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A pilot-scale synthesis of (1*R*)-*trans*-2-(2,3-dihydro-4-benzofuranyl)cyclopropanecarboxylic acid: a practical application of asymmetric cyclopropanation using a styrene as a limiting reagent

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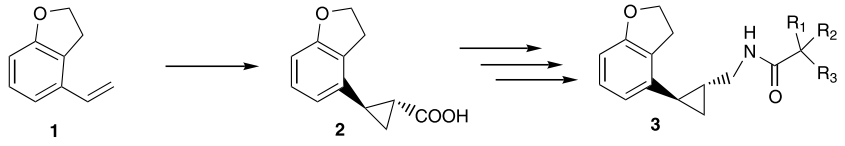
Abstract—Asymmetric cyclopropanation of styrene **1** (as the limiting reagent) was demonstrated using excess ethyl diazoacetate and catalytic Ru(ip-Pybox). Selective hydrolysis of the resulting 90:10 *trans*:*cis* mixture of cyclopropane **4** generated cyclopropyl acid **2** as a 96:4 *trans*:*cis* mixture with 84% e.e. for the *trans*-cyclopropane. Further purification and enantiomeric enrichment was achieved by diastereoselective crystallization with (+)-dehydroabeitylamine to afford the (*R*,*R*)-isomer with ≥99.9% e.e in 60–65 M% yield starting from styrene **1**.

1. Introduction

Recently, several melatonin agonists with generic structure **3** (Scheme 1) were identified at Bristol-Myers Squibb.[1] For the synthesis of these compounds, cyclopropyl carboxylic acid **2** was viewed as a pivotal intermediate since the *trans*-substituted cyclopropane fragment was common in all the compounds. As this program progressed into larger clinical studies, the requirements for the active pharmaceutical ingredient increased to multi-kilogram quantities, thus requiring an efficient synthesis of the cyclopropyl acid **2**. Herein, we report the preparation of **2**, which features a practical application of an asymmetric cyclopropanation chemistry using a styrene as a limiting agent[2] to afford a stereocontrolled cyclopropanation on multi-kilogram scale.

Early in the development of the synthesis of **2**, 4-vinyl-2,3-dihydrobenzofuran **1** was considered as a key starting material because of its ready availability from the industrial intermediate 5,8-dihydro-1-naphthol.[3,4] The vinyl group in **1** provided a potential handle for introduction of the cyclopropane ring with the desired stereochemistry. Asymmetric cyclopropanation using diazoacetate esters in the presence of a chiral metal



Scheme 1.

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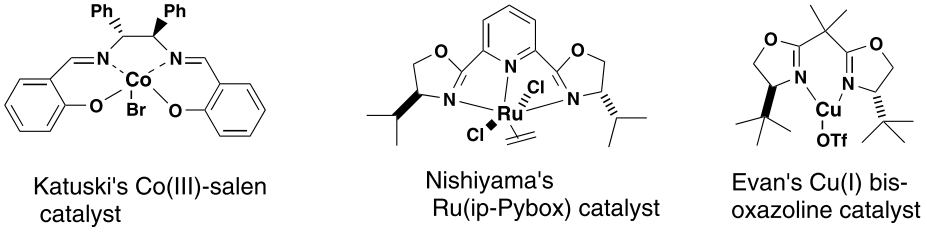
catalyst was attractive because of the ability to construct a functionalized cyclopropane ring from a styrene in a single step with proper stereocontrol. Several metal catalysts were known to enable highly enantioselective intermolecular cyclopropanation,[5] providing us with some flexibility in the selection of a suitable process for scale-up operations. However, a key drawback of most of the published methods is the employment of the styrene in substantial excess to suppress competing dimerization of the carbinoid derived from the diazoacetate. Since preparation of styrene **1** required multiple chemical conversions, use of this intermediate in excess would have been prohibitively expensive. This presented a unique challenge in that the literature procedures needed to be modified to allow the use of the olefin as the limiting reagent while delivering the desired cyclopropanation without impacting the chemical and stereochemical outcomes.

2. Results and discussion

Catalytic asymmetric cyclopropanations are well documented and a wide choice of metals and ligands are available for this transformation. Catalytic systems (Scheme 2) as reported by Evans,[6] Katsuki,[7] and Nishiyama[8] were evaluated for reactivity and selectivity against styrene **1**.[9] In contrast to these publications, where the olefin was used in large excess, the focus of the work described herein was to develop a cyclopropanation procedure which would allow styrene **1** to be used as the limiting reagent.

The overwhelmingly favored reaction pathway is dimerization of the metal–carbene complex to afford either maleate or fumerate (see Scheme 3). In the presence of an excess of an electron-rich olefin (e.g. styrene), the metal–carbene can be trapped by the olefin to form a cyclopropane. When using an expensive styrene as the limiting reagent, the diazoacetate needs to be added at such a rate that the metal carbene complex has a chance to react preferably with the olefin. Consequently, initial experiments using distilled styrene **1**, catalyst, and 90% EDA (ethyl diazoacetate) were focused on the addition rate of EDA and the molar ratio necessary to drive the reaction to completion. As expected, as styrene was consumed, dimerization became the predominant reaction. However, after several attempts, complete consumption of the styrene was accomplished by the addition of 2.5 equiv. of EDA over 16 h. Having established proof of concept, we next needed to identify a catalyst system that would impart high stereoselectivity and enantioselectivity.

Three catalysts were evaluated by monitoring the conversion of styrene **1** to the cyclopropyl ester as a function of catalyst loading while adding 2.5 equiv. of EDA over 16 h. The *cis*/*trans* selectivity was directly monitored by HPLC; but to determine the enantioselectivity, the ester was hydrolyzed to the acid prior to analysis on a chiral HPLC system. The Evans' Cu(I) bis-oxazoline catalyst was prepared as reported[6] and used for the cyclopropanation without further isolation or purification. This catalyst was active at 0.1 M%, leading to complete conversion of the styrene with 74% *trans*-selectivity; the *trans*-isomer was exclusively the (*R*,*R*)-isomer. Reaction conditions that would improve the *trans* to *cis* ratio and take advantage of the high enantioselectivity of the Evans' catalyst were not found beyond increasing the size of the ester. In addition, cyclopropanations with the (salen)Co(III) bromide[7] proceeded at best to 72% conversion and were only 81% selective for the (*R*,*R*)-isomer under the conditions studied. Nishiyama's Ru(ip-Pybox) catalyst was pre-

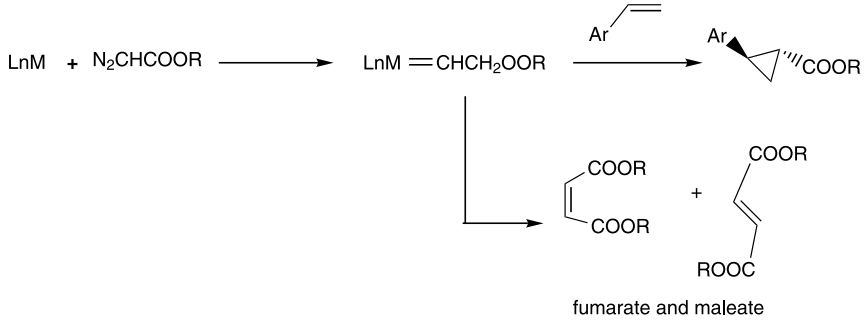


Katuski's Co(III)-salen catalyst

Nishiyama's Ru(ip-Pybox) catalyst

Evan's Cu(I) bis-oxazoline catalyst

Scheme 2.



fumarate and maleate

Scheme 3.

pared and purified by silica chromatography as reported.[10] Use of this catalyst at 2.0 M% afforded 95% conversion with 90% *trans*-selectivity, and an asymmetric induction of 83% for the (*R*,*R*)-isomer. Thus there were no surprises regarding stereoselectivity results from all three catalysts and in all aspects it compared well with the published literature. Consequently, the Ru(ip-Pybox) catalyst was chosen for further development since it afforded the highest molar yield of the (*R*,*R*)-isomer.

Further refinement of the Ru(ip-Pybox) reaction conditions revealed that the percentage conversion and stereoselectivity of the cyclopropanation e.e. was independent of solvent and temperature (see Tables 1 and 2). A 2^{4-1} statistically designed experiment[11] indicated that the reaction was highly sensitive to the molar ratio of EDA and the rate of EDA addition, but showed little response to changes in the concentration of either the EDA or styrene. Consistent with most reports, a slightly enhanced *trans* selectivity ($\sim$5%) was observed using *t*-butyl diazoacetate in place of the ethyl ester however, development was continued with the ethyl ester due to its greater availability (vide infra). These studies led to an optimized cyclopropanation process using 1.0 M% Ru(ip-Pybox) in ethyl acetate at 60°C with 2.5 equiv. of EDA added over 16 h. A graphic representation of the HPLC data for conversion of the styrene **1** to cyclopropane **4** is shown in Figure 1. For successful implementation on scale, these promising reaction conditions had to be adopted to actual process streams. In addition, workup conditions that would allow for isolation of the (*R*,*R*)-isomer in >99% enantiomeric purity needed to be developed.

Table 1. Solvent study

Solvent	% Conv.	% *trans*	% (*R*,*R*) (acid)
EtOAc	99	91	85
$Cl(CH_2)_2Cl$	99	88	82
t-BuOMe	97	91	85
THF	98	92	86
Cyclohexane	98	91	84
DME	99	91	84
MEK	99	91	83
IPA	97	86	80
Toluene	98	91	85

These reactions were run using 2.0 M% Ru(ip-Pybox) at ca. 60°C with 2.5 equiv. of ethyl diazoacetate added over 16 h.

Table 2. Temperature study

T (°C)	Solvent	% Conv.	% *trans*	% (*R*,*R*) (acid)
0	CH_2Cl_2	75	91	85
20	CH_2Cl_2	86	91	85
40	CH_2Cl_2	99	90	85
60	EtOAc	99	91	85
77	EtOAc	99	90	84
100	Toluene	99	90	83

These reactions were run using 2.0 M% Ru(Pybox) with 2.5 equiv. of ethyl diazoacetate added over 16 h.

EDA used during the initial screening experiments was purchased from Aldrich. However, to use EDA on multi-kilogram scale, a practical and high yielding process was developed.[12] Also, early in development, the Ru(ip-Pybox) catalyst was prepared according to the published procedure, which involved chromatographic purification of the catalyst. However, to avoid the need for large scale chromatographic purification, a simplified ligand preparation procedure and an improved preparation of the Ru-catalyst were developed.[13] With these improvements, large quantities of the air stable catalyst were prepared and used as needed.

Styrene **1** used in the screening studies had been purified by distillation and stabilized with 0.05 wt/wt% hydroquinone to inhibit radical catalyzed dimerization. For processing on scale, it was advantageous to employ **1** as an organic extract directly in the cyclopropanation sequence. Poor conversions plagued the use of a rich MTBE extract following the aqueous workup in the synthesis of styrene **1**. Upon testing several variations it was determined that the rich MTBE extract had to be washed to a neutral pH, and the residual water content lowered to <0.1%. An azeotropic distillation from toluene proved to work quite well. These developments led to a working process whereby a toluene solution of **1** and 2.0 M% of Ru(ip-Pybox) was prepared and warmed to 60°C. The catalyst loading was increased from 1 to 2 M% to consistently achieve $\geq$97% conversions. A solution of EDA (2.5 molar equiv.) in toluene prepared specifically for each cyclopropanation reaction was then added over 16 h while maintaining the batch at 60°C.

Once the desired cyclopropyl ester process was in hand, the preparation of acid **2** was accomplished via hydrolysis and diastereoselective crystallization (Scheme 4). Hydrolysis of the cyclopropyl ester **4** was accomplished by addition of water, NaOH, and tetrabutylammonium hydroxide to the crude cyclopropanation reaction mixture at 60°C. Hydrolysis was typically complete in 6 to 8 h with no detectable epimerization. A 4% enrichment in the *trans*/*cis* diastereomeric mixture was observed due to the selective hydrolysis of the *trans*-isomer. A graphic representation of the HPLC data for conversion of the hydrolysis reaction is shown in Figure 2.

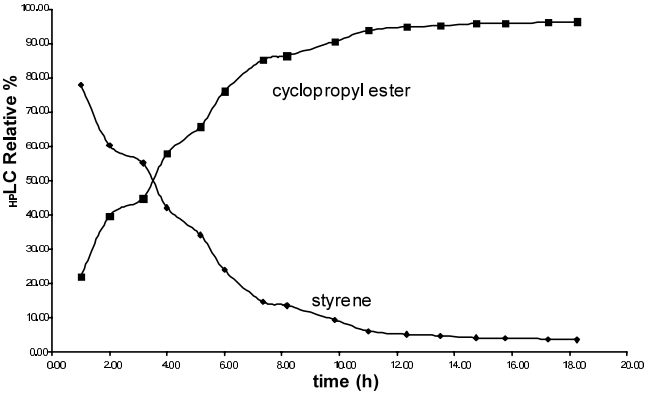
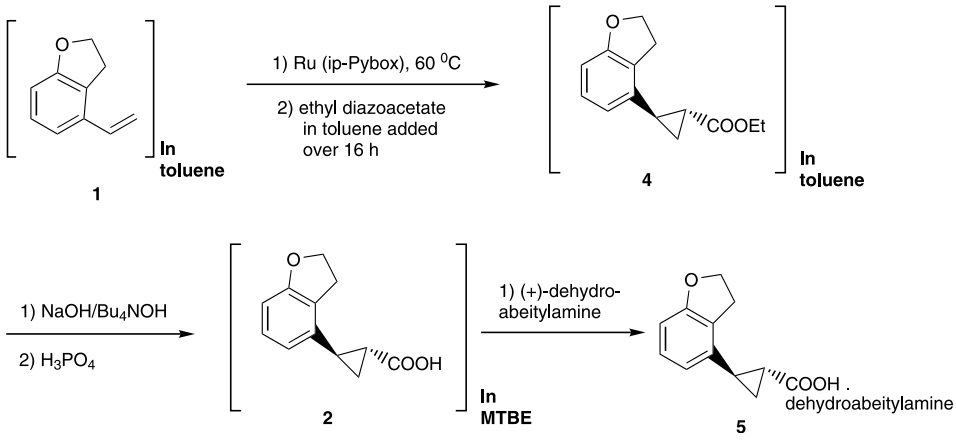


Figure 1. A typical cyclopropanation reaction profile with addition of EDA over 16 h.



Scheme 4.

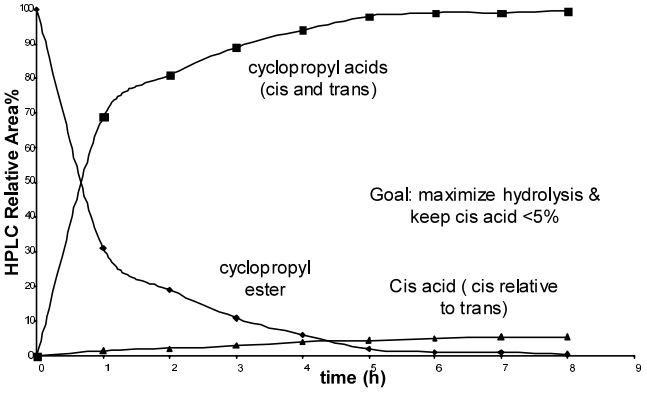


Figure 2. A typical hydrolysis reaction profile.

Removal of undesired fumaric and maleic acids was accomplished by adjusting the pH to 4.0–4.5 with phosphoric acid. The cyclopropyl acid was selectively extracted into MTBE and washed free of fumaric acid and maleic acid. Quantitation of the rich MTBE stream at this stage usually was 80–85 M% with a typical stereoisomer ratio of (1*R*,2*S*)- 3.7%; (1*S*,2*R*)- 0.5%; (1*R*,2*R*)- 90.0%; and (1*S*,2*S*)- 5.8%.

The enantiomeric purity of the *trans*-cyclopropyl acid was enriched further by diastereoselective crystallization using (+)-dehydroabeitylamine.[14] Upon crystallization, the product was isolated by filtration and dried to afford ca. 60–65 M% (based on **1**) of the (*R*,*R*)-dehydroabeitylamine salt having ×99.9% diastereomeric purity (Scheme 4).

Table 3. Yields of (1*R*)-*trans*-2-(2,3-dihydro-4-benzofuranyl)cyclopropanecarboxylic acid as its dehydroabeitylamine salt

Run	Input **1** (kg)	Output **5** (kg)	M% Yield	% Enantiomeric purity
1	0.025	0.0537	64.2	≥99.9
2	0.0658	0.143	64.8	≥99.9
3	52	113	65	≥99.9

All of these process modifications were integrated into a sequential process and demonstrated by the preparation of 56 g of enantiomerically pure **5** as recorded in Section 4. With documented safe laboratory procedures, this asymmetric cyclopropanation was further implemented in the pilot plant with 50 kg inputs of **1**.[15] The results of laboratory and pilot plant scale batches are summarized in Table 3; note that the pilot plant implementation of the procedure proceeded as expected without any scale-up issues.

3. Summary

In summary, a highly enantioselective cyclopropanation process suitable for manufacturing scale was developed. The chemistry demonstrated the use of a valuable styrene intermediate as the limiting reagent while delivering the desired cyclopropanation without affecting the chemical and stereochemical outcomes of the literature procedure.

4. Experimental

4.1. General

Preparation of the Ru(ip-Pybox) catalyst needed is described in Ref. 4. Toluene and MTBE were used without any purification or drying. The moisture content in toluene should be ≤0.05% w/w. Moisture content was determined by coulometric titration on a Mitsubishi CA-06 moisture meter on a w/w basis. Proton and carbon NMR were recorded on Bruker AC-300 spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C in $CDCl_3$ solution using Me_4Si as an internal standard. HPLC analysis was run under the following conditions: Equipment: Hewlett Packard 1090 Series HPLC, Column: YMC ODS-AQ S5μ, 4.6×250 mm, Isocratic: 55 V% water (containing 1.0 mL of 85% phosphoric acid per 1000 mL of water) 45 V% acetonitrile, Flow rate: 1.0 mL/min, Detection: 210 nm, Injection volume: 10 μL, Temperature: room temperature. Typical retention times were 1.9 min for fumaric and maleic acid, 4.2 min for ethyl diazoacetate, 4.4 min for *cis*-cyclopropyl acid, 5.1 min for *trans*-cyclopropyl acid, 5.9 min ethyl maleate, 9 min for ethyl fumarate, 15 min for *cis*-cyclo-

propyl ester, 15.7 min for toluene, 16.8 min for the styrene **1**, and 21.1 min for *trans*-cyclopropyl ester.

The following Chiral LC method was used for determining the enantiomeric ratio for the four possible stereoisomers of the cyclopropyl acid. Equipment: Hewlett Packard 1090 Series HPLC, Column: Chiralcel OJ-R OCD-HJ019 S5μ, 4.6×150 mm, Isocratic: 35 V% water, 65 V% methanol (containing 0.5 mL of trifluoroacetic acid per 1000 mL of water and methanol solution), Flow rate: 1.0 mL/min, Detection @ 285 nm, Injection volume:10 μL, Temperature: room temperature. Typical retention times were 6.7 min for (1*R*,2*S*)-isomer, 7.5 min for (1*S*,2*R*)-isomer, 10.2 min for (1*R*,2*R*)-isomer, 12.5 min for (1*S*,2*S*)-isomer.

4.2. Ethyl diazoacetate

To a solution of 18.9 g (135 mmol) of sodium tetraborate decahydrate[16] in 380 mL of water was added 98.2 (1423 mmol) of sodium nitrite and 190 g (1355 mmol) of ethyl glycine hydrochloride. Dissolution was endothermic, so the mixture was warmed to 20°C. To the aqueous solution was added 440 mL of toluene, and the reaction mixture was cooled to −5±5°C. At 5°C, 860 mL of a phosphoric acid solution was charged at a rate such that the batch temperature did not exceed 20°C. The phosphoric acid solution was prepared by charging 18.9 g of 85% phosphoric acid to 930 mL of water. The temperature of the reaction mixture was maintained at 10±10°C until an aqueous sample indicated the presence of nitrous acid by a positive starch-iodide test. The bottom aqueous waste was separated and treated as described in 'A Safe and Practical Procedure to Prepare Ethyl Diazoacetate'.[12] The upper rich organic layer was washed with 190 mL of water followed by 380 mL of 8 wt/wt% sodium bicarbonate in water. The ethyl diazoacetate solution in toluene was quantitated by GC analysis against a standard solution prepared from Aldrich supplied material. GC quantitation indicated that the 535 mL solution contained 128 g (83 M%). This material was kept at 5±5°C for use in the cyclopropanation reaction.

4.3. (1R-*trans*)-2-(2,3-Dihydro-4-benzofuranyl)cyclopropanecarboxylic acid 2

To a reaction vessel was charged 4.5 g (9.00 mmol) of Ru(ip-Pybox) and 65.8 g (450 mmol, 130 mL of the toluene solution) of 4-vinyl-2,3-dihydrobenzofuran **1**.[3] At 60±10°C, 128 g (1125 mmol, 513 mL of the toluene solution) of ethyl diazoacetate was added at a constant rate over 16 h. Upon complete addition of the ethyl diazoacetate, ≤2% of **1** remained by HPLC analysis. To the reaction mixture was added 450 mL of water, 66 g (140 mmol) of 55 wt/wt% tetrabutylammonium hydroxide (note: 55% was preferred over 40% because 55% remains a liquid whereas 40% crystallizes), and 110 g (1350 mmol) of 50 wt/wt% sodium hydroxide. The reaction mixture was maintained at 60°C for 8 h when ≤2% of the ethyl ester remained by HPLC analysis. To the reaction mixture was added 660 g of water and the batch was cooled to 20°C. The phases were separated, keeping the product rich aqueous phase; the upper organic phase was extracted with 65 mL of water. (Note that even though phase separation was rapid, the phase separations were difficult due to both phases having the same dark purple color and the presence of a dense rag layer.) The two aqueous streams were combined, and 730 g of MTBE were added. The mixture was cooled to 0–10°C and the pH was adjusted to pH 4.0–4.5 with 132 g of 85 wt/wt% phosphoric acid while maintaining the batch temperature at ≤25°C. (Note that at pH <4.0, it is more difficult to remove the fumaric acid by-products.) The phases were separated, and the upper rich organic layer was washed with two 130 g portions of water, whereby the fumaric acid by-products in the organic phase were ≤0.2 area% by HPLC analysis. The rich organic layer was quantitated by HPLC analysis to contain 78.1 g (85 M%). This solution was further diluted with 736 g (1000 mL) of MTBE and 172 g (210 mL) of SDA 3A alcohol (90 V% ethanol, 5 V% methanol, and 5 V% water). At 50±5°C the cyclopropyl acid(ca. 382 mmol)in MTBE was treated with a solution of (+)-dehydroabietylamine prepared by dissolving 191 g (401 mmol based on 60 w/w%) of 60 w/w% (+)-dehydroabietylamine in 626 mL of MTBE. The batch temperature was maintained at 50±5°C for 15 min, then 100 mg of seed crystals were added. The batch was cooled over 2 h to 25±5°C, then further cooled to 0–5°C over 1 h, and finally maintained at 0–5°C for 1 h. The crystalline material was collected by filtration, washed with two 200 mL portions of MTBE and dried under reduced pressure at ≤65°C to afford 143 g (64.8M%) of the salt.

(Samples for chiral HPLC analysis were converted to the free acid by the procedure described in the next paragraph, except that MTBE was used as the extracting solvent). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.9 (m, 1H), 1.0 (s, 3H), 1.1 (m, 1H), 1.2–1.9 (m which includes d, 19H), 2.1 (m, 2H), 2.65 (dd, 2H), 2.85 (m, 2H), 3.1 (apparent t, 2H), 4.5 (m, 2H), 6.3 (br. S, 3H), 6.35 (d, 1H), 6.6 (d, 1H), 6.85 (s, 1H), 7.0 (m, 2H), 7.15 (d, 1H). ^{13}C NMR (CDCl3) δ 16.45, 17.57, 18.44, 18.95, 22.98, 24,01, 25.19, 26.03, 28.70, 29,84, 33.45, 35.38, 36.07, 37.42, 38.06, 46.66, 51.76, 70.97, 106.96, 115.69, 123.97, 124,12, 126.08, 126.78, 128.19,134.31, 138.31,145.75, 146.71, 159.67, 179.82.

If needed, the free acid **2** was liberated by dissolving 143 g (293 mmol) of the DAA-salt in 1430 mL of toluene and 439 mL (878 mmol) of 2N sodium hydroxide. This mixture was stirred at 20±5°C for 1 h, followed by separating the phases and keeping the bottom rich aqueous phase. To the aqueous phase was added 43 g of sodium chloride, 430 mL *n*-butyl acetate, and 73 mL of conc. hydrochloric acid while maintaining the batch temperature ≤25°C. This mixture was stirred for 1 h before separating the phases. The bottom aqueous phase was back-extracted with 430 mL of *n*-butyl acetate, and the two organic streams were combined. The organics were concentrated by distillation at atmospheric pressure to 330 mL. Quantitation by HPLC analysis indicated 56.8 g (278 mmol, 61.8 M% from the 'styrene') of (1*R*)-*trans*-2-(2,3-dihydro-4-benzofuranyl)-

cyclopropanecarboxylic acid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.4 (m, 1H), 1.65 (m, 1H), 1.9 (m, 1H), 2.5 (m, 1H), 3.25 (t, 2H), 4.6 (t, 2H), 6.45 (d, 1H), 6.7 (d, 1H), 7.05 (t, 1H).

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14. Initially, the diastereoselective crystallization using (+)-dehydroabeitylamine was developed by our colleague Dr. Brian Kaller for the resolution of racemic **2**. During this development 26 homochiral amines under various solvent conditions were evaluated prior to selection of (+)-dehydroabeitylamine.
15. In the pilot plant, the dehydroabeitylamine salt **5** was not dried due to dust hazards associated with it. Although the salt was found to be thermally stable, it was electrically non-conductive and was highly sensitive to electrical ignition. Therefore, after MTBE washes, the salt was washed with water, centrifuged and isolated as ca. 50 wt% water wet material. Authors would like to thank D. Domina and W. Merkl and Dr. S. Wang for providing safety assessment on the salt and the New Brunswick Pilot Plant staff for successful scale-up operations.
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