the starting material, the contents of the flask were cooled to room temperature and poured into water (~300 mL). The product mixture was extracted with dichloromethane (3 × 25 mL), dried (anhydrous $MgSO_4$), and subjected to GLC analyses after concentration on a Buchi rotavapor. Only (*E*)-stilbene and dimethyl fumarate were detected from 1 and 3, respectively, and no trace of (*Z*)-alkene. The solvent was removed completely and the product dried under vacuum to yield (*E*)-alkene, confirmed by melting point, mixed melting point, and superimposable IR spectra.

The reaction mixtures from benzalacetophenone dibromide and benzalacetone dibromide were separated by column chromatography (silica gel, 100–200 mesh) with benzene as eluent to yield the corresponding olefin and the α-bromo olefin.

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Transition-Metal-Assisted Asymmetric Synthesis of Amino Acid Analogues. A New Synthesis of Optically Pure D- and L-Pyridylalanines

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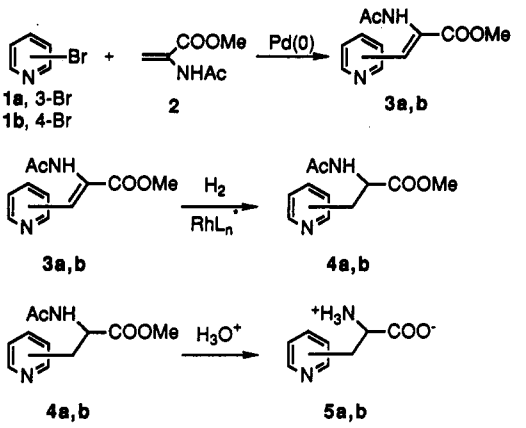
Pyridylalanines and substituted pyridylalanines, structural analogues of the naturally occurring amino acids histidine, phenylalanine, and tyrosine, exhibit a diverse range of effects when introduced into biological systems.[2] Pyridylalanines have been incorporated as histidine replacements in angiotensin II[3] and the N-terminal tetradecapeptide of ribonuclease A and ribonuclease S.[4] As enzyme substrates, the pyridylalanines are found to be antagonists of phenylalanine[5] and inhibitors of histidine decarboxylase.[6] Pyridylalanines have been studied as pharmaceutical agents and show antiinflammatory activity[7] and are components of both new antibacterial cepholasporins[8] and antiovulatory peptides.[9] As part of our program to use transition-metal catalysts in the synthesis of biologically active molecules, we report a new asymmetric route to both the D and L isomers of 3- and 4-pyridylalanine. To our knowledge, this is the first report of a direct asymmetric synthesis of these heterocyclic amino acid analogues. Although other methods have been reported for the synthesis of pyridylalanines,[10] the principal drawback to these approaches is that resolution is required to obtain the pure enantiomer. Our approach is shown in Scheme I. Treatment of 3- or 4-bromopyridine (**1a** or **1b**) in a nitrile solvent (6–8 mL/mmol of heteroaromatic bromide) with olefin **2** in the presence of 2–3 mol % of $Pd_2(dba)_3$, 8–12 mol % $P(o\text{-}tol)_3$, and 1.1 equiv of Et_3N for 18 h at 110°C under an inert atmosphere gives good yields of prochiral enamides **3a** or **3b**. The enamide is hydrogenated in the presence of a chiral Rh catalyst to give the optically active pyridylalanine precursors **4a** or **4b**. The free amino acids **5a** and **5b** are released by hydrolysis of **4**.

Scheme I



The key step in the process is the initial palladium-catalyzed coupling of **2** and the bromopyridine. The product enamides are normally prepared by conversion of an aromatic aldehyde to the corresponding azalactone using classical Erlenmeyer methodology,[11] followed by hydrolysis or reaction of the azalactone with an alkoxide. However, an Erlenmeyer approach for the synthesis of **4b** starting from 4-pyridinecarboxaldehyde was unsuccessful and gave instead only polymeric material.

The conditions used for the palladium-catalyzed coupling are important. Initial experiments showed that standard conditions reported by Heck[12] and others[13] are not successful for the preparation of **3** from the cross-coupling of **1** and **2**. At the high reactant concentrations

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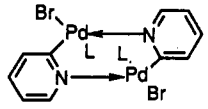
Table I

compd	yield, %	ee, %
3a	64	
3b	60	
4a, *l* isomer	86	>99[a]
4a, *d* isomer	60	86[a]
4b, *l* isomer	71	94[a]
4b, *d* isomer	91	92[a]
5a, *l* isomer	59	88[b]
5a, *d* isomer	48	84[b]
5b, *l* isomer	70	96[b]
5b, *d* isomer	14	86[b]

[a] Determined by GLC. [b] Determined by HPLC.

normally employed in the Heck reaction, the bromopyridine undergoes homocoupling to give either 3,3′- or 4,4′-bipyridyl as the primary product; cross-coupling product **3** is observed in less than 10% yield. However, performing the reaction under more dilute conditions (5–8 mL/mmol of starting bromopyridine) affords **3** in 60–80% yield. The coupling reaction is amenable to scaleup; we have performed the reaction on up to 25 g of starting bromide with no noticeable loss in yield. The reaction of 4-bromopyridine is more sluggish, requires longer reaction times, and gives greater amounts of colored byproducts. In both cases, analysis by NMR spectroscopy shows that the reaction proceeds to give a roughly 90:10 mixture of *Z* and *E* olefins, respectively.[14] $Pd_2(dba)_3$ is a markedly superior catalyst. Other common palladium sources such as $Pd(OAc)_2$ and $Pd(PPh_3)_4$ give considerably lower yields of **3**.

The coupling reaction fails with 2-bromopyridine. While the catalyst undergoes oxidative addition to the bromoarene, the resulting adduct presumably dimerizes to form the stable complex **6**.[15] Formation of this complex renders



6

the palladium catalyst unavailable for further reaction. The reaction also fails when iodopyridines are substituted for bromopyridines and gives homocoupled material as the only isolable product.

The chiral center of pyridylalanine precursor **4** is introduced by asymmetric reduction of **3** with the chiral rhodium catalyst $[Rh(DIPAMP)(COD)]^+(BF_4^-)$.[16] Either the D or L isomer of **4** may be prepared with use of (*S,S*)- or (*R,R*)-$[Rh(DIPAMP)(COD)]^+(BF_4^-)$ as a catalyst.[17] The hydrogenations of the heterocyclic substrates are considerably slower than those reported for nonheterocyclic systems, which may be attributed to the presence of the ligating nitrogen of the pyridine ring. The reactions are performed in MeOH with 1.5–5 mol % catalyst at 50 °C under 60–65 psi of H_2 overnight. The reduced material is obtained in greater than 85% isolated yield and normally in greater than 95% ee. The reaction can also be performed to give the D isomer using a commercially available DIOP ligand, however, the ee drops to about 70%.

The free amino acid is obtained by hydrolytic removal of the protecting groups. During hydrolysis, a small amount of racemization is noted and the ee drops to about 90%. The product is crystallized from acetone/water to give the pyridylalanine in about 60–70% yield.

The yields for each of the steps are given in Table I. Preliminary results indicate that this procedure is general for a variety of heterocyclic bromides. This reaction sequence is being used for the preparation of a number of different amino acid analogues, and the results will be reported in due course.

Experimental Section

Methods and Materials. ^1H nuclear magnetic resonance spectra were measured at 300 MHz and ^{13}C spectra at 75.4 MHz on a Varian VXR-300 spectrometer with tetramethylsilane for spectra measured in organic solvents and 3-(trimethylsilyl)-propionic-*2,2,3,3-d*$_4$ acid, sodium salt (Aldrich), for spectra taken in aqueous solution as internal standards (chemical shifts in δ). Infrared spectra were measured on an IBM IR30 instrument (cm^{-1}). Chiral GC measurements were performed on a Hewlett-Packard HP5890 instrument with a 25-m Chirasil-Vol III column. Chiral LC measurements were performed with use of a Daicel Crownpak 15 cm × 4.6 mm column and aqueous $HClO_4$ (pH 2) as the mobile phase, flow rate 0.4 mL/min at a temperature of 4 °C and observed at 210 or 225 nm. Optical rotations were measured at room temperature at the sodium D line with a Rudolph Research Autopol III polarimeter and have been converted to specific rotations. Concentrations of the specific rotations are given as grams/100 mL. Routine chromatography was performed with use of Fisher Chromatographic silica gel, 100–200 mesh. Radial chromatography was performed on a Harrison Research chromatotron with use of silica gel and a variety of solvent systems. "Degassed" refers to the technique of alternately evacuating a system on a vacuum double manifold and refilling with an inert gas, usually argon. If solvent is included, the solution is allowed to bubble gently during the vacuum portion of the degas. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Melting points are uncorrected.

Propionitrile was purchased from Aldrich and was distilled from CaH_2 before use. Butyronitrile (Aldrich) was used as received. Triethylamine (Aldrich) was distilled from CaH_2 before use. Methyl 2-acetamidoacrylate was available by custom synthesis from Lancaster Chemical. All glassware was dried in a 130 °C oven overnight before use, assembled under a slow flow of argon, and cooled under vacuum. The (*R,R*)-DIPAMP ligand used in the preparation of (*S,S*)-DIPAMP and Rh catalysts for asymmetric hydrogenation was obtained from the G. D. Searle, Augusta, GA. All other materials were commercially available and were used as received.

General Procedure for the Palladium-Catalyzed Coupling of Heteroaromatic Bromides with Methyl 2-Acetamidoacrylate. An oven-dried Fisher-Porter bottle is charged with nitrile solvent (6–10 mL/mmol of substrate), the heteroaromatic bromide (1 equiv), methyl 2-acetamidoacrylate (1.1 equiv), $P(o\text{-tol})_3$ (8–12 mol %), and Et_3N (1.1 equiv). The bottle is capped with a pressure head and the system degassed on the vacuum line. $Pd_2(dba)_3$ (2–3 mol %) is added and the bottle recapped and degassed again. The reaction is heated to 110–120 °C in an oil bath overnight, which generates 10–15 psi. Completion of the reaction is often indicated by the presence of a shiny mirror of palladium(0) on the walls of the reaction vessel although final determination is made by thin-layer chromatography. The reaction is cooled to room temperature and the solvent removed on the rotary evaporator. The residue is dissolved in a large amount of CH_2Cl_2 (300–500 mL for reactions performed on a 10–20-mmol scale) and is washed 3 × 20 mL of H_2O. The organic phase is dried over $MgSO_4$ and filtered and the solvent removed on the rotary evaporator. The residue is washed with small amounts of Et_2O or Et_2O/hexane mixtures to remove some of the

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remaining phosphine and unreacted methyl 2-acetamidoacrylate. The crude product is purified by column or radial chromatography. Residual phosphine and methyl 2-acetamidoacrylate is eluted with Et_2O/hexane mixtures. The coupling product is eluted with EtOAc or EtOAc containing 3–4% MeOH. This procedure can be performed on a larger scale at atmospheric pressure at the reflux temperature of the solvent in a four-necked round-bottom flask fitted with a Friedrichs condenser, mechanical stirrer, thermometer, and nitrogen inlet. The mixture is kept under a nitrogen atmosphere over the course of the reaction.

Preparation of Methyl 2-Acetamido-3-(3-pyridyl)acrylate (3a). 3-Bromopyridine (2460 mg, 15.57 mmol, 1.5 mL), methyl 2-acetamidoacrylate (2450 mg, 17.13 mmol), P(*o*-tol)$_3$ (377 mg, 1.24 mmol), Et_3N (1573 mg, 15.57 mmol, 22 mL), and $Pd_2(dba)_3$ (142 mg, 0.31 mmol) were mixed in butyronitrile (84 mL), and the resultant mixture was heated at 110 °C overnight. Purification of a 943-mg sample of the crude product from normal workup by radial chromatography gave 512 mg of **3a** (64%) as a white powder: mp 113–114 °C; ^{1}H NMR (94:6 mixture of *Z* and *E* isomers) (acetone-d_6) 2.13 (s, 3 H, NHC(O)CH_3), 3.83 (s, 3 H, COOCH_3), 7.30 (s, 1 H, olefinic), 7.45 (m, 1 H, aromatic), 8.06 (d, 1 H, *J* = 8 Hz, aromatic), 8.55 (m, 1 H, aromatic), 8.80 (s, 1 H, aromatic), 9.06 (br s, 1 H, NH); ^{13}C NMR (acetone-d_6) 22.88, 52.65, 124.24, 128.39, 128.97, 130.94, 136.98, 150.38, 157.51, 165.99, 169.83; IR (KBr disk) 3250, 1738, 1723, 1669, 1512, 1289, 1266, 1250, 1132, 704; MS (FAB) [M + 1] *m/e* 221. Anal. C, H, N.

Preparation of Methyl 2-Acetamido-3-(4-pyridyl)acrylate (3b). 4-Bromopyridine hydrochloride (5000 mg, 25.71 mmol), methyl 2-acetamidoacrylate (4047 mg, 28.3 mmol), P(*o*-tol)$_3$ (626 mg, 2.06 mmol), Et_3N (5202 mg, 51.5 mmol, 7.2 mL), and $Pd_2(dba)_3$ (296 mg, 0.323 mmol) were mixed in propionitrile (340 mL) according to the general procedure. Normal workup and isolation after 22 h gave 3410 mg (60%) of **3b** as a light yellow powder. An analytical sample from acetone/hexane showed the following data: mp 152.5–157.5 °C; ^{1}H NMR ($CDCl_3$) 2.21 (s, 3 H, NHC(O)CH_3), 3.89 (s, 3 H, COOCH_3), 7.11 (s, 1 H, olefinic), 7.28 (d, 2 H, *J* = 7 Hz, aromatic), 8.16 (br s, 1 H, NH), 8.54 (d, 2 H, *J* = 7 Hz, aromatic); ^{13}C NMR ($CDCl_3$) 23.19, 52.85, 123.17, 127.59, 127.77, 141.72, 149.70, 165.0, 165.68; IR (Nujol mull) 3145, 1716, 1688, 1289, 1256, 1130; MS (EI, CI) *m/e* 220. Anal. C, H, N.

General Procedure for Catalytic Asymmetric Hydrogenation. A dry Fisher-Porter bottle is charged with the substrate and MeOH (5 mL/mmol of substrate). A pressure head is affixed, and the solution is degassed three to four times on the vacuum line. The rhodium catalyst is added under a slow flow of argon, the bottle recapped, and the system degassed again. The bottle is pressurized to 65–70 psi of H_2 and is heated overnight at 45–50 °C in an oil bath. The reaction is cooled and filtered through a bed of Celite and the solvent removed on the rotary evaporator. The residue is purified by column or radial chromatography, most conveniently with EtOAc or EtOAc/MeOH mixtures to elute the product.

Preparation of *l*-Methyl 2-Acetamido-3-(3-pyridyl)propanoate (4a, *l* Isomer). **3a** (500 mg, 2.27 mmol) and (*R*,*R*)-[Rh(DIPAMP)(COD)]$^+$(BF_4^-) (60 mg, 0.079 mmol) were combined in MeOH (12 mL) and pressurized to 65 psi with H_2 according to the general procedure. Normal workup and isolation followed by radial chromatography (4% MeOH/EtOAc) gave 432 mg (86%) of the *l* isomer of **4a** as a clear oil that solidified upon standing: ^{1}H NMR ($CDCl_3$) 1.99 (s, 3 H, NHC(O)CH_3), 3.06 (dd, 1 H, CH_2CH), 3.74 (s, 3 H, COOCH_3), 4.92 (q, 1 H, CH$_2$C*H*), 7.21 (m, 2 H, aromatic), 7.50 (dt, 1 H, aromatic), 8.35 (d, 1 H, aromatic), 8.42 (dd, aromatic); ^{13}C NMR ($CDCl_3$) 22.56, 34.77, 52.14, 52.66, 123.18, 131.76, 136.50, 147.99, 150.03, 169.83, 171.51; IR (KBr disk) 3193, 3031, 1742, 1671, 1557, 1437, 1429, 1374, 1300, 1285, 1211, 1196, 1167, 718; MS (CI) [M + H] *m/e* 223. An analytical sample from $CHCl_3$/hexane gave mp 105–106 °C and $[\alpha]^{25}$ 105.1° (*c* 1.08, $CHCl_3$); GC >99% ee. Anal. C, H, N.

Preparation of *d*-Methyl 2-Acetamido-3-(3-pyridyl)propanoate (4a, *d* Isomer). **3b** (2000 mg, 9.1 mmol) and (*R*,*R*)-[Rh(DIPAMP)(COD)]$^+$(BF_4^-) were combined in MeOH (42 mL) and pressurized with H_2 according to the general procedure. Normal workup and isolation gave 1200 mg (60%) of the *d* isomer of **4a** as a clear oil that crystallized upon standing. An analytically pure sample was obtained from acetone/hexane: mp 105.5–108.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.01 (s, 3 H, NHC(O)CH_3), 3.07 (dd, 1 H, CH_2CH), 3.19 (dd, 1 H, CH_2CH), 3.75 (s, 3 H, COOCH_3), 4.93 (q, 1 H, CH$_2$C*H*), 6.64 (br d, 1 H, NH), 7.22 (dd, 1 H, aromatic), 7.47 (dt, 1 H, aromatic), 8.34 (d, 1 H, aromatic), 8.45 (dd, 1 H, aromatic); ^{13}C NMR ($CDCl_3$) 22.86, 34.99, 52.37, 52.76, 123.31, 131.66, 136.59, 148.32, 150.26, 169.74, 171.60; IR (KBr disk) 3192, 3033, 1742, 1672, 1557, 1438, 1429, 1375, 1301, 1285, 1211, 1196, 1167, 718; MS (FAB) [M + 1] *m/e* 223; GC, 93:7 mixture of *d* to *l* isomers ee 86%; $[\alpha]^{25}$ −105.6° (*c* 1.8, $CHCl_3$). Anal. C, H, N.

Preparation of *l*-Methyl 2-Acetamido-3-(4-pyridyl)propanoate (4b, *l* Isomer). Methyl 2-acetamido-3-(4-pyridyl)acrylate (500 mg, 2.27 mmol) and (*R*,*R*)-[Rh(DIPAMP)(COD)]$^+$(BF_4^-) (60 mg, 0.079 mmol) were combined in MeOH (12 mL) and pressurized to 65 psi with H_2 according to the general procedure. Normal workup and isolation followed by radial chromatography (4% MeOH/EtOAc) gave 360 mg (71%) of the *l* isomer of **4b** as a clear oil that crystallized slowly upon standing for 3 months: ^{1}H NMR ($CDCl_3$) 1.99 (s, 3 H, NHC(O)CH_3), 3.07 (dd, 1 H, CH_2CH), 3.18 (dd, 1 H, CH_2CH), 3.75 (s, 3 H, COOCH_3), 4.94 (q, 1 H, CH$_2$C*H*), 6.88 (br s, 1 H, NH), 7.08 (d, 2 H, aromatic), 8.45 (d, 2 H, aromatic); ^{13}C NMR ($CDCl_3$) 22.51, 36.81, 52.17, 123.11, 124.31, 145.42, 149.31, 169.88, 171.43; IR (neat) 3272, 3038, 2955, 1744, 1661, 1605, 1549, 1437, 1420, 1374, 1285, 1217, 1179, 1003; MS (CI) [M + H] *m/e* 223; GC, 97:3 ratio of isomers, ee 94%; $[\alpha]^{25}$ +84.7° (*c* 1.04, $CHCl_3$); high-resolution MS, calcd 222.1083, found 222.1016.

Preparation of *d*-Methyl 2-Acetamido-3-(4-pyridyl)propanoate (4b, *d* Isomer). Methyl 2-acetamido-3-(4-pyridyl)acrylate (380 mg, 1.73 mmol) and (*S*,*S*)-[Rh(DIPAMP)(COD)]$^+$(BF_4^-) (46 mg, 0.061 mmol) were combined in MeOH (10 mL) and pressurized to 65 psi with H_2 according to the general procedure. Normal workup and isolation followed by radial chromatography gave 349 mg (91%) of the d-isomer of **4b** as a clear oil: ^{1}H NMR ($CDCl_3$) 2.00 (s, 3 H, NHC(O)CH_3), 3.08 (dd, 1 H, CH_2CH), 3.18 (dd, 1 H, CH_2CH), 3.75 (s, 1 H, COOCH_3), 4.95 (m, 1 H, CH$_2$C*H*), 7.10 (d, 2 H, aromatic), 7.29 (br m, 1 H, NH), 8.46 (d, 2 H, aromatic); ^{13}C NMR ($CDCl_3$) 22.49, 36.78, 52.16, 124.29, 145.43, 149.28, 169.89, 171.42; IR (neat) 3274, 3033, 2955, 1748, 1661, 1603, 1545, 1437, 1418, 1374, 1285, 1217, 1179, 789, 762; MS (CI) [M + H] *m/e* 223; GC, 96:4 mixture of isomers, ee 92%; $[\alpha]^{25}$ −78.5° (*c* 1.36, $CHCl_3$); high-resolution MS, calcd 222.1083, found 222.0985.

General Procedure for the Hydrolysis of the Products of Asymmetric Reduction. The reduction product is dissolved in 6 N HCl (3 mL/mmol of substrate), and the resultant mixture is heated at 100–110 °C for 3 h. The reaction mixture is cooled, and the solvent is removed on the rotary evaporator. The solid is redissolved in H_2O and filtered. The pH of the solution is adjusted to between 6.5 and 7.0 with 10% NaOH, and the solvent is removed on the rotary evaporator. The residue is washed with small amounts of EtOH. Occasionally this preferentially dissolves the product and separates it from the NaCl generated during the base treatment. More commonly, it aids in removal of colored impurities. Crude yields of material at this point are quite high. Analytically pure samples are obtained by dissolving the product in H_2O and preciptating it with acetone. The process is repeated until an acidic aqueous sample of the product gives a negative reaction with added aqueous $AgNO_3$.

Preparation of *l*-3-Pyridylalanine (5a, *l* Isomer). The *l* isomer of **4a** (1600 mg, 7.21 mmol) was dissolved in 6 N HCl (40 mL) and the resultant mixture heated at reflux according to the general procedure. Normal workup and isolation gave 701 mg (59%) of *l*-3-pyridylalanine as a white powder: ^{1}H NMR (D_2O) 3.26 (m, 2 H, CH_2CH), 4.05 (t, 1 H, CH$_2$C*H*), 7.47 (dd, 1 H, aromatic), 7.82 (d, 1 H, aromatic), 8.46 (m, 2 H, aromatic); ^{13}C NMR (D_2O) 36.32, 58.25, 127.18, 134.33, 141.11, 150.47, 157.78, 176.07; IR (KBr disk) broad absorption 3150–2100, 1622, 1561, 1492, 1429, 1412, 1347, 1330, 1308, 1153; MS (FAB) [M + 1] *m/e* 167; decomposition at 278 °C; $[\alpha]^{25}$ −9.6° (*c* 1.37, H_2O); chiral LC, 6:94 mixture of *d* and *l* isomers, ee 88%. Anal. C, H, N.

Preparation of *d*-3-Pyridylalanine (5a, *d* Isomer). The *d* isomer of **4a** (4572 mg, 20.6 mmol) was dissolved in 6 N HCl (115 mL) and the resultant mixture heated at reflux according to the general procedure. Normal workup and isolation gave 1632 mg (48%) of *d*-3-pyridylalanine as a white powder: ^{1}H NMR (D_2O) 3.27 (m, 2 H, CH_2CH), 4.06 (t, 1 H, CH$_2$C*H*), 7.48 (dd, 1 H,

aromatic), 7.83 (d, 1 H, aromatic), 8.46 (m, 2 H, aromatic); ^{13}C NMR (D_2O) 36.93, 58.87, 127.81, 134.96, 141.74, 151.11, 152,12, 176.69; IR (KBr disk) broad absorption 3130–2100, 1565, 1447, 1429, 1411, 1346, 1329, 1308, 1153, 853, 718, 685; MS (FAB) [M + 1] *m/e* 167; decomposed at 285 °C; $[\alpha]^{25}$ 9.68 (*c* 1.5, H_2O); chiral LC, 92:8 mixture of *d* and *l* isomers, ee 84%. Anal. C, H, N.

Preparation of *l*-4-Pyridylalanine (5b, *l* Isomer). The *l* isomer of **4b** (3307 mg, 14.90 mmol) was dissolved in 6 N HCl (60 mL) and the resultant mixture heated according to the general procedure. Normal workup and isolation gave 1725 mg (70%) of *l*-4-pyridylalanine as a white powder: ^1H NMR (D_2O) 3.20 (dd, 1 H, CH_2CH), 3.33 (dd, 1 H, CH_2CH), 4.08 (dd, 1 H, CH_2CH), 7.40 (d, 2 H, aromatic), 8.49 (d, 2 H, aromatic); ^{13}C NMR (D_2O) 38.73, 57.97, 128.01, 148.95, 151.74, 176.13; IR (KBr disk) broad absorption 3250–2250, 1609, 1559, 1406, 1360, 1345, 1316, 1217, 1005, 878, 839, 783, 627; MS (FAB) [M + 1] *m/e* 167; chiral LC, ee 96%; decomposed at 290 °C; $[\alpha]^{25}$ −8.3° (*c* 1.8, H_2O); high-resolution MS, calcd (M + H) 167.0821, found 167.0818.

Preparation of *d*-4-Pyridylalanine (5b, *d* Isomer). The *d* isomer of **4b** (348 mg, 1.57 mmol) was dissolved in 6 N HCl (5 mL) and the resultant mixture heated according to the general procedure. Normal workup and isolation gave 37 mg (14%) of *d*-4-pyridylalanine as a white powder: ^1H NMR (D_2O) 3.20 (dd, 1 H, CH_2CH), 3.33 (dd, 1 H, CH_2CH), 4.06 (dd, 1 H, CH_2CH), 7.40 (d, 2 H, aromatic), 8.49 (d, 2 H, aromatic); ^{13}C NMR (D_2O) 38.62, 57.87, 127.92, 148.88, 151.65, 176.02; IR (KBr disk) broad absorption 3250–2250, 1613, 1559, 1541, 1408, 1360, 1345, 1316, 1217, 1005, 839, 783; MS (CI) [M + H] *m/e* 167; chiral LC, 93:7 mixture of *d* and *l* isomers, 86%; decomposed at 280 °C; high-resolution MS, calcd (M + H) 167.0821, found 167.0826.

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Registry No. **1a**, 626-55-1; **1b**·HCl, 19524-06-2; **2**, 35356-70-8; **3a**, 115167-43-6; **3b**, 131905-72-1; L-**4a**, 95200-94-5; D-**4a**, 95200-93-4; L-**4b**, 131905-73-2; D-**4b**, 131905-74-3; L-**5a**, 64090-98-8; D-**5a**, 70702-47-5; L-**5b**, 37535-49-2; D-**5b**, 37535-50-5; (*R,R*)-[Rh(DIPAMP)(COD)]$^+BF_4^-$, 56977-92-5; (*S,S*)-[Rh(DIPAMP)(COD)]$^+BF_4^-$, 71423-54-6.

Supplementary Material Available: Copies of ^1H and ^{13}C NMR spectra of isomers of **4b** and **5b** (11 pages). Ordering information is given on any current masthead page.

Reformatsky Reaction: Carboxymethylenation of Cyclic Anhydrides and Reactions of Products Thereof†

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Methylidenephthalides 1, which have been prepared by exposing phthalic anhydride to either Perkin (R = H) or Wittig reaction conditions (R = Et),[1-3] are valuable precursors for the preparation of phthalazinone-1-acetic acid, **2** (R = H).[4] Certain derivatives of these acids have been identified as potent aldose reductase enzyme inhibitors targeted for treatment of diabetic complications.[5] In this connection, we were interested in preparing α-substituted phthalazinone-1-acetic acids which required access to α-substituted 3-((alkoxycarbonyl)methylidene)phthalides. The Perkin and Wittig reactions are of little value for the preparation of α,α-disubstituted compounds. However, the easy access to a variety of α-halo esters prompted us to explore the potential of the Reformatsky reaction as a method for the preparation of both 3-((alkoxycarbonyl)-methylidene)phthalides and their α-monosubstituted and α,α-disubstituted derivatives, even though the use of cyclic anhydrides in the reaction was unprecedented.

Scheme I

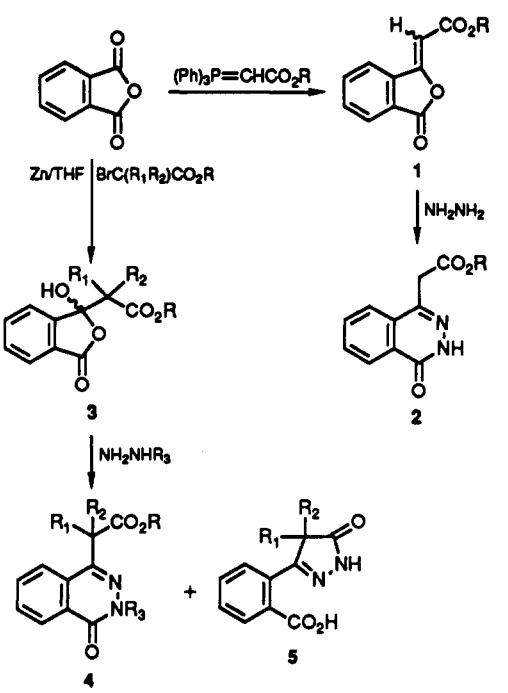
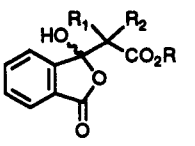


Table I



bromo ester		product R_1	R_2	R_3	yield, %
$BrCH_2CO_2Et$	**3a**	H	H	Et	40
$BrCH_2CO_2t$-Bu	**3b**	H	H	t-Bu	60
$BrCH(CH_3)CO_2Et$	**3c**	CH_3	H	Et	60
$BrCH(Ph)CO_2Et$	**3d**	Ph	H	Et	65
$BrC(CH_3)_2CO_2Et$	**3e**	CH_3	CH_3	Et	76
$BrC(CH_3)_2CO_2t$-Bu	**3f**	CH_3	CH_3	t-Bu	89

Results and Discussion

Exposure of phthalic anhydride and zinc in benzene or tetrahydrofuran to ethyl bromoacetate gave upon work up a crude oily product (Scheme I). Purification of this product by chromatography gave **3a** in low yield (15%). The yield in the Reformatsky reaction is often improved by switching from zinc to a zinc–copper couple.[6] Repetition of the above reaction using zinc–copper couple in tetrahydrofuran did significantly improve the yield (40%) and more importantly gave reproducible yields even when the reaction was run on a large scale. A further increase in the yield of **3a** to 60% was achieved by the addition of

† Dedicated to Professor Ernest Wenkert for his 65th birthday.

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