Synthesis of New Optically Active and Racemic Phenylsuccinamic Acids

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Abstract: The synthesis, isolation, and characterization of new (*S*)-(+)- and racemic phenylsuccinamic acids, obtained from the reaction of (*S*)-(+)-phenylsuccinic anhydride (**1**) with five different primary amines (**2a**–**e**) is described. Ring opening of anhydride **1** led to the formation of two isomeric phenylsuccinamic acid products with the phenyl substituent β to the amide function being the preferred product. Complete racemization occurred with all of the α-phenylsuccinamic acids (**3a**–**e**) and β-phenylsuccinamic acids **4b** and **4c**. However, β-phenylsuccinamic acids **4a**, **4d**, and **4e** were found to be optically active.

Key words: anhydride, chirality, nucleophilic addition, racemization, ring opening

Recently, we reported[1] the auto-resolution of nonracemic antihistamines under achiral conditions. During our initial attempts to improve upon existing methods[2–5] of antihistamine resolution by HPLC, we prepared several *n*-propylamino silica gel columns modified by various (*S*)-(+)-phenylsuccinamic acids. Although these modified columns did not prove successful, several interesting results were observed when (*S*)-(+)-phenylsuccinic anhydride (**1**) was reacted with different amines (**2**) to obtain the desired phenylsuccinamic acids. Therefore, the reaction of anhydride **1** with various primary amines (**2a**–**e**) was further investigated and the results are reported here.

Succinamic acids (4-amino-4-oxobutanoic acids) contain both the carboxylic acid and amide functionalities. When one of the methylene hydrogens is replaced by a different substituent (i.e. phenyl), two regioisomers are possible. The substituent will either be alpha (α-succinamic acid) or beta (β-succinamic acid) to the amide.

Richard Anschütz[6], in 1907, was the first to report the synthesis of a phenylsuccinamic acid by reacting racemic phenylsuccinic anhydride with ammonia. He reported that the β-isomer of phenylsuccinamic acid (mp 144–145 °C) was the major product. He also reacted phenylsuccinic anhydride with aniline and reported that the β-phenylsuccinanilic acid (mp 169–170 °C) was the only product formed. From these results, Anschütz concluded that the carbonyl carbon β to the phenyl substituent of the anhydride is more susceptible to attack by the amine and that ring opening will result in the formation of the β-phenylsuccinamic acid as the major product.

In 1940, Naps and Johns[7] synthesized optically active (+)-β-phenylsuccinamic acid and (+)-β-phenylsuccinanilic acid. No mention was made of the α-isomers and in the case of the (+)-β-phenylsuccinamic acid, the authors reported that some racemization occurred during purification.

Eleven years later, Miller and Long[8] synthesized a number of *N*-substituted phenylsuccinamic acids by reacting racemic phenylsuccinic anhydride with various amines, (methylamine, ethylamine, *n*-propylamine, isopropylamine, allylamine, *n*-butylamine, isobutylamine, and *sec*-butylamine). Although they reported that a mixture of α- and β-phenylsuccinamic acid isomers formed, only the β-isomers were isolated and their melting points reported. Neither the ratio of α- to β-isomer nor the isolation and characterization of the α-isomers for any of these reactions were given.

André Foucaud[9], was the first to report how varying the substituents on one of the methylene carbons of succinic anhydride affected the ratio of α- to β-isomer formation. A phenyl group was one of the substituents studied. Foucaud reported, on the basis of column chromatography, that the ratio of α- to β-phenylsuccinamic acid was 46.5% to 53.5% when phenylsuccinic anhydride was reacted with ammonia and 23% (α) to 77% (β) when phenylsuccinic anhydride was reacted with dimethylamine. However, neither of the isomers was isolated.

To our knowledge, no α-phenylsuccinamic acids have ever been isolated or characterized and only two optically active β-phenylsuccinamic acids have been reported.[7] In addition, although the ratio of α- to β-succinamic acid formation has been investigated when varying the substituent on one of the methylene carbons,[9] no study has been reported concerning the effects that varying the amine would have on the α- to β-phenylsuccinamic acid ratio. Given these facts, we report the isolation and characterization of several new α- and β-phenylsuccinamic acids and their percent composition when (*S*)-(+)-phenylsuccinic anhydride (**1**) is reacted with five primary amines (**2a**–**e**).

The racemic phenylsuccinic acid was resolved[10,11] and the (*S*)-(+)-phenylsuccinic anhydride (**1**) was synthesized[7] from (*S*)-(+)-phenylsuccinic acid using published methods. The optical activity, $[\alpha]_D^{25}$ +97.8° (c 0.3, benzene), melting point, 83–85 °C, and the infrared carbonyl stretching bands, 1860 and 1788 cm^{-1} of anhydride **1** are in agreement with the literature[7] reported values. The amines chosen for this study were *n*-propylamine (**2a**),

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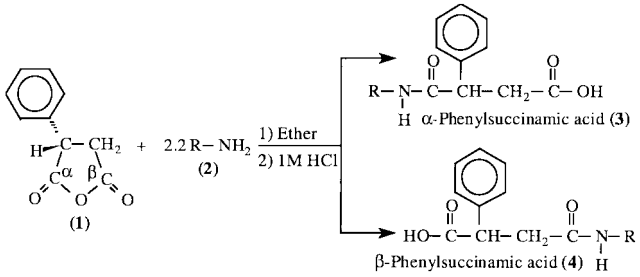


Scheme 1 Reaction between (*S*)-(+)-phenylsuccinic anhydride (**1**) and amines **2a**–**e**

isopropylamine (**2b**), *tert*-butylamine (**2c**), aniline (**2d**), and benzylamine (**2e**).

The general reaction of (*S*)-(+)-phenylsuccinic anhydride (**1**) with amines **2a**–**e** in ether is shown in Scheme 1. Using 2.2 equivalents of amine **2** ensured ring opening of anhydride **1** and complete salt formation of the α- and β-phenylsuccinamic acids **3** and **4**. The isomeric products **3** and **4** were isolated by cooling the reaction mixture to 0°C and dissolving their amine salts in distilled water. After the ether was removed, the resulting solution was acidified to approximately pH 1 using 1 M HCl and the α-, β-isomer mixture was collected by filtration.

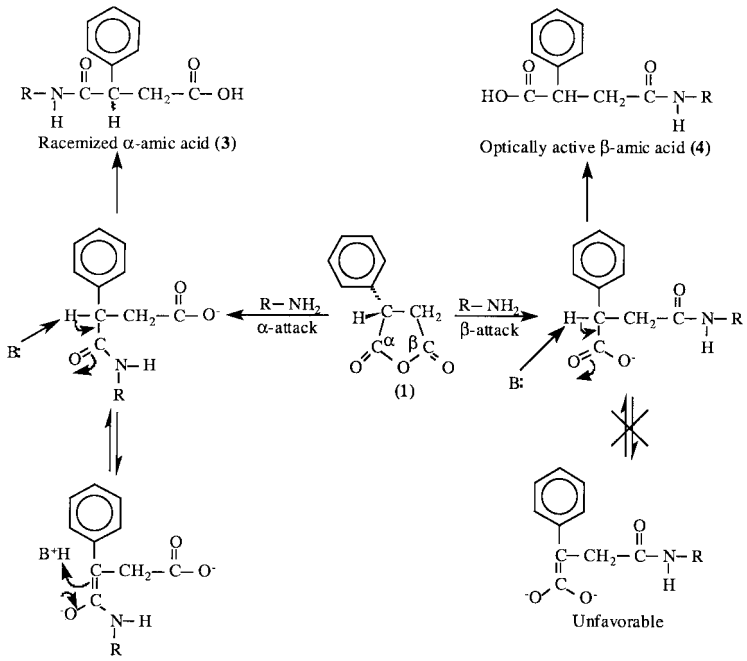
The ratio of α- to β-isomer for these reactions was determined by HPLC and is shown in Table 1, along with the overall yields.

From Table 1 it can be seen that the overall yield of isomeric products **3** and **4** decreases as the bulkiness of the R-group of the amine increases. For example, the yields decreased as anhydride **1** was reacted with *n*-propylamine (97%), isopropylamine (89%), or *tert*-butylamine (80%). In addition, no matter which amine was reacted with anhydride **1**, β-isomer **4** was always the major product (55–71%). However, for each reaction there was also a significant formation of α-isomer **3** (29–45%). The reaction of anhydride **1** with amines **2a**–**d** at lower temperatures (0 °C or –60 °C) had no effect on the ratio of product formation, however, the overall yields decreased. For example, when anhydride **1** was reacted with *n*-propylamine (**2a**), there was no change (±2%) in the ratio of product formation (**3** and **4**), but the overall yield decreased form 97% at 25 °C to 85% at –60 °C.

Table 1 Yields and Percent Composition of α- and β-Phenylsuccinamic Acid Isomers

	R-Group	Product Ratio[a]	Yield (%)[c]	Yield (%)[d]
3a	*n*-C_3H_7	45	97	85
4a	*n*-C_3H_7	55		
3b	*i*-C_3H_7	38	89	73
4b	*i*-C_3H_7	62		
3c	*t*-C_4H_9	39	80	62
4c	*t*-C_4H_9	61		
3d	C_6H_5	29[b]	93	74
4d	C_6H_5	71[b]		
3e	C_6H_5-CH_2	41	96	-
4e	C_6H_5-CH_2	59		

[a]Determined by HPLC, mobile phase: *n*-hexane–THF–HOAc, 70:25:5, flow rate: 0.25 mL/min.
[b]Mobile phase: *n*-hexane–THF–HOAc, 80:17:3, flow rate: 0.25 mL/min.
[c] Total yield of both isomer at r.t.
[d] Total yield of both isomers at –60 °C.



Scheme 2 A possible mechanism for the racemization of the α-phenylsuccinamic acids **3**

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The α- and β-phenylsuccinamic acids **3** and **4** were separated by cooling the initial reaction mixture to 0 °C, dissolving their amine salts in distilled water and then removing the ether. Dropwise acidification[12] of the aqueous solution to approximately pH 4 using 1 M HCl and stirring the resulting mixture for 30 minutes, led to the selective precipitation of the α-product. Further acidification of the filtrate to about pH 1 caused the precipitation of the β-isomer. However, complete separation of the two regioisomers of phenylsuccinanilic acids **3d** and **4d** could not be achieved by the above procedure. Thus, 98% pure β-isomer **4d** was isolated as determined by HPLC (it contained 2% of the α-isomer), while α-isomer **3d** was found to contain 15% of β-isomer **4d**. Other attempts to isolate pure **3d** were not successful. The melting points, specific rotations, and IR properties of phenylsuccinamic acids **3** and **4** are listed in Table 2.

The specific rotations presented in Table 2 show that racemization occurred in all of the α-phenylsuccinamic acids isolated **3a**–**c**, **3e**. A rationale for the racemization of the α-products is shown in Scheme 2.

When the α-carbonyl of the anhydride ring **1** is attacked (α-attack) by the basic nitrogen of the amine, the anhydride ring opens to obtain a carboxylate anion in the β-position and an amide in the α-position. The α-hydrogen, which is benzylic and therefore somewhat acidic, can be abstracted by a base, such as another amine molecule. The resulting enol tautomer is stabilized by conjugation with the phenyl ring, thus facilitating racemization. With β-attack, formation of the carboxylate anion occurs at the α-position, therefore abstraction of the α-hydrogen is less likely to occur due to the fact that this would place two negative charges in close proximity to each other, hence impeding racemization.

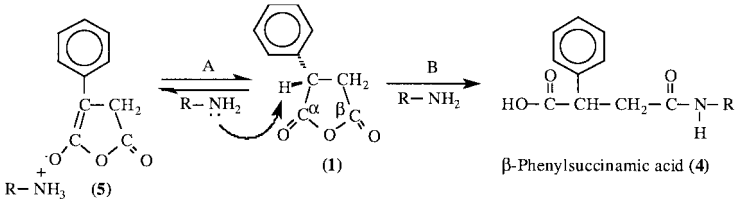
A more interesting observation was that racemization also occurred in formation of β-phenylsuccinamic acids **4b** and **4c**, when anhydride **1** was reacted with isopropylamine (**2b**) and *tert*-butylamine (**2c**), respectively. However, β-phenylsuccinamic acids **4a**, **4d**, and **4e** resulting from the reaction of anhydride **1** with *n*-propylamine (**2a**), aniline (**2d**), and benzylamine (**2e**), respectively, remained optically active. A possible mechanism explaining the racemization of only the β-phenylsuccinamic acid products **4b** and **4c** is shown in Scheme 3.

Isopropylamine (**2b**) and *tert*-butylamine (**2c**) are stronger in base strength, yet are weaker nucleophiles than *n*-propylamine (**2a**) or benzylamine (**2e**). Therefore, amines **2b** and **2c** act more as a base (pathway A) and racemization of anhydride **1** can occur via intermediate **5** before nucleophilic attack of the carbonyl carbon (pathway B). With the less hindered amines, *n*-propylamine (**2a**) and benzylamine (**2e**), or with the less basic amine, aniline (**2d**), nucleophilic attack (pathway B) can occur before racemization takes place (pathway A). An alternative possibility is

Table 2 Physical Data for Amic Acids **3** and **4**

	R-Group	mp °C	$[\alpha]_D$[a]	IR: N–H cm^{-1}	IR: amide C=O cm^{-1}
3a	*n*-C_3H_7	166–167	*rac*.	3290	1640
4a	*n*-C_3H_7	124–125	+122.7	3360	1615
3b	*i*-C_3H_7	175–177	*rac*.	3276	1638
4b	*i*-C_3H_7	122–125	*rac*.	3341	1641
3c	*t*-C_4H_9	197–200	*rac*.	3307	1641
4c	*t*-C_4H_9	143–146	*rac*.	3356	1612
4d	C_6H_5[b]	138–139	+148.7	3352	1662
3e	$C_6H_5CH_2$	162–165	*rac*.	3289	1638
4e	$C_6H_5CH_2$	136–138	+85.6	3341	1648

[a]For conditions, see experimental.
[b]Pure **3d** was not isolated.



Scheme 3 A possible mechanism for racemization of β-phenylsuccinamic acids **4b** and **4c**

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that acid catalyzed racemization occurred during the HCl work up. If this were the case, then racemization would have occurred in all β-phenylsuccinamic acid products (**4a**–**e**). This was not observed, and products **4a**, **4d**, and **4e** are all optically active.

As expected, due to the presence of the chiral center, the adjacent methylene protons of phenylsuccinic anhydride (**1**) and all of the phenylsuccinamic acid products (**3** and **4**) are diastereotopic and therefore exhibit an ABX system in the ^{1}H NMR; that is, the methylene protons split each other and are split by the adjacent methine proton. This splitting results in the formation of a symmetrical multiplet of eight lines (two doublets of doublets). However, surprisingly, a second ABX system was also observed in the ^{1}H NMR spectra of the *N*-benzylphenylsuccinamic acids **3e** and **4e**. Even though the benzylic methylene group is separated from the chiral center by as many as five bonds, the splitting of the two diastereotopic benzylic protons by each other and the N–H proton results in a total of eleven lines. Other examples[13] of methylene protons which are not adjacent to a chiral center, yet are diastereotopic, have been reported. The geminal coupling between the benzylic methylene protons prevails even after the N–H has been exchanged for N–D (by DMSO-d_6/CF_3COOD), resulting in a pair of doublets (an AB-quartet). This indicates that the diastereotopic benzylic methylene protons are caused by the chiral center, not by the adjacent N–H.

In summary the reaction of (*S*)-(+)-phenylsuccinic anhydride (**1**) with various primary amines (**2a**–**e**) led to the formation of two isomeric products and the percentage of each isomer was determined. In each case, the β-phenylsuccinamic acid (**4a**–**e**) was the major product. The isolation and characterization of the first α-phenylsuccinamic acids (**3a**–**c**, **3e**) are also reported. In addition, several new β-phenylsuccinamic acids (**4a**–**e**) were also synthesized and characterized. It was determined that racemization occurs during α-product (**3a**–**e)** formation and in β-products (**4b**, **4c**), where the attacking amine is a somewhat stronger base, but a poor nucleophile.

Elemental analyses were performed by Atlantic Laboratory, Inc. (Norcross, GA). Nuclear magnetic resonance spectra (^{13}C and ^{1}H NMR) were recorded by NuMega Resonance Labs, Inc. (San Diego, CA) on a 500 MHz Bruker instrument or a 400 MHz Bruker NMR spectrophotometer. All chemical shifts (δ) are quoted in ppm downfield from TMS and coupling constants (*J*) in Hz. All NH and OH protons undergo deuterium exchange in DMSO-d_6 values given are for NMR carried out in D_2O–TFD. The infrared spectra were obtained as a KBr pellet on a Perkin Elmer Fourier Transform (FTIR) Spectrophotometer Spectrum 1000. Optical rotations were obtained using a Perkin Elmer 241 Polarimeter. HPLC analyses were performed on a WatersTM 600 Controller equipped with a WatersTM 996 Photodiode Array Detector. A 15-cm WatersTM Resolve Silica Gel (5 μm) column was used for all separations. Melting points were obtained using a Thomas-Hoover capillary melting point apparatus.

Commercially available reagents and solvents were used without further purification except aniline and benzylamine, which were distilled before use.

(*S*)-(+)-3-Phenyldihydrofuran-2,5-dione (1)
The procedure of Naps and Johns[7] was followed. The yield of pure (+)-**1** was 96.5%.

Mp 83–85 °C, lit.[7] mp 82 °C.

$[\alpha]_D^{25}$ +97.8° (c 0.3, benzene), lit[7] $[\alpha]_D^{29}$ +99.8° (c 0.751, benzene).

IR (KBr): 1860 (C=O), 1788 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$): δ = 3.15 (dd, *J* = 19 Hz, C*HC*H*H, 1 H), 3.45 (dd, *J* = 7 Hz, C*HCH*H*, 1 H), 4.33 (dd, C*H, 1 H), 7.27–7.41 (m, Ph, 5 H).

^{13}C NMR ($CDCl_3$): δ = 37.08 (CH_2), 46.94 (C*H), 127.69 (Ph_{para}), 129.12 (Ph_{meta}, 2 × C), 129.92 (Ph_{ortho}, 2 × C), 135.03 (Ph), 169.88 (β CO), 171.96 (α CO).

α-Amic acids (3) and β-Amic acids (4); General Procedure
A solution of amine **2** (56.3 mmol) in Et_2O (50 mL) was added dropwise to a solution of (*S*)-(+)-phenylsuccinic anhydride (**1**) (4.50 g, 25.6 mmol) in Et_2O (250 mL) at 0 °C. The reaction mixture was stirred for 30 min, distilled water (100 mL) was added, and the reaction mixture stirred for an additional 30 min. The 2 phases were separated and the organic layer was washed with distilled water (100 mL). The aqueous layers were combined and 1 M HCl (ca 15 mL) was added dropwise, until a turbid mixture was observed, (ca pH 4). The mixture was stirred for 30 minutes at 0 °C, the solid was filtered, and washed twice with distilled water (25 mL) to yield a crude sample of α-amic acid **3**. After recrystallization from distilled water, an analytical sample of **3** was obtained. The filtrate, of **3**, was treated with 1 M HCl until the pH was ca 1. After stirring the mixture for 30 minutes at 0 °C, the solid was filtered and washed twice with distilled water (25 mL) to yield a crude sample of β-amic acid **4**. After recrystallization from distilled water, an analytical sample of **4** was obtained.

(±)-4-Oxo-3-phenyl-4-(propylamino)butanoic Acid (3a)
Mp 166–167 °C.

IR (KBr): 3290 (N–H), 1700 (C=O, acid), 1640 cm^{-1} (C=O, amide).

^{1}H NMR (DMSO): δ = 0.74 (t, *J* = 7 Hz, CH_3, 3 H), 1.33 (sextet, *J* = 8 Hz, CH_3CH_2, 2 H), 2.50 (dd, *J* = 17 Hz, C*HCH*H*, 1 H), 2.97 (m, C*HCHH, NCH_2, 3 H), 3.88 (dd, *J* = 10 Hz, C*H, 1 H), 7.19–7.52 (m, Ph, 5 H), 7.99 (t, *J* = 6 Hz, NH, 1 H), 12.11 (br s, OH, 1 H).

^{13}C NMR (DMSO): δ = 11.11 (CH_3), 22.18 (CH_3CH_2), 37.27 (C*HCH$_2$), 40.26 (NCH_2), 47.02 (C*H), 126.62 (Ph_{para}), 127.39 (Ph_{meta}, 2 × C) 128.19 (Ph_{ortho}, 2 × C), 140.23 (Ph), 171.59 (NCO), 172.62 (COOH).

Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.10; H, 7.21; N, 5.93.

(+)-(2*S*)- 4-Oxo-2-phenyl-4-(propylamino)butanoic Acid (4a)
Mp 124–125 °C. $[\alpha]_D^{25}$ +122.7° (c 0.3, acetone).

IR (KBr): 3360 (N–H), 1710 (C=O, acid), 1615 cm^{-1} (C=O, amide).

^{1}H NMR (DMSO): δ = 0.76 (t, *J* = 7 Hz, CH_3, 3 H), 1.33 (sextet, *J* = 8 Hz, CH_2CH_3, 2 H), 2.42 (dd, *J* = 17 Hz, C*HC*H*H, 1 H), 2.81 (dd, *J* = 17 Hz, C*HCH*H*, 1 H), 2.94 (m, NCH_2, 2 H); 3.93 (dd, *J* = 10 Hz, C*H, 1 H), 7.24–7.34 (m, Ph, 5 H), 7.81 (t, *J* = 6 Hz, NH, 1 H), 12.29 (br s, OH proton, 1 H).

^{13}C NMR (DMSO): δ = 11.19 (CH_3), 22.24 (CH_3CH_2), 39.62 (C*HCH$_2$), 41.07 (NCH_2), 47.96 (C*H), 126.89 (Ph_{para}), 127.62 (Ph_{meta}, 2 × C), 128.37 (Ph_{ortho}, 2 × C), 139.05 (Ph), 169.61 (NCO), 174.08 (COOH).

Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.25; H, 7.22; N, 5.93.

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(±)-4-Oxo-3-phenyl-4-(isopropylamino)butanoic Acid (3b)
Mp 175–177 °C.

IR (KBr): 3276 (N–H), 1700 (C=O, acid), 1638 cm^{-1} (C=O, amide).

^{1}H NMR (DMSO): δ = 0.98 (dd, *J* = 7 Hz, 2 × CH_3, 6 H), 2.50 (dd, *J* = 16 Hz, C*HC*H*H*, 1 H), 2.93 (dd, *J* = 14 Hz, C*HCH*H*, 1 H), 3.76 (septet, *J* = 7 Hz, NCH, 1 H), 3.85 (dd, C*H, 1 H), 7.20–7.29 (m, Ph, 5 H), 7.89 (d, *J* = 8 Hz, NH, 1 H), 12.10 (br s, OH, 1 H).

^{13}C NMR (DMSO): δ = 22.20 (2 × CH_3), 37.53 (CH_2), 40.40 (NCH), 47.02 (C*H), 126.67 (Ph_{para}), 127.46 (Ph_{meta}, 2 × C), 128.28 (Ph_{ortho}, 2 × C), 140.35 (Ph), 170.85 (NCO), 172.76 (COOH).

Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N 5.95. Found: C, 66.20; H, 7.28; N, 6.06.

(±)-4-Oxo-2-phenyl-4-(isopropylamino)butanoic Acid (4b)
Mp 122–125 °C, lit.[8] mp 117–119 °C.

IR (KBr): 3341 (N–H), 1717 (C=O, acid), 1641 cm^{-1} (C=O, amide).

^{1}H NMR (DMSO): δ = 0.96 (dd, *J* = 7 Hz, 2 × CH_3, 6 H), 2.39 (dd, *J* = 15 Hz, C*HC*H*H*, 1 H), 2.79 (dd, *J* = 15 Hz, C*HCH*H*, 1 H), 3.76 (septet, NCH, 1 H), 3.92 (dd, *J* = 9 Hz, C*H, 1 H), 7.25–7.31 (m, phenyl protons, 5 H), 7.67 (d, *J* = 8 Hz, NH, 1 H), 12.29 (br s, OH, 1 H).

^{13}C NMR (DMSO): δ = 22.34 (2 × CH_3), 38.82 (CH_2), 40.16 (NCH), 47.11 (C*H), 126.96 (Ph_{para}), 127.73 (Ph_{meta}, 2 × C), 128.43 (Ph_{ortho}, 2 × C), 139.12 (Ph), 168.86 (NCO), 174.19 (COOH).

Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.34; H, 7.23; N, 5.95.

(±)-4-*tert*-Butylamino-4-oxo-3-phenylbutanoic Acid (3c)
Mp 197–200 °C.

IR (KBr): 3307 (N–H), 1701 (C=O, acid),1641 cm^{-1} (C=O, amide).

^{1}H NMR (DMSO): δ = 1.18 (s, 3 × CH_3, 9 H), 2.45 (dd, *J* = 16 Hz, C*HC*H*H*, 1 H), 2.89 (dd, *J* = 16 Hz, C*HCH*H*, 1 H), 3.90 (dd, *J* = 10 Hz, C*H, 1 H), 7.18–7.33 (m, Ph, 5 H), 7.60 (s, NH, 1 H), 12.10 (br s, OH, 1 H).

^{13}C NMR (DMSO): δ = 28.39 (3 × CH_3), 37.68 (CH_2), 47.20 (C*H), 49.94 (NC), 126.48 (Ph_{para}), 127.37 (Ph_{meta}, 2 × C), 128.16 (Ph_{ortho}, 2 × C), 140.59 (Ph), 171.32 (NCO), 172.75 (COOH).

Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.67; H, 7.77; N, 5.54.

(±)-4-*tert*-Butylamino-4-oxo-2-phenylbutanoic Acid (4c)
Mp 143–146 °C.

IR (KBr): 3356 (N–H), 1704 (C=O, acid),1612 cm^{-1} (C=O amide).

^{1}H NMR (DMSO): δ = 1.17 (s, 3 × CH_3, 9 H), 2.39 (dd, *J* = 15 Hz, C*HC*H*H*, 1 H), 2.80 (dd, *J* = 15 Hz, C*HCH*H*, 1 H), 3.90 (dd, *J* = 9 Hz, C*H, 1 H), 7.28 (s, Ph, 5 H), 7.41 (s, NH, 1 H), 12.20 (s, OH, 1 H).

^{13}C NMR (DMSO): δ = 28.51 (3 × CH_3), 39.48 (CH_2), 47.24 (C*H), 49.90 (NC), 126.95 (Ph_{para}), 127.82 (Ph_{meta}, 2 × C), 128.43 (Ph_{ortho}, 2 × C), 139.23 (Ph), 169.52 (NCO), 174.32 (COOH).

Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.72; H, 7.80; N, 5.49.

(±)-4-Anilino-4-oxo-3-phenylbutanoic Acid (3d)
Crude **3d** was isolated and consisted of 85% **3d** and 15% **4d**, as determined by HPLC. Further attempts to separate this mixture not successful.

(+)-(2*S*)- 4-Anilino-4-oxo-2-phenylbutanoic Acid (4d)
Mp 138–139 °C, lit.[7] mp 125–127 °C. $[\alpha]_D^{25}$ +148.7° (c 0.300, MeOH), lit.[7] $[\alpha]_D^{33}$+151.8° (c 0.876, EtOH).

IR (KBr): 3350 (N–H), 1718 (C=O, acid), 1662 cm^{-1} (C=O, amide).

^{1}H NMR (DMSO): δ = 2.70 (dd, *J* = 16 Hz, C*HC*H*H*, 1 H), 3.11 (dd, *J* = 16 Hz, C*HCH*H*, 1 H), 4.05 (dd, *J* = 10 Hz, C*H, 1 H), 7.01–7.57 (m, 2 × Ph, 10 H), 9.97 (s, NH, 1 H), 12.38 (br s, OH, 1H).

^{13}C NMR (DMSO): δ = 39.74 (CH_2), 46.80 (C*Ph), 118.93 (C*HPh_{ortho}, 2 × C), 123.11 (C*HPh_{para}), 127.13 (Ph_{para}), 127.73 (Ph_{ortho}, 2 × C), 128.60 (Ph_{meta}, 2 × C), 128.68 (C*HPh_{meta}, 2 × C), 138.98 (Ph), 139.29 (C*HPh), 169.07 (NCO), 174.16 (COOH).

Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.38; H, 5.60; N, 5.23.

(±)-4-Benzylamino-4-oxo-3-phenylbutanoic Acid (3e)
Mp 163–165 °C.

IR (KBr): 3289 (N–H), 1702 (C=O, acid), 1638 cm^{-1} (C=O, amide).

^{1}H NMR (DMSO): δ = 2.55 (dd, *J* = 17 Hz, C*HC*H*H*, 1 H), 3.05 (dd, *J* = 17 Hz, C*HC*H*H, 1 H), 3.98 (dd, *J* = 10 Hz, C*H, 1 H), 4.18 (dd, *J* = 15 Hz, C*H*HPh, 1 H), 4.32 (dd, *J* = 15 Hz, CH*H*Ph, 1 H), 7.13–7.54, (m, 2 × Ph, 10 H), 8.57 (t, *J* = 16 Hz, NH, 1 H), 12.21 (br s, OH, 1 H).

^{13}C NMR (DMSO): δ = 38.13 (CH_2), 42.84 (CH_2Ph), 47.96 (C*H), 127.45 (Ph_{para}), 127.74 (CH_2Ph_{para}), 128.45 (Ph_{meta}, CH_2Ph_{meta}, 4 × C), 128.96 (CH_2Ph_{ortho}, 2 ×C), 129.21 (Ph_{ortho}, 2 × C), 140.33 (CH_2Ph), 140.94 (Ph), 172.80 (NCO), 173.67 (COOH).

Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 72.09; H, 6.12; N, 5.07.

(+)-(2*S*)-Benzylamino-4-oxo-2-phenylbutanoic Acid (4e)
Mp 138–140 °C. $[\alpha]_D^{25}$+85.6° (c 0.305, MeOH).

IR (KBr): 3341 (N–H), 1716 (C=O, acid),1648 cm^{-1} (C=O, amide).

^{1}H NMR (DMSO): δ = 2.56 (dd, *J* = 15 Hz, C*HC*H*H*, 1 H), 2.92 (dd, *J* = 15 Hz, C*HCH*H*, 1 H), 4.00 (dd, *J* = 9 Hz, C*H, 1 H), 4.21 (dd, *J* = 15 Hz, CH*H*Ph, 1 H), 4.27 (dd, *J* = 15 Hz, C*H*HPh, 1 H), 7.09–7.34, (m, Ph, 10 H), 8.37 (t, *J* = 6 Hz, NH, 1 H), 12.38 (br s, OH, 1 H).

^{13}C NMR (DMSO): δ = 39.62 (CH_2), 42.72 (CH_2Ph), 48.01 (C*H), 127.45 (Ph_{para}), 127.80 (CH_2Ph_{para}), 127.92 (Ph_{meta}, 2 × C), 128.71 (CH_2Ph_{meta}, 2 × C), 129.02 (CH_2Ph_{ortho}, 2 × C), 129.38 (Ph_{ortho}, 2 × C), 139.91 (CH_2Ph), 140.26 (Ph), 170.84 (NCO), 175.07 (COOH).

Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 72.00; H, 6.09; N, 4.98.

To Determine the Percentage Composition and Total Yield of Amic Acids (3 and 4); General Procedure
A solution of amine **2** (2.2 mmol) in Et_2O (10 mL) was added dropwise to a solution of (*S*)-(+)-phenylsuccinic anhydride (**1**) (176 mg, 1.0 mmol) in Et_2O (10 mL) at r.t. (or –60 °C). The reaction mixture stirred for 30 min, distilled water (20 mL) was added and the reaction mixture stirred for an additional 5 min. HCl (6 M, 2 mL) was added and the mixture stirred for 10 min. The pH of the aqueous layer was approximately 1. The two layers were then separated and the aqueous layer was washed with Et_2O (20 mL). The two ether layers were combined and dried over anhyd Na_2SO_4. The ether was removed under reduced pressure to afford a mixture of **3** and **4**. The percent composition of these mixtures was determined by HPLC on a mixture of **3a**–**e** and **4a**–**e**, dissolved in a solution of *n*-hexane–MeOH (50:50) (Table 1).

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