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A Scalable Asymmetric Synthesis of (*R*)-2-Amino-1-(3-pyridinyl)ethanol Dihydrochloride via an Oxazaborolidine Catalyzed Borane Reduction

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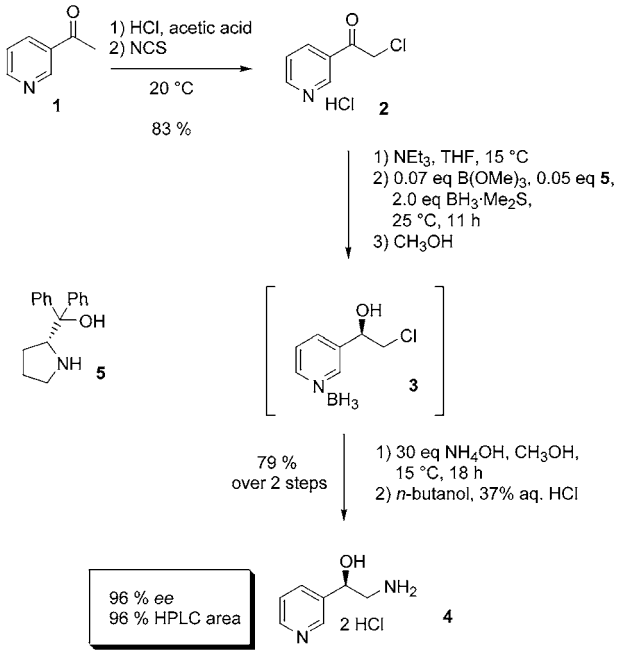
Abstract:

This report describes a scalable process for the asymmetric synthesis of (*R*)-2-amino-1-(3-pyridinyl)ethanol dihydrochloride. The stereochemistry of the product is set via a reduction of 3-chloroacetyl pyridine with 2 equiv of borane-dimethyl sulfide and a catalytic amount of an in situ generated oxazaborolidine. The enantiomeric excess (ee) of the reductive step depends on the addition rate of the substrate and the temperature. The authors hypothesize that the low ee observed during a fast addition of the substrate or at low temperatures is due to the slow regeneration of the active catalyst from the catalyst−product complex.

Introduction

Recently we had a need to produce kilogram quantities of amino alcohol **4** (Scheme 1). Previously, our group obtained this intermediate enantiomerically pure via chiral chromatography of racemic **3**[1] and subsequent Gabriel synthesis.[2,3] To obviate the need for chromatography and to facilitate the rapid chemical development of a preclinical candidate, we investigated the asymmetric synthesis of **4** via an oxazaborolidine catalyzed borane reduction. Oxazaborolidines have demonstrated tremendous scope and efficiency in asymmetric catalytic borane reductions of unsymmetrical ketones.[4] For example, Quallich[5] and Masui[6] have reported their use in catalytically reducing ketones containing heterocyclic functionality. Specifically, Quallich obtained 96% ee and Masui obtained 99% ee with 3-acetylpyridine, in excellent yields.[7] Quallich,[5] Corey,[8] and Hett[9] also reported the reduction of the α-haloacetophenone moiety, with Hett further demonstrating the scalability of this reaction.[10] Chiral stoichiometric reductions of α-haloacetylpyridines have been reported,[11,12] as has a poor-yielding catalytic reduction.[13] However, this report describes the first example of an efficient catalytic asymmetric reduction on 3-chloroacetyl pyridine and the subsequent large-scale synthesis of its corresponding amino alcohol.

Scheme 1. **Enantioselective Synthesis of (*R*)-2-Amino-1-(3-pyridinyl)ethanol**



Results and Discussion

Earlier work demonstrated that high yields are achievable for the chlorination of the hydrochloride salt of 3-acetylpyridine (Scheme 1).[12] In the referenced procedure, 3-acetylpyridine was precipitated as the HCl salt by treatment with 1 M HCl in ether. The product was filtered, added to 1 M HCl in acetic acid, treated with NCS, and filtered again. To avoid the use of a highly flammable solvent on a large scale and to eliminate a time-consuming isolation step, the in situ generation of the 3-acetylpyridine HCl salt was investigated.

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(1) Chromatography was performed on borane-free chlorohydrin.
(2) Bayer Co. U.S. Patent 6,051,586, April 18, 2000.
(3) The enantiomerically pure chlorohydrin is also obtainable via a fermentation process. Kaneka Co. WO Patent 00/48997, August 24, 2000.
(4) Singh, V. K. *Synthesis* **1992**, 605−617.
(5) Quallich, G. J.; Woodall, T. M. *Tetrahedron Lett.* **1993**, *34*, 785−788.
(6) Masui, M.; Shioiri, T. *Synlett* **1997**, 273−274.
(7) Quallich used 5 mol % and Masui used 10 mol % catalyst.
(8) Corey, E. J.; Shibata, S. J.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861−2863.
(9) Hett, R.; Senanayake, C. H.; Wald, S. A. *Tetrahedron Lett.* **1998**, *39*, 1705−1708.
(10) Hett, R.; Fang, Q. K.; Gao, Y.; Wald, S. A.; Senanayake, C. H. *Org. Process Res. Dev.* **1998**, *2*, 96−99.
(11) Naylor, E. M.; Colandrea, V. J.; Candelore, M. R.; Cascieri, M. A.; Colwell, L. F.; Deng, L.; Feeney, W. P.; Forrest, M. J.; Hom, G. J.; MacIntyre, D. E.; Strader, C. D.; Tota, L.; Wang, P.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3087−3092.
(12) Merck & Co. U.S. Patent 5,561,142, October 1, 1996.
(13) (a) Hu, B.; Ellingboe, J.; Gunawan, I.; Han, S.; Largis, E.; Li, Z.; Malamas, M.; Mulvey, R.; Oliphant, A.; Sum, F.; Tillett, J.; Wong, V. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 757−760. (b) American Home Products Co. WO Patent 02/0623, January 24, 2002. (c) The optically active bromohydrin obtained in the previous references was converted into the epoxide and opened with ammonia/methanol to yield the optically active amino alcohol. No ee was reported.

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In the current method, an ~2 M HCl solution in acetic acid was easily prepared with gaseous HCl and glacial acetic acid.[14] 3-Acetylpyridine was then added to the solution, followed by the addition of NCS, and the product was isolated by filtration with yields and purity comparable to those of the previous method.[15]

Chloroketone **2** was then converted to the free base in preparation for the reduction. Initially, the HCl salt was dissolved in water, slowly treated with solid sodium bicarbonate, and extracted with dichloromethane. The organic extracts were then dried with sodium sulfate, filtered, concentrated *in vacuo*, and redissolved in THF. Two concerns about the scalability of this step prompted us to explore alternative methods. First, the procedure seemed unnecessarily lengthy for such a simple step. Second, earlier work in our lab showed that the free base of the chloroketone had poor solution stability. This instability might lead to decomposition during the removal of dichloromethane on a large scale. Two other methods more amenable to large-scale synthesis were developed. The free base of the chloroketone is insoluble in water, so it could be isolated by a simple filtration and a solution prepared as needed. The other approach was to prepare a slurry of the HCl salt in THF, basify the salt with triethylamine, and remove the resulting triethylamine hydrochloride solid by filtration. The latter approach was chosen for scale-up because it permitted the direct use of the filtrate for the subsequent step. Despite the heterogeneity of this procedure, only small amounts of the product were found in the solid triethylamine salt. Additionally, only a trace of triethylamine was found in the filtrate.[16] This new procedure eliminated the need to perform a slow solid addition, an extraction, and a concentration and thus improved the efficiency of the process.

The oxazaborolidine catalyzed borane reduction was performed next. The active catalytic species for the reduction was prepared in situ by mixing (*R*)-α,α-diphenyl-2-prolinol and trimethylborate in THF for 1 h. By using trimethyl borate, the active catalyst has a methoxy group attached to boron (Scheme 2). Masui[6] proposed that, by modifying the Lewis acidity of the boron, the binding rate of the catalyst to the ketone should increase and so should the relative rate of the catalytic reduction versus the background reduction. Thus, this procedure was chosen because it provided excellent results with 3-acetylpyridine and precedent for an increase in ee versus catalysts with other[17] boron substituents. After the generation of the active catalyst, 2 equiv of borane-dimethyl sulfide in THF were then charged to the reaction. Excess borane was necessary to facilitate the reaction, as 1 equiv coordinates to the pyridine nitrogen.[5,18] The chloroketone solution was then added slowly to the reaction solution to effect the asymmetric reduction.

Scheme 2. **Putative Catalytic Cycle**

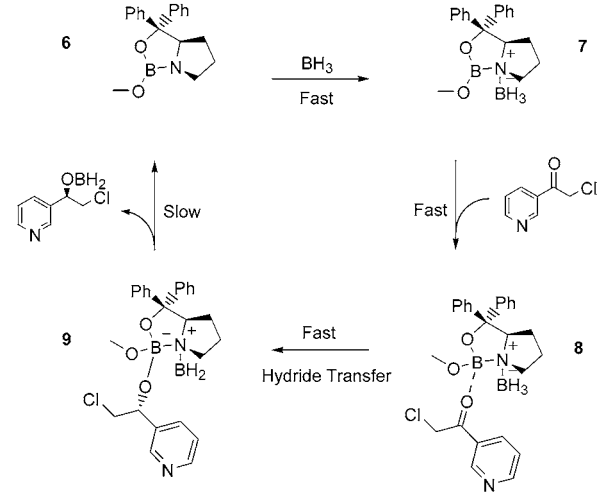
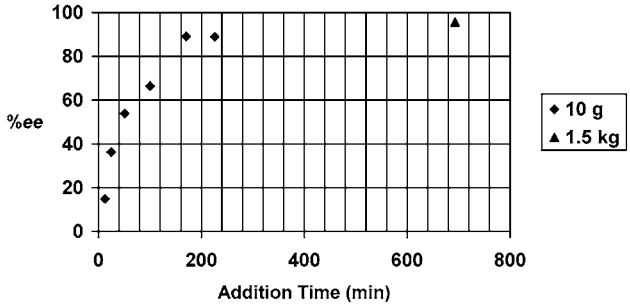


Chart 1. **Percent of Enantiomeric Excess versus Addition Time of the Free Base of 2[a−c]**



[a] Scale shown is for the HCl salt. [b]The temperature was maintained between 23 and 25 °C during the addition. [c]The catalyst appears saturated at less than 170 min. The authors believe that the lower ee's for the 10 g runs at 170 min (89% ee) and 226 min (89% ee) versus the 1.5 kg run (96% ee) are due to the presence of adventitious water (ref 22) that was introduced into the chloroketone solution during the open-to-air filtration. A closed filter, inerted with dry nitrogen, was used for the 1.5 kg run.

Table 1. **Effect of Temperature on Percent of Enantiomeric Excess[a]**

addition time (min:s)	% ee	temp[b] (°C)
48:55	7.3	2−3
49:53	53.9	24−25
47:47	88.9	43−44

[a] Runs were performed on 10 g of **2**. [b]Internal temperature.

Small-scale experiments demonstrated that the addition time (Chart 1) and reaction temperature (Table 1) were critical in determining the enantiomeric excess. To the best of our knowledge, it has never been reported in the literature that the enantiomeric excess can depend on the substrate addition time for an oxazaborolidine catalyzed reduction of a ketone.[19] Most efforts at improving the ee have focused on modifying the ligand structure and the boron substituent.[9]

(14) In the preliminary experiments, the flask containing acetic acid and the HCl cylinder were tared to determine that the desired amount was transferred into the solution. On the kilogram scale, only the cylinder tare was used. No other method was used to determine the precise molarity of the solution.

(15) The impurities in the reaction mixture for both methods are 3-acetylpyridine, the bis-chlorinated byproduct, and succinimide. However, the bis-chlorinated byproduct and succinimide are more soluble in the reaction mixture and are not detected in the isolated solid. Based on the relative ratio of the methyl (2.69 ppm) and methylene (5.30 ppm) protons in the ^{1}H NMR (DMSO-d_6), there was 3% 3-acetylpyridine hydrochloride in the solid.

(16) By ^{1}H NMR, less than 2 mol % of the product was found in the triethylamine hydrochloride solid and less than 2 mol % of triethylamine was found in the filtrate.

(17) Quallich, G. J.; Woodall, T. M. *Synlett* **1993**, 929−930.

(18) After quenching with methanol, a broad peak is observed in the ^{1}H NMR at 2.5 ppm, which is consistent with a borane−pyridine complex.

Presumably, an optimized ligand should offer greater enantioselectivity during the reductive step in the catalytic cycle. In our case, since the ee was high during a slow addition, the enantioselectivity of the catalytic species must be high, thus suggesting that the low ee at high addition rates is due to a low catalyst turnover frequency. Previous experiments in our lab showed that the background reduction of the chloroketone was fast. If the putative catalytic cycle is correct (Scheme 2),[20] then the binding of the substrate and the hydride transfer must be even faster. This conclusion is reached because the ee was high with a slow addition in the presence of a large excess of borane. Other data suggest that borane binding is also fast. For example, the reduction of acetophenone reported by Masui, with 0.05 equiv of the enantiomer of **6**, yielded a high ee with an addition time of 10 min at 25−30 °C. This duration is much less than the addition time needed to obtain a high ee for **2**.[21−23] Thus, we hypothesize that the low ee at high addition rates was due to the slow release of the product from the catalyst relative to the background reduction.[24] Temperature also had a dramatic effect on the ee, with higher temperatures yielding a higher ee for a constant addition time. We reason that the rate of product release from the catalyst depends more on temperature than does the background reduction, resulting in a higher relative rate at higher temperatures and thus a higher ee.

After the completion of the chloroketone addition, the reaction mixture was slowly quenched with methanol[18] to liberate **3** and then was concentrated *in vacuo.* Methanol and 30 equiv of ammonium hydroxide were added, and the reaction was stirred for 18 h. No effort was made to reduce the number of equivalents of ammonia, but the excess was used to avoid significant formation of the dialkylated byproduct.[25] The solvent was then swapped with *n*-butanol via a combination of ambient and azeotropic vacuum distillation. This also removed most of the ammonia.[26] Concentrated aqueous hydrochloric acid was then added to form the dihydrochloride salt.[27] The water was then removed via azeotropic vacuum distillation,[28] and the resulting white solid was filtered to give crude amino alcohol **4** in 66% yield over three steps with 96% ee and 96% purity by HPLC area.[29] The product can be used without further purification. Alternatively, enrichment by a hot reslurry in 190 proof ethanol delivers a 79% recovery with 99.5% ee and 99.8% purity by area.

Summary

An efficient and scalable asymmetric synthesis of enantiomerically enriched 2-amino-1-(3-pyridinyl)ethanol dihydrochloride was developed using commercially available starting materials. The desired compound is produced in 3 steps, in high purity and with an overall yield of 66% and an ee of 96%. The catalytic cycle appears to be limited by the regeneration of the active catalyst from the catalyst−product complex.

Experimental Section

General. ^{1}H NMR and ^{13}C NMR spectra were measured with a Varian NMR spectrometer with residual protonated solvent (^{1}H NMR, DMSO-d_6 δ 2.50; $CDCl_3$ δ 7.27; ^{13}C NMR, DMSO-d_6 δ 39.51) as the reference standard. Chemical shifts are reported in part per million. Elemental analysis was performed by Robertson Microlit Laboratories in Madison, NJ. Unless otherwise noted, all reagents were obtained from Acros, Aldrich, or Lancaster and were used without further purification. All solvents were obtained from EM Science or Pharmco. The pump system used to examine the effect of addition rate was the MasterFlex Digital Console L/S Pump Drive (Cole-Parmer #7524-50) with a PTFE tubing pump head (Cole-Parmer #77390-00) and PTFE tubing assembly (2 mm ID, 4 mm OD, Cole-Parmer #77390-50). For the kilogram scale run, a Fluid Metering Inc. pump

(19) Hett showed (ref 9) that the same ee was obtained in the reduction of 2-bromo-4′-(benzyloxy)-3′-nitroacetophenone when the substrate addition time was 2 h or 30 min.

(20) Corey, E. J.; Bakshi; R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551−5553.

(21) High *ee*s have been obtained with oxazaborolidine catalyzed borane reductions during which borane was added into a solution of the catalyst and ketone (ref 22). These results also suggest that borane binding is fast.

(22) Jones, T. K.; Mohan, J. J.; Xavier, L. C.; Blacklock, T. J.; Mathre, D. J.; Sohar, P.; Jones, E. T. T.; Reamer, R. A.; Roberts, F. E.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 763−769.

(23) For the addition of ketone, excess borane is always in solution with the catalyst and intermediate **7** can form upon regeneration of **6**. In this addition sequence, the borane binding rate required for a high ee is less than the rate required for a high ee under the addition of borane.

(24) This low turnover frequency might be due to the stabilization of intermediate **9** via the electron withdrawing effect of the chloro substituent and the consequent delocalization of the negative charge on boron. For example, without the chloro substituent, only a 1 h addition time at 0−5 °C was needed to reduce 3-acetylpyridine in 99% ee with 10 mol % of the enantiomer of catalyst **6** and with borane-dimethyl sulfide as the reducing agent (ref 6). Furthermore, it has been reported that the *simultaneous* addition of ketone and reducing reagent was necessary to ensure high enantioselectivity in the reduction of 2-bromo-4′-(benzyloxy)-3′-nitroacetophenone (ref 10), α-chloroacetophenone (ref 8, 31), and 2-bromo-cyclohex-2-eneone (ref 32). The only explanation provided on the need for simultaneous addition is that it "suppress[es] uncatalyzed reduction pathways" (ref 31). However, there are also examples on the reduction of 2-bromo-4′-(benzyloxy)-3′-nitroacetophenone (ref 9) and α-chloroacetophenone (ref 17, 32) for which simultaneous addition was not necessary, using a different catalyst, a different borane source, or both a different catalyst and a different borane source. This may be due to the role the catalyst and borane source play in the stabilization or destabilization of intermediate **9**. Another possible counterexample is that trihalomethyl ketones were reduced with excellent enantioselectivity (ref 33). However, no description of the addition mode, addition time, or time for complete conversion was provided. Also, the trihalomethyl group inverts the stereo configuration of the catalyst complex relative to the corresponding monohalomethyl ketone, which may in itself have a consequence on the rate of catalyst regeneration.

(25) A minor amount of the ion (MH^+ = 260.1) believed to correspond to the dialkylated product was observed in the LCMS (APCI) of one of the impurities detected in the isolated solid. The impurity (t_r = 8.57 min) was present in 2 area % based on the achiral method outlined in ref 29. The major ion detected was 224.1. Also a minor amount of 265.1 was detected.

(26) Because of its insolubility, ammonium chloride has no ^{1}H NMR spectrum in DMSO-d_6, but when a sample of pure **4** is spiked with ammonium chloride, a triplet is observed at 7.4 ppm. This triplet was observed by ^{1}H NMR in the final product, but its intensity was reduced by the reslurry. See the Experimental Section for more information.

(27) The monohydrochloride salt is partially soluble in *n*-butanol and also can be isolated by filtration, albeit in lower yields.

(28) It was later observed that water appears to aid the removal of some of the organic impurities. Future work might include eliminating the final azeotrope.

(29) Chiral conditions: Crownpak CR(+) 4.0 mm × 150 mm; A = 0.5% $HClO_4$ in H_2O, B = MeOH; 0.5 mL/min; isocratic run with 1% B for 10 min; room temp; UV 265 nm; t_r = 5.2 min. Achiral conditions: Metachem Diol. 5.0 mm × 60 mm; A = 0.1% TFA in hexane, B = 0.1% TFA in 1:1 MeOH/EtOH; 3.0 mL/min; ramp from 1% B to 30% B over 9.5 min; room temp; UV 254 nm; t_r = 7.7 min.

(QSY-1) was used. The kilogram scale synthesis was performed in a Büchi 100-L reactor train.

2-Chloro-1-(3-pyridinyl)ethanone Hydrochloride (2). Glacial acetic acid (24 L) was charged to the reactor, and gaseous HCl (1.7 kg, 47 mol) was introduced above the surface of the liquid at 17 °C over 1 h. The temperature was raised to 20 °C, and 3-acetylpyridine (2.3 L, 21 mol) was added dropwise in 40 min, resulting in the formation of a vapor cloud and a clear solution. The sides of the reactor were rinsed with more glacial acetic acid (2 L). *N*-chlorosuccinimide (3.0 kg, 22.5 mol) was then dissolved in the solution at 22 °C. After 1 h, the product began to crystallize from the reaction mixture, resulting in a rise in temperature. The mixture was stirred overnight at 20 °C, cooled to 15 °C the next morning, and filtered. The cake was washed with acetic acid (2 L), washed with ethyl acetate (4 L), and dried under vacuum at 25 °C to yield 3.3 kg (83%) of white powder. *Compound is an irritant*. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.26 (s, 1H), 8.95 (d, J = 5.2 Hz, 1H), 8.59 (d, J = 8.3 Hz, 1H), 7.86 (dd, J = 5.2, 8.3 Hz, 1H), 5.30 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 188.6, 147.8, 144.2, 140.4, 131.0, 125.6, 48.1.

Borane-(*R*)-2-chloro-1-(3-pyridinyl)ethanol (3). 2 (1.50 kg, 7.81 mol) and THF (11.3 L) were charged to the reactor. A solution of triethylamine (1.09 L, 7.81 mol) in THF (1.25 L) was then added dropwise over 10 min. The mixture was stirred for 1 h at 17 °C and filtered. The reactor was rinsed with THF (2.5 L), and the rinse was filtered over the solid. The filtrate (14 L) was kept under inert atmosphere at room temperature during the addition, and no precipitation was observed. A sample of the filtrate was concentrated and analyzed by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.79 (d, J = 4.7 Hz, 1H), 8.23 (d, J = 7.9 Hz, 1H), 7.45 (dd, J = 4.7, 7.9 Hz, 1 H), 4.70 (s, 2H).

To the same reactor previously mentioned, without further rinsing, was added THF (7.8 L), (*R*)-(+)-α,α-diphenylprolinol (Yunichem, 98.9 g, 391 mmol) and trimethyl borate (58.7 mL, 523 mmol). The mixture was stirred for 1 h at 25 °C. A bleach scrubber was connected to the vent line of the reactor, and 2 M borane-dimethyl sulfide in THF (6.87 kg, 16.1 mol) was then charged to the solution. The chloroketone solution previously mentioned was then added at 23 mL/min for a total addition time of 11.3 h. After the addition was complete, the solution was stirred for 1 h and quenched with methanol (2.5 L) over a period of 2 h to avoid rapid hydrogen evolution. Solvent (24 L) was then removed *in vacuo*. A sample of the reaction mixture was analyzed prior to distillation. Chiral HPLC[30] indicated 95.7% ee. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (s, 1H), 8.49 (d, J = 5.7 Hz, 1H), 8.15 (d, J = 8.0 Hz, 1H), 7.69 (dd, J = 5.7, 8.0 Hz, 1H), 6.20 (d, J = 4.7 Hz, 1H), 5.05 (q, J = 4.9 Hz, 1H), 3.85 (dq, J = 5.1, 8.5 Hz, 2H), 2.50 (b, 3H).

(*R*)-2-Amino-1-(3-pyridinyl)ethanol Dihydrochloride (4). To the solution previously mentioned was added methanol (13 L) and 30% ammonium hydroxide (30 L, 220 mol). The mixture was stirred at 25 °C for 3 days, but a sample after 18 h indicated the reaction was complete. Next, methanol was distilled under ambient pressure. About one-half of the water and ammonia were then removed via vacuum distillation. The remaining water and most of the ammonia were removed via azeotropic vacuum distillation with *n*-butanol (53 L). HCl (37% aq, 1.5 L) was then added at 10 °C over 10 min. The mixture was again distilled under vacuum until the distillate contained a single phase, and the final volume was ~18 L. The white solid was filtered, rinsed with *n*-butanol (4 L), and dried in the vacuum oven at 35 °C to yield 1.30 kg (79%).

The solid previously mentioned (1.30 kg) was charged to a flask with 5.2 L of ethanol/water (95:5), heated to reflux, and allowed to cool to room temperature overnight. The solid was filtered, rinsed with ethanol (500 mL), and dried in a vacuum oven at 35 °C to yield 1.03 kg (79%) with 99.8% purity by area and 99.5% ee. The solid was determined to be partially crystalline by the observation of some birefringence under an optical microscope with a differential interface contrast filter. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.87 (s, 1H), 8.84 (d, J = 5.7 Hz, 1H), 8.54 (d, J = 8.2 Hz, 1H), 8.28 (b, 2H), 8.01 (dd, J = 5.7, 8.2 Hz, 1H), 5.15 (dd, J = 3.9, 7.8 Hz, 2H), 3.21 (m, 1H), 3.05 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 142.5, 140.5, 140.4, 139.5, 126.2, 66.0, 44.6. HRMS +esi (m/z): $[M + H]^+$ calcd for $C_7H_{12}Cl_2N_2O$, 139.086589; found, 139.08697. Anal. Calcd for $C_7H_{12}Cl_2N_2O \cdot 0.15H_4ClN$: C, 38.37; H, 5.80; Cl, 34.79; N, 13.74. Found: C, 38.35; H, 5.89; Cl, 34.66; N, 13.77. Based on the elemental analysis, the estimated ammonium chloride content is 4 wt %.

An analytical sample was obtained by an additional recrystallization. Anal. Calcd for $C_7H_{12}Cl_2N_2O$: C, 39.83; H, 5.73; Cl, 33.59; N, 13.27. Found: C, 39.80; H, 5.64; Cl, 33.95; N, 13.23. Melting point 205−208 °C.

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Supporting Information Available

Table of data for Chart 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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(30) Chiralpak AD 4.6 mm × 250 mm; 1:9 (v/v) ethanol/hexane; 1.0 mL/min; isocratic 25 min; room temp; UV 254 nm.

(31) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986−2012.

(32) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925−7926.

(33) Corey, E. J.; Link, J. O.; Bakshi, R. K. *Tetrahedron Lett.* **1992**, *33*, 7107−7110.