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Efficient Crystallization-Induced Dynamic Resolution of α-Substituted Carboxylic Acids

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Herein we present a novel route to enantiomerically enriched chiral α-substituted carboxylic acids by crystallization-induced dynamic resolution (CIDR) of their diastereomeric salts with chiral amines. Thus, the racemic α-bromo acid **3** is converted reliably with *(1R,2S)*-2-amino-1,2-diphenylethanol in the presence of a catalytic amount of tetrabutylammonium bromide into its *R*-enantiomer **4** in 90% yield with 88% ee. Similarly, the racemic α-thiobenzoyl acid **5** could be resolved to 90% ee in 74% yield. Further enrichment to enantiomeric homogeneity could be achieved in both cases by crystallization. In a telescoped, two-step process, *S*-α-thiobenzoyl acid **6** (≥99.6% ee) was prepared from the racemic bromide **3** in 63% yield. State-of-the-art parallel experimentation enabled rapid screening for suitable dynamic resolution conditions. Kinetic studies defined the influence of temperature, tetrabutylammonium bromide concentration, molarity, and solvent polarity on the resolution rate, product yield, and enantiomeric excess.

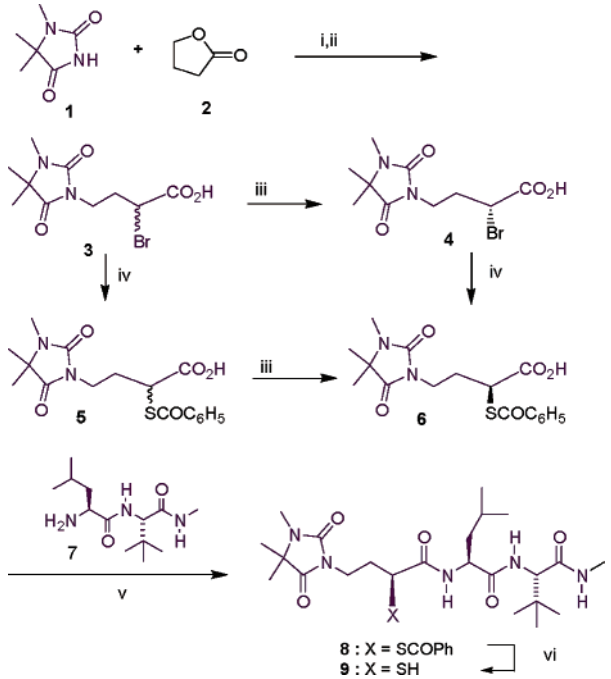
Introduction

We recently required a practical synthesis of the chiral dipeptide analogue **9**. Although there are many potential syntheses of this compound, our early analysis indicated that the route outlined in Scheme 1, proceeding via the enantiomerically pure *S*-α-thiobenzoyl acid **6**, was the most viable from both ease of practice and economical perspectives.

Classical resolution via chiral amine salts[2a] is the obvious choice for converting the readily available carboxylic acids **3** and **5** to **4** and **6**, respectively. Equally obvious is the economic disadvantage of the maximum 50% yield in these resolutions. Therefore, we were intrigued by the possibility of simultaneously racemizing the undesired enantiomer of **4** or **6** during the resolution process (a dynamic resolution),[2b] thus converting all of the racemate to the desired enantiomer. A number of dynamic resolutions of α-substituted carboxylic acids have been reported.[3,4] To the best of our knowledge, however, in all of these examples the carboxylic acid was first covalently bound, e.g., as an amide or ester, to a chiral auxiliary before resolution was affected by reaction with an appropriate nucleophile[3] or crystallization.[4]

This approach suffers from the disadvantage of requiring two additional steps in the process, specifically those

SCHEME 1. Synthesis of 9[a]



[a] Conditions: (i) K_2CO_3, 140 °C; (ii) PCl_3, Br_2, 1,2-DCP, 80 °C; (iii) resolution; (iv) PhC(O)SH, K_2CO_3, MTBE; (v) Vilsmeier Reagent, EtOAc, −25 °C; (vi) DAPA, Dithiothreitol, ^{i}PrOAc.

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involving attachment and detachment of the chiral auxiliary to the substrate and product, respectively. A conceptually superior alternative to this approach is to dynamically resolve the chiral amine salt(s), utilizing the solubility differential of the diastereomeric salts in a given solvent system, in the presence of an agent capable of affecting racemization. This concept of a crystallization-induced dynamic resolution (CIDR) via a pair of salt diastereomers has been demonstrated for various racemic amines and amino acids[5] but not, until this work, in the complementary fashion for carboxylic acids. Herein we report the first CIDR of a diastereomeric pair of α-substituted carboxylic acid salts.

Results and Discussion

Working Model. Our proposed resolution of bromo acid **3** is indicated in Scheme 2. Thus, treatment of a mixture of **3** with the appropriate chiral amine R^*NH_2 under conditions in which the undesired enantiomer undergoes epimerization to the desired enantiomer would lead to complete conversion to the desired diastereomeric salt. Treatment with aqueous acid would then lead to the enantiomerically pure acid **4**.

Experimental success in this proposed reaction would depend on satisfying several conditions:

(1) The salt(s) of the carboxylic acid with the chiral amine must be only partially soluble in the chosen solvent(s).

SCHEME 2. Proposed Dynamic Resolution of 3

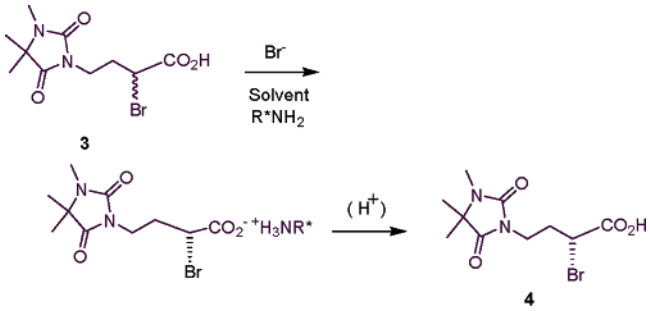

TABLE 1. Screening of Chiral Amines and Solvents for CIDR of Racemic Acid 3

amine	solvent	salt % *R*[a]	% *R* after CIDR
S-α-methylbenzylamine	*n*-BuOAc	48.0	20
S-diphenylpyrrolidinemethanol	*n*-BuOAc	51.0	86
1*S*,2*R*-2-amino-1,2-diphenylethanol	*n*-BuOAc	42.9	7
1*R*,2*S*-2-amino-1,2-diphenylethanol	1:1 *i*-PrOAc−MTBE	52.0	94
R-ephedrine	CH_3CN	49.6	∼50

[a] Determined by chiral column HPLC; all values ±0.5%.

(2) The desired salt diastereomer must have a lower solubility in the chosen solvent(s); e.g. the chiral amine must be of the right absolute configuration to give, ultimately, the *R*-acid **4**.

(3) An equilibrium must occur between the diastereomeric salts in solution, e.g., by nucleophilic substitution reaction in the presence of a bromide source.

Establishing the CIDR. The first step toward affecting the proposed CIDR involved treatment of the racemic acid **3** with 47 commercially available chiral amines. In a parallel experimentation approach, using reactor block technology, a total of 341 amine/solvent combinations were screened at 50 °C. The amine/solvent conditions leading to crystalline materials are indicated in Table 1; full details of the screening protocol are included in the Supporting Information.

Of the amines leading to crystalline salts, those derived from *S*-α-methylbenzylamine, 1*S*,2*R*-2-amino-1,2-diphenylethanol, and *R*-ephedrine gave slight excesses of the undesired *S*-acid salt, suggesting the desired differential solubility of the diastereomeric *R*- and *S*-acid salts could be obtained. The absolute stereochemistry was assigned by converting the obtained salt(s) into the chiral dipeptide and comparison against a reference sample of **9** by chiral column HPLC. Correction of the absolute stereochemistry of the product was readily achieved by using amines of the opposite absolute configuration. To demonstrate that the CIDR was feasible and, at the same time, to choose among these amines, suspensions of the salt mixtures were treated with catalytic amounts of potassium bromide or tetrabutylammonium bromide at temperatures ≥50 °C. At lower temperatures racemization was unacceptably slow. Thus, after heating of a 1:1 mixture of racemic acid **3** and 1*R*,2*S*-2-amino-1,2-diphenylethanol in *n*-butyl acetate in the presence of catalytic amounts of tetrabutylammonium bromide at 55 °C for 24 h, the diastereomerically enriched salt **10** with a 94:6 *R*:*S* ratio was isolated from the mixture by filtration in 90% yield

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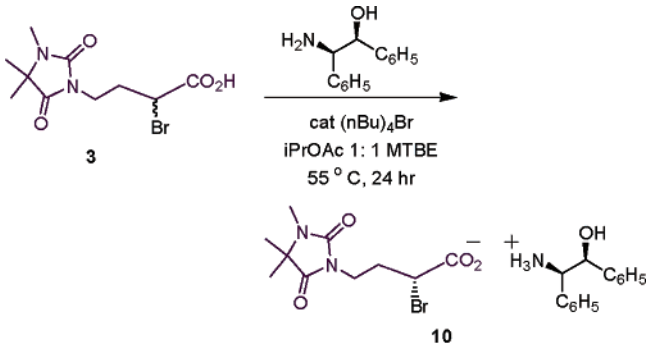
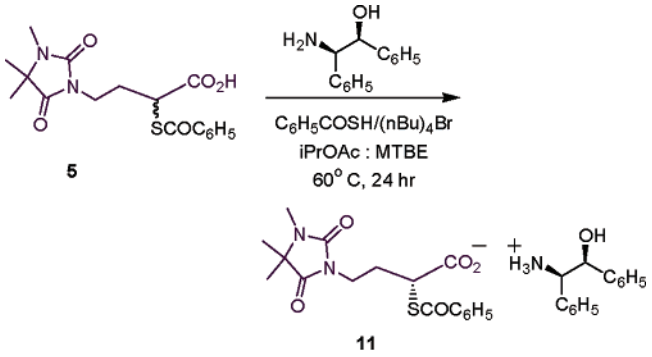
SCHEME 3. Crystallization-Induced Dynamic Resolution (CIDR) of 3



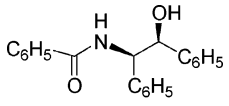
SCHEME 4. Crystallization-Induced Dynamic Resolution (CIDR) of 5



(Scheme 3)**.** As indicated in Table 1, the other amines gave less satisfactory results under similar conditions.

With this result in hand, we turned our attention to the CIDR of racemic thiobenzoyl acid **5** (Scheme 4). Using the same methodology (66 amines and 6 solvents) as for the bromo acid, we found that 1*R*,2*S*-2-amino-1,2-diphenylethanol in the presence of tetrabutylammonium thiobenzoate (generated in situ from thiobenzoic acid and tetrabutylammonium bromide) gave a 95:5 diastereomeric ratio of the *R*-salt **11** and its diastereomer.

Our efforts on this reaction (including using the opposite enantiomer of the amine to obtain the desired *S*-acid **6**) were cut short by the finding that a significant byproduct in these reactions was the cross-acylated amine **12** in up to 15% yield. We thus turned our attention back to the CIDR of bromo acid **3**.



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Optimization of the CIDR of Bromo Acid 3. We began the optimization of the enantiomeric enrichment and yield of the CDIR by statistically designed experiments. A Plackett−Burman experimental design scanning eight variables (solvent, bromide source, equivalents of bromide, equivalents of 1*R*,2*S*-2-amino-1,2-diphenylethanol, temperature, molarity, presence of water, reaction time) was carried out. It was found that **3** could be resolved in the presence of NBu_4Br as well as KBr, although in less polar solvents the use of KBr was less effective due to its low solubility. The variables with the strongest primary effects were identified as concentration of **3** and reaction time. Since the results of the experiment were confounded with multiple two-way interactions between the variables, we systematically investigated the various factors independently.

If not otherwise noted, resolutions were performed at a 0.12 M concentration of **3** with 0.97 equiv of 1*R*,2*S*-2-amino-1,2-diphenylethanol at 55 °C in 1:1 MTBE−^{i}PrOAc in the presence of 0.02 equiv of tetrabutylammonium bromide. The reaction time factor was eliminated by measuring the resolution rate expressed as diasteromeric enrichment of the reaction mixture with time under all experimental conditions. After approximately 20 h the mixture was cooled to room temperature and the diastereomerically enriched salt was isolated by filtration.

(a) Temperature. The resolution was significantly faster at higher temperatures, while yield and the final diastereomeric ratio were not affected. However, at reaction temperatures above 65 °C, the diastereomeric ratio of the reaction mixture declined with time and the isolated yield was low. For example, when the resolution was performed in EtOAc at 76 °C, a maximum diastereomeric ratio of 92:8 *R*:*S* was reached after 2 h. After 8 h, however, the diastereomeric ratio of the reaction mixture had declined to 75:25 *R*:*S* (Figure 1). The salt was isolated in only 75% yield. It was found that under the reaction conditions significant amounts of the N-acetylated chiral amine were formed. Loss of the chiral amine enabled dissolution and subsequent racemization of the now free bromo acid.**(b) Tetrabutylammonium Bromide (TBAB) Concentration**. In the range between 0.002 and 0.07 equiv of tetrabutylammonium bromide the resolution rate increased linearly with the bromide concentration. Yield and achievable diastereomeric ratio remained unaffected (Table 2).

However, in the presence of ≥0.2 equiv of tetrabutylammonium bromide lower yields were observed. In the presence of 0.05 equiv of tetrabutylammonium bromide 90% of resolved salt with a diastereomeric ratio of 94:6 was isolated after filtration. However, in the presence of 0.2 equiv of tetrabutylammonium bromide only 82% of the resolved salt was recovered, with a slightly lower diastereomeric ratio (88:12 *R*:*S*). This observation was rationalized by competing complexation of **3** with the tetrabutylammonium cation. ^{1}H NMR verified the presence of tetrabutylammonium cations in the isolated solids (1 M % in the presence of 0.02 equiv; up to 25 M % in the presence of 0.40 equiv of TBAB). Because of its racemic nature this tetrabutylammonium salt of **3** depresses the diastereomeric ratio of the isolated salt **10** and, assuming a higher solubility than **10**, leads to lower yields. To verify our hypothesis further, the resolution was carried out with 0.05 equiv of tetrabutylammonium bromide in the presence of 0.2 equiv of tetrabutylammonium hexafluorophosphate. This resolution yielded the diastereomerically enriched salt (*R*:*S* = 91:9) in only 80% yield.

(c) Concentration of 3. Resolutions at higher concentrations required longer reaction times to reach the final enantiomeric ratio of 94:6 (*R*:*S*) than less concentrated reactions. In fact, the resolution rate and the concentration of **3** were found to be nearly inversely proportional. At the same time, yields were higher at

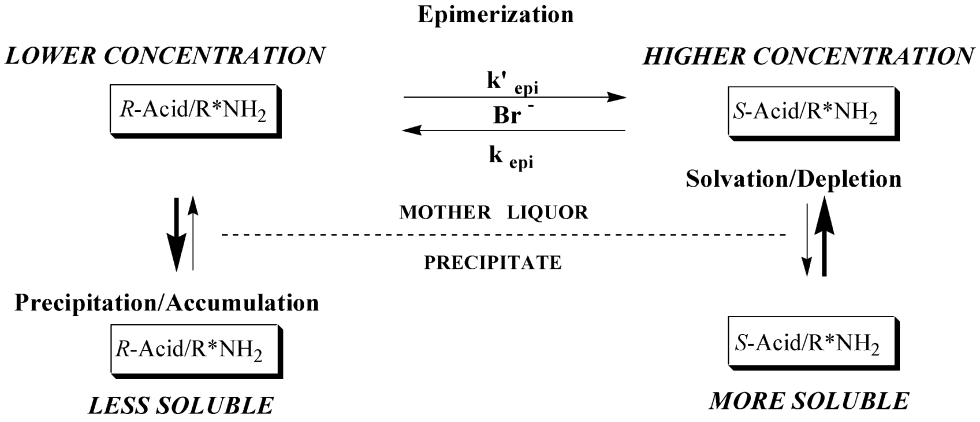


FIGURE 1. Proposed scheme for the dynamic resolution of **3**.

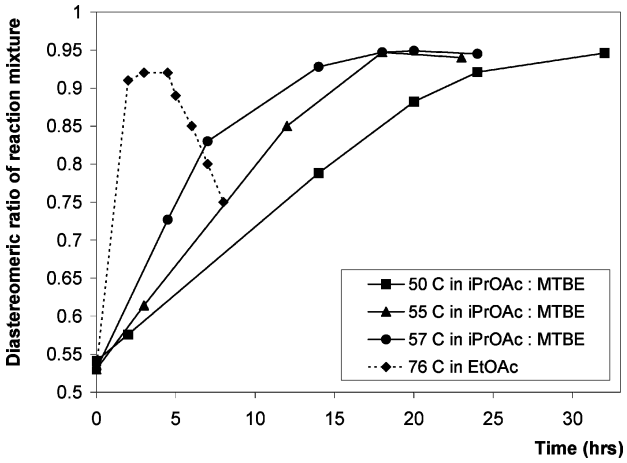


FIGURE 2. Diastereomeric ratio of the reaction mixture vs time at different temperatures.

TABLE 2. Resolution Rate, Diastereomeric Ratio, and Yield at Different TBAB Concentrations

TBAB concn, M	mol equiv rel to **3**	reacn time to reach 90:10 *R*:*S*, h	diastereomeric ratio of isolated **10**	yield, %
0.00025	0.002	60	94:6	90
0.0015	0.012	17	94:6	90
0.0020	0.016	15	94:6	90
0.0025	0.020	14	94:6	90
0.0069	0.055	4	94:6	90
0.0080	0.068	3	94:6	90

TABLE 3. Resolution Rate, Yield, and Diastereomeric Ratio at Different Concentrations of 3

concn **3**, M	reacn time to reach 90:10 *R*:*S*, h	diastereomeric ratio of **10**, isolated at 55 °C	Diastereomeric ratio of **10**, isolated at 25 °C	yield, %
0.045	3.5	94:6	83:17	71
0.064	7	94:6	85:15	82
0.107	11	95:5	93:7	87
0.143	15	95:5	94:6	90
0.286	36	93:7[a]	92:8[a]	94

[a] Resolution stopped uncompleted after 60 h.

higher concentrations of **3**, since the percentage of resolved salt **10** lost to the mother liquor is diminished (Table 3).

To compare the diastereomeric ratios achieved at different molarities, it was important to distinguish between the diastereomeric ratios of the solids isolated at ~ 55 °C and after cooling to 25 °C. At all molarities investigated, the diastereomeric ratios of the solids reached ≥94:6 "in-situ" at 55 °C. However, the diastereomeric ratios were significantly lower after cooling to 25 °C, especially at low molarities. For example, at 0.045 M molarity the diasteromeric ratio of the solids dropped from 94:6 to 83:17 after cooling the reaction mixture to 25 °C, while at 0.13 M molarity the diastereomeric ratio remained mostly unaffected by cooling. This was rationalized by the observation that the lower solubility of the salt at 25 °C (0.002 M) compared to 55 °C (0.010 M) caused additional precipitation from the mother liquor upon cooling. Because of the equilibrium established in solution, this precipitate was racemic and thus depressed the overall diastereomeric purity.

TABLE 4. Resolution Rate and Yield in Different Solvent Systems

solvent	reacn time to reach 90:10 *R*:*S*, h	yield, %	diastereomeric ratio of isolated **10**[a]
MTBE	not reached within 30 h	97	76:24
2:1 MTBE−^{i}PrOAc	28	90	91:9
1:1 MTBE−^{i}PrOAc	14	90	93:7
1:2 MTBE−^{i}PrOAc	8	89	92:8
^{i}PrOAc	6	85	92:8

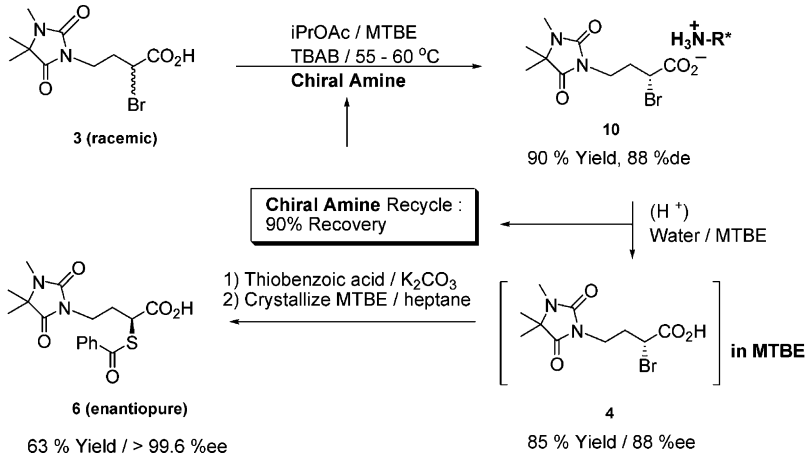
[a] Isolated after 30 h.

(d) Solvent Composition. While the resolution proceeded faster in more polar solvent systems, the higher solubility of the diastereomeric salts resulted in lower yields due to increased losses to the mother liquor. The diastereomeric ratio of the isolated salt **10** remained unaffected (Table 4).

(e) Equivalents of 1*R*,2*S*-2-Amino-1,2-diphenylethanol. The yield (90%) and enantiomeric ratio (94:6) were unchanged over the range of chiral amine concentrations examined (0.90, 0.97, 1.00, and 1.10 equiv of 1*R*,2*S*-2-amino-1,2 diphenylethanol relative to **3**). Interestingly, the resolution rate was generally slightly faster with an undercharge of the chiral amine.

Overall, the factors of temperature, tetrabutylammonium bromide concentration, solvent composition, equivalents of 1*R*,2*S*-2-amino-1,2 diphenylethanol, and molarity of **3** influenced the reaction rate as well as the yield of the resolution. Generally it was found that reaction parameters which accelerated the resolution (higher temperature, more polar solvent system, lower salt

SCHEME 5. Synthesis of 6



molarity, or higher tetrabutylammonium bromide concentration) inherently lowered the yield, either by adverse side reactions or losses to the mother liquor.

It was somewhat surprisingly to find that there were no reaction parameters that had an effect on the final diastereomeric ratio of 94:6. The latter finding as well as more detailed mechanistic investigations, also explaining the observed rate increase with an undercharge of the chiral amine, will be the topic of a future publication.

Preparation of *S*-Thiobenzoyl Acid 6 via CIDR of Bromo Acid 3. The optimized resolution conditions were a compromise between yield and reaction time. Salt **10** was thus obtained in 90% yield, containing **3** in a 94:6 *R*:*S* ratio of the enantiomers, after heating a 0.13 M mixture of racemic **3** and 1*R*,2*S*-2-amino-1,2-diphenylethanol (0.97 equiv) in 1:1 MTBE−^{i}PrOAc to 55−60 °C for 16 h.

The enantioenriched bromo acid **4** (*R*:*S* = 94:6) could be isolated from the diastereoenriched salt **10** by treatment with 1 N HCl or 1 N MSOH and extraction into MTBE in 90% yield. Treatment of the solution of **4** with K_2CO_3/thiobenzoic acid yielded **6** via inversion of stereochemistry to afford an enantiomeric ratio of 94:6 (*S*:*R*) in 94% yield. Under the reaction conditions (30 °C/3 h), compounds **4** and **6** were stable to racemization. In addition, it was demonstrated that, after extractive removal of the base K_2CO_3 and acidification to pH = 4 with acetic acid, the reaction mixture could be heated to 80 °C for >12 h without change in the enantiomeric ratio of **6**. However, when the reaction mixture was heated in the presence of the base, partial racemization of **6** to a ratio of *S*:*R* = 60:40 was observed after 2 h at 80 °C. Enantioenrichment of **6** to ≥99.8% ee was achieved by crystallization from *n*-heptane−MTBE in 74% crystallized yield. In comparison, enantiopurification of **4** by crystallization was much less efficient. Several crystallizations from toluene−*n*-heptane or MTBE−*n*-heptane were necessary to enrich **4** from 88% ee to 96% ee in an overall yield of 35%.

Overall, the reaction sequence accomplished the transformation of racemic **3** to enantiopure **6** in a two-step process in an overall yield of 63% (Scheme 5). Furthermore, the chiral amine 1*R*,2*S*-2-amino-1,2-diphenylethanol was recovered in 90% yield and >99% ee from the aqueous streams by treatment with 1 N NaOH and was successfully recycled into subsequent resolutions up to 5 times.

Conclusions

A novel route to enantiomerically enriched chiral α-substituted carboxylic acids by crystallization-induced asymmetric transformation (CIDR) of their diastereomeric salts with chiral amines has been presented. Because the α-substituent can be displaced via nucleophilic substitution, these chiral α-substituted carboxylic acids represent an excellent means of accessing chiral building blocks (potentially on large scale >100 kg) having either *R* or *S* configuration α to a carboxylic acid. State-of-the-art parallel experimentation enabled rapid screening for suitable resolution conditions. Detailed kinetic studies defined the influence of temperature, tetrabutylammonium bromide concentration, molarity, and solvent on the resolution rate, product yield, and enantiomeric excess.

Subsequently enantiopure *S*-α-thiobenzoyl acid **6** (≥99.6% ee) was prepared in a two-step process via CIDR of racemic α-bromo acid **3** in 68% yield.

Experimental Section

Materials. Racemic bromo acid **3** as well as the chiral amines and solvents were commercially available.

General Methods. (a) Amine/Solvent Screening. **3** and the chiral amine were dispensed in a 1:1 molar ratio into HPLC vials as 1 M methylene chloride solutions. The solvent was removed on the Savant Speed-Vac, and the test solvent was added into the appropriate containers to an approximate 0.05−0.10 M concentration. The mixtures were heated for 0.5 h to 50 °C and then judged visually. In case of a crystalline slurry, a sample of the solids was taken, and after identification as salt of **3** by ^{1}H NMR and HPLC, the diastereomeric ratio of the precipitate was determined by HPLC.

(b) Mechanistic Investigations Dynamic Resolutions of 3. Carboxylic acid **3** (1.00 equiv), chiral amine (0.90−1.10 equiv), and catalytic amounts of NBu_4Br were mixed in the solvent and heated to 55−60 °C. Samples of the resulting slurry were taken after certain times, and the progress of the reaction was followed as the increase of the diastereomeric ratio in the reaction mixture. Up to 90% conversion all resolutions progressed linearly with time.

After resolution completion, the reaction mixture was cooled to room temperature and the diastereoenriched salt isolated

by filtration. The resolution yield was determined as amount of isolated diasteroenriched salt (94:6 *R*:*S*) over the amount of input **3** or chiral amine whichever is smaller.

Dynamic Resolutions of 5 were carried out as described for **3** in the presence of catalytic amounts of thiobenzoic acid equivalent to the amount of NBu_4Br.

Analytical Methods. **Diastereomeric ratios** were determined by chiral column HPLC as the AP ratio of the *R*-enantiomer over the sum of both enantiomers. HPLC conditions: Chiralpak AD (0.46 × 25 cm, 10 μm) column; eluant 40% (v/v) EtOH (absolute) in hexane with 0.1% (v/v) TFA; flow rate 1.0 mL/min; detection at 230 nm. Bromo acid **3**: (*R*)-enantiomer $R_t = 12.0$ min; (*S*)-enantiomer $R_t = 10.4$ min. Thiobenzoxy acid **5**: (*R*)-enantiomer $R_t = 9.9$ min; (*S*)-enantiomer $R_t = 8.0$ min. Byproduct **12**: $R_t = 13.0$ min.

Concentrations of 3, 5, and 1,2-amino-1,2-diphenylethanol in solution were determined by HPLC area count after calibraton with respective reference samples. HPLC conditions: Zorbax SB-C18 (0.46 × 7.5 cm) column; eluant 65% (v/v) water in acetonitrile adjusted to pH = 2.5 with phosphoric acid; flow rate 0.5 mL/ min; detection at 210 nm. Bromo acid **3**: $R_t = 3.5$ min; correction factor = 1.00×10^{-8} g L^{-1} $area^{-1}$. Thiobenzoxy acid 5: $R_t = 8.5$ min; correction factor = 0.23×10^{-8} g L^{-1} $area^{-1}$. 2-Amino-1,2-diphenylethanol: $R_t = 1.8$ min; correction factor = 1.30×10^{-9} g L^{-1} $area^{-1}$.

Synthesis of (α*R*)-α-Bromo-3,4,4-trimethyl-2,5-dioxo-1-imidazolidinebutanoic acid, (α*R*,*β*S)-*β*-Amino-α-phenylbenzeneethanol Salt (1:1) (10). At room temperature, 30.0 g (0.098 mol) of 3, 20.2 g (0.095 mol) of 1,2-diphenyl-2-aminoethanol, and 0.75 g (2.3 mmol) of tetrabutylammonium bromide were dissolved in a mixture of 360 mL of isopropyl acetate and 360 mL of MTBE. After approximately 3 min the salt precipitated from the solution. The resulting slurry was heated to 55−60 °C for 24 h. After being cooled to room temperature, the reaction mixture was filtered on a Buchner funnel and the cake washed with 240 mL of MTBE and dried to weight constant.

Yield: 45.6 g (0.088 moL) (90%) of **10** as white powder (93.3% *R*)

^{1}H NMR ($CDCl_3$): δ (ppm) = 7.16 (m, 8 H), 7.08 (m, 2 H), 5.60 (br s, 4 H), 5.49 (d, 3 Hz, 1 H), 4.54 (d, 3 Hz, 1 H), 4.09 (t, 7 Hz, 1 H), 3.49 (m, 2 H), 2.73 (s, 3 H), 2.23 (m, 1H), 2.11 (m, 1H), 1.28 (s, 3H), 1.27 (s, 3H). ^{13}C NMR (acetone-d_6): δ (ppm) = 22.0, 24.5, 34.4, 37.2, 45.1, 61.8, 67.2, 82.7, 127.2, 127.3, 127.7, 128.0, 128.1, 128.3, 128.3, 128.4, 128.5, 130.1, 139.3, 141.5, 155.6, 171.1, 177.3. Anal. Calcd: C, 55.39; H, 5.81; N, 8.07; Br, 15.35; O, 15.37. Found: C, 55.52; H, 5.91; N, 8.00; Br, 15.45.

Synthesis of (*R*)-α-Bromo-3,4,4-trimethyl-2,5-dioxo-1-imidazolidinebutanoic Acid (4). A 25.0 g amount (0.048 mol) of **10** was dissolved in 350 mL of water and acidified to a pH of 1.0 with concentrated HCl. The solution was extracted 6 times with 150 mL of MTBE. The combined organic layers were washed with 125 mL of water and then azeotropically concentrated to 400 mL under atmospheric pressure. A 100 mL volume of toluene was added, and distillation was continued until the reaction mixture reached 80 °C. At 80 °C 80 mL of *n*-heptane was added until clouding was evident. The solution was cooled to room temperature within 2 h and stirred for 1 h at room temperature. The resulting slurry was filtered on a Buchner funnel to yield 8.5 g (0.028 mol) of **4** as white crystals (95.2% *R*). A 3.0 g amount of the enantioenriched bromo acid was recrystallized from toluene and MTBE−*n*-heptane to yield 1.9 g of **4** (0.006 mol) (35%) with an enantiomeric ratio of 98:2 *R*:*S*.

^{1}H NMR ($CDCl_3$): δ (ppm) = 4.30 (m, 1H), 3.72 (m, 2H), 2.96 (s, 3 H), 2.48 (m, 1H), 2.27 (m, 1H), 1.39 (s, 6H). ^{13}C NMR ($CDCl_3$): δ (ppm) = 176.7, 172.2, 155.2, 61.4, 41.7, 36.6, 33.2, 24.4, 21.9, 21.9. IR (KBr): ν (cm^{-1}) = 3000 (br), 1740 (s), 1680 (s), 1450 (br), 1250 (s). Anal. Calcd: C, 39.10; H, 4.92; N, 9.12; Br, 26.01. Found: C, 39.31; H, 4.94; N, 9.06; Br, 25.63.

Synthesis of (*S*)-α-(Benzoylthio)-3,4,4-trimethyl-2,5-dioxo-1-imidazolidinebutanoic Acid (6). A 45.6 g amount (0.088 mol) of **10** was dissolved in a mixture of 600 mL of water and 6 mL of methanesulfonic acid and extracted four times with 0.5, 0.4, 0.3, and 0.3 L of MTBE. The combined organic layers were washed with 100 mL of water and azeotropically dried to a KF of 0.26% and a volume of 380 mL. Under nitrogen 11.7 mL (0.100 mol) of thiobenzoic acid and 11.5 g (0.083 mol) of potassium carbonate were added and the resulting slurry was stirred at 30 °C for 3 h. The reaction was quenched by addition of a mixture of 120 mL of water and 40 mL of acetic acid, and after phase separation, the organic layer was washed with 90 mL of water. After addition of 0.25 mL of acetic acid, the reaction mixture was azeotropically dried to a KF of 0.27% and concentrated to 240 mL. The solution was heated to 50 °C, and 120 mL of *n*-heptane was added within 30 min. The resulting crystal slurry was cooled to 0 °C within 1.5 h. After 2 h the crystal slurry was filtered on a Buechner funnel and the cake washed with 60 mL of a 1:1 mixture of MTBE and *n*-heptane. Yield: 22.3 g of off-white crystals (0.061 mol) (70%) (99.8% *S*).

^{1}H NMR ($CDCl_3$): δ (ppm) = 7.98 (d, 8.0 Hz, 2 H), 7.60 (t, 8 Hz, 1H), 7.48 (t, 8.0 Hz, 2H), 4.40 (m, 1H), 3.78 (m, 2H), 2.96 (s, 3 H), 2.42 (m, 1H), 2.10 (m, 1H), 1.47 (s, 3H), 1.43 (s, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) = 189.6, 176.9, 172.7, 155.3, 135.9, 133.8, 128.6, 127.3, 61.4, 42.7, 36.5, 30.7, 24.4, 21.8, 21.7. IR (KBr): ν (cm^{-1}) = 3000 (br), 1740 (s), 1680 (s), 1450 (br), 1220 (s), 1180 (s), 900 (s), 780 (s), 690 (s). Anal. Calcd: C, 56.03; H, 5.53; N, 7.68; S, 8.79. Found: C, 55.97; H, 5.58; N, 7.64; S, 8.89.

Resolution of 5 via Its (α*R*,*β*S)-*β*-Amino-α-phenylbenzeneethanol Salt (11). At room temperature, 0.50 g (1.37 mmol) of **5**, 0.27 g (1.27 mmol) of 1,2 diphenyl-2-aminoethanol, 13 mg (0.06 mmol) of tetrabutylammonium bromide, and 10 μL of thiobenzoic acid (0.12 mmol) were dissolved in 10 mL of isopropyl acetate. The resulting slurry was heated to 55−60 °C for 24 h. After being cooled to room temperature, the reaction mixture was filtered on a Buchner funnel and the cake washed with 40 mL of MTBE and dried to weight constant. Yield: 0.54 g (0.94 moL; 74%) of **11** as a white powder (94.7% *R*).

^{1}H NMR (acetone-d_6): δ (ppm) = 7.95 (d, 7 Hz, 2 H), 7.70 (m, 1H), 7.54 (m, 2H), 7.16 (m, 2 H), 7.08 (m, 8 H), 5.34 (d, 3 Hz, 1 H), 4.98 (d, 3 Hz, 1 H), 4.40 (t, 7 Hz, 1 H), 3.63 (m, 2 H), 2.85 (s, 3 H), 2.42 (m, 1H), 2.04 (m, 1H), 1.32 (s, 6H). ^{13}C NMR (acetone-d_6): δ (ppm) = 22.0, 24.5, 31.6, 37.1, 44.0, 61.8, 67.2, 82.7, 127.2, 127.3, 127.6, 127.7, 127.8, 127.9, 128.0, 128.2, 128.3, 128.4, 128.5, 129.8, 129.9, 134.9, 137.3, 139.4, 141.6, 155.7, 172.2, 177.3, 190.1.

The isolated material was dissolved in 40 mL of water and acidified to a pH of 1.35 with MSA. An insoluble residue remained. The aqueous solution was filtered on a Buchner funnel to yield 0.06 g of byproduct **12** (0.19 mmol) (15%) as a white powder.[6]

Mp: 225 °C. ^{1}H NMR (DMSO-d_6): δ (ppm) = 8.52 (d, 8 Hz, 1 H), 7.63 (d, 7 Hz, 2 H), 7.40 (m, 6 H), 7.28 (m, 7 H), 5.50 (br s, 1 H), 5.18 (t, 8 Hz, 1H), 4.97 (d, 8 Hz, 1 H). The filtrate contained 0.36 g (0.98 mmol) (77%) of *S*-α-thiobenzoyl acid **6**, based on HPLC analysis.

Supporting Information Available: Characterization of compounds **4**, **6**, **10**, and **11** (^{1}H NMR, ^{13}C NMR) and a table detailing all screened amines and solvents. This material is available free of charge via the Internet at http://pubs.acs.org.

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