Efficient Chemoenzymatic Synthesis of Enantiomerically Pure α-Amino Acids**

Matthias Beller,* Markus Eckert, Holger Geissler,* Bernd Napierski, Heinz-Peter Rebenstock, and E. Wolfgang Holla*

Dedicated to Professor Boy Cornils on the occasion of his 60th birthday

Abstract: A general two-step chemoenzymatic synthesis for enantiomerically pure natural and nonnatural α-amino acids is presented. In the first step of the sequence, the ubiquitous educts aldehyde, amide and carbon monoxide react by palladium-catalyzed amidocarbonylation to afford the racemic *N*-acyl amino acids in excellent yields. In the second step, enzymatic enantioselective hydrolysis yields the free optically pure α-amino acid and the other enantiomer as the *N*-acyl derivative, both in optical purities of 85–99.5% *ee*. The advantage of the chemoenzymatic process compared to other amino acid synthesis are demonstrated by the preparation of various functionalized (-OR, -Cl, -F, -SR) α-amino acids on a 10-g scale.

Keywords: amino acids · amidocarbonylation · enzymes · homogeneous catalysis · palladium

Introduction

Enantiomerically pure α-amino acids play a central role in chemistry and biology owing to their function as building blocks of proteins, peptides and other natural compounds. From an industrial point of view amino acids and certain derivatives are important as food additives, agrochemicals, even as detergents and metal-chelating agents.[1] In addition, α-amino acid derivatives are highly important in synthetic organic chemistry as chiral, nonracemic starting materials and auxiliaries.[2] Although the synthesis of enantiomerically pure α-amino acids has been a field of intensive research for years,[3] there is no general, environmentally friendly and economical concept for the preparation of many important nonnatural amino acids. The present common chemical enantioselective synthesis routes have a number of disadvantages, and are therefore not attractive for amino acid preparation even on a hundred-gram scale, not to mention technical applications.

Not only the well-known and powerful synthetic techniques developed by Schöllkopf,[4] Seebach,[5] Evans,[6] Williams[7] and others,[8] but also very recent methods,[9] are predominantly not catalytic and utilize some expensive or not commercially available reactants. Moreover, they frequently require low-temperature reaction steps and mostly need at least four reaction steps to yield the desired amino acid starting from inexpensive educts. Further, the synthetic routes utilizing valuable catalytic processes such as asymmetric hydrogenation[10] most often require expensive starting materials.[11] Hence, the classical Strecker reaction[12] combined with a resolution step is still often favourable for multigram to kilogram synthesis of nonnatural amino acids despite the large amount of salt by-products produced by this reaction sequence. There is obviously still a need for a general and convergent approach towards nonnatural amino acids that would allow an easy, inexpensive and technically feasible synthesis.

Results and Discussion

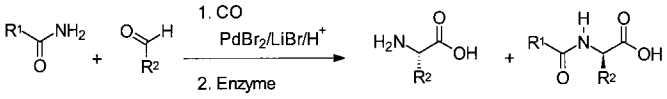
We present for the first time a simple chemoenzymatic sequence as a general method for the synthesis of enantio-

[*] Prof. Dr. M. Beller, Dipl.-Chem. M. Eckert
Anorganisch-chemisches Institut
der Technischen Universität München
Lichtenbergstrasse 4, D-85747 Garching (Germany)
Fax: (+ 49) 89-2891-3473
E-mail: mbeller@arthur.anorg.chemie.tu-muenchen.de
Dr. E. W. Holla, Dr. B. Napierski, H.-P. Rebenstock
Hoechst Marion Roussel Deutschland GmbH
Chemical Research, D-65926 Frankfurt am Main (Germany)
Fax: (+ 49) 69-3058-0226
E-mail: wolfgang.holla@hmrag.com
Dr. H. Geissler
Hoechst AG, Corporate Research & Technology
D-65926 Frankfurt am Main (Germany)
E-mail: geissler@msmwia.hoechst.com

[**] Palladium-Catalyzed Reactions for Fine Chemical Synthesis, Part 6; for Part 5, see M. Beller, T. H. Riermeier, *Eur. J. Inorg. Chem.* **1998**, 29–35.

  0947-6539/98/0405-0935 $ 17.50+.25/0

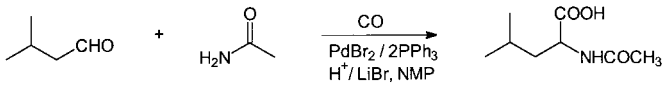
merically pure α-amino acids (Scheme 1). The two-step procedure relies on our recently disclosed palladium-catalyzed amidocarbonylation[13] and a subsequent enzymatic racemic resolution. In the first step of the reaction sequence, the racemic *N*-acyl amino acid is prepared by amidocarbonylation from an aldehyde, an acid amide and CO in the present of palladium catalysts. Originally, this atom-economical three-component reaction for the synthesis of *N*-acyl amino acids



Scheme 1. Chemoenzymatic two-step sequence of amidocarbonylation and enzymatic hydrolysis.

was accidentally discovered by Wakamatsu et al. using synthesis gas and cobalt catalysts in 1971.[14] Later, Ojima and coworkers used this method and developed elegant tandem procedures[15] based on the amidocarbonylation. Despite improvements by some of us, such as acid cocatalysis[16] of the cobalt-catalyzed variant, the methodology is limited in its product spectrum so far. In addition, the activity of the cobalt catalysts is quite low.

Stimulated by the initial experiments of Jägers[17] we could demonstrate that Pd(II) salts in combination with phosphines and halide and acid cocatalysis constitute an excellent catalyst system that is superior to all published amidocarbonylation catalysts.[13] Optimization studies using the amidocarbonylation of isovaleraldehyde revealed excellent yields and superior catalyst productivities (turnover number TON = 25000, turnover frequency TOF > 400 h^{-1}) under appropriate conditions (Scheme 2).



Scheme 2. Racemic *N*-acyl amino acid synthesis by palladium-catalyzed amidocarbonylation; NMP = *N*-methylpyrrolidone.

Our initial studies also showed that other simple aliphatic and aromatic aldehydes could be efficiently amidocarbonylated. The next goal was to extend this chemistry to use more functionalized aldehydes as well as amides as substrates for the palladium-catalyzed amidocarbonylation. In the presence of the catalyst system $PdBr_2/H_2SO_4$/LiBr (0.25 mol%/1 mol%/35 mol%) at 60 bar CO pressure and 120 °C, it is possible to prepare racemic *N*-acyl derivatives of important proteinogenic and nonproteinogenic amino acids. For example, methionine and substituted phenylglycines are obtained in good to excellent yields (not optimized) from simple low-cost starting materials (Table 1).

As shown in Table 1, interesting functional groups like -OR, halides (-Cl, -F) and even -SR are tolerated without any problems. In addition, a sterically hindered aldehyde such as cyclohexyl carbaldehyde yielded the corresponding *N*-acyl amino acids in very good yields. For the purpose of comparison of the classical cobalt catalysts with the new palladium catalyst system, amidocarbonylations of acetamide with cyclohexane carbaldehyde and 4-fluorobenzaldehyde were carried out in the presence of dicobaltoctacarbonyl (3 mol% Co, 100 bar CO/H_2 (1:1), 120 °C, 3 h).[18] Both reactions revealed the superiority of the palladium-catalyzed variant. While the cobalt-catalyzed amidocarbonylation of cyclohexane carbaldehyde afforded *N*-acetyl-α-cyclohexylglycine in 88% yield (TON = 29), the palladium-catalyzed reaction yielded the desired product in 95% yield (TON = 380). Even more evident are the advantages for the reactions using 4-fluorobenzaldehyde. With cobalt catalysts no amidocarbonylation occurred (this can be explained by hydrogenation side reactions), whereas *N*-acetyl-4-fluorophenylglycine was obtained in 85% yield with the palladium catalyst system.

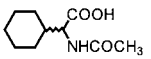
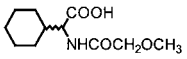
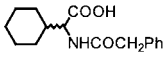
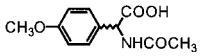
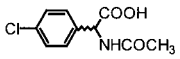
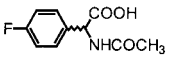
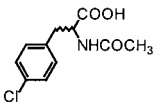
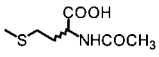
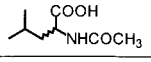
With the palladium-catalyzed amidocarbonylation in hand, we are interested in the efficient production of optically pure *N*-acyl amino acids and the corresponding amino acids. Apart from the development of catalytic asymmetric variants, which we are pursuing, the combination of amidocarbonylation with an enzyme-catalyzed resolution step attracted our attention in particular. In principle, the enzymatic cleavage of the *N*-acyl group leads to both enantiomerically enriched free amino acid and *N*-acyl-protected amino acid. Biocatalytic processes of this kind are well known[19] and are employed on a large scale.[20] The obtained optical purities are generally good to very good and many enzymes for amide hydrolysis are commercially available. In this respect the amino hydrolases (EC 3.5.1.14) from *Aspergillus spp.* and from porcine kidneys as well as penicillin acylase are particularly suited. Interestingly, these amide hydrolases accept substrates with a wide range of structure and functionality in both the amino acid and acyl moities of substrates. However, they reveal some interesting and significant differences.[19, 20] For instance, the *Aspergillus* acylase shows higher relative activities with aromatic and β-branched amino acids than does porcine kidney acylase. *N*-Phenacetyl derivatives enable the application of penicillin acylase, which is known for a rather lax substrate specificity.

A remarkable feature of palladium-catalyzed amidocarbonylation is that it is double-convergent and gives products with various side chains. This feature allows also a fine tuning of the stereoselectivity of the enzymatic resolution by a simple variation of the amide group. Thus, that amide-protecting

Abstract in German: *Es wird eine allgemeine zweistufige chemoenzymatische Synthese von enantiomerenreinen natürlichen und nicht-natürlichen α-Aminosäuren beschrieben. Im ersten Schritt der Sequenz werden die ubiquitären Edukte Aldehyd, Amid und Kohlenmonoxid mittels palladiumkatalysierter Amidocarbonylierung zu den racemischen N-Acylaminosäuren in guten bis sehr guten Ausbeuten umgesetzt. Im zweiten Schritt führt die enzymatische enantioselektive Hydrolyse zu der freien optisch reinen α-Aminosäure und dem N-Acylderivat des anderen Enantiomers, beide in optischen Reinheiten von 85 bis 99.5% ee. Der Vorteil dieses chemoenzymatischen Prozesses gegenüber anderen Aminosäuresynthesen wird demonstriert durch die Darstellung von verschiedenen funktionalisierten (-OR, -Cl, -F, -SR) α-Aminosäuren im 10-g-Maßstab.*

  0947-6539/98/0405-0936 $ 17.50+.50/0 *Chem. Eur. J.* **1998**, *4*, No. 5

Table 1. Synthesis of enantiomerically pure α-amino acids by palladium-catalyzed amidocarbonylation and enzymatic hydrolysis.

	Amidocarbonylation			Enzymatic Hydrolysis				
					(*S*)-Amino Acid		(*R*)-*N*-Acyl Amino Acid	
	Yield [%] [b]	TON	(*R,S*)-*N*-Acyl-AA	Enzyme [a]	Yield [%] [b]	*ee* [%]	Yield [%] [b]	*ee*[%]
1	95	380		AA [c]	43.9	≥ 99.5	47.2	95.6
2	85	340		PKA [d]	43.9	98.8	42.5	95
3	83	332		PA [e]	38	≥ 99.5	49	≥ 94
4	72	288		AA [c]	41.3	96.5	44.2	96.8
5	88	356		AA [c]	43.3	98.9	48.3	89.7
6	85	340		AA [c]	45.8	≥ 99.5	40	≥ 94
7	75	300		AA [c]	40.4	≥ 99.5	45.6	94.4
8	75	300		PKA [e]	32 [f]	≥ 99.5	40	85.6
9	99	396		AA [c]	39	≥ 99.5	46	89.2

[a] Amount of enzyme, reaction time and work-up procedure are not optimized. [b] Isolated yields. [c] Acylase from *Aspergillus spp.* [d] Porcine kidney acylase. [e] ChiroCLEC®-EC (penicillin acylase). [f] After incomplete precipitation.

group can be used which is known to give the best stereoselectivities or higher reaction rates with the subsequently employed enzyme. For instance, in many cases methoxyacetic acid amides are hydrolyzed faster by porcine kidney acylase than the corresponding acetamide derivatives. To the best of our knowledge, *N*-methoxyacetic acid amides and *N*-phenylacetic acid amides have never been used in amidocarbonylation reactions. *N*-acetyl-, *N*-α-methoxyacetyl- and *N*-phenacetylamino acids are accessible in yields of 72–99% by amidocarbonylation employing our standard reaction conditions.

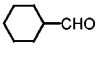
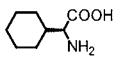
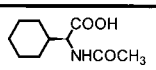
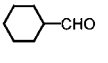
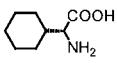
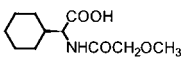
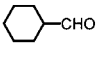
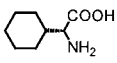
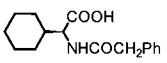
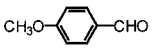
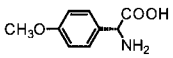
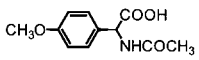
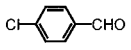
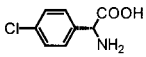
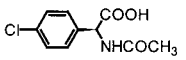
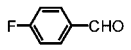
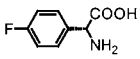
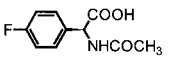
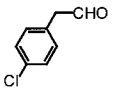
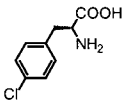
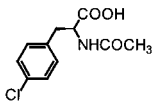
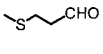
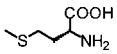
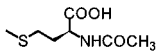
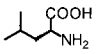
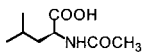
To demonstrate the utilization of the overall process we subjected nine different amidocarbonylation products representing a wide range of structure and functionality to enzymatic hydrolysis. The results are summarized in Table 1. The acylase-mediated resolutions were performed on 2–30 g scale under standard conditions. Initial concentrations of racemic substrates were 0.18–0.58 M, in most cases ≥0.4 M. Periodic addition of a few drops of aqueous NaOH maintained the pH at 7.6–7.9, and the temperature was kept at 37–40 °C.

Acylase from *Aspergillus spp.* (AA) and porcine kidney acylase (PKA) were used as lyophilized powders. To avoid autoxidation of PKA, substrate solutions were purged with nitrogen before addition of the enzyme and then kept under an atmosphere of nitrogen during the reaction. To accelerate the reaction rates of AA- or PKA-catalyzed hydrolysis ≥0.5 mM $CoCl_2 \cdot 6H_2O$ was included in the reaction mixtures. Amount of enzymes, duration of the reaction, and the work-up procedure were not optimized. In most cases the work-up protocol involved acidification of the reaction mixture to pH 5–6, filtration of the (*S*)-amino acid, acidification to pH 1–2 and subsequent filtration or extraction of the (*R*)-*N*-acyl amino acid. The enantiomeric excesses of the (*S*)-amino acids are in all cases >96%, in most cases >99%. The corresponding (*R*)-*N*-acyl amino acids, which can be further used for (*R*)-amino acid synthesis, are available[21] without recrystallization in optical purities of >85%. The yields of the overall process are 24–42% of (*S*)-amino acid and 30–46% of (*R*)-*N*-acyl amino acid (Table 2).

Although our chemoenzymatic procedure can theoretically give a maximum yield of 50%, of the (*S*)-amino acid as well as of the remaining (*R*)-acyl amino acids, it is important to note that the yield of the (*S*)-amino acid can be easily increased. After racemization of the (*R*)-acyl amino acid by heating in acetic acid and acetic acid anhydride at 110–115 °C, the resulting racemic mixture can be reused for the resolution process.[22] In order to prove this principle we racemized the obtained *N*-acetyl-(*R*)-4-chlorophenylglycine and performed an additional enzymatic resolution. The yield of (*S*)-4-chlorophenylglycine was increased to 63% (99% *ee*). On a large scale, a continuous process would increase the yield up to 80–90%.

The advantages of the presented chemoenzymatic process compared to other stereoselective synthetic methods for amino acids appear in particular if the desired product needs to be prepared on a scale of 10–100 g or even larger. As an example we prepared (*S*)-4-chlorophenylglycine, which is a topically interesting subunit of pharmaceutically active agents. Starting from inexpensive 4-chlorobenzaldehyde (21 g) and acetamide (9 g) we performed the amidocarbonylation in a 300 mL autoclave and obtained 30 g of the racemic

Table 2. Overall isolated yields of the chemoenzymatic synthesis of enantiomerically pure α-amino acids.

	Starting materials		(*S*)-Amino Acid		(*R*)-*N*-Acyl Amino Acid	
	Aldehyde	Amide		Yield [%]; *ee* [%]		Yield [%]; *ee* [%]
1		$AcNH_2$		42; ≥ 99.5		45; 95.6
2		$MeOAcNH_2$		37; 98.8		36; 95
3		$PhAcNH_2$		32; ≥ 99.5		42; ≥ 94
4		$AcNH_2$		30; 96.5		32; 96.8
5		$AcNH_2$		38; 98.9		40; 89.7
6		$AcNH_2$		39; 99.5		34; ≥ 94
7		$AcNH_2$		30; ≥ 99.5		41; 94.4
8		$AcNH_2$		24; ≥ 99.5		30; 85.6
9		$AcNH_2$		39; ≥ 99.5		46; 89.2

N-acetyl-4-chlorophenylglycine. Subsequent enzymatic resolution gave 10.6 g of enantiomerically pure (*S*)-4-chlorophenylglycine.

In conclusion, we have developed an extremely easy to perform two-step procedure for the synthesis of α-amino acids. It might initially appear that this procedure, containing a resolution step and thus giving only a maximum yield of 50% of the desired amino acid for a batch reaction, is not competitive with spectacular catalytic asymmetric procedures, for example hydrogenations, or one of the numerous elegant diastereoselective reactions, which can lead in principle to a 100% yield. However, all these methods must be compared considering the availability of the precursors, the number of reaction steps and the possibility of performing large-scale reactions ($>10-100$ g). By comparing these critical issues we believe that in many or most cases the methodology described herein is the state of the art synthesis for α-amino acids.

Experimental Section

General: A 300 mL stirred reactor (Parr 4561) with a magnet-driven propeller stirrer was used for the high-pressure reactions. Melting points were determined on a Büchi 535 melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 141 polarimeter. The enantiomeric purities of the amino acids were determined by GC analysis (HP 5890 with auto injector HP 7673) after derivatization with propanol/HCl (110 °C, 1 h) and perfluoropropionic acid anhydride (110 °C, 1 h) on a 25 m Chirasil L-Val capillary column (Alltech) at 80–160 °C, inj. 240 °C, det. (FID) 260 °C, 0.8 bar H_2 carrier gas. The enantiomeric purities of the *N*-acyl amino acids were determined by GC analysis under similar conditions after derivatization with propanol/HCl or methanol/HCl. ^{1}H NMR and ^{13}C NMR spectra (internal standard TMS) were recorded in [D_6]DMSO and trifluoroacetic acid on a Varian Gemini 200 (200 MHz), a Varian Unity plus 300 (300 MHz) and a Bruker AM 400 (400 MHz) spectrometer. Mass spectra were determined on a Micromass TRIO-2000 (DCI), a Micromass BIO-Q (ESI) and a Finnigan MAT 90 (CI). Infrared spectra were taken with a Perkin–Elmer 683 and a Perkin–Elmer FT-IR 1600 spectrometer.

Materials: Acylase Amano 30000 from *Aspergillus spp.*, 30 u/mg (AA) was obtained from Amano Enzyme Europe, acylase I, grade II, from porcine kidney, 720 u/mg (PKA) from Sigma Chemical, and ChiroCLEC-EC (PA) from Altus Biologics Inc.

General procedure for amidocarbonylation: *N*-Methylpyrrolidone (NMP) solution (1M, 25.0 mL) in aldehyde and amide, [$(PPh_3)_2PdBr_2$] (0.25 mol%), H_2SO_4 (1 mol%) and LiBr (35 mol%) were allowed to react under 60 bar CO at 120 °C for 12 h. The volatile components were removed under high vacuum, and the residue was taken up in a saturated aqueous solution of $NaHCO_3$ and then washed with chloroform and ethyl acetate. The aqueous phase was adjusted to pH 2 with phosphoric acid. The precipitate was filtered off, washed with water and dried under high vacuum. The combined aqueous phases were then extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, and the solvent was removed under vacuum. The precipitate and the residue were combined and recrystallized.

(*R,S*)-*N*-acetylcyclohexylglycine (1): Following the general procedure, cyclohexane carbaldehyde (14.1 g, 0.125 mol), acetamide (7.4 g, 0.125 mol), [$(PPh_3)_2PdBr_2$] (247 mg, 0.3125 mmol), H_2SO_4 (0.12 g, 1.25 mmol) and LiBr (3.8 g, 44 mmol) in 100 mL NMP were converted to yield 23.7 g (95%) (*R,S*)-*N*-acetylcyclohexylglycine (CAS 14328-56-4); m.p. 185 °C; ^{1}H NMR (400 MHz, [D_6]DMSO): $\delta = 0.9-1.3$ (m, 5H), 1.5–1.8 (m, 6H), 1.86 (s, 3H), 4.1 (dd, $J_1 = 8$ Hz, $J_2 = 6$ Hz, 1H), 7.96 (d, $J = 8$ Hz, 1H), 12.47 (s, 1H); ^{13}C NMR (400 MHz, [D_6]DMSO): $\delta = 173.3$, 169.5, 56.9, 29.3, 28.2, 25.8, 25.7, 22.4; MS (CI): m/z (%) = 200.2 ([M^++H], 100); IR (KBr): $\tilde{\nu} = 3339.7$, 2929.3, 1699.9, 1615.7, 1563.2 cm^{-1}.

Enzymatic hydrolysis of (*R,S*)-*N*-acetylcyclohexylglycine: (*R,S*)-*N*-acetylcyclohexylglycine (19.9 g, 0.1 mol) was dissolved at 20–25 °C in a mechanically stirred solution of NaOH pellets (4.0 g, 0.1 mol) in water (250 mL). After addition of $CoCl_2 \cdot 6H_2O$ (32.6 mg, 0.14 mmol) the clear solution was adjusted to pH 7.9 with HCl (2N) and heated to 37–40 °C. Acylase from *Aspergillus spp.* (100 mg Amano 30000, 30 u/mg) was added and the reaction mixture was stirred at 37–40 °C for 41 h. The resultant heterogenous reaction mixture was stirred for 1 h at 0–5 °C. Filtration of the precipitate under suction and drying in vacuo at 60 °C afforded 6.9 g

0947-6539/98/0405-0938 $ 17.50+.50/0 *Chem. Eur. J.* **1998**, *4*, No. 5

(43.9%) of the desired (*S*)-cyclohexylglycine; m.p. > 300 °C; $[\alpha]_D^{20} = +31$ ($c = 1$, 1N HCl); ≥ 99.5% *ee* (GC); ^{1}H NMR (200 MHz, TFA): $\delta = 1.1-1.6$ (m, 5H), 1.7–2.1 (m, 5H), 2.1–2.3 (m, 1H), 4.3 (d, $J = 4$ Hz, 1H), 11.6 (s, 1H); MS (DCI): *m/z* (%) = 158 ([M^++H], 100); IR (KBr): $\tilde{\nu} = 2927.7$, 1583.9, 1508.8 cm^{-1}.

The remaining solution was acidified to pH ≈ 1.5 with conc. HCl (10–13 mL), cooled to 0–5 °C and stirred for 30–45 min. Filtration of the precipitate under suction and drying in vacuo at 60 °C afforded 9.4 g (47.2%) of (*R*)-*N*-acetylcyclohexylglycine; m.p. 210–211 °C; $[\alpha]_D^{20} = -23$ ($c = 1$, MeOH); 95.6% *ee* (GC); ^{1}H NMR, ^{13}C NMR, MS and IR data were in agreement with data from (*R,S*)-*N*-acetylcyclohexylglycine.

(*R,S*)-*N*-methoxyacetylcyclohexylglycine (2): Following the general procedure, cyclohexane carbaldehyde (2.8 g, 0.025 mol), 2-methoxyacetamide (2.23 g, 0.025 mol), [$(PPh_3)_2PdBr_2$] (49 mg, 0.063 mmol), H_2SO_4 (0.025 g, 0.25 mmol) and LiBr (0.76 g, 8.8 mmol) in 25 mL NMP were converted to yield 4.9 g (85%) (*R,S*)-*N*-methoxyacetylcyclohexylglycine; m.p. 110 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 0.9-1.32$ (m, 5H), 1.5–1.84 (m, 6H), 3.32 (s, 3H), 3.86 (s, 2H), 4.18 (dd, $J_1 = 9$ Hz, $J_2 = 6$ Hz, 1H), 7.57 (d, $J =$ 9 Hz, 1H), 12.8 (brs, 1H); ^{13}C NMR (400 MHz, [D$_6$]DMSO): $\delta = 172.8$, 169.0, 71.1, 58.6, 56.2, 29.3, 28.1, 25.7, 25.6; MS (CI): *m/z* (%) = 230 ([M^++H], 100); IR (KBr): $\tilde{\nu} = 3372.3$, 2922.7, 1734.0, 1631.9, 1549.4 cm^{-1}; anal. calcd for $C_{11}H_{19}NO_4$: C 57.63, H 8.35, N 6.11; found: C 57.30, H 8.43, N 6.22.

Enzymatic hydrolysis of (*R,S*)-*N*-methoxyacetylcyclohexylglycine: (*R,S*)-*N*-methoxyacetylcyclohexylglycine (4.0 g, 17.4 mmol) was dissolved at 20–25 °C in a mechanically stirred solution of NaOH pellets (0.7 g, 17.5 mmol) in water (45 mL) under nitrogen. After addition of $CoCl_2 \cdot 6H_2O$ (5 mg, 0.021 mmol) the clear solution was adjusted to pH 7.9 with HCl (2N) and heated to 37–40 °C. Porcine kidney acylase (4 mg, 720 u/mg) was added and the reaction mixture was stirred at 37–40 °C for 72 h (pH was monitored periodically and kept at ≈ 7.9 with 1N NaOH). The resultant heterogenous reaction mixture was adjusted to pH 6 with 2N HCl and stirred for 30 min at 0–5 °C. Filtration of the precipitate under suction at 60 °C afforded 1.2 g (43.9%) of (*S*)-cyclohexylglycine; m.p. > 300 °C; $[\alpha]_D^{20} = +30.7$ ($c = 1$, 1N HCl); 98.8% *ee* (GC).

The remaining solution was acidified to pH ≈ 1 with conc. HCl, cooled to 0–5 °C and stirred for 1 h. Filtration of the precipitate under suction and drying in vacuo afforded 1.5 g of (*R*)-methoxyacetylcyclohexylglycine. Evaporation of the remaining solution under reduced pressure, trituration of the blue solid residue with a small amount of 2N HCl, filtration under suction and drying in vacuo afforded further 0.2 g of (*R*)-methoxyacetylcyclohexylglycine; total yield: 1.7 g (42.5%); m.p. 106–107 °C; $[\alpha]_D^{20} = -35$ ($c = 1$, MeOH); 95% *ee* (GC); ^{1}H NMR, ^{13}C NMR, MS and IR data were in agreement with data from (*R,S*)-*N*-methoxyacetylcyclohexylglycine.

(*R,S*)-*N*-phenacetylcyclohexylglycine (3): Following the general procedure, cyclohexane carbaldehyde (3.4 g, 0.03 mol), 2-phenylacetamide (4.1 g, 0.03 mol), [$(PPh_3)_2PdBr_2$] (59 mg, 0.08 mmol), H_2SO_4 (0.03 g, 0.3 mmol) and LiBr (1.0 g, 11 mmol) in 30 mL NMP were converted to yield 6.8 g (83%) (*R,S*)-*N*-phenacetylcyclohexylglycine; m.p. 193 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 0.86-1.30$ (m, 5H), 1.50–1.80 (m, 6H), 3.46, 3.54 (AB system, $J_{AB} = 14$ Hz, 2H), 4.13 (dd, $J_1 = 9$ Hz, $J_2 = 6$ Hz, 1H), 7.13–7.37 (m, 5H), 8.20 (d, $J = 9$ Hz, 1H), 12.53 (brs, 1H); ^{13}C NMR (400 MHz, [D$_6$]DMSO): $\delta = 173.2$, 170.3, 136.6, 129.0, 128.2, 126.3, 56.9, 41.9, 29.3, 28.1, 25.7, 25.6; MS (CI): *m/z* (%) = 276 ([M^++H], 100); IR (KBr): $\tilde{\nu} = 3340.1$, 2925.4, 1705.8, 1620.1, 1553.7 cm^{-1}; anal. calcd for $C_{16}H_{21}NO_3$: C 69.79, H 7.69, N 5.09. found: C 69.59, H 7.80; N 4.99.

Enzymatic hydrolysis of (*R,S*)-*N*-phenacetylcyclohexylglycine: (*R,S*)-*N*-phenacetylcyclohexylglycine (6.00 g, 21.78 mmol) was dissolved in a mechanically stirred potassium phosphate buffer (0.02M, pH = 7.6, 120 mL). The mixture was heated to 37–40 °C, ChiroCLEC-EC (penicillin acylase) was added and the reaction mixture was stirred at 37–40 °C for 48 h (pH was monitored periodically and kept at ≈ 7.6 with 1N NaOH). The resultant heterogenous reaction mixture was stirred for 30–45 min at 0–5 °C. Filtration of the precipitate under suction and drying in vacuo afforded 1.3 g (38%) of (*S*)-cyclohexylglycine; m.p. > 300 °C; $[\alpha]_D^{20} = +31.3$ ($c = 1$, 1N HCl); ≥ 99.5% *ee* (GC).

The remaining solution was acidified to pH ≈ 1.5 with conc. HCl, cooled to 0–5 °C and stirred for 30–45 min. Filtration of the precipitate under suction and drying in vacuo afforded 3.0 g of white (*R*)-*N*-phenacetylcyclohexylglycine, nearly free (≤ 2%) of phenylacetic acid; yield (corr.): 2.94 g (49%); m.p. 202–203 °C; $[\alpha]_D^{20} = -0.3$ ($c = 1$, MeOH); ≥ 94% *ee* (HPLC on (*S,S*)-Whelk-O 1 (E. Merck, Darmstadt), monitoring at 225 nm, eluting with hexane/ethanol, 5/1+0.1% HOAc; flow rate: 1 mL/min; 25 °C); ^{1}H NMR, ^{13}C NMR, MS and IR data were in agreement with data from (*R,S*)-*N*-phenacetyl-cyclohexylglycine.

(*R,S*)-*N*-acetyl-4-methoxyphenylglycine (4): Following the general procedure, 4-anisaldehyde (3.4 g, 0.025 mol), acetamide (1.48 g, 0.025 mol), [$(PPh_3)_2PdBr_2$] (49 mg, 0.063 mmol), H_2SO_4 (0.025 g, 0.25 mmol) and LiBr (0.76 g, 8.8 mmol) in 25 mL NMP were converted to yield 4.0 g (72%) (*R,S*)-*N*-acetyl-4-methoxyphenylglycine; m.p. 210 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 1.88$ (s, 3H), 3.75 (s, 3H), 5.13 (d, $J = 7.5$ Hz, 1H), 6.92 (m, 2H), 7.30 (m, 2H), 8.50 (d, $J = 7.5$ Hz, 1H), 12.67 (brs, 1H); ^{13}C NMR (400 MHz, [D$_6$]DMSO): $\delta = 172.2$, 169.0, 159.0, 129.3, 128.8, 113.9, 55.7, 55.2, 22.3; MS (DCI/MeOH): *m/z* (%) = 224 ([M^++H], 65), 165 (100); IR (KBr): $\tilde{\nu} = 3358.9$, 1705.5, 1618.4, 1546.3, 1516.7 cm^{-1}; anal. calcd for $C_{11}H_{13}NO_4$: C 59.19, H 5.87, N 6.27. found: C 58.98, H 5.97, N 6.30.

Enzymatic hydrolysis of (*R,S*)-*N*-acetyl-4-methoxyphenylglycine: (*R,S*)-*N*-acetyl-4-methoxyphenylyglycine (2.00 g, 8.96 mmol) was dissolved at 20–25 °C in a mechanically stirred solution of NaOH pellets (0.5 g, 12.5 mmol) in water (20 mL). After addition of $CoCl_2 \cdot 6H_2O$ (3.3 mg, 0.014 mmol) the clear solution was adjusted to pH 7.9 with HCl (2N) and heated to 37–40 °C. Acylase from *Aspergillus spp.* (15 mg Amano 30000, 30 u/mg) was added and the reaction mixture was stirred at 37–40 °C for 48 h (pH was checked periodically and kept at ≈ 7.9 with 1N NaOH). The resultant reaction mixture was stirred for 1 h at 0–5 °C. Filtration of the precipitate under suction and drying in vacuo afforded 0.67 g (41.3%) of the desired (*S*)-4-methoxyphenylglycine; m.p. 260 °C (decomp.); $[\alpha]_D^{20} = 139.1$ ($c = 1$, 1N HCl); 96.5% *ee* (GC); ^{1}H NMR (200 MHz, TFA): $\delta = 4.20$ (s, 3H), 5.43 (s, 1H), 7.17 (d, $J = 10$ Hz, 2H), 7.54 (d, $J = 10$ Hz, 2H), 11.60 (s, 1H); MS (DCI): *m/z* (%) = 182 ([M^++H], 8), 165 (61), 136 (100); IR (KBr): $\tilde{\nu} =$ 3442.0, 2954.6, 1586.2, 1516.7 cm^{-1}.

The remaining solution was acidified to pH ≈ 1.5 with conc. HCl, cooled to 0–5 °C and stirred for 1 h. Filtration of the precipitate under suction and drying afforded 0.88 g (44.2%) of (*R*)-*N*-acetyl-p-methoxyphenylglycine as an off-white solid; m.p. 211–212 °C; $[\alpha]_D^{20} = 211.2$ ($c = 1$, MeOH); 96.8% *ee* (GC); ^{1}H NMR, ^{13}C NMR, MS and IR data were in agreement with data from (*R,S*)-*N*-acetyl-4-methoxyphenylglycine.

(*R,S*)-*N*-acetyl-4-chlorophenylglycine (5): Following the general procedure, 4-chlorobenzaldehyde (21.1 g, 0.15 mol), acetamide (8.9 g, 0.15 mol), [$(PPh_3)_2PdBr_2$] (300 mg, 0.38 mmol), H_2SO_4 (0.15 g, 1.5 mmol) and LiBr (4.5 g, 52 mmol) in 100 mL NMP were converted to yield 30.1 g (88%) (*R,S*)-*N*-acetyl-4-chlorophenylglycine; m.p. 196 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 1.90$ (s, 3H), 5.35 (d, $J = 7.5$ Hz, 1H), 7.42 (m, 4H), 8.65 (d, $J = 7.5$ Hz, 1H), 12.94 (brs, 1H); ^{13}C NMR (400 MHz, [D$_6$]DMSO): $\delta =$ 171.9, 169.2, 136.7, 132.6, 129.6, 128.5, 55.7, 22.4; MS (DCI): m/z (%) = 228 (M+H$^+$, 100); IR (KBr): $\tilde{\nu} = 3342.0$, 1710.0, 1620.5, 1541.4, 1494.1 cm^{-1}; anal. calcd for $C_{10}H_{10}ClNO_3$: C 52.76, H 4.43, N 6.15. found: C 52.50, H 4.20, N 6.20.

Enzymatic hydrolysis of (*R,S*)-*N*-acetyl-4-chlorophenylglycine: (*R,S*)-*N*-acetyl-4-chlorophenylglycine (30.00 g, 0.132 mol) was dissolved at 20–25 °C in a mechanically stirred solution of NaOH pellets (6.0 g, 0.15 mol) in water (300 mL). After addition of $CoCl_2 \cdot 6H_2O$ (50 mg, 0.21 mmol) the clear solution was adjusted to pH 7.9 with HCl (2N) and heated to 37–40 °C. Acylase from *Aspergillus spp.* (225 mg Amano 30000, 30 u/mg) was added and the reaction mixture was stirred at 37–40 °C for 48 h (pH was monitored periodically and kept at ≈ 7.9 with 1N NaOH). The resultant heterogenous reaction mixture was stirred for 1 h at 0–5 °C. Filtration of the precipitate under suction and drying in vacuo afforded 10.6 g (43.3%) (*S*)-4-chlorophenylglycine; m.p. > 300 °C; $[\alpha]_D^{20} = 143.1$ ($c = 1$, 1N HCl); 98.9% *ee* (GC); ^{1}H NMR (300 MHz, TFA): $\delta = 5.45$ (s, 1H), 7.50 (m, 4H), 11.60 (s, 1H); MS (DCI/MeOH): *m/z* (%) = 186 ([M+H]$^+$, 100); IR (KBr): $\tilde{\nu} = 2936.0$, 1611.8, 1507.3 cm^{-1}.

The remaining solution was acidified to pH ≈ 1.5 with conc. HCl, cooled to 0–5 °C and stirred for 1 h. Filtration of the precipitate under suction and drying in vacuo afforded 14.5 g (48.3%) of (*R*)-*N*-acetyl-4-chlorophenylglycine as an off-white solid; m.p. 208–209 °C; $[\alpha]_D^{20} = 193.2$ ($c = 1$, MeOH); 89.7% *ee* (GC); ^{1}H NMR, ^{13}C NMR, MS and IR data were in agreement with data from (*R,S*)-*N*-acetyl-4-chlorophenylglycine.

Racemization of (*R,S*)-*N*-acetyl-4-chlorophenylglycine: (*R*)-*N*-acetyl-4-chlorophenylglycine (14.5 g, 64 mmol), conc. acetic acid (65 mL) and acetic acid anhydride were stirred at 110–115 °C for 3.5 h. The mixture was

evaporated under reduced pressure, water (30–40 mL) was added and the mixture was again evaporated to dryness. Trituration with water (30–40 mL), filtration and drying in air afforded 13.6 g (94%) (*R,S*)-*N*-acetyl-4-chlorophenylglycine as an off-white solid, which can be used without further purification (recrystallization from EE/*i*PrOH); m.p. 196 °C; $[\alpha]_D^{20} = \pm 0$ ($c = 1$, MeOH). ^{1}H NMR and MS data were in agreement with data from (*R,S*)-*N*-acetyl-4-chlorophenylglycine used as starting material.

(*R,S*)-*N*-acetyl-4-fluorophenylglycine (**6**): Following the general procedure, 4-fluorobenzaldehyde (6.2 g, 0.05 mol), acetamide (2.96 g, 0.05 mol), $[(PPh_3)_2PdBr_2]$ (99 mg, 0.125 mmol), H_2SO_4 (0.05 g, 0.5 mmol) and LiBr (1.52 g, 18 mmol) in NMP (50 mL) were converted to yield 9.0 g (85%) (*R,S*)-*N*-acetylfluorophenylglycine; m.p. 188 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 1.88$ (s, 3H), 5.33 (d, $J = 7.5$ Hz, 1H), 7.20 (m, 2H), 7.43 (m, 2H), 8.60 (d, $J = 7.5$ Hz, 1H), 12.86 (br, 1H); ^{13}C NMR (400 MHz, [D$_6$]DMSO): $\delta = 172.0$, 169.2, 163.1 + 160.6, 133.7, 129.8, 115.2, 55.6, 22.4; MS (CI): *m/z* (%) = 212 ([M^++H], 100); IR (KBr): $\tilde{\nu} = 3354.6$, 1716.7, 1614.9, 1547.3, 1509.2, 1225.2 cm^{-1}; anal. calcd for $C_{10}H_{10}FNO_3$: C 56.87, H 4.77, N 6.63. found: C 56.47, H 4.96, N 6.62.

Enzymatic hydrolysis of (*R,S*)-*N*-acetyl-4-fluorophenylglycine: (*R,S*)-*N*-acetyl-4-fluorophenylglycine (6.00 g, 28 mmol) was dissolved at 20–25 °C in a mechanically stirred solution of NaOH pellets (1.2 g, 30 mmol) in water (60 mL). After addition of $CoCl_2 \cdot 6H_2O$ (10 mg, 0.042 mmol) the clear solution was adjusted to pH 7.9 with HCl (2N) and heated to 37–40 °C. Acylase from *Aspergillus spp.* (45 mg Amano 30000, 30 u/mg) was added and the reaction mixture was stirred at 37–40 °C for 48 h (pH was checked periodically and kept at ≈7.9 with 1N NaOH). The resultant reaction mixture was stirred for 45 min at 0–5 °C. Filtration of the precipitate under suction and drying in vacuo afforded 2.2 g (45.8%) (*S*)-4-fluorophenylglycine; m.p. 295–300 °C (sublimed); $[\alpha]_D^{20} = +134.7$ ($c = 0.9$, 6N HCl); $[\alpha]_D^{20} = +141$ ($c = 1$, 1N HCl); ≥99.5% *ee* (HPLC on Crownpak CR(+) 15 mm × 0.4 cm [Daicel Chemical Industries], monitored at 212/260 nm, eluted with 0.0162M $HClO_4$, pH = 2.09; flow rate: 1 mL min^{-1}; 40 °C); ^{1}H NMR (200 MHz, TFA): $\delta = 5.46$ (s, 1H), 7.23 (m, 2H), 7.53 (m, 2H), 11.58 (s, 1H); MS (ESI): *m/z* (%) = 170 ([M^++H], 100); IR (KBr): $\tilde{\nu} = 2935.9$, 1611.1, 1505.8 cm^{-1}.

The remaining solution was acidified to pH ≈ 1.0 with conc. HCl, cooled to 0–5 °C and stirred for 1 h. Filtration of the precipitate under suction and drying in vacuo afforded 2.4 g (40%) of (*R*)-*N*-acetyl-p-fluorophenylglycine as an off-white solid; m.p. 180–181 °C; $[\alpha]_D^{20} = -193.8$ ($c = 1$, MeOH); ≥94% *ee* (HPLC on (*S,S*)-Whelk-O 1 [E. Merck, Darmstadt], monitored at 225 nm, eluted with hexane/ethanol (7/1 + 0.2% HOAc, flow rate: 1 mL min^{-1}, 40 °C); ^{1}H NMR, ^{13}C NMR, MS and IR data were in agreement with data from (*R,S*)-*N*-acetyl-4-fluorophenylglycine.

(*R,S*)-*N*-acetyl-3-(4-chlorophenyl)-alanine (**7**): Following the general procedure, 2-(4-chlorophenyl)acetaldehyde (3.9 g, 0.025 mol), acetamide (1.48 g, 0.025 mol), $[(PPh_3)_2PdBr_2]$ (49 mg, 0.063 mmol), H_2SO_4 (0.025 g, 0.25 mmol) and LiBr (0.76 g, 8.8 mmol) in NMP (25 mL) were converted to yield 4.5 g (75%) (*R,S*)-*N*-acetyl-3-(4-chlorophenyl)glycine (CAS 14091-10-2); m.p. 179 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 1.78$ (s, 3H), 2.85, 3.02 (ABX system, $J_{AB} = 14$ Hz, $J_{AX} = 10$ Hz, $J_{BX} = 5$ Hz, 2H), 4.40 (ddd, $J_1 = 10$ Hz, $J_2 = 8$ Hz, $J_3 = 5$ Hz, 1H), 7.28 (m, 4H), 8.17 (d, $J = 8$ Hz, 1H), 12.3 (br s, 1H); ^{13}C NMR (400 MHz, [D$_6$]DMSO): $\delta = 173.3$, 169.2, 136.8, 128.9, 128.0, 126.3, 53.8, 36.8, 22.4; MS (CI): *m/z* (%) = 242 ([M^++H], 100); IR (KBr): $\tilde{\nu} = 3314.6$, 2923.0, 1743.9, 1616.0, 1559.8 cm^{-1}.

Enzymatic hydrolysis of (*R,S*)-*N*-acetyl-3-(4-chlorophenyl)alanine: (*R,S*)-*N*-acetyl-3-(4-chlorophenyl)alanine (24.1 g, 0.10 mol) was dissolved at 20–25 °C in a mechanically stirred solution of NaOH pellets (4.0 g, 0.1 mol) in water (250 mL). After addition of $CoCl_2 \cdot 6H_2O$ (36 mg, 0.15 mmol) the clear solution was adjusted to pH 7.7–7.9 with HCl (2N) and heated to 37–40 °C. Acylase from *Aspergillus spp.* (100 mg Amano 30000, 30 u/mg) was added and the reaction mixture was stirred at 37–40 °C for 42 h (pH was monitored periodically and kept at ≈7.9 with 1N NaOH). The resultant heterogenous reaction mixture was stirred for 1 h at 0–5 °C. Filtration of the precipitate under suction and drying in vacuo afforded 8.6 g (40.4%) of the desired (*S*)-3-(4-chlorophenyl)alanine; m.p. 255–256 °C (decomp.); $[\alpha]_D^{20} = 2.5$ ($c = 1$, 1N HCl); ≥99.5% *ee* (GC); ^{1}H NMR (200 MHz, TFA): $\delta = 3.39$, 3.61 (ABX system, $J_{AB} = 15$ Hz, $J_{AX} = 7.5$ Hz, $J_{BX} = 5$ Hz, 2H), 4.68 (dd, $J_1 = 7.5$ Hz, $J_2 = 5$ Hz 1H), 7.35 (m, 4H), 11.55 (s, 1H); MS (DCI): *m/z* (%) = 200 (M+H$^+$, 100); IR (KBr): $\tilde{\nu} = 3412.0$, 3084.5, 1587.8, 1513.3, 1492.5, 1408.5 cm^{-1}.

The remaining solution was acidified to pH ≈ 1.5 with conc. HCl, cooled to 0–5 °C and stirred for 30–45 min. Filtration of the precipitate under suction and drying in vacuo at 60 °C afforded 11.0 g (45.6%) of (*R*)-*N*-acetyl-3-(4-chlorophenyl)-alanine; m.p. 132–133 °C; $[\alpha]_D^{20} = -44.8$ ($c = 1$, MeOH); 94.4% *ee* (GC); ^{1}H NMR, ^{13}C NMR, MS and IR data were in agreement with data from (*R,S*)-*N*-acetyl-3-(4-chlorophenyl)alanine.

(*R,S*)-*N*-acetylmethionine (**8**): Following the general procedure, 3-(methylmercapto)propionaldehyde (10.4 g, 0.1 mol), acetamide (5.9 g, 0.1 mol), $[(PPh_3)_2PdBr_2]$ (198 mg, 0.25 mmol), H_2SO_4 (0.1 g, 1.0 mmol) and LiBr (3.0 g, 35 mmol) in 100 mL NMP were converted to yield 14.3 g (75%) (*R,S*)-*N*-acetylmethionine (CAS 1115-47-5); m.p. 84 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 1.70–2.05$ (m, 2H), 1.85 (s, 3H), 2.03 (s, 3H), 2.40–2.57 (m, 2H), 4.28 (m, 1H), 8.13 (d, $J = 8$ Hz, 1H), 12.5 (br s, 1H); ^{13}C NMR (400 MHz, [D$_6$]DMSO): $\delta = 173.6$, 169.6, 51.0, 30.8, 29.8, 22.5, 14.7; MS (CI): *m/z* (%) = 192 (M+H$^+$, 100); IR (KBr): $\tilde{\nu} = 3335.5$, 2923.7, 1706.5, 1621.4, 1556.1 cm^{-1}.

Enzymatic hydrolysis of (*R,S*)-*N*-acetylmethionine: (*R,S*)-*N*-acetylmethionine (10.00 g, 52.28 mmol) was dissolved at 20–25 °C in a mechanically stirred potassium phosphate buffer (0.02M, pH = 7.8, 100 mL) under an atmosphere of nitrogen. After addition of $CoCl_2 \cdot 6H_2O$ (16.5 mg, 0.069 mmol) the solution was heated to 37–40 °C. Porcine kidney acylase (6.25 mg, 720 u/mg) was added and the reaction mixture was stirred at 37–40 °C for 72 h (pH was checked periodically and kept at ≈7.8 with 1N NaOH). The resultant reaction mixture was adjusted to pH = 1 with 5N HCl and extracted with ethyl acetate (4 ≈ 100 mL). The combined extracts were dried with $MgSO_4$ and concentrated in vacuo. The solid residue was triturated with a small amount of *t*BuOMe. Filtration and drying gave 4.0 g (40%) (*R*)-*N*-acetylmethionine; m.p. 99–100 °C; $[\alpha]_D^{20} = +7.4$ ($c = 1$, MeOH); 85.6% *ee* (GC); ^{1}H NMR (200 MHz, [D$_6$]DMSO): $\delta = 1.70–2.05$ (m, 2H), 1.85 (s, 3H), 2.03 (s, 3H), 2.40–2.57 (m, 2H), 4.28 (m, 1H), 8.13 (d, $J = 8$ Hz, 1H), 12.5 (br s, 1H); MS (DCI/MeOH): *m/z* (%) = 192 ([M^++H], 100); IR (KBr): $\tilde{\nu} = 3335.5$, 2923.7, 1706.5, 1621.4, 1556.1 cm^{-1}.

The remaining aqueous phase was adjusted to pH = 5.5 with 11N NaOH, concentrated under reduced pressure to 40–50 mL, cooled to 0–5 °C and stirred for 30–45 min. Filtration after incomplete precipitation and drying afforded 2.5 g (32%) (*S*)-methionine; m.p. 287–288 °C (decomp); $[\alpha]_D^{20} = +22.8$ ($c = 1$, 1N HCl); ≥99.5% *ee* (GC); ^{1}H NMR, ^{13}C NMR, MS and IR data were in agreement with data from (*R,S*)-*N*-acetylmethionine.

(*R,S*)-*N*-acetylleucine (**9**): Following the general procedure, isovaleraldehyde (8.6 g, 0.1 mol), acetamide (5.9 g, 0.1 mol), $[(PPh_3)_2PdBr_2]$ (198 mg, 0.25 mmol), H_2SO_4 (0.1 g, 1.0 mmol) and LiBr (3.0 g, 35 mmol) in 100 mL NMP were converted to yield 17.1 g (99%) (*R,S*)-*N*-acetylleucine (CAS 99-15-0); m.p. 160 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 0.84$ (d, $J = 7$ Hz, 3H), 0.88 (d, $J = 7$ Hz, 3H), 1.42–1.52 (m, 2H), 1.6 (m, 1H), 1.83 (s, 3H), 4.2 (q, $J = 7$ Hz, 1H), 8.05 (d, $J = 7$ Hz, 1H), 12.43 (s, 1H); ^{13}C NMR (400 MHz, [D$_6$]DMSO): $\delta = 174.3$, 169.3, 50.2, 40.1, 24.3, 22.9, 22.4, 21.3; MS (CI): *m/z* (%) = 174 ([M+H]$^+$, 100); IR (KBr): $\tilde{\nu} = 3335.2$, 2961.3, 1701.6, 1624.6, 1561.1 cm^{-1}.

Enzymatic hydrolysis of (*R,S*)-*N*-acetylleucine: (*R,S*)-*N*-acetylleucine (10.00 g, 57.73 mmol) was dissolved at 20–25 °C in a mechanically stirred solution of NaOH pellets (2.5 g, 62.5 mmol) in water (100 mL). After addition of $CoCl_2 \cdot 6H_2O$ (16.5 mg, 0.069 mmol) the clear solution was adjusted to pH 7.7–7.9 with HCl (2N) and heated to 37–40 °C. Acylase from *Aspergillus spp.* (75 mg Amano 30000, 30 u/mg) was added and the reaction mixture was stirred at 37–40 °C for 48 h (pH was checked periodically and kept at ≈7.9 with 1N NaOH). The resultant heterogenous reaction mixture was stirred for 1 h at 0–5 °C. Filtration of the white precipitate under suction and drying in vacuo afforded 1.28 g (16.5%) of (*S*)-leucine; m.p. 288 °C (decomp.); $[\alpha]_D^{20} = +12.1$ ($c = 1$, 1N HCl); ≥99.5% *ee* (GC).

The remaining reaction mixture was adjusted to pH = 1 with 5N HCl and stirred for 1 h at 0–5 °C. The white precipitate was filtered off and the resultant solution was extracted with ethyl acetate (4 × 100 mL). The combined extracts were dried with $MgSO_4$, concentrated in vacuo and added to the white precipitate; total yield: 4.6 g (46%) of (*R*)-*N*-acetylleucine; m.p. 188–190 °C; $[\alpha]_D^{20} = +24$ ($c = 1$, MeOH); 89.2% *ee* (GC).

The remaining aqueous phase was adjusted to pH = 5.5 with 11N NaOH, concentrated under reduced pressure to 30–40 mL, cooled to 0–5 °C and

0947-6539/98/0405-0940 $ 17.50+.50/0 *Chem. Eur. J.* **1998**, *4*, No. 5

stirred for 15–30 min. Filtration and drying afforded a further 1.70 g (22.5%) of (*S*)-leucine; m.p. 288 °C (decomp.); $[\alpha]_D^{20} = +12.1$ ($c = 1$, 1N HCl); ≥99.5% *ee* (GC); total yield: 2.98 g (39%); ^{1}H NMR, ^{13}C NMR, MS and IR data were in agreement with data from (*R,S*)-*N*-acetylleucine.

Acknowledgments: M.B., M.E. and H.G. thank Prof. Dr. K. Kühlein for stimulating discussions. This work was financially supported by the Deutsche Forschungsgemeinschaft (BE1931/1-1; BE1931/1-2). V. Backes, W. Hofmann and R. Saric are thanked by E.W.H. for the GC and HPLC analyses.

Received: November 26, 1997 [F908]

[1] H. H. Szmant, *Organic Building Blocks for the Chemical Industry*, Wiley, New York, **1989**.

[2] a) G. M. Coppola, H. F. Schuster, *Asymmetric Synthesis*, Wiley, New York, **1987**; b) H. Waldmann, *Synlett* **1995**, 133; c) M. T. Reetz, *Angew. Chem*. **1991**, *103*, 1559–1573; *Angew. Chem. Int. Ed. Engl*. **1991**, *30*, 1531–1546; d) K. Drauz, A. Kleemann, J. Martens, *ibid*. **1982**, *94*, 590–613 and **1982**, *21*, 584–608.

[3] a) R. O. Duthaler, *Tetrahedron* **1994**, *50*, 1539; b) M. J. O'Donnell, *ibid*. **1988**, *44*, 5253.

[4] a) U. Schöllkopf, *Tetrahedron* **1983**, *39*, 2085; b) U. Schöllkopf, *Top. Curr. Chem*. **1983**, *109*, 65.

[5] a) D. Seebach, R. Imwinkelried, T. Weber, *Modern Synthetic Methods, Vol. 4*, Springer, Heidelberg, **1986**; b) D. Seebach, A. R. Sting, M. Hoffmann, *Angew. Chem*. **1996**, *108*, 2880–2921; *Angew. Chem. Int. Ed. Engl*. **1996**, *35*, 2708–2748.

[6] a) D. A. Evans, A. E. Weber, *J. Am. Chem. Soc*. **1987**, *109*, 7151; b) D. A. Evans, T. C. Britton, J. A. Ellman, R. L. Dorow, *ibid*. **1990**, *112*, 4011.

[7] R. M. Williams, P. J. Sinclair, D. Zhai, D. Chen, *J. Am. Chem. Soc*. **1988**, *110*, 1547.

[8] R. M. Williams, *Synthesis of Optically Active α-Amino Acids* in *Organic Chemistry Series, Vol. 7* (Ed.: J. E. Baldwin, P. D. Magnus), Pergamon, **1989**.

[9] a) N. A. Petasis, I. A. Zavialov, *J. Am. Chem. Soc*. **1997**, *119*, 445–446; b) Y. S. Park, P. Beak, *J. Org. Chem*. **1997**, *62*, 1574–1575; c) A. G. Myers, J. L. Gleason, T. Yoon, D. W. Kung, *J. Am. Chem. Soc*. **1997**, *119*, 656–673.

[10] a) J. P. Genet, *Advanced Asymmetric Synthesis* (Ed.: G. R. Stephenson), Chapman & Hall, **1996**; b) H. Takaya, T. Ohta, R. Noyori, *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), VCH, Weinheim, **1993**; c) M. J. Burk, J. E. Feaster, W. A. Nugent, R. L. Harlow, *J. Am. Chem. Soc*. **1993**, *115*, 10125; d) A. Kumar, G. Oehme, J. P. Roque, M. Schwarze, R. Selke, *Angew. Chem*. **1994**, *106*, 2272–2275; *Angew. Chem. Int. Ed. Engl*. **1994**, *33*, 2197–2199; e) J. Albrecht, U. Nagel, *ibid*. **1996**, *108*, 444–446 and **1996**, *34*, 404–407; f) J. A. Wiles, S. H. Bergens, *J. Am. Chem. Soc*. **1997**, *119*, 2940–2941.

[11] a) B. M. Trost, G. R. Dake, *J. Am. Chem. Soc*. **1997**, *119*, 7595–7596; b) U. Schmidt, A. Lieberknecht, J. Wild, *Synthesis* **1988**, 159.

[12] A. Strecker, *Liebigs Ann. Chem*. **1850**, *75*, 57.

[13] a) M. Beller, M. Eckert, F. Vollmüller, S. Bogdanovic, H. Geissler, *Angew. Chem*. **1997**, *109*, 1534–1536; *Angew. Chem. Int. Ed. Engl*. **1997**, *35*, 1494–1496; b) M. Beller, M. Eckert, F. Vollmüller, S. Bogdanovic, H. Geissler, German patent applied for; c) G. Dyker, *Angew. Chem*. **1997**, *109*, 1777–1779; *Angew. Chem. Int. Ed. Engl*. **1997**, *35*, 1700–1702.

[14] a) H. Wakamatsu, J. Uda, N. Yamakami, *J. Chem. Soc. Chem. Commun*. **1971**, 1540; b) J. F. Knifton in *Applied Homogeneous Catalysis with Metal Complexes* (Eds.: W. A. Herrmann, B. Cornils), VCH, Weinheim, **1996**, p. 159.

[15] I. Ojima, *Chem. Rev*. **1988**, *88*, 1011–1030.

[16] M. Beller, H. Fischer, P. Gross, T. Gerdau, H. Geissler, S. Bogdanovic (Hoechst AG), DE-4.415.712, **1995** [*Chem. Abstr*. **1996**, *124*, 149264a].

[17] E. Jägers, H.-P. Koll (Hoechst AG), EP-338.330 **1989**; *Chem. Abstr*. **1990**, *112*, 77951z.

[18] Acetamide (5.9 g, 0.1 mol), cyclohexane carbaldehyde (11.2 g, 0.1 mol) and dicobaltoctacarbonyl (0.5 g, 3 mol% Co) were suspended in dimethoxyethane (DME; 40 g). The reaction mixture was stirred for 3 h at 100 bar CO/H_2 (1:1) and 120 °C, during which time the pressure decreased by 23 bar. After cooling and depressurizing the product was collected by filtration and dried. 16.7 g (88%) *N*-acetyl-α-cyclohexylglycine was obtained. Under the same conditions benzaldehydes did not react to give the desired glycine derivatives. Identical experiments with benzaldehyde and 4-fluorobenzaldehyde resulted in hydrogenation of the educts.

[19] a) H. K. Chenault, J. Dahmer, G. M. Whitesides, *J. Am. Chem. Soc*. **1989**, *111*, 6354. b) M. A. Verkhovskaja, I. A. Yamskov, *Russ. Chem. Rev*. **1991**, *60*, 1163.

[20] K. Drauz, H. Waldmann, *Enzyme Catalysis in Organic Synthesis*, VCH, Weinheim, **1995**.

[21] T. Wieland, *Methoden Org. Chem*. (Houben-Weyl), 4th ed. **1958**, *Vol. XI/2*, pp. 316 ff.

[22] M. Bergmann, L. Zervas, *Biochem. Z*. **1929**, *203*, 280–292.