Efficient Synthesis of *N*-Acyl-α-arylglycines via Palladium-Catalyzed Amidocarbonylation: Application to the Central Amino Acid of Chloropeptin†

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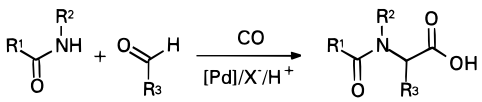
Arylglycines are of actual interest in organic and medicinal chemistry because of their antimicrobial and enzyme inhibitory properties.[1] They constitute an important integral part of the growing class of clinically effective glycopeptide antibiotics such as vancomycin, β-avoparcin, and chloropeptin.[2] Of key importance for the practical synthesis of these cyclic peptides as well as of pharmacologically interesting analogues is an easy and general access to nonproteinogenic α-amino acids of the arylglycine type. Although a number of elegant strategies for stereoselective *N*-acyl amino acid synthesis were published during the past decade,[3] to our knowledge none of them is applied in industry on a larger scale. This is explained by the fact that most developed procedures use fairly expensive starting materials and are limited to the millimole scale.

Due to our interest to develop catalytic reactions for organic synthesis which are applicable also in industry on a larger scale, we looked for alternative methods for the synthesis of amino acid derivatives. In this respect the so-called amidocarbonylation developed by Wakamatsu in 1971 seems to be an industrially feasible procedure: starting from aldehydes, amides, and CO the desired *N*-acyl α-amino acids are obtained in the presence of cobalt catalysts (eq 1).[4] Up to now, this methodology



(1)

has not found broad use in amino acid synthesis because high catalyst concentrations of the cobalt catalyst $HCo(CO)_4$ and harsh reaction conditions are required for the reaction to take place. More important the substrate variety is limited to nonfunctionalized aliphatic aldehydes—e.g., aromatic aldehyde derivatives *cannot* be amidocarbonylated using cobalt catalysts to give aryl glycine derivatives.[5] To overcome the limitations of the cobalt-catalyzed reaction, we developed recently a new protocol for the amidocarbonylation utilizing palladium catalysts.[6] On the basis of our new amidocarbonylation process herein, we report for the first time a general and efficient catalytic amidocarbonylation of all kinds of substituted benzaldehydes. The corresponding *N*-acyl-α-arylglycines are obtained in one step in good to excellent yields. The synthetic potential of the method is illustrated by the asymmetric synthesis of the characteristic amino acid derivative of chloropeptin: (*S*)-*N*-acetyl-3,5-dichloro-4-hydroxyphenylglycine.

Our initial attempts focused on the amidocarbonylation of benzaldehyde and 4-methoxybenzaldehyde with acetamide. In the presence of only 0.25 mol % $PdBr_2$, 0.5 mol % PPh_3 as catalyst system, and 30 mol % LiBr and 1 mol % H_2SO_4 as cocatalysts, the reaction proceeded smoothly in NMP as solvent to give (*R*,*S*)-*N*-acetyl-α-phenylglycine and (*R*,*S*)-*N*-acetyl-α-(4-methoxyphenyl)-glycine in 70% and 75% yields, respectively. These results encouraged us to use the palladium-catalyzed amidocarbonylation for a general synthesis of functionalized arylglycine derivatives. Table 1 summarizes the results obtained for the reaction of a variety of substituted benzaldehydes.

The characteristic features of the results are as follows: (1) the palladium-catalyzed amidocarbonylation of aromatic aldehydes takes place under much milder conditions (e.g., 80 °C, 60 bar CO) compared to the classical cobalt-catalyzed reaction[7] of even more reactive aliphatic aldehydes; (2) benzaldehydes bearing electron-donating or weakly electron-withdrawing substituents (entries 1−4) react more smoothly than those with strong electron-withdrawing groups[8] (entries 5−10); (3) nevertheless, deactivated benzaldehydes underwent success-

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(7) Amidocarbonylations of benzaldehydes with cobalt catalysts did not yield the desired *N*-acyl amino acid in any of our reference experiments. Beside the aldehydes only hydrogenated starting material could be detected in some cases.

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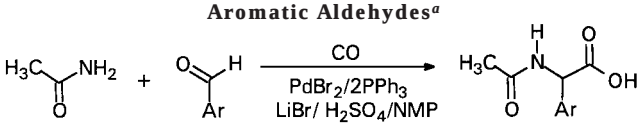
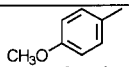
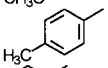
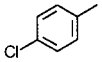
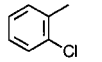
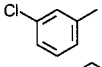
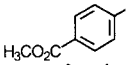
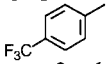
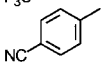
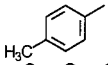
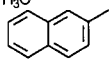
Table 1. Palladium-Catalyzed Amidocarbonylation of Aromatic Aldehydes[a]



		Ar	σ_p [b]	(100 °C, 12 h)[a,c] yield [%]	TON[f]	(120 °C, 15 h)[a,c] yield [%]	TON[f]
1	**1**		- 0.27	75	300	-	-
2	**2**		- 0.17	86	344	95	380
3	**3**		0.00	70	280	92	368
4	**4**		0.06	65	260	-	-
5	**5**		0.30	65	260	-	-
6	**6**		-	56	224	-	-
7	**7**		-	63	252	-	-
8	**8**		0.39	52	208	89	356
9	**9**		0.54	42	168	82	328
10	**10**		0.66	37	148	-	-
11	**2**[d]		- 0.17	-	-	70	280
12	**11**		-	76	304	-	-
13	**12**		-	-	-	42[e]	168

[a] Reactions using 25.0 mL of a 1 M NMP (*N*-methylpyrrolidone) solution of aldehyde and amide and 0.25 mol % $PdBr_2/2PPh_3$, 1 mol % H_2SO_4, and 35 mol % LiBr. [b] Hammett para substituent constants. [c] Isolated yield. [d] Reaction using 0.025 mol % $PdBr_2/2PPh_3$. [e] Reaction time 60 h. [f] TON = turnover number.

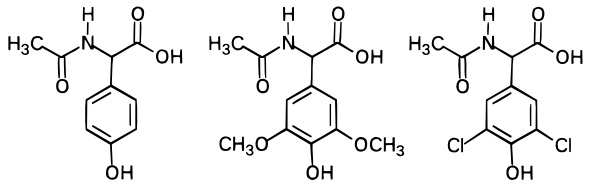
ful amidocarbonylation with excellent yields when the reaction temperature was slightly raised from 100 to 120 °C and the reaction time was prolonged; (4) in addition to para-substituted benzaldehydes, meta- and ortho-substituted benzaldehydes were amidocarbonylated in the presence of the palladium catalyst without a significant decrease in the yield (entries 5−7). Interestingly, heteroaromatic aldehydes such as 3-thiophenecarbaldehyde also gave access to the corresponding *N*-acetyl amino acid **12**, albeit at lower yield (42%).

The only byproducts observed in the amidocarbonylation of substituted benzaldehydes in significant amounts were the bisamides of the corresponding aldehydes. Usually these bisamides were easily filtered off from sodium bicarbonate solution.

It should be pointed out that most of the aforementioned reactions have not been optimized in detail. For some derivatives (Table 1, entries 2, 3, 8, and 9) we demonstrated that the rise of temperature and prolongation of reaction time increased the yield of desired products to a synthetically useful level. However, we believe that if someone has a particular interest in a special *N*-acyl arylglycine, it should be possible to further increase the yield by additional variations of the reaction parameters, especially temperature and CO pressure. To prove the catalyst efficiency we performed the amidocarbonylation of 4-tolylaldehyde with a reduced amount of palladium(II)bromide (0.01 mol %). Turnover numbers of 2800 and turnover frequency of 200 h^{-1} were obtained. Thus, we recommend for these type of amidocarbonylations a catalyst load of 0.05−0.25 mol % in order to get good yields.

The catalytic mechanism of the palladium-catalyzed amidocarbonylation has not yet been fully elucidated; however, it is clear that the addition of halide ions is prerequisite for catalysis. In contrast, even without acid as cocatalyst the reaction takes place, albeit in lower yield. The substrate profile of the benzaldehyde derivatives (see Table 1) shows a clear but not essential dependence of the electron properties of the substituents on reactivity and only a small influence on the position of substitution. In general, electron-rich aromatic aldehydes give better yields of the desired *N*-acyl amino acids. This is explained by a better stabilization of an intermediate benzylic cation. According to these preliminary mechanistic observations we propose the following mechanism: The reaction of acetamide and the aromatic aldehyde in the presence of the acid and halide ions as cocatalysts leads to several intermediates in equilibrium (α-hydroxyamides, bisamides), most importantly a benzylic α-haloamide. This benzylic α-haloamide undergoes an oxidative addition to a coordinatively unsaturated Pd(0) phosphine complex giving a palladium(II) alkyl species. Subsequent insertion of CO and hydrolysis lead to the *N*-acyl aryl amino acid.

To demonstrate the possibilities of the amidocarbonylation as a powerful tool for natural product synthesis, we turned our interest toward the synthesis of arylglycine residues **13**−**15** which constitute key amino acid building blocks found in pharmaceutically important natural products such as vancomycin, *β*-avoparcin, and chloropeptins. Among these active agents the recently isolated and characterized hexapeptide chloropeptin I, which selectively inhibits HIV replication in peripheral human lymphocytes,[9] is particularly important. The total synthesis of chloropeptin has not been reported, although a synthetic approach toward subunits was very recently disclosed.[10] Two of the three different arylglycine residues found in chloropeptin are 4-hydroxyphenylglycine (**13**) and 3,5-dichloro-4-hydroxyphenylglycine (**15**).



13 (90%) **14** (65%) **15** (73%)

13 was directly obtained by palladium-catalyzed amidocarbonylation in one step from inexpensive and readily available 4-hydroxybenzaldehyde in excellent yield (90%). 3,5-Dichloro-4-hydroxyphenylglycine (**15**) was prepared as follows: reduction of the commercially available ester

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(9) Gouda, H.; Matsuzaki, K.; Tanaka, H.; Hirono, S. *J. Am. Chem. Soc.* **1996**, *118*, 13087−13088.
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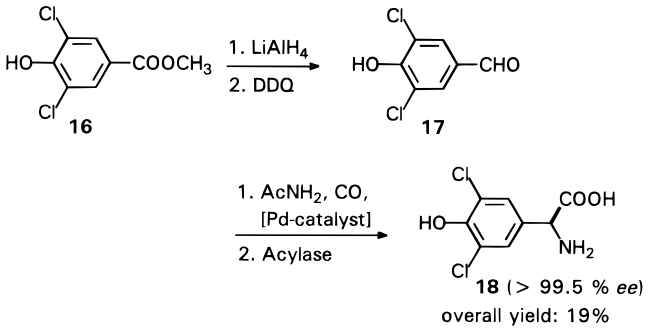
Scheme 1



16 with $LiAlH_4$ and selective oxidation with DDQ lead to 3,5-dichloro-4-hydroxybenzaldehyde (**17**) in almost quantitative yield (Scheme 1).[11] Palladium-catalyzed amidocarbonylation (yield 73%) and enzymatic resolution provided the chiral arylglycine **18** with >99.5% ee in 19% overall yield (and the (*R*)-enantiomer of **15** in >99.5% ee in 18% overall yield). To increase the yield of **18** it should be possible to racemize and additionally enzymatically hydrolyze the (*R*)-enantiomer of **15**.[6] The efficiency of the amidocarbonylation as a key step for complex aryl amino acid synthesis is demonstrated unambiguously if one compares the shown reaction sequence with the preparation of the related *N*-Boc-3,5-dichloro-4-methoxyphenylglycine. The synthesis of this latter compound was reported in five reaction steps starting from 3,5-dichloro-4-methoxybenzaldehyde![10]

Antibiotics such as vancomycin[12] and β-avoparcin[13] are characterized by a central arylglycine residue bearing a 3,5-dialkoxy-4-hydroxy substitution pattern on the aromatic ring. Thus, we prepared 3,5-dimethoxy-4-hydroxyphenylglycine (**14**) via amidocarbonylation of the commercially available 3,5-dimethoxy-4-hydroxybenzaldehyde. The reaction proceeded in good yield (65%). Initially the purification of the desired hydroxy-substituted *N*-acetyl aryl amino acids turned out to be more difficult. However, by applying longer reaction times (48 h) and in the case of **14** 2 equiv of aldehyde, minor amounts of bisamides were produced, which could be removed by recrystallization.

In conclusion, we have developed a general synthetic strategy for the preparation of *N*-acetylarylglycines based on the palladium-catalyzed amidocarbonylation. Utilizing the ubiquitous commercially available feedstock of benzaldehydes, this atom economic multicomponent reaction offers the most efficient straightforward route to various racemic arylglycines. In combination with enzymatic hydrolysis also enantiomerically pure arylglycines are available. The usefulness of the methodology for organic synthesis is demonstrated by the synthesis of naturally occurring arylglycines **13**−**15**, which constitute key structural components of important cyclopeptides.

Experimental Section

General. All high-pressure reactions were carried out with a 300-mL stirred reactor (no. 4561 from Parr Co.) with a magnet-driven propeller stirrer. Commercial reagents were used as received without additional purification. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded using solvent shifts for calibration. Melting points are uncorrected.

General Protocol. A 25.0-mL portion of a *N*-methylpyrrolidone (NMP) solution (1 M) in aldehyde and amide, 0.25 mol % $(PPh_3)_2PdBr_2$, 1 mol % H_2SO_4, and 35 mol % LiBr were allowed to react at 60 bar CO and 100 °C for 12 h. After the reaction mixture had cooled, the volatile components were removed in vacuo, and the residue was taken up in a saturated aqueous solution of sodium bicarbonate and then washed with chloroform and ethyl acetate. The aqueous phase was adjusted to pH 2 with phosphoric acid and extracted five times with ethyl acetate. The combined organic phases were dried over magnesium sulfate, and the solvent was removed in vacuo. The product was recrystallized from water/2-propanol mixtures or ethyl acetate.

(*R,S*)-*N*-Acetyl-α-(4-methoxyphenyl)glycine (1): mp 210 °C; ^{1}H NMR (DMSO-d_6) δ 12.7 (bs, 1H), 8.50 (d, J = 7.03 Hz, 1H), 7.30 (d, J = 8.53 Hz, 2H), 6.93 (d, J = 8.53 Hz, 2H), 5.24 (d, J = 7.53 Hz, 1H), 3.75 (s, 3H), 1.88 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 172.2, 169.0, 159.0, 129.3, 128.8, 113.9, 55.7, 55.2, 22.3; FT-IR (KBr) ν = 3341s, 1718s, 1600s, 1545s, 1514s; CI-MS m/z 224 (M + H$^+$). 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.

(*R,S*)-*N*-Acetyl-α-(4-tolyl)glycine (2): mp 230 °C; ^{1}H NMR (DMSO-d_6) δ 12.5 (bs, 1H), 8.35 (d, J = 7.53 Hz, 1H), 7.08 (d, J = 8.03 Hz, 2H), 6.98 (d, J = 8.03 Hz, 2H), 5.06 (d, J = 7.53 Hz, 1H), 2.10 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 172.3, 169.2, 137.3, 134.4, 129.1, 127.6, 124.3, 56.1, 22.4, 20.8; FT-IR (KBr) ν = 3338s, 1718s, 1601s, 1545s; CI-MS m/z 208 (M + H$^+$). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.66; H, 6.54; N, 6.79.

(*R,S*)-*N*-Acetyl-α-phenylglycine (3): mp 199 °C; ^{1}H NMR (DMSO-d_6) δ 12.6 (bs, 1H), 8.50 (d, J = 7.03 Hz, 1H), 7.30 (d, J = 8.53 Hz, 2H), 6.93 (d, J = 8.53 Hz, 2H), 5.24 (d, J = 7.53 Hz, 1H), 3.75 (s, 3H), 1.88 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 172.1, 169.2, 137.4, 128.7, 128.0, 127.6, 56.4, 22.4; FT-IR (KBr) ν = 3342s, 1716s, 1669s, 1604s, 1540s; CI-MS m/z 194 (M + H$^+$). Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.45; H, 5.99; N, 7.30.

(*R,S*)-*N*-Acetyl-α-(4-fluorophenyl)glycine (4): mp 188 °C; ^{1}H NMR (DMSO-d_6) δ 12.8 (bs, 1H), 8.59 (d, J = 7.03 Hz, 1H), 7.41 (dd, J = 8.53, 5.52 Hz, 2H), 7.19 (m, 2H), 5.32 (d, J = 7.53 Hz, 1H), 1.88 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 171.8, 169.0, 160.5, 133.7, 129.7, 115.2, 55.5, 22.2; FT-IR (KBr) ν = 3341s, 1724s, 1616s, 1542s, 1512s; CI-MS m/z 212 (M + H$^+$). 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.

(*R,S*)-*N*-Acetyl-α-(4-chlorophenyl)glycine (5): mp 196 °C; ^{1}H NMR (DMSO-d_6) δ 12.9 (bs, 1H), 8.70 (d, J = 7.53 Hz, 1H), 7.42 (m, 4H), 5.33 (d, J = 7.53 Hz, 1H), 1.90 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 171.5, 169.3, 135.5, 133.2, 129.8, 129.6, 129.2, 127.6, 53.2, 22.3; FT-IR (KBr) ν = 3339s, 1717s, 1602s, 1541s; CI-MS m/z 227/229 (M + H$^+$). 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.

(*R,S*)-*N*-Acetyl-α-(2-chlorophenyl)glycine (6): mp 160 °C; ^{1}H NMR (DMSO-d_6) δ 12.6 (bs, 1H), 8.69 (d, J = 7.53 Hz, 1H), 7.3−7.5 (m, 4H), 5.76 (d, J = 8.03 Hz, 2H), 1.88 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 171.4, 169.2, 135.5, 133.1 129.8, 129.6, 129.2, 127.6, 53.2, 22.3; FT-IR (KBr) ν = 3359s, 1717s, 1609s, 1538s; CI-MS m/z 227/229 (M + H$^+$). Anal. Calcd for $C_{10}H_{10}ClNO_3$: C, 52.76; H, 4.43; N, 6.15. Found: C, 53.02; H, 4.51; N, 6.18.

(*R,S*)-*N*-Acetyl-α-(3-chlorophenyl)glycine (7): mp 169 °C; ^{1}H NMR (DMSO-d_6) δ 12.6 (bs, 1H), 8.70 (d, J = 6.53 Hz, 1H), 7.4 (m, 4H), 5.39 (d, J = 7.03 Hz, 1H), 1.89 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 171.6, 169.3, 139.9, 133.2, 130.5, 128.0, 127.5, 126.6, 55.8, 22.4; FT-IR (KBr) ν = 3348s, 1719s, 1607s, 1534s; CI-MS m/z 227/229 (M + H$^+$). Anal. Calcd for $C_{10}H_{10}ClNO_3$: C, 52.76; H, 4.43; N, 6.15. Found: C, 52. 92; H, 4.15; N, 6.30.

(*R,S*)-*N*-Acetyl-α-(4-(methoxycarbonyl)phenyl)glycine (8): mp 227 °C; ^{1}H NMR (DMSO-d_6) δ 12.8 (bs, 1H), 8.73 (d, J = 7.53 Hz, 1H), 7.95 (d, J = 8.53 Hz, 2H), 7.55 (d, J = 8.03 Hz, 2H), 5.44 (d, J = 7.53 Hz, 1H), 3.83 (s, 3H), 1.90 (s, 3H); ^{13}C

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NMR (DMSO-d_6) δ 171.7, 169.3, 166.1, 143.0, 129.6, 129.4, 128.0, 56.2, 52.3, 22.4; FT-IR (KBr) ν = 3338s, 1727s, 1610m, 1545s; CI-MS m/z 252 (M + H$^+$). Anal. Calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.46; H 5.31; N, 5.56.

(*R,S*)-*N*-Acetyl-α-(4-(trifluoromethyl)phenyl)glycine (9): mp 211 °C; ^{1}H NMR (DMSO-d_6) δ 12.7 (bs, 1H), 8.78 (d, J = 7.53 Hz, 1H), 7.75 (d, J = 8.03 Hz, 2H), 7.60 (d, J = 8.03 Hz, 2H), 5.49 (d, J = 7.53 Hz, 1H), 1.88 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 171.5, 169.3, 142.3, 128.8, 125.5, 56.0, 22.4; FT-IR (KBr) ν = 3358s, 1725s, 1600s, 1539s; CI-MS m/z 262 (M + H$^+$). Anal. Calcd for $C_{11}H_{10}F_3NO_3$: C, 50.58; H, 3.86; N, 5.36. Found: C, 50.96; H, 4.08; N, 5.35.

(*R,S*)-*N*-Acetyl-α-(4-cyanophenyl)glycine (10): mp 232 °C; ^{1}H NMR (DMSO-d_6) δ 12.8 (bs, 1H), 8.79 (d, J = 8.03 Hz, 1H), 7.85 (d, J = 8.03 Hz, 2H), 7.59 (d, J = 8.03 Hz, 2H), 5.49 (d, J = 7.53 Hz, 1H), 1.91 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 171.3, 169.4, 143.2, 132.5, 128.7, 118.8, 110.8, 56.1, 22.4; FT-IR (KBr) ν = 3329s, 2234s, 1729s, 1616s, 1533s; CI-MS m/z 219 (M + H$^+$). Anal. Calcd for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.08; H, 4.33; N, 12.70.

(*R,S*)-*N*-Acetyl-α-(*β*-naphthyl)glycine (11): mp 208 °C; ^{1}H NMR (DMSO-d_6) δ 12.6 (bs, 1H), 8.80 (d, J = 7.53 Hz, 1H), 8.0 (m, 4H), 7.6 (m, 3H), 5.58 (d, J = 7.53 Hz, 1H), 1.95 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 172.1, 169.2, 135.1, 132.7, 132.5, 128.2, 127.9, 127.6, 126.5, 126.4, 56.6, 22.4; FT-IR (KBr) ν = 3394s, 1734s, 1617s, 1534s; CI-MS m/z 244 (M + H$^+$). Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.25; H, 5.48; N, 5.70.

(*R,S*)-*N*-Acetyl-α-(3-thiopheneyl)glycine (12): departing from general protocol, the reaction was allowed to react for 60 h; mp 190 °C; ^{1}H NMR (DMSO-d_6) δ 12.8 (bs, 1H), 8.61 (d, J = 7.53 Hz, 1H), 7.52 (m, 1H), 7.48 (m, 1H), 7.12 (d, J = 5.02 Hz, 1H), 5.43 (d, J = 7.53 Hz, 1H), 1.88 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 172.0, 169.3, 137.3, 127.3, 126.7, 123.5, 52.3, 22.4; FT-IR (KBr) ν = 3339s, 1717s, 1652s, 1602s, 1538s; CI-MS m/z 200 (M + H$^+$). Anal. Calcd for $C_8H_9NO_3S$: C, 48.23; H, 4.55; N, 7.03. Found: C, 48.00; H, 4.80; N, 6.93.

(*R,S*)-*N*-Acetyl-α-(4-hydroxyphenyl)glycine (13): departing from general protocol, the reaction was allowed to react for 48 h; mp 199 °C; ^{1}H NMR (DMSO-d_6) δ 12.6 (bs, 1H), 9.48 (bs, 1H), 8.44 (d, J = 7.53 Hz, 1H), 7.17 (d, J = 8.53 Hz, 2H), 6.75 (d, J = 8.53 Hz, 2H), 5.16 (d, J = 7.03 Hz, 1H), 1.90 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 172.5, 169.1, 157.3, 129.0, 127.4, 115.3, 55.9, 22.3; FT-IR (KBr) ν = 3342s, 1716s, 1669s, 1604s, 1540s; CI-MS m/z 210 (M + H$^+$). Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.15; H, 5.62; N, 6.55.

(*R,S*)-*N*-Acetyl-α-(3,5-dimethoxy-4-hydroxyphenyl)glycine (14): departing from general protocol, the reaction was allowed to react for 48 h and 2 equiv of aldehyde was used; mp > 240 °C; ^{1}H NMR (DMSO-d_6) δ 12.6 (bs, 1H), 8.46 (d, J = 7.53 Hz, 1H), 8.45 (s, 1H), 6.66 (s, 2H), 5.16 (d, J = 7.03 Hz, 1H), 3.76 (s, 6H), 1.89 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 172.4, 169.1, 147.9, 135.5, 126.8, 105.5, 56.2, 56.1, 22.4; FT-IR (KBr) ν = 3373s, 1729s, 1616s, 1569s, 1520s, 1216s; CI-MS m/z 270 (M + H$^+$). Anal. Calcd for $C_{12}H_{15}NO_6$: C, 53.53; H, 5.62; N, 5.20. Found: C, 54.00; H, 5.75; N, 5.23.

(*R,S*)-*N*-Acetyl-α-(3,5-dichloro-4-hydroxyphenyl)glycine (15): departing from general protocol, the reaction was allowed to react for 48 h; mp 232 °C; ^{1}H NMR (DMSO-d_6) δ 12.9 (bs, 1H), 10.24 (bs, 1H), 8.57 (d, J = 7.53 Hz, 1H), 7.35 (s, 2H), 5.23 (d, J = 7.53 Hz, 1H), 1.86 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 171.6, 169.2, 148.9, 130.3, 127.9, 122.2, 54.9, 22.4; FT-IR (KBr) ν = 3356s, 1717s, 1622m, 1559s, 1490m, 1419m; CI-MS m/z 279 (M + H$^+$). Anal. Calcd for $C_{10}H_9Cl_2NO_4$: C, 43.19; H, 3.26; N, 5.04. Found: C, 42.91; H, 3.35; N, 5.30.

3,5-Dichloro-4-hydroxybenzaldehyde (17). A 1.4-g (38 mmol) portion of lithium aluminum hydride in a 250-mL three-necked flask equipped with a reflux condenser and a dropping funnel was suspended in 100 mL of dry THF under nitrogen atmosphere. As the mixture stirred vigorously a solution of 6.0 g (25 mmol) of methyl 3,5-dichloro-4-hydroxybenzoate hydrate (**16**) (Aldrich, #38,909-9) in 50 mL of dry THF was added dropwise, and the suspension was heated under reflux for 12 h. After the mixture cooled to room temperature water was added dropwise till hydrogen formation stopped; then aqueous sulfuric acid (10%) was added to dissolve the precipitation. Extraction with ether, combining the organic layers, drying over sodium sulfate, and removing the solvent yielded 4.6 g (24 mmol) of 3,5-dichloro-4-hydroxybenzyl alcohol: mp 86 °C; ^{1}H NMR (DMSO-d_6) δ 9.95 (s, 1H), 7.29 (s, 2H), 5.24 (t, J = 5.52 Hz, 1H), 4.48 (d, J = 5.52 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 147.6, 135.8, 126.6, 122.1, 61.5; FT-IR (KBr) ν = 3332s, 2959m, 2928m, 2871m, 2606m, 2468m, 1700s, 1623s, 1559s, 1448m, 1439m; CI-MS m/z 194 (M + H$^+$). 3,5-Dichloro-4-hydroxybenzyl alcohol (4.6 g, 24 mmol) was dissolved in 150 mL of dioxane, and 5.5 g (24 mmol) of DDQ was added to this solution. The reaction mixture was stirred for 12 h at room temperature, then the solvent was removed, and the precipitation was dissolved in 150 mL of methylene chloride. After filtration the solution was dried over $MgSO_4$, and the solvent was removed. Recrystallization from ethyl acetate yielded 4.4 g (23 mmol) of **17**: mp 157 °C; ^{1}H NMR (DMSO-d_6) δ 9.95 (s, 1H), 7.29 (s, 2H), 5.24 (t, J = 5.52 Hz, 1H), 4.48 (d, J = 5.52 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 147.6, 135.8, 126.6, 122.1, 61.5; FT-IR (KBr) ν = 3355s, 2966m, 2928m, 1700s, 1557s, 1448m, 1375m; CI-MS m/z 191 (M + H$^+$).

(*S*)-α-(3,5-Dichloro-4-hydroxyphenyl)glycine (18). (*R,S*)-*N*-Acetyl-3,5-dichloro-4-hydroxyphenylglycine (0.89 g, 3.2 mmol) was dissolved at 20−25 °C in a mechanically stirred solution of NaOH pellets (0.25 g, 6.25 mmol) in water (20 mL). After addition of $CoCl_2 \cdot 6H_2O$ (1.7 mg, 0.007 mmol) the clear solution was adjusted to pH 7.9 with hydrochloric acid (2 N) and heated to 37−40 °C. Acylase from *Aspergillus sp.* (30 mg of Amano 30.000, 30 U/mg) was added, and the reaction mixture was stirred at 37−40 °C for 94 h (pH was controlled periodically and kept at ∼7.9 with 1 N NaOH). The resulting reaction mixture was stirred for 1 h at 0−5 °C, but no precipitation occurred. The reaction mixture was concentrated under reduced pressure to 10 mL, 2−5 mL of ethanol was added, and the reaction mixture was concentrated under reduced pressure to 5−10 mL. Filtration of the precipitate under suction and drying in vacuo afforded 0.2 g (26.5%) of the desired (*S*)-3,5-dichloro-4hydroxyphenylyglycine: mp 204 °C dec; $[\alpha]_D^{20}$ +104 (c = 1, 1 N HCl); >99.5% ee (HPLC on Crownpak CR (+) 15 cm × 0.4 cm (Daicel Chemical Industries), monitoring at 205/280 nm, eluting with 0.016 M $HClO_4$, pH = 2.06; flow rate 1 mL/min; 40 °C); ^{1}H NMR (300 MHz, TFA) δ 5.4 (s, 1H), 7.52 (s, 2H), 11.5 (s, 1H); MS (ESI) m/z (%) 235.9 (M + H$^+$, 100).

The remaining solution was acidified to pH ∼ 1.5 with concentrated hydrochloric acid and extracted with ethyl acetate. The combined extracts were dried with $MgSO_4$ and concentrated in vacuo. Trituration with *tert*-butyl methyl ether and drying afforded 0.223 g (25%) of (*R*)-*N*-acetyl-3,5-dichloro-4-hydroxyphenylyglycine as an off-white solid: mp 234 °C dec; $[\alpha]_D^{20}$ −28° (c = 1, MeOH); >99.5% ee (HPLC on (*S,S*)-Whelk-O 1 (E. Merck, Darmstadt), monitoring at 225/215 nm, eluting with hexane/ethanol, 4/1, + 0.1% HOAc; flow rate 1 mL/min; 25 °C); MS (ESI) m/z (%) 278.0 (M + H$^+$, 100); ^{1}H NMR data were in agreement with data from (*R,S*)-*N*-acetyl-3,5-dichloro-4-hydroxyphenylglycine.

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