

# A Kilolaboratory Preparation of the CNRS Chiral Auxiliary

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## Abstract:

An improved preparation at kilolaboratory scale of the CNRS chiral auxiliary is presented.

## Introduction

The CNRS reagent, 2-cyano-6-phenyloxazolopiperidine (**1**), is a chiral auxiliary developed by Husson and colleagues<sup>1</sup> and has shown great utility in the asymmetric synthesis of various cyclic alkaloids. This chiral auxiliary was used to asymmetrically synthesize simple piperidines such as coniine,<sup>1</sup> dihydropinidine,<sup>1</sup> and monomorine **2** as well as more complex alkaloids like those found in the 3-aminoazepanes series.<sup>3,4</sup> It also shows utility as a starting point for the asymmetric synthesis of spiro-piperidines<sup>5,6</sup> and an NK1 antagonist.<sup>7</sup> A polyhydroxylated analogue of **1** was successfully used in the asymmetric syntheses of trihydroxypipicolic acid<sup>8</sup> and 1-deoxynojirimycin.<sup>9</sup> Kindon recently reported the use of **1** in the synthesis of an orexin receptor antagonist and also documented minor improvements to the preparation of **1**.<sup>10</sup>

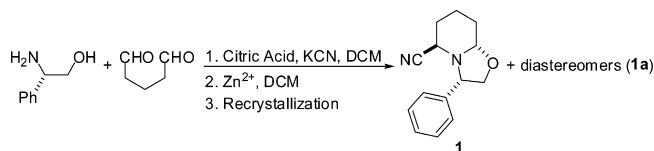
The reported preparation of **1** describes a Robinson–Schopf condensation<sup>11</sup> between phenylglycinol, glutaraldehyde, and potassium cyanide to provide a crude solution of **1**, its diastereomers, and related oligomers (Scheme 1).<sup>12</sup> After the initial condensation reaction, the resulting multicomponent system is converted to the presumed thermodynamically stable diastereomer **1** using zinc bromide. Careful column chromatography and a hexanes recrystallization affords **1** in 65% yield.

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## Scheme 1



A recent project in our chemical development laboratories required kilogram quantities of **1** for the asymmetric synthesis of a potential drug candidate. While the reported procedure<sup>12</sup> was amenable for producing 10–25 g lots of **1**, it proved too cumbersome for lots greater than 50 g. Using the reported procedure as a starting point, we developed a process to produce larger amounts of **1**. Described herein is a kilolaboratory-scale preparation of the CNRS reagent.

## Results and Discussion

Process optimization was focused on four critical areas: volume optimization, removal of column chromatography, choice of a process-friendly Lewis acid, and alternative reaction solvents.

It was immediately noted that the reported procedure<sup>12</sup> utilizes large volumes of aqueous and organic solvents for the Robinson–Schopf formation of crude **1**—a 10-g reaction requires approximately 1.3 L of reaction volume. We found that the total aqueous volume could be reduced 10-fold, the volume of dichloromethane could be reduced by half, and commercially available 50 wt % aqueous glutaraldehyde solutions could be substituted for 24 wt % aqueous glutaraldehyde solutions without adversely affecting the reaction and purity profile of the initial condensation reaction. For a 10-g reaction using these optimized volumes, the bulk reaction volume is 0.51 L, an approximate 2.5-fold reduction. Changing the reaction quench to 4.5 M aqueous KOH (buffered with K<sub>2</sub>HPO<sub>4</sub> to prevent a potential pH swing into strongly basic conditions)<sup>13</sup> instead of solid sodium bicarbonate increased the bulk reaction volume to 0.55 L. We concluded that the small increase in bulk reaction volume using an aqueous base quench was a good trade-off for the removal of the gas-evolving, solid sodium bicarbonate quench.

The removal of the formal silica gel column to purify **1** was investigated next. A wide variety of solvent systems was investigated to crystallize the desired chiral auxiliary **1** away from the crude reaction products, but successful conditions were not found. While a silica gel purification could not be excluded entirely, we discovered that a silica gel plug filtration coupled with a recrystallization was a viable alternative. Passing crude dichloromethane solutions of **1** (post zinc treatment) through a short

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**Table 1.** Diastereomeric purity of **1** post-epimerization with selected Brønsted and Lewis acids<sup>a</sup>

epimerization agent	diastereomeric ratio <b>1</b> : <b>1a</b>	
ratio of <b>1</b> : <b>1a</b> prior to the zinc-mediated epimerization reaction	44.4	55.6
ZnBr <sub>2</sub>	93.4	6.6
ZnCl <sub>2</sub>	92.7	7.3
Zn(CF <sub>3</sub> CO <sub>2</sub> ) <sub>2</sub>	92.2	7.8
Zn(OTf) <sub>2</sub>	85.4	14.6
Zn(pTSA) <sub>2</sub>	80.0	20.0
methanesulfonic acid	77.5	22.5
Yb(OTf) <sub>3</sub>	71.1	28.9
trifluoroacetic acid	69.0	31.0
Zn(OAc) <sub>2</sub>	63.3	36.7
Zn(CN) <sub>2</sub>	46.3	53.7

<sup>a</sup> A catalyst loading of 15 mol % and a 24-h epimerization time was used for the above 0.5-g test reactions.

silica plug yielded samples of **1** that would readily crystallize from aqueous alcoholic mixtures. A volume efficient 3:2 isopropanol/water recrystallization (4.5 volumes to phenylglycinol) was developed and substituted for the hexanes crystallization. The isopropanol/water recrystallization produced granular, crystalline samples of **1** in high overall and diastereomeric purity (>98 LC area percent (LCAP),  $\geq$  99:1 **1/1a** dr),<sup>14</sup> low water content ( $\leq$ 0.3 wt %), and in a single crystal form. Recovered yields of **1** were less than those reported in the published procedure (53% versus 65%).<sup>12</sup> While the complete removal of silica gel from the process would have been ideal, the substitution of the silica plug filtration for the formal column chromatography greatly improved the overall process and material throughput.

Zinc bromide efficiently converts the crude mixture of diastereomers and related oligomers of **1** formed in the Robinson-Schopf reaction (dr  $\approx$  45:55 **1/1a**) to significantly upgraded samples of **1** (dr  $\geq$  85:15 **1/1a**). Unfortunately, zinc bromide deliquesces quickly in the open atmosphere, making weighing and charging large quantities of the reagent somewhat of a challenge. Moreover, the postequilibration zinc bromide byproduct adheres to the reactor walls, requiring repeated 6 N hydrochloric acid washes followed by methanol washes. It was thus desirable to find a Lewis acid that was easy to handle and provided facile reactor cleanup, but provided a conversion profile similar to that of zinc bromide.

A number of Brønsted and Lewis acids were investigated (Table 1) as potential epimerization agents. Many common acids, for example LiBr, MgSO<sub>4</sub>, CsCl, AcOH, TsOH hydrate, and Ti(OiPr)<sub>4</sub>, failed to enhance the **1/1a** diastereomeric ratio of crude reaction products. Zinc triflate, zinc *p*-toluenesulfonic acid, methanesulfonic acid, and ytterbium triflate were constructive conversion agents, but they did not transform the crude CNRS reagent mixture to the diastereomeric purity levels achieved by the bromide, chloride, and trifluoroacetate salts of zinc. Zinc chloride was not further investigated because of its ability to quickly deliquesce in the open atmosphere. A potential candidate was zinc trifluoroacetate hydrate, a white powder that can be easily manipulated in the open atmosphere and was thus chosen for additional investigation.

(14) The diastereomers of **1** were identified by LC/MS analysis, but a rigorous structure proof of individual diastereomers was not performed. The LCAP sum of the three possible diastereomers (**1a**) is reported, relative to **1**.

Small-scale test runs as well as multiple 0.5 kg demonstration runs (based on phenylglycinol) proved that zinc trifluoroacetate hydrate was an ideal replacement for zinc bromide. The crude conversion profiles with zinc trifluoroacetate hydrate were essentially identically to those of zinc bromide. The change in zinc counterion did not affect the quality or quantity of postsilica gel product collected. Semisolids still formed on the sides of the reactor, but cleanup required only a single acetonitrile wash followed by 0.5 N HCl and methanol washes, far superior to the prior protocol. While the per kilo cost of zinc trifluoroacetate hydrate ( $\sim$ \\$480/kilo) is higher than the per kilo cost of both zinc bromide ( $\sim$ \\$112/kilo, ACS grade) and zinc chloride ( $\sim$ \\$80/kilo, ACS grade), the higher catalyst cost is justified by the significantly less solvent and processing time required for equipment cleaning. Zinc trifluoroacetate hydrate may also be readily prepared from inexpensive raw materials.<sup>15,16</sup>

Toluene, MTBE, and MeTHF<sup>17</sup> were briefly investigated as alternative reaction solvents. Each of these common process solvents was chosen because of their stability to strongly acidic media. With toluene, the in-process reaction characteristics were less than desirable, as large amounts of thick semisolids formed on the side of the reactor flask during the Robinson-Schopf reaction. The Robinson-Schopf reaction with MTBE and MeTHF proceeded smoothly, but the zinc-mediated equilibrations did not achieve the diastereomeric purities ( $\leq$ 76:24 **1/1a**) of similar equilibrations in dichloromethane, presumably because of competitive coordination of Zn<sup>2+</sup> with the solvent.<sup>18</sup> Dichloromethane proved to be the only solvent capable of being telescoped through the Robinson-Schopf reaction, zinc-mediated conversion reaction, and the silica gel plug with excellent product purities and overall product recovery, and was thus selected as our process solvent.

A demonstration reaction on 0.5-kg scale (based on phenylglycinol) using the described optimizations provided **1** in 98.3 LCAP purity, 99.6:0.4 dr (**1/1a**), and 53% yield.

## Conclusion

A kilolaboratory-scale process for the efficient synthesis of **1** is described. Process optimization highlights include a reduced reaction volume, an easy to manipulate zinc trifluoroacetate hydrate-mediated equilibration reaction, a silica gel plug filtration purification, and a straightforward isopropanol/water recrystallization that produces **1** in  $\geq$ 98% LCAP,  $\geq$  99:1 dr (**1/1a**) and moderate yields.

## Experimental Section

**General.** A Waters liquid chromatograph (model 2695) equipped with a photodiode array detector (model 2996) was used for in-process and final analytical release. The in-process analysis used an 8-min linear method ramping from 95:5 to 15:85 water (0.1% TFA)/acetonitrile (0.1% TFA) at 2 mL/min with a ThermoElectron BetaBasic 18, 50 mm  $\times$  4.6 mm, 5  $\mu$ m column at 25 °C, with PDA analysis 214 nm. The LC analysis release method used a 30-min method ramping from 90:10 to 50:

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50 10 mM pH = 2.55 aqueous phosphate buffer/acetonitrile over 20 min, and then ramped to 20:80 10 mM pH = 2.55 aqueous phosphate buffer/acetonitrile over 10 min at 1.0 mL/min with a Waters Xterra RP18 4.6 mm × 150 mm, 3.5 μm column, ambient temperature, with PDA analysis at 215 nm. All reactions were run under positive nitrogen flow. A Dräger PAC III gas monitor, equipped with an HCN sensor, was used throughout the process development. The Robinson–Schopf reaction was scrubbed with aqueous KOH and/or aqueous KOH/KMnO<sub>4</sub>.

(2-Cyano-6-phenyloxazolopiperidine, (3*S*,5*R*,8*aS*)-3-Phenylhexahydro-2*H*-oxazolo[3,2-*a*]pyridine-5-carbonitrile), **1**. A mixture of distilled water (10 L), citric acid monohydrate (1991 g, 9.48 mol, 2.6 equiv), and (*S*)-(+)-phenylglycinol (500 g, 3.64 mol, 1.0 equiv.) was cooled to 5 °C, and glutaric dialdehyde (1167 g, 5.83 mol, 1.6 equiv., 50% by weight in water) was charged over 50 min at ≤5 °C. Dichloromethane (5 L) was charged, and the temperature equilibrated ≤5 °C. A solution of potassium cyanide (356 g, 5.47 mol, 1.5 equiv) in water (1 L) was charged over 25 min at ≤5 °C, and the contents were stirred at 2–5 °C for 4 h. The temperature was maintained below 5 °C to ensure any HCN formed during the reaction remained in the liquid state (HCN bp = 25.6 °C). The reaction was quenched by charging dibasic potassium phosphate (508 g, 2.92 mol, 0.8 equiv) followed by aqueous 4.5 M potassium hydroxide (1.2 kg of 90 wt % potassium hydroxide in 4.8 L water). The potassium hydroxide solution was charged over 43 min at ≤15 °C. The pH of the reaction solution was monitored during the last part of the base addition to ensure that the pH did not exceed 8.<sup>13</sup> When the pH of the reaction solution was between 7 and 8, the phases were allowed to separate for 10 min. After removing the bottom organic phase, dichloromethane (1.5 L) was charged and stirred for 10 min. The aqueous and organic phases were allowed to separate for 10 min. The bottom organic phase was removed, combined with the bulk organic solution, and dried for 16 h with anhydrous sodium sulfate (500 g). LC analysis of the crude Robinson–Schopf condensation reaction revealed a product purity of **1** at 46.2 LCAP with a dr of 49.5:50.5 (**1/1a**). KF analysis after 12 h of drying returned a water content of 0.28 wt %.

The drying agent was filtered and washed with dichloromethane (250 mL). The organic solution was degassed with dry nitrogen for 10 min, and zinc trifluoroacetate hydrate (113 g, 0.36 mol, 10 mol %, MW calculations assume 1 mol of water) charged. The contents were stirred at 20–25 °C until a dr of ≥85:15 **1/1a** was achieved (16 h), resulting in a dark-red solution of **1** (83.0 LCAP, 89.7:10.3 **1/1a**). The organic solution was passed through a plug of silica gel (1.6 kg Merck grade 9385, 40–60 μm, 230–400 mesh silica gel, prewashed with dichloromethane, 3.3 wt equiv to phenylglycinol) using gentle vacuum. An additional 5 L of dichloromethane was passed through the silica gel plug to yield a clear, colorless organic solution that was concentrated to a transparent oil using a rotary evaporator (30 °C bath temperature, 25–50 Torr pressure).<sup>19</sup> The residual dichloromethane was chased with isopropanol (3 × 500 mL) to yield a crude, white solid.<sup>20</sup> Analysis of the solid revealed an 87.4 LCAP purity of **1** and 90.1:9.9 dr (**1/1a**). The resulting crude solid was suspended in isopropanol (1.5 L, 3

vol to phenylglycinol) and warmed to a temperature of 60 °C; 1 L of water (2 volumes to phenylglycinol) was charged at a rate that maintained the reaction solution temperature ≥50 °C (45 min). The solution was cooled to 20 °C over 6 h using a linear ramp, and the reactor contents were stirred an additional 8 h at 20 °C. Crystals began to form at a reaction solution temperature of 44 °C. After 16 h, the reaction solution had turned from pale-yellow to yellow, and a white, granular, crystalline solid was present. The solids were collected and washed with a 1:1 water/isopropanol solution (2 × 500 mL). The resulting white, granular solid was dried at 45 °C for 14 h to yield 411 g (53% yield, 98.34 LCAP purity, 99.6:0.4 dr (**1/1a**)) of **1**. KF analysis of **1** was 0.23 wt %. OVI analysis by GC headspace revealed **1** contained 14 ppm dichloromethane and 1090 ppm isopropanol. XRPD analysis showed a single-crystal form was isolated. DSC analysis gave a sharp endotherm of 79.16 °C with an onset temperature of 77.15 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 7.34 (m, 5H), 4.25 (t, *J* = 8.0 Hz, 1H), 4.12 (dd, *J* = 9.8 Hz, 2.0 Hz, 1H), 3.89 (t, *J* = 8.0 Hz, 1H), 3.83 (m, 1H), 3.73 (t, *J* = 8.0 Hz, 1H), 2.11 (m, 1H), 1.95–1.67 (m, 4H), 1.59–1.52 (m, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 137.0, 128.8 (2), 128.4, 127.8 (2), 115.8, 89.6, 72.8, 63.7, 47.2, 29.8, 27.8, 19.2. Calcd for C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.37; H, 7.03; N, 12.16.

**Reactor Cleaning.** The reactor used to perform the zinc trifluoroacetate hydrate epimerization reaction was charged with 2 L of acetonitrile, and the contents were stirred for 15 min. The resulting red solution was removed, and 2 L of 0.5 N aqueous HCl was charged and stirred for 15 min. After removing the aqueous HCl solution, the reactor was charged with 1 L of methanol and stirred for 15 min. Removal of the methanol wash solution gave a reactor flask free of visible inorganic and organic impurities.

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### Supporting Information Available

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- (19) Our kilolaboratory manufacturing used a rotary evaporator to exchange dichloromethane for IPA for the sake of convenience; however, two larger-scale manufacturing campaigns (based on 5 kg of phenylglycinol, ZnBr<sub>2</sub> as the epimerization reagent) at our CMO demonstrated that an atmospheric pressure solvent exchange from dichloromethane to IPA does not adversely affect the yield (54%, 50%) or quality (> 98% LCAP, > 99:1 dr) of the finished product (**1**). The CMO noted the difficulty cleaning the reactors post-zinc equilibration (a phenomenon we also experienced in our kilolaboratory) which prompted us to search for the alternative epimerization catalysts.
- (20) It was critical to remove as much dichloromethane as possible before the isopropanol/water recrystallization. The high solubility of **1** in dichloromethane (>35 mg/mL) can lead to depressed product yields if dichloromethane is not effectively removed.