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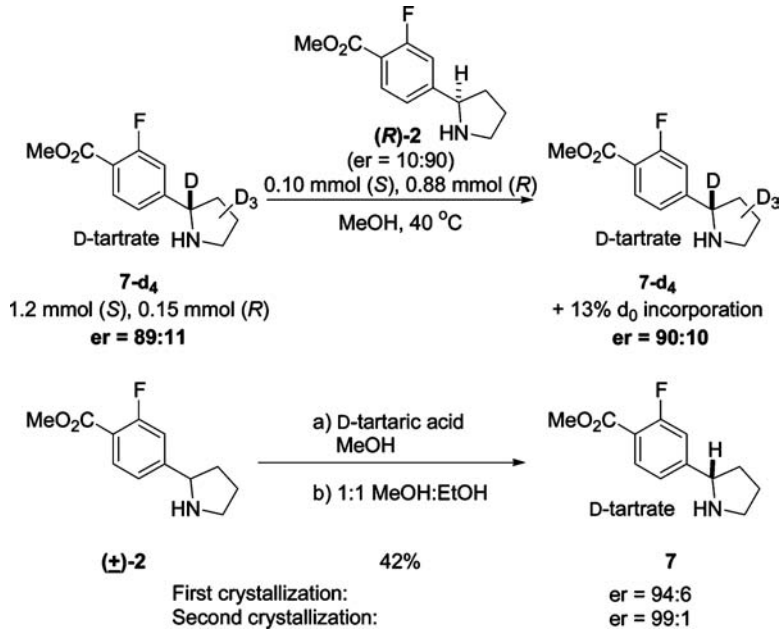

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Impact of Entropic Effects in the Classical Resolution of a 2-Arylpyrrolidine†

David M. Barnes,* Jufang Barkalow, Yong Chen, Ashok Gupta, Anthony R. Haight, John E. Hengeveld, Francis A. J. Kerdesky, Brian J. Kotecki, Bryan Macri, and Agnes Pal

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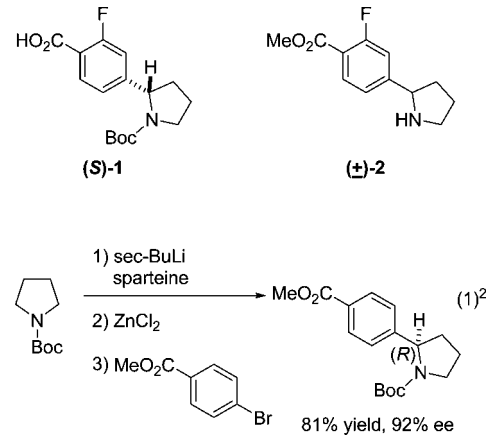
Abstract:

The impact of entropic effects on the classical salt resolution of a 2-arylpyrrolidine is described. We have found that the crystallization of a racemic mixture of the base with tartaric acid led to a salt in which the undesired enantiomer is incorporated into the crystal lattice as a solid solution. The product enantiomer ratio was later determined to be at the thermodynamic well when the racemate is crystallized. In order to circumvent this effect, an efficient two-crystallization resolution was developed. The bulk of the undesired enantiomer is removed in the first crystallization so that the second crystallization can result in material of acceptable optical purity.



Introduction

Single-enantiomer chiral compounds constitute an increasingly important fraction of new chemical entities in the pharmaceutical industry. While enormous strides have been made in the development of asymmetric catalysts for the enantioselective synthesis of chiral compounds, the classical approach of separating a single enantiomer from a racemic mixture by formation of diastereomeric salts remains an important strategy for asymmetric synthesis.[1]

For a recent project, we required the (*S*)-isomer of 4-(pyrrolidin-2-yl)benzoic acid **(*S*)-1**. An elegant approach to the synthesis of (*R*)-2-arylpyrrolidines has been reported recently, employing a Beak (−)-sparteine-mediated enantioselective lithiation of Boc-pyrrolidine, followed by transmetalation to zinc and cross-coupling (eq 1).[2,3] However, for our purposes this strategy is limited by the lack of inexpensive surrogates for (+)-sparteine.[4]

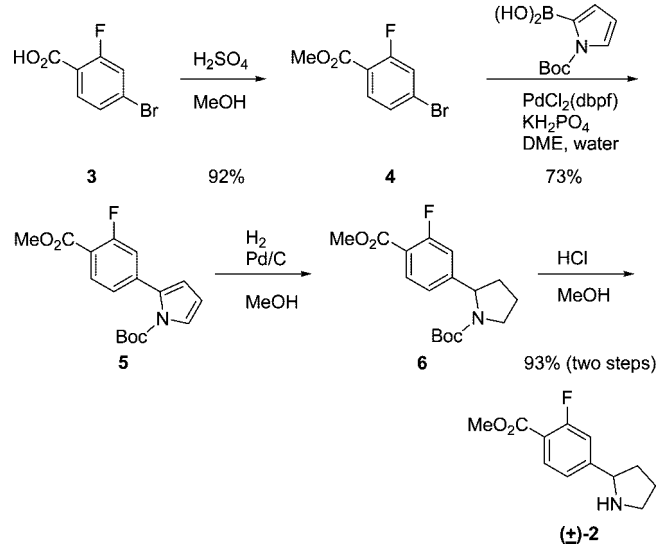
An alternate approach to the asymmetric synthesis of benzoic acid **(*S*)-1** would employ the classical salt resolution of racemic amine **(±)-2**. Although the maximum theoretical yield of a diastereomeric salt resolution is 50%, this can still be an attractive strategy when the racemic substrate is readily prepared.

Results and Discussion

The development of a classical resolution optimally employs single-enantiomer reagents from which the diastereomeric salt pairs are prepared. The relative solubilities of these diastereomeric salts are then compared in order to identify optimal resolving agents and conditions.

We developed an efficient synthesis of the racemic amine **(±)-2** starting from 4-bromo-2-fluorobenzoic acid (Scheme 1).

Scheme 1. **Synthesis of racemic amine (±)-2**



Following esterification, the Suzuki−Miyaura coupling with 1-Boc-pyrrole-2-boronic acid[5] employing 1,1′-bis(di-*tert*-butylphosphino)ferrocene (dbpf)[6] afforded the corresponding

† This paper is dedicated to the memory of Chris Schmid.

* Author to whom the correspondence may be sent. E-mail: david.barnes@abbott.com.

(1) Fogassy, E.; Nogradi, M.; Kozma, D.; Egri, G.; Palovics, E.; Kiss, V. *Org. Biomol. Chem.* **2006**, *4*, 3011–2020.

(2) Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C.-y. *J. Am. Chem. Soc.* **2006**, *128*, 3538–3539.

(3) The enantiomerically enriched 2-lithiopyrrolidine has also been transmetallated to copper, the products of which undergo palladium-catalyzed cross coupling. See: (a) Dieter, R. K.; Oba, G.; Chandupatla, K. R.; Topping, C. M.; Lu, K.; Watson, R. T. *J. Org. Chem.* **2004**, *69*, 3076–3086. (b) Dieter, R. K.; Li, S. *J. Org. Chem.* **1997**, *62*, 7726–7735.

(4) (a) Dearden, M. J.; Firkin, C. R.; Hermet, J.-P. R.; O'Brien, P. *J. Am. Chem. Soc.* **2002**, *124*, 11870–11871. For a list of ligands screened in the lithium metallation see: (b) Gallagher, D. J.; Wu, S.; Nikolic, N. A.; Beak, P. *J. Org. Chem.* **1995**, *60*, 8148–8154 It should also be noted that Beak and co-workers have reported a synthesis of 2-arylpyrrolidines by the asymmetric metalation and cyclization of (chloropropyl)benzylamines. (c) Wu, S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 715–721.

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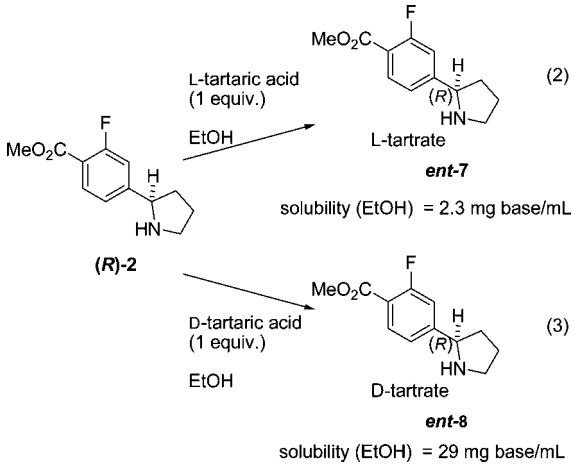
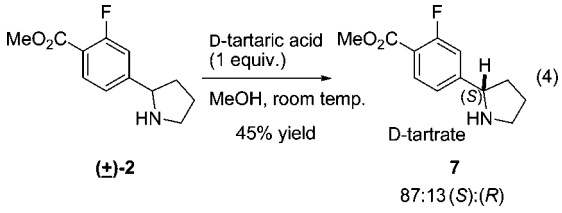
2-arylpyrrole. Reduction occurred readily using Pd/C, and finally the Boc protecting group was removed with HCl in MeOH.

When the (*R*)-amine **(*R*)-2** (obtained via chiral chromatography of the Boc-intermediate **6**) was treated with a series of enantiomeric pairs of chiral acids, the tartrate salts ***ent*-7** and ***ent*-8** exhibited a promising differentiation in solubilities (~12:1, eqs 2,3). If one assumes that these solubilities accurately reflect the behavior of the intended system, one would predict that the crystallization of racemic base could be carried out to remove all of the undesired enantiomer, with minimal (~10%) loss of the desired enantiomer.[7]



When the resolution of racemic amine was attempted using D-tartaric acid in MeOH at room temperature, the salt came out of solution immediately, being formed with an enantiomer ratio of only 87:13 (*S*):(*R*) (eq 4). At first, we assumed that this was a kinetic result, and that the crystallization was occurring too rapidly to allow discrimination between enantiomers in the growing crystals. Therefore, an experiment was run in which the initial slurry was held at 40 °C in order to allow equilibration of the solids with the liquors. However, over 18 h at 40 °C no change was observed in the composition of the liquors ((*S*):(*R*) = 18:82 to 17:83), and the solids were still obtained with a ratio of 91:9 (*S*):(*R*) after cooling to ambient temperature



Few differences were observed by X-ray powder diffraction between diastereomerically pure and impure salt samples (Figure 1). Indeed, although line broadening is observed with less optically pure samples, even at a 2:1 er, XRPD indicates

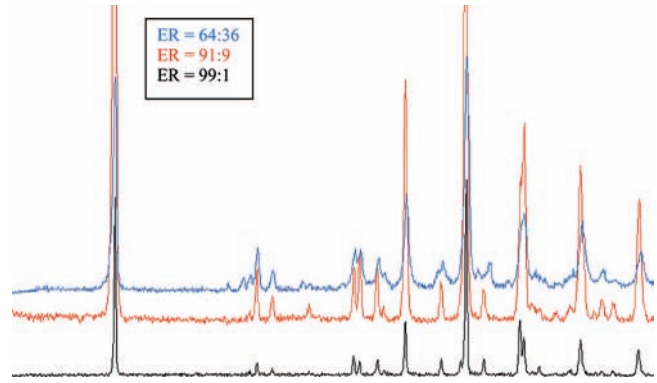
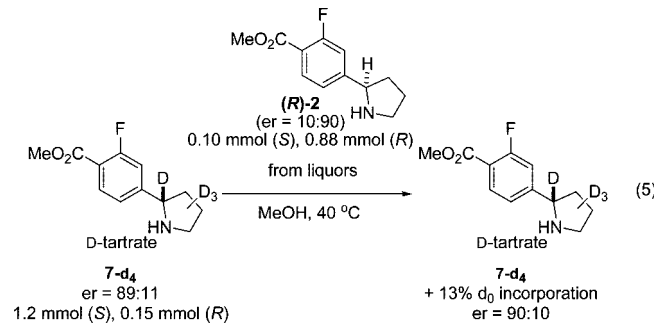


Figure 1. **XRPD of samples of varying diastereomer composition.**

that the crystal structure is still that of the expected major diasteromer. This indicated that the low ratio was not the result of crystallization of a new polymorph of the undesired salt diastereomer but rather of incorporation of the minor enantiomer into the salt crystal lattice as a solid solution.[8,9]

As the above results contradicted our hypothesis of a kinetically unselective crystallization, we ran another experiment in which a deuterated substrate (er = 89:11 (*S*):(*R*)) was incubated in the presence of unlabeled liquors (er = 10:90 (*S*):(*R*)) at 40 °C for 22 h (eq 5). The enantiomer ratio of the recovered solids (90:10 (*S*):(*R*)) was unchanged, although by NMR they now contained 13% of the unlabeled compound. Because complete randomization of the labeled and unlabeled materials would result in only 15% incorporation of the unlabeled compound into the solids (see Experimental Section for details), we conclude that under these conditions, a 9:1 enantiomer ratio is indeed the thermodynamic well for the system.



The practical implication of the observation that the observed enantiomer ratio is under thermodynamic control is that it becomes increasingly challenging to find conditions that will yield sufficiently enriched product after a single crystallization. We believe that the enthalpy (ΔH) of the process favors crystallization to generate a diastereomerically pure salt. However, when resolving the racemate, the (*S*)-enantiomer exists at a very high concentration of about 100 mg/mL in the supernatant. Entropically (ΔS), having all of the undesired enantiomer in the supernatant, represents an ordered system. We therefore

(5) Martina, S.; Enkelmann, V.; Wegner, G.; Schluter, A.-D. *Synthesis* **1991**, *61*, 3–615. (b) Johnson, C. N.; Stemp, G.; Stephen, S. C.; Gallagher, T. *Synlett* **1998**, 1025–1027.

(6) Itoh, T.; Sato, K.; Mase, T. *Adv Synth. Catal.* **2004**, *346*, 1859–1867. (a) Itoh, T.; Mase, T. *Tetrahedron Lett.* **2005**, *46*, 3573–3577.

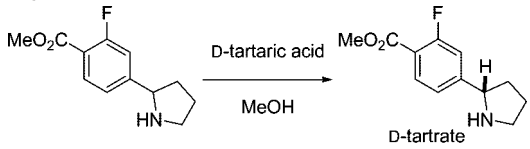
(7) In a resolution in which the solubility ratio is 12:1, a crystallization in which all of the undesired enantiomer is rejected (i.e. 100% of the undesired material) will also in theory lose 100%/12 = 8% of the desired enantiomer to the liquors. Of course, in practice the presence of the other enantiomer will likely increase the solubility of the desired salt form, but this rough calculation provides a convenient starting point for experimental design.

(8) Kozma, D.; Tomor, K.; Novak, C.; Pokol, G.; Fogassy, E. *J. Therm. Anal.* **1996**, *46*, 1613–1623.

(9) Products with er's as low as 2:1 were analyzed by X-ray powder diffraction and found to contain no additional peaks.

(10) Another report has noted a similar entropic contribution to a classical resolution. See: (a) Anandamanoharan, P. R.; Cains, P. W.; Jones, A. G. *Tetrahedron: Asymmetry* **2006**, *17*, 1867–1874.

Table 1. **Effect of tartaric acid stoichiometry on resolution efficiency**



(±)-2 7

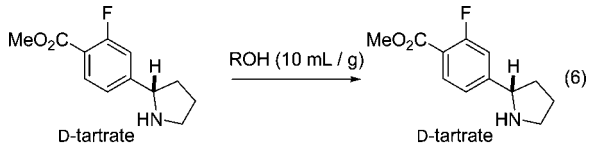
	equiv of D-tartaric acid	yield (%)	product (*S*):(*R*)
1	1.2	50	92.5:7.5
2	1.0	42	93.8:6.2
3	0.9	43	94.8:5.2
4	0.8	42	95.2:4.8
5	0.7	24	96.8:3.2

propose that under these circumstances the entropics of the system lead to incorporation of the minor enantiomer in spite of the small enthalpic cost.[10]

As a result, we abandoned a single-crystallization strategy in favor of a two-step approach. In this manner, the first crystallization removes most of the undesired (*R*) enantiomer from the system. Recrystallization of the resulting enantiomerically enriched product takes place in a system in which the level of (*R*) enantiomer in the supernatant is relatively low; this second crystallization therefore affords product of acceptable optical purity.

We first optimized the initial crystallization by examining the effect of stoichiometry. While the diastereomeric purity of the isolated solids does improve with an excess of base relative to acid, the effect is mild and offset by a corresponding decrease in recovery (Table 1). We therefore employed an excess of acid to maximize the yield of the desired enantiomer in the first crystallization.

We next looked at the effect of the crystallization medium on the second crystallization. Important to the success of this approach is the realization that losses of desired product (enthalpy driven) are primarily determined by its solubility in the recrystallization medium. On the other hand, rejection of the minor enantiomer is entropy driven. This will therefore be favored by the use of large volumes of solvent. As an example of the above discussion, when salt (er = 91:9 (*S*):(*R*)) was recrystallized from 10 mL/g of either MeOH or EtOH, the final ratios were substantially similar, although the losses to the MeOH liquors (14.6%, er = 49:51 (*S*):(*R*)) were triple the losses to the EtOH liquors (4.8%, er = 19:81 (*S*):(*R*)) (eq 6).

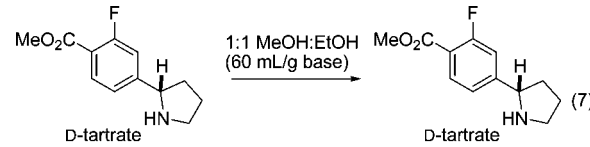


7 7

er = 91:9 (*S*):(*R*)

MeOH: 84%, er = 96.5:3.5 (*S*):(*R*)
EtOH: 92%, er = 95.8:4.2 (*S*):(*R*)

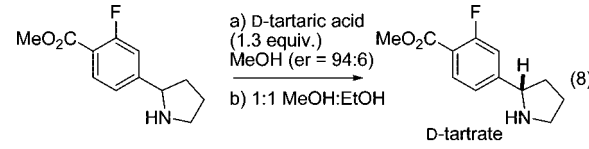
Therefore, we observe that in order to achieve optimal recoveries and purities the recrystallization requires a large volume of a medium in which the desired diastereomeric salt has low solubility. Thus, recrystallization of salt with a starting ratio of 92.5:7.5 (*S*):(*R*) from 60 mL/g of 1:1 MeOH:EtOH afforded a 74% yield of product **7** with a final ratio of 99.5:0.5 (eq 7).



7 74% 7

er = 92.5:7.5 er = 99.5:0.5

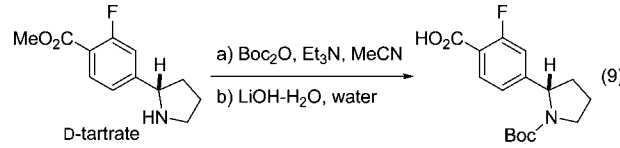
On scale, the process was run more efficiently by not drying the intermediate wetcake. The two-crystallization sequence was carried out to yield 42% of the salt **7** (84% of theory) as a 99:1 mixture of (*S*):(*R*) isomers (eq 8).



(±)-2 42% 7

er = 99:1

With the resolved salt in hand, we completed the preparation of Boc-acid **(*S*)-1** in a one-pot procedure (eq 9). First, the salt was reacted with Boc_2O without need of freebasing, in the presence of triethylamine in MeCN to form the intermediate Boc-ester. Although we could work up this reaction, we found that hydrolysis could be effected by the addition of aqueous LiOH to the reaction mixture; after stirring overnight at ambient temperature, the saponified product was crystallized directly from the reaction mixture in 93% yield by neutralization with hydrochloric acid.



7 93% (*S*)-1

In conclusion, during the development of a classical resolution of a 2-arylpyrrolidine derivative, we determined that the thermodynamic reaction mixture afforded salt containing a significant quantity of the undesired enantiomer. This observation prompted us to focus on a two-crystallization sequence designed to overcome the entropic liabilities inherent to the system. As a result, a process was developed in which the desired enantiomer was obtained in 42% yield (84% of theory) with excellent optical purity (99:1) through the two crystallizations, in which the second crystallization was optimized for minimal losses due to enthalpy (via low solubility of the desired salt) and maximal purification due to entropy (via a large volume of crystallization).

Experimental Section

Methyl 4-Bromo-2-fluorobenzoate (4). 4-Bromo-2-fluorobenzoic acid (24.7 kg, 113 mol) was dissolved in 135 kg of MeOH. H_2SO_4 (3 kg, 30.6 mol, 0.3 equiv) was added, and the reaction was heated to reflux for 20 h. After cooling to ambient temperature, the product was crystallized by adding the reaction mixture to 500 kg of cold (5 °C) water and isolated by filtration. After washing the cake with water, the product was dried at ambient temperature to afford 23.95 kg (92%) of the product as a white solid. Drying at higher temperatures led to loss of the product by sublimation.

Mp 58−60 °C. ^{1}H NMR (MeOH-d_4, 400 MHz) δ 7.82 (dd, J = 8.5, 7.8 Hz, 1H), 7.60−7.31 (m, 2H), 3.89 (s, 3H). ^{13}C NMR (MeOH-d_4, 400 MHz) δ 164.8, 163.6, 161.9, 133.8, 128.53, 128.45, 128.42, 121.4, 121.1, 118.7, 118.6, 52.9, 49.0.

Anal. Calcd for $C_8H_6BrFO_2$: C, 41.23; H, 2.60. Found C, 41.23; H, 2.38.

***tert*-Butyl 2-(3-fluoro-4-(methoxycarbonyl)phenyl)-1H-pyrrole-1-carboxylate (5).** Methyl 4-bromo-2-fluorobenzoate (12.3 kg, 53 mol) was dissolved in 234 kg of 1,2-dimethoxyethane, and the solution was purged with nitrogen. To a separate reactor was charged 1-Boc-pyrrole-2-boronic acid (13.4 kg, 63.5 mol, 1.2 equiv), dibasic potassium phosphate (9.2 kg, 53 mol, 1 equiv), tribasic potassium phosphate (11.2 kg, 53 mol, 1 equiv), and the reactor was purged with nitrogen. To the solids were added 170 kg of purged water and 57.7 kg of purged EtOH, followed by the ester solution. Finally, $PdCl_2$(1,1′-di-*tert*-butylphosphinoferrocene) (390 g, 0.53 mol, 0.01 equiv) was added, and the reaction was stirred at ambient temperature for 4 h.

The reaction was partitioned between 417 kg of EtOAc and 588 kg of 20% NaCl. The aqueous layer was extracted twice with EtOAc, and the combined organic layers were concentrated and filtered through 70 kg of silica gel with 10% EtOAc/heptane. The product solution was concentrated and solvent switched to MeOH, and was isolated by crystallization from 200 L of MeOH and 140 L water. After drying, 11.75 kg (73%) of the product was isolated.

Mp 54−56 °C. ^{1}H NMR (MeOH-d_4, 400 MHz) δ 7.87 (t, J = 7.9 Hz, 1H), 7.37 (dd, J = 3.4, 1.7 Hz, 1H), 7.20 (dd, J = 8.1, 1.7 Hz, 1H), 7.15 (dd, J = 11.9, 1.7 Hz, 1H), 6.31 (dd, J = 3.4, 1.8 Hz, 1H), 6.24 (t, J = 3.4 Hz, 1H), 3.90 (s, 3H), 1.39 (s, 9H). ^{13}C NMR (MeOH-d_4, 400 MHz) δ 165.4, 163.2, 160.6, 149.8, 142.0, 141.9, 133.4, 131.8, 125.4, 125.3, 124.7, 118.0, 117.7, 117.4, 117.3, 116.8, 111.7, 85.3, 52.7, 49.0, 28.0.

Anal. Calcd for $C_{17}H_{18}FNO_4$: C, 63.94; H, 5.68; N, 4.39. Found C, 63.88; H, 5.67; N, 4.37.

***tert*-Butyl 2-(3-fluoro-4-(methoxycarbonyl)phenyl)pyrrolidine-1-carboxylate (6).** MeOH (128 kg) was added to *tert*-butyl 2-(3-fluoro-4-(methoxycarbonyl)phenyl)-1H-pyrrole-1-carboxylate (24.0 kg, 75 mol) and 5% wet Pd/C (0.5 kg), and was pressurized with 40 psi H_2 for 3 h. The catalyst was removed by filtration (rinsed with 128 kg of MeOH) to yield 24.75 kg (103%) by assay.

^{1}H NMR (MeOH-d_4, 400 MHz) δ 7.87 (t, J = 7.55 Hz, 1H), 7.09 (d, J = 8.1 Hz, 1H), 7.06−6.95 (m, 1H), 4.97−4.73 (m, 1H), 3.88 (s, 3H), 3.71−3.45 (m, 2H), 2.49−2.26 (m, 1H), 1.97−1.70 (m, 2H), 1.56−1.07 (two br s, 9H). ^{13}C NMR (MeOH-d_4, 400 MHz) δ 165.4, 164.0, 161.4, 155.5, 154.3, 154.2, 132.7, 122.0, 117.5, 117.4, 114.8, 114.6, 81.0, 62.3, 61.7, 52.7, 48.3, 36.8, 35.7, 28.8, 28.5, 24.6, 24.3.

2-(3-Fluoro-4-(methoxycarbonyl)phenyl)pyrrolidine (2). The MeOH solution of *tert*-butyl 2-(3-fluoro-4-(methoxycarbonyl)phenyl)pyrrolidine-1-carboxylate (24 kg assay, 74 mol) was treated with conc. HCl solution (9.0 kg, 88 mol, 1.2 equiv) at reflux for 4 h. The MeOH was then removed by distillation and the reaction diluted with 300 kg of dichloromethane and washed with 110 kg of 10% Na_2CO_3 (the aqueous layer was extracted twice with dichloromethane). The combined organic layers were washed with 150 kg of 20% NaCl, and the reaction was solvent switched into MeOH to yield 15.0 kg by assay (90%) of the product as a solution in MeOH.

(*S*)-2-(3-Fluoro-4-(methoxycarbonyl)phenyl)pyrrolidine D-Tartaric Acid Salt (7). A solution of D-tartaric acid (13.0 kg, 87 mol, 1.3 equiv) in 61 kg of MeOH at 45 °C was added to the above MeOH solution of 2-(3-fluoro-4-(methoxycarbonyl)phenyl)pyrrolidine (15 kg assay, 67 mol), preheated to 63 °C. The salt formation was stirred at 65 °C for two hours, then cooling was started. At 64 °C solids began to form, and the reaction was cooled to 20 °C over 6.5 h before the product was collected by filtration and washed with 51 kg of EtOH. The wetcake exhibited an isomer ratio of 94:6 (*S*):(*R*).

The wetcake was taken up in a mixture of 200 kg of MeOH and 200 kg of EtOH, heated to reflux, and then cooled. The solids were collected by filtration and washed with EtOH to afford, after drying, 10.6 kg (42%) of the salt as a 99:1 mixture of (*S*):(*R*) isomers. HPLC method Chiralpak AD-H, 250 mm × 4.6 mm, 30 °C, 1 mL/min, elute with 95:2:3 hexanes/EtOH/MeOH with 0.05% diethylamine. (*S*)-enantiomer: 17 min, (*R*)-enantiomer: 15 min.

$[\alpha]^{26}_{589}$ −5.8 (*c* 1.07, water). Mp 196−198 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.89 (t, J = 7.9 Hz, 1H), 7.47 (dd, J = 12.1, 1.6 Hz, 1H), 7.40 (dd, J = 8.3, 1.4 Hz, 1H), 4.52 (dd, J = 9.5, 7.0 Hz, 1H), 4.01 (s, 2H), 3.84 (s, 3H), 3.35−3.11 (m, 2H), 2.41−2.23 (m, 1H), 2.13−1.76 (m, 3H). ^{13}C NMR (DMSO-d_6, 400 MHz) δ 173.6, 163.0, 161.4, 158.8, 145.6, 145.5, 131.5, 123.3, 123.2, 117.2, 117.1, 115.7, 115.5, 71.7, 60.6, 52.4, 45.0, 39.5, 31.6, 23.8.

Anal. Calcd for $C_{16}H_{20}FNO_8$: C, 51.47; H, 5.40; N, 3.75. Found C, 51.54; H, 5.39; N, 3.74.

(*S*)-4-(1-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl)-2-fluorobenzoic Acid ((*S*)-1). A solution of Boc_2O (6.2 kg, 28.4 mol, 1.0 equiv) and triethylamine (8.6 kg, 85 mol, 3 equiv) was added to (*S*)-2-(3-fluoro-4-(methoxycarbonyl)phenyl)pyrrolidine D-tartaric acid salt **7** (10.6 kg, 28.4 mol) in 58 kg of MeCN. After one hour, the reaction was complete, and $LiOH \cdot H_2O$ (5.9 kg, 140 mol, 5 equiv) in 72 kg of water was added, and the saponification was stirred for 8 h. The reaction was quenched with 207 kg of 1 N HCl solution followed by 69 kg of water. The product was isolated by filtration and washed with water to afford, after drying, 8.15 kg (93%) of (*R*)-4-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorobenzoic acid.

$[\alpha]^{25}_{589}$ −104 (*c* 1.06, $CHCl_3$). Mp 181−183 °C. ^{1}H NMR (MeOH-d_4, 400 MHz) δ 7.88 (t, J = 7.8 Hz, 1H), 7.08 (d, J = 8.1 Hz, 1H), 7.01 (br d, J = 11.5 Hz, 1H), 4.85−4.76 (m, 1H), 3.68−3.46 (m, 2H), 2.48−2.27 (m, 1H), 2.02−1.72 (m, 3H),

1.59−1.08 (br d, 9H). ^{13}C NMR (MeOH-d_4, 400 MHz) δ 166.6, 166.5, 164.2, 161.6, 155.5, 154.0, 153.9, 153.1, 153.0, 133.0, 121.9, 118.1, 118.0, 114.8, 114.5, 81.0, 62.3, 61.7, 48.3, 36.8, 35.8, 28.8, 28.6, 24.6, 24.3.

Anal. Calcd for $C_{16}H_{20}FNO_4$: C, 62.12; H, 6.52; N, 4.53. Found C, 61.76; H, 6.42; N, 4.56.

Incubation of Labeled Salt d_4-7 in the Presence of Unlabeled (*R*)-Liquors. Labeled d_4-salt (500 mg salt, er = 89:11 (*S*):(*R*), 267 mg (*S*)-base, 33 mg (*R*)-base) was incubated in unlabeled MeOH liquors from a crystallization (1.7 g, 0.22 g base assay, er = 10:90 (*S*):(*R*), 22 mg (*S*), 196 mg (*R*)) at 40 °C for 22 h. Thus, the system contained (*S*)-isomer d_4:d_0 = 92:8, and (*R*)-isomer d_4:d_0 = 14:86. The recovered salt was found to have an er of 90:10 (*S*):(*R*) and contained 13% unlabeled d_0 base. Assuming complete randomization, one would expect in the 90:10 solids 83% d_4-(*S*), 7% d_0-(*S*), 1.5% d_4-(*R*), and 8.5% d_0-(*R*), or 15.5% d_0. Because 13% was observed by NMR, we conclude that almost complete randomization was achieved without affecting the er.

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