR (400 MHz, $CDCl_3$): δ=7.99 (d, $J$=6.8 Hz, 1H),

7.09 (d, $J=6.8$ Hz, 1H), 3.24 (t, $J=7.8$ Hz, 2H), 3.07 (d, $J=7.7$ Hz, 2H), 2.19–2.27 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta=154.4$, 140.7, 139.4, 127.0, 125.1, 31.8, 31.2, 21.8; IR (film): $\nu=3406$, 3077, 2962, 1662, 1437, 1311, 1264, 1236, 1014, 825, 726 cm$^{-1}$; LR-MS (ES/APCI): calcd. for $C_8H_8ClNO$ [M+H$^+$]: 170.6; found: 170.0.

### 4-Pyrrolidino-6,7-dihydro-1,5-pyrindane *N*-Oxide (7a)

Pyrrolidine (189 g, 221 mL, 2.65 mol) was added slowly (to avoid an exotherm) to a solution of 4-chloro-6,7-dihydro-1,5-pyrindane *N*-oxide (**6**; 90.0 g, 0.53 mol) and $K_2CO_3$ (89.4 g, 0.54 mol) in distilled water (300 mL) in a 2-L round-bottomed flask. The flask was fitted with a reflux condenser, and the mixture was heated, with stirring, under air at 90–95 °C for 17 h. Then, the reaction mixture was cooled to room temperature, and the solvent was removed on a rotary evaporator, furnishing a black solid. Toluene (100 mL) was added in order to azeotropically remove the remaining water. The product was extracted from the black solid with 1:1 acetone:$CH_2Cl_2$ (6×300 mL). The dark-purple extracts were combined, dried over anhydrous $Na_2SO_4$, filtered, and concentrated on a rotary evaporator. The resulting purple-black solid was dissolved in warm acetone (120 mL; 40–50 °C), and then methyl *tert*-butyl ether (600 mL) was added. This solution was heated to 70 °C for 10 min, and then it was cooled in an ice bath, leading to the precipitation of *N*-oxide **7a**. The product was collected by filtration, washed with methyl *tert*-butyl ether (300 mL) to remove a purple impurity and then dried under vacuum overnight, affording a gray, free-flowing solid; yield: 100 g (92%).

The product was judged to be >99% pure by $^1$H NMR spectroscopy; m.p. 80–83 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta=7.84$ (d, $J=7.1$ Hz, 1H), 6.20 (d, $J=7.1$ Hz, 1H), 3.47–3.50 (m, 4H), 3.27 (t, $J=7.5$ Hz, 2H), 3.15 (t, $J=7.8$ Hz, 2H), 2.06–2.14 (m, 2H), 1.97–2.02 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$); $\delta=153.7$, 145.2, 137.4, 122.8, 107.7, 49.5, 33.1, 29.9, 25.6, 22.3; IR (film): $\nu=3375$, 2963, 1624, 1495, 1457, 1230, 982 cm$^{-1}$; LR-MS (ES/APCI): calcd. for $C_{12}H_{16}N_2O$ [M+H$^+$]: 205.3; found: 205.1.

### 4-(Dimethylamino)-6,7-dihydro-1,5-pyrindane *N*-Oxide (7b)

With stirring, 4-chloro-6,7-dihydro-1,5-pyrindane *N*-oxide (**6**; 40.0 g, 236 mmol) was dissolved in a solution of $Me_2NH$ in water (40 wt%; 100 mL, 790 mmol) in a 500-mL round-bottomed flask. The solution was transferred to a 250-mL stainless steel Parr apparatus (due to the volatility of $Me_2NH$) using additional $Me_2NH$ solution (80 mL, 632 mmol) in order to ensure quantitative transfer. The Parr apparatus was sealed and heated to 75 °C in an oil bath with stirring for 24 h (behind a blast shield, as a precaution). Next, the Parr apparatus was cooled in an ice bath, and the reaction mixture was poured into an Erlenmeyer flask. $K_2CO_3$ (39.8 g, 241 mmol) was added, and the mixture was stirred for 30 min. The solution was transferred to a 1-L round-bottomed flask, and the solvent was removed on a rotary evaporator, leading to a black solid. The product was extracted from the solid with 1:1 acetone:$CH_2Cl_2$ (6×200 mL). The dark-purple extracts were combined, dried over anhydrous $Na_2SO_4$, filtered, and concentrated on a rotary evaporator, providing a black crystalline solid that was judged to be 95% pure by $^1$H NMR spectroscopy; yield: 38.7 g (92%); mp 150–156 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta=7.90$ (d, $J=7.2$ Hz, 1H), 6.40 (d, $J=7.2$ Hz, 1H), 3.16 (t, $J=7.8$ Hz, 2H), 3.11 (t, $J=7.4$ Hz, 2H), 2.96 (s, 6H), 2.13 (pent. $J=7.5$ Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta=153.7$, 147.9, 137.3, 126.4, 109.3, 41.4, 33.1, 29.7, 22.6; IR (film): $\nu=3379$, 2957, 1621, 1509, 1434, 1236, 976, 816, 735 cm$^{-1}$; LR-MS (ES/APCI): calcd, for $C_{10}H_{14}N_2O$ [M+H$^+$]: 179.2; found: 179.2.

### 4-Pyrrolidino-7-acetoxy-6,7-dihydro-1,5-pyrindane–Acetic Acid Adduct (8a)

In a 1-L flask, a mixture of acetic anhydride (200 g, 185 mL, 1.96 mol) and distilled water (2.1 mL, 117 mmol)[7] was stirred at room temperature for 10 min under nitrogen. The flask was then cooled in an ice bath, and 4-pyrrolidino-6,7-dihydro-1,5-pyrindane *N*-oxide (**7a**; 50.0 g, 0.24 mol) was added slowly *via* a glass funnel over 15 min (to prevent an exotherm). The flask was purged with nitrogen, and the mixture was stirred at room temperature for 1 h. The flask was then fitted with a reflux condenser, and the reaction mixture was heated to 80 °C with stirring under nitrogen for 25 h. The solvent was removed on a rotary evaporator from the resulting dark-brown reaction mixture, leading to a brown solid. This solid was dissolved in the minimum amount of $CH_2Cl_2$ (~100 mL), and the solution was passed through a 7-cm pad of silica gel on a 2-L sintered coarse glass frit. The silica gel was rinsed with 30:70 EtOAc:hexane (1 L), 30:60:10 EtOAc:hexane:$Et_3N$ (~1.5 L), and 60:30:10 EtOAc:hexane: $Et_3N$ (5 L), collecting 1-L "fractions". The solvent was removed on a rotary evaporator from the appropriate fractions (as judged by TLC). The resulting beige solid was suspended in methyl *tert*-butyl ether (150 mL) and filtered through a Buechner funnel. The solid was rinsed with additional portions of methyl *tert*-butyl ether (2×50 mL; the product ***is*** somewhat soluble in this solvent, so large volumes should not be used), resulting in a free-flowing, cream-colored solid. The desired product was dried under vacuum overnight (98–99% pure according to $^1$H NMR spectroscopy; acetic acid adduct); yield: 43.5 g (58%); mp 119–120 °C; $R_f=0.51$ (9:1 EtOAc:$Et_3N$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta=11.38$ (br s, 1H), 8.17 (d, $J=6.0$ Hz, 1H), 6.28 (d, $J=6.0$ Hz, 1H), 6.05 (dd, $J=7.5$, 5.1 Hz, 1H), 3.54–3.58 (m, 4H), 3.33–3.42 (m, 1H), 3.11–3.18 (m, 1H), 2.50–2.59 (m, 1H), 2.13 (s, 3H), 2.07 (s, 3H), 1.95–2.02 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta=175.6$, 171.1, 158.7, 152.0, 147.3, 120.4, 107.2, 49.3, 30.5, 29.4, 25.6, 22.0, 21.3; IR (film): $\nu=2976$, 2871, 1736, 1606, 1515, 1372, 1243, 834 cm$^{-1}$; LR-MS (ES/APCI): calcd. for $C_{14}H_{18}N_2O_2$ [M+H$^+$]: 247.3; found: 247.1.

### 4-(Dimethylamino)-7-acetoxy-6,7-dihydro-1,5-pyrindane–Acetic Acid Adduct (8b)

Acetic anhydride (149 g, 138 mL, 1.46 mol) was added to a 1-L flask (in a 0 °C ice bath) that contained 4-(dimethylamino)-6,7-dihydro-1,5-pyrindane *N*-oxide (**7b**; 26.0 g, 0.146 mol). Distilled water (1.25 mL, 69.4 mmol)[7] was added, and the solution was stirred at 0 °C for 30 min. The flask was then fitted with a reflux condenser and heated to 75–80 °C for 24 h under nitrogen. Next, the dark-brown reaction mix-

ture was concentrated on a rotary evaporator, leading to a brown solid, which was dissolved in the minimum amount of $CH_2Cl_2$ (~50 mL) and passed through a pad of silica gel, eluting with 2:3 EtOAc:hexane (500 mL) and then 45:45:10 EtOAc:hexane:$Et_3N$ (800 mL). The desired product was dried under vacuum overnight (tan solid; 98–99% pure according to $^1$H NMR spectroscopy; acetic acid adduct); yield: 30.4 g (74%); m.p. 62–67 °C; $R_f$ = 0.53 (9:1 EtOAc:$Et_3N$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 11.03 (br s, 1H), 8.22 (d, $J$ = 5.9 Hz, 1H), 6.43 (d, $J$ = 5.9 Hz, 1H), 6.05 (dd, $J$ = 7.4, 5.2 Hz, 1H), 3.16–3.22 (m, 1H), 3.05 (s, 6H), 3.00–3.05 (m, 1H), 2.52–2.58 (m, 1H), 2.14 (s, 3H), 2.07 (s, 3H), 1.97–2.03 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 174.9, 170.9, 159.8, 155.0, 148.1, 122.3, 108.0, 41.2, 30.7, 29.7, 21.8, 21.2; IR (film): $\nu$ = 3383, 2945, 1733, 1587, 1509, 1439, 1371, 1243, 1024, 962, 816 cm$^{-1}$; LR-MS (ES/APCI): calcd. for $C_{12}H_{16}N_2O_2$ [M + H$^+$]: 221.3; found: 221.1.

## 4-Pyrrolidinopyrindine [4-(Pyrrolidin-1-yl)-7*H*-cyclopenta[*b*]pyridine; 9a]

4-Pyrrolidino-7-acetoxy-6,7-dihydro-1,5-pyrindane acetic acid adduct (**8a**; 20.0 g, 65.9 mmol) was slowly added in small portions (to avoid an exotherm) to a flask that contained concentrated $H_2SO_4$ (35 mL; in a 0 °C ice bath). The flask was capped under air with a septum and a needle (vent), and then it was heated to 60–65 °C in an oil bath for 80 min. Next, the reaction mixture was cooled in an ice bath, and ice was added. A solution of NaOH (6 N; ~240 mL) was added slowly over 30–40 min until pH ~12 (heavy white precipitate formed). The reaction mixture was extracted with EtOAc (3 × 300 mL) and $CH_2Cl_2$ (3 × 250 mL), and the organic extracts were dried over $Na_2SO_4$ [$Et_3N$ (15 mL) was added, since the product is stabilized by the presence of a weak base], filtered, and concentrated on a rotary evaporator. The resulting brown residue was purified by column chromatography, eluting with 45:45:10 EtOAc:hexane:$Et_3N$ (200 mL) and then 90:10 EtOAc:$Et_3N$ (600 mL). The product, a yellow-green crystalline solid, was judged to be > 98% pure by $^1$H NMR spectroscopy (~60:40 mixture of olefin isomers); yield:10.1 g (83%).

*Note:* This compound is somewhat sensitive, and it is best to use it immediately. Alternatively, it can be stored in a freezer under an inert atmosphere for several weeks without noticeable degradation; mp 84–86 °C (mix of isomers); $R_f$ = 0.27 (45:45:10 EtOAc:hexanes:$Et_3N$); $^1$H NMR (400 MHz, $CDCl_3$): (major isomer) δ = 8.17 (d, $J$ = 5.9 Hz, 1H), 6.98 (dt, $J$ = 5.7, 1.8 Hz, 1H), 6.80 (dt, $J$ = 5.7, 2.0 Hz, 1H), 6.26 (d, $J$ = 5.9 Hz, 1H), 3.74–3.78 (m, 2H), 3.60–3.66 (m, 4H), 2.00–2.11 (m, 4H); (minor isomer) δ = 8.10 (d, $J$ = 5.9 Hz, 1H), 7.22 (dt, $J$ = 6.1, 2.0 Hz, 1H), 6.37 (dt, $J$ = 6.2, 2.1 Hz, 1H), 6.34 (d, $J$ = 5.9 Hz, 1H), 3.60–3.66 (m, 4H), 3.46–3.48 (m, 2H), 2.00–2.11 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$): (major isomer) δ = 164.6, 149.4, 148.5, 136.9, 134.1, 118.7, 104.7, 48.6, 38.9, 25.5; (minor isomer) δ = 166.9, 147.0, 146.0, 130.6, 128.1, 121.7, 105.7, 49.5, 40.8, 25.7; IR (film): $\nu$ = 3367, 2969, 2868, 1693, 1591, 1570, 1484, 1395, 1357, 1059, 900, 800, 708 cm$^{-1}$; LR-MS (ES/APCI): calcd. for $C_{12}H_{14}N_2$ [M + H$^+$]: 187.3; found: 187.1.

## 4-(Dimethylamino)pyrindine (*N*,*N*-Dimethyl-7*H*-cyclopenta[*b*]pyridin-4-amine; 9b)

4-(Dimethylamino)-7-acetoxy-6,7-dihydro-1,5-pyrindane acetic acid adduct (**8b**; 20.0 g, 71.3 mmol) was added in one portion to concentrated $H_2SO_4$ (44 mL) in an ice bath. The mixture was stirred for 10 min at 0 °C, and then it was heated to 60–65 °C in an oil bath for 75 min. Next, the reaction mixture was cooled in an ice bath, and ice was added. The reaction was then slowly quenched over 15 min by the dropwise addition of NaOH (6 N solution; ~350 mL) until pH ~12 (heavy white precipitate formed). The reaction mixture was extracted with EtOAc (6 × 200 mL), and the organic extracts were dried over $Na_2SO_4$ [$Et_3N$ (15 mL) was added, since the product is stabilized by the presence of a weak base], filtered, and concentrated on a rotary evaporator. The resulting yellow residue was purified by column chromatography, eluting with 45:45:10 EtOAc:hexane:$Et_3N$ (1.0 L), which yielded a yellow-green crystalline solid (judged to be > 99% pure by $^1$H NMR spectroscopy; ~85:15 mixture of olefin isomers); yield: 9.04 g (79%).

*Note:* This compound is somewhat sensitive, and it is best to use it immediately. Alternatively, it can be stored in a freezer under an inert atmosphere for several weeks without noticeable degradation; mp 59–63 °C (mix of isomers); $R_f$ = 0.39 (9:1 EtOAc:$Et_3N$); $^1$H NMR (400 MHz, $CDCl_3$): (major isomer) δ = 8.18 (d, $J$ = 5.9 Hz, 1H), 6.93–6.96 (m 1H), 6.76–6.78 (m, 1H), 6.35 (d, $J$ = 5.9 Hz, 1H), 3.63 (s, 2H), 3.14 (s, 6H); (minor isomer) δ = 8.10 (d, $J$ = 5.9 Hz, 1H), 7.14 (dt, $J$ = 8.1, 1.9 Hz, 1H), 6.46 (d, $J$ = 5.9 Hz, 1H), 6.42 (dt, $J$ = 6.1, 2.1 Hz, 1H), 3.43 (s, 2H), 3.11 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): (major isomer) δ = 165.2, 152.6, 148.8, 137.0, 134.2, 120.1, 105.5, 41.4, 39.6; (minor isomer) δ = 167.1, 150.8, 146.3, 130.4, 129.4, 123.9, 106.8, 42.2, 40.9; IR (film): $\nu$ = 2885, 1691, 1589, 1570, 1386, 1373, 1189, 1029, 801 cm$^{-1}$; LR-MS (ES/APCI): calcd. for $C_{10}H_{12}N_2$ [M + H$^+$]: 161.2; found: 161.1.

## 4-Pyrrolidinopyrindinyl-pentamethylcyclopentadienyl-iron (1)

A solution of *n*-BuLi (1.6 M in hexanes; 24.1 mL, 38.6 mmol) was added dropwise over 2 min to a solution of pentamethylcyclopentadiene (5.26 g, 38.6 mmol) in anhydrous THF (200 mL) in a 0 °C ice bath under nitrogen. The resulting white suspension was stirred for 1 h at 0 °C.

Separately, anhydrous THF (80 mL) was added to powdered $FeCl_2$ (4.90 g, 38.6 mmol) in a 2-L round-bottomed flask. The mixture was sonicated for 1 h, resulting in a fine suspension. Next, the mixture was cooled to 0 °C, and the solution that contained the Cp*Li was added by cannula over 10 min to the suspension of $FeCl_2$, leading to a homogeneous green solution, which was stirred at 0 °C for 2.5 h.

In a 250-mL round-bottomed flask, a 0 °C solution of 4-pyrrolidinopyrindine (6.54 g, 35.1 mmol) in anhydrous THF (80 mL) was treated with *n*-BuLi (1.6 M solution in hexanes; 22.4 mL, 35.8 mmol; dropwise addition), and the resulting dark yellow-brown solution was stirred at 0 °C for an additional 1.5 h. This solution was then added by cannula over 15 min to the 0 °C solution of Cp*FeCl, resulting in a dark-purple solution. This mixture was stirred for 18 h, during which time it was allowed to slowly warm to room temperature. Next, the reaction mixture was poured onto a column

of silica gel, eluting first with 65:30:5 hexane:EtOAc:$Et_3N$ (600 mL) and then with 90:10 EtOAc:$Et_3N$ (1.5 L). The purple fractions were collected, and the solvents were removed on a rotary evaporator, thereby providing racemic **1** in >99% purity as judged by $^1$H NMR spectroscopy; yield: 12.0 g (91%).

This reaction has also been conducted on a larger scale: 4-pyrrolidinopyrindine: 10.0 g, 53.7 mmol; product yield: 17.8 g (88%); mp 116–120 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 8.21$ (d, $J = 5.1$ Hz, 1H), 5.59 (d, $J = 5.2$ Hz, 1H), 4.54 (dd, $J = 2.7$, 1.1 Hz, 1H), 4.35 (dd, $J = 2.8$, 1.1 Hz, 1H), 3.74 (t, $J = 2.8$ Hz, 1H), 3.57 (br s, 4H), 2.07–2.10 (m, 4H), 1.65 (s, 15H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 156.3$, 156.3, 152.1, 111.3, 93.8, 78.4, 74.4, 73.2, 67.1, 64.0, 49.3 , 25.7 (br), 9.9; IR (KBr): $\nu = 2966$, 2902, 2865, 1538, 1487, 1380, 1338, 1021, 907, 730 cm$^{-1}$; LR-MS (ES/APCI): calcd. for $C_{22}H_{28}FeN_2$ [M+H$^+$]: 377.3; found: 377.2; anal. calcd. for $C_{22}H_{28}FeN_2$: C 70.22, H 7.50, N 7.44; found: C 70.02, H 7.54, N 7.44.

## Classical Resolution of 4-Pyrrolidinopyrindinyl-pentamethylcyclopentadienyliron (1)

*First crystallization:* Under nitrogen, a solution of di-*p*-toluoyl-D-tartaric acid (3.59 g, 9.30 mmol) in nitrogen-purged EtOAc (270 mL) was added dropwise over 5 min to a stirred solution of pure, racemic 4-pyrrolidinopyrindinyl-pentamethylcyclopentadienyliron (**1**; 14.0 g, 37.2 mmol) in anhydrous $CH_2Cl_2$ (135 mL) in a 1-L flask. The resulting dark-purple suspension was stirred at room temperature for 14 h under nitrogen, and then it was allowed to stand for 1–3 h. Next, the suspension was filtered, and the solid was rinsed with hexanes (120 mL). The filtrate was concentrated and then purified by passage through a column of silica gel (the column should be loaded using 100% EtOAc), washing first with EtOAc to remove traces of degradation products (yellow-brown bands) and then with 90:10 EtOAc:$Et_3N$ (~500 mL) to elute catalyst **1** as a blood-red solution. The appropriate fractions were collected and concentrated on a rotary evaporator. HPLC analysis revealed an enantiomeric excess of 70% (6.65 g, 48%; fast-eluting enantiomer on chiral HPLC, [(+)-(*R*) configuration]. Daicel OD column, flow: 1.0 mL/min, eluent: 50:50:0.4 2-propanol:hexane:$Et_2NH$. $t_r$ (+)-(*R*): 4.67 min; (−)-(*S*): 11.22 min.

The purple solid from the filter cake was dissolved in $CH_2Cl_2$ (100 mL), and the solution was treated with a small amount of $Et_3N$ (15 mL) and passed through a column of silica gel, eluting with 90:10 EtOAc:$Et_3N$ (~500 mL). The bright-red fractions were collected. HPLC analysis revealed an enantiomeric excess of 94% (5.84 g, 42%; slow-eluting enantiomer on chiral HPLC, [(−)-(*S*) configuration].

*Note:* Column chromatography of catalyst **1** can be performed in the air. However, solutions of catalyst **1** that are exposed to air for extended periods of time (i.e., hours) will decompose slightly, leading to the formation of a polar compound that leaves a brown band on the top of silica gel columns.

*Recrystallization of the solid from the first crystallization:* Calculation of the required amount of resolving agent: mmol of resolving agent = (mmol of catalyst **1**) × 0.5 × [fraction of the major enantiomer (e.g., 0.97 for 94% *ee*)].

A solution of di-*p*-toluoyl-D-tartaric acid (2.90 g, 7.50 mmol) in nitrogen-purged EtOAc (102 mL) was added dropwise over 5 min to a stirred solution of enantioenriched **1** (the solid from the first crystallization; 5.84 g, 15.5 mmol, 94% *ee*) in anhydrous $CH_2Cl_2$ (58 mL) in a 500-mL flask under nitrogen. The resulting dark-purple suspension was stirred at room temperature for 14 h under nitrogen, and then it was allowed to stand for 1–3 h. The suspension was filtered, and the purple solid was "worked-up" as described for the first crystallization: yield: 5.23 g (37%, based on the starting amount of racemic **1**). HPLC analysis revealed >99% enantiomeric excess of the slow-eluting enantiomer on chiral HPLC, (−)-(*S*)-configuration.

*Recrystallization of the filtrate from the first crystallization:* A solution of di-*p*-toluoyl-L-tartaric acid (2.90 g, 7.51 mmol) in nitrogen-purged EtOAc (125 mL) was added dropwise over 5 min to a stirred solution of enantioenriched **1** (the filtrate from the first crystallization; 6.65 g, 17.7 mmol, 70% *ee*) in anhydrous $CH_2Cl_2$ (63 mL) in a 500-mL flask under nitrogen. Within a few minutes, a dark-purple suspension had formed. This mixture was stirred at room temperature for 14 h under nitrogen, and then it was allowed to stand for 1–3 h. The suspension was filtered, and the purple solid was "worked-up" as described for the first crystallization: yield: 5.25 g (38% based on the starting amount of racemic **1**). HPLC analysis revealed >99% enantiomeric excess of the fast-eluting enantiomer on chiral HPLC, (+)-(*R*) configuration.

(−)-(*S*)-**1**: $[\alpha]_D^{20}$: −2,280° (*c* 0.00046, $CHCl_3$); mp 155–160 °C (decomp.; >99% *ee*).

## 4-(Dimethylamino)pyrindinyl-pentaphenylcyclopentadienyliron (2)

A solution of *n*-BuLi (1.6 M in hexanes; 5.45 mL, 8.73 mmol) was added dropwise over 2 min to a mixture of pentaphenylcyclopentadiene (3.90 g, 8.72 mmol) suspended in anhydrous THF (86 mL) under nitrogen. The solution, which was initially homogeneous and yellow, was allowed to stir for 2 h, at which time it was red-orange.

Separately, anhydrous THF (40 mL) was added to powdered $FeCl_2$ (1.07 g, 8.44 mmol) in a 500-mL round-bottomed flask. The mixture was sonicated for 30 min, yielding a fine suspension. The solution that contained the pentaphenylcyclopentadienyl anion was then added by cannula over 2 min to the suspension of $FeCl_2$, resulting in a beige solution. The reaction mixture was stirred at room temperature for 2 h.

A solution of *n*-BuLi (1.6 M solution in hexanes; 4.54 mL, 7.27 mmol) was added dropwise over 2 min to a solution of 4-(dimethylamino)pyrindine (1.17 g, 7.27 mmol) in anhydrous THF (35 mL) at 0 °C in a 250-mL round-bottomed flask. The resulting dark yellow-brown solution was stirred at 0 °C for 1.5 h. Then, this solution was added by cannula over 2 min to the solution of $C_5Ph_5FeCl$ (at room temperature), resulting in a brown solution. The reaction mixture was heated to 60 °C for 3.5 h. Next, the reaction mixture was poured onto a column of silica gel, which was eluted with 45:45:10 EtOAc:hexane:$Et_3N$ (200 mL). The resulting solution was concentrated to a dark-purple solid on a rotary evaporator, and this crude material was purified by column chromatography, first eluting with $CH_2Cl_2$ (400 mL) to remove the excess $C_5Ph_5H$ and then with 90:10 $CH_2Cl_2$:$Et_3N$ (400 mL), which provided the catalyst as a tight purple

band. The purple fractions were collected and concentrated on a rotary evaporator to afford the title compound in >99% purity as judged by $^1$H NMR spectroscopy (purple powder; yield: 4.51 g, 93%).

This reaction has also been conducted on a larger scale: 4-(dimethylamino)pyrindine: 2.50 g, 15.6 mmol; product yield: 8.15 g (79%); mp 238–241 °C; $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.17 (d, $J$ = 5.2 Hz, 1H), 7.13–7.16 (m, 5H), 7.05–7.12 (m, 10H), 6.94–6.96 (m, 10H), 5.87 (d, $J$ = 5.2 Hz, 1H), 5.11 (br s, 1H), 4.92–4.94 (m, 1H), 4.28–4.30 (m, 1H), 2.94 (br s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 158.6, 153.9, 135.3, 132.6, 127.1, 126.2, 113.4, 99.5, 86.0, 77.9, 77.7, 69.6, 66.1, 41.7; IR (film): $\nu$ = 3055, 2952, 1537, 1502, 1351, 1075, 1027, 741, 700 cm$^{-1}$; LR-MS (ES/APCI): calcd. for $C_{45}H_{36}FeN_2$ [M+H$^+$]: 661.6; found: 661.2; anal. calcd. for $C_{45}H_{36}FeN_2$: C 81.81, H 5.49, N 4.24; found: C 81.62, H 5.49, N 4.41.

### Classical Resolution of 4-(Dimethylamino)pyrindinyl-pentaphenylcyclopentadienyliron (2)

*First crystallization:* In the air, a suspension of racemic 4-(dimethylamino)pyrindinyl-pentaphenylcyclopentadienyliron (**2**; 11.5 g, 17.4 mmol) and $CH_2Cl_2$ (200 mL) in a 500-mL flask was sonicated for ~10 min until all of catalyst **2** had dissolved. Next, the solution was diluted with THF (79 mL), and then a solution of anhydrous dibenzoyl-L-tartaric acid (3.12 g, 8.70 mmol)[14] in THF (79 mL)[15] was added dropwise by pipette over 10 min to the stirred solution of catalyst **2**. The resulting dark-purple solution was sonicated for ~6 min. The flask was then fitted with a septum, and the flask was vigorously stirred and purged with nitrogen until a purple suspension formed. This suspension was stirred for 20 h, and then it was allowed to stand for 1.5 h without stirring. Next, the mixture was filtered, and the purple solid that was collected was rinsed with hexanes (100 mL). The material in the filtrate was purified by passing it through a column of silica gel, rinsing first with EtOAc to remove traces of degradation products (yellow or brown) and then with 90:10 EtOAc:$Et_3N$ (~1.0 L) to elute the catalyst as a dark-purple band. The highly colored fractions were collected and concentrated on a rotary evaporator. HPLC analysis revealed an enantiomeric excess of 52% [7.44 g, 65%; fast-eluting enantiomer on chiral HPLC, (+)-(*R*) configuration]; Regis Whelk O column, flow: 0.9 mL/min, eluent: 60:40:0.4 $CH_2Cl_2$:hexanes:$Et_2NH$. $t_r$ (+)-(*R*): 4.6 min; (−)-(*S*): 5.5 min.

The purple solid from the filter cake was dissolved in $CH_2Cl_2$ (44 mL) and $Et_3N$ (4.5 mL). This solution was passed through a column of silica gel, eluting with 90:10 EtOAc:$Et_3N$ (~800 mL). The dark-purple fractions were collected and concentrated on a rotary evaporator. HPLC analysis revealed an enantiomeric excess of 98% [4.18 g, 36%; slow-eluting enantiomer on chiral HPLC, (−)-(*S*) configuration].

*Notes:* 1) Column chromatography of catalyst **2** can be performed in the air with essentially no concern for decomposition. 2) The equivalents of the resolving agent that are used for the resolution of catalyst **2** is double that used in the resolution of catalyst **1.**

*Recrystallization of the solid from the first crystallization:* Calculation of the required amount of resolving agent: mmol of resolving agent = (mmol of catalyst **2**) × [fraction of the major enantiomer (e.g., 0.99 for 98% *ee*)].

A mixture of enantioenriched **2** (the solid from the first crystallization; 4.18 g, 6.33 mmol; 98% *ee*) and $CH_2Cl_2$ (96 mL) in a 500-mL flask under air was sonicated until all of catalyst **2** had dissolved (~10 min). Next, the solution was diluted with THF (41 mL), and then a solution of anhydrous dibenzoyl-L-tartaric acid (2.24 g, 6.25 mmol) in THF (46 mL; this solution was filtered before use) was added dropwise *via* pipette over 10 min to the stirred solution of **2**. The resulting dark-purple mixture was sonicated for ~5 min, leading to the formation of a large amount of a purple precipitate. The mixture was stirred for ~20 min, during which time it became less viscous. The flask was purged with nitrogen for 2–3 min, and then it was stoppered with a septum and allowed to stir for 20 h. Next, the mixture was allowed to stand without stirring for 3 h, and then it was filtered. The purple solid was "worked-up" as described for the first crystallization. HPLC analysis revealed an enantiomeric excess >99% [3.17 g, 28% (based on the starting amount of racemic **2**); slow-eluting enantiomer on chiral HPLC, (−)-(*S*) configuration].

*Recrystallization of the filtrate from the first crystallization:* A mixture of enantioenriched **2** (the filtrate from the first crystallization; 7.44 g, 11.3 mmol; 52% *ee*) and $CH_2Cl_2$ (170 mL) in a 500-mL flask was sonicated until all of the catalyst had dissolved (~10 min). Next, the solution was diluted with THF (74 mL), and a solution of dibenzoyl-D-tartaric acid monohydrate (3.22 g, 8.58 mmol) in THF (74 mL; this solution was filtered before use) was added dropwise *via* pipette over 10 min to the stirred solution of **2**. The resulting dark-purple mixture was sonicated for ~6 min. Next, while stirring the mixture, the flask was purged with nitrogen for 2–3 min. Stirring was continued overnight (20 h), leading to a slurry. The mixture was allowed to stand without stirring for 1 h, and then it was filtered through a sintered glass frit. The purple solid was rinsed with hexanes (100 mL) and then suspended in $CH_2Cl_2$ (100 mL). $Et_3N$ (~10 mL) was added until the solution was homogeneous. The solution was passed through a column of silica gel, eluting with 95:5 EtOAc:$Et_3N$ (~900 mL). The dark-purple fractions were collected and concentrated on a rotary evaporator. HPLC analysis revealed an enantiomeric excess of >99% [5.07 g, 44% (based on the starting amount of racemic **2**); fast-eluting enantiomer on chiral HPLC, (+)-(*R*) configuration]. (+)-(*R*)-**2**: $[\alpha]_D^{20}$: +940° (*c* 0.00024, $CHCl_3$); mp 280–281 °C (decomp.; >99% *ee*).

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[15] Because the solution was somewhat cloudy, it was filtered before it was used.


  