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A New Improved Palladium-Catalyzed Amidocarbonylation

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Abstract: A new and improved variant of the palladium-catalyzed amidocarbonylation[1)] to yield *N*-acyl-α-amino acids is described. Using Pd/C as catalyst the products were prepared in good to excellent yields (up to 98 %). Advantages of the Pd/C-catalyst with regard to former catalyst systems are demonstrated by the preparation of *N*-substituted non-natural amino acids which are of current interest as structural units of peptoids.

Enantiomerically pure *N*-acyl α-amino acids are of enormous interest to organic chemistry and biology owning to their function as components in proteins and peptides.[2)] Moreover, this class of compounds is used as food additives, pharmaceuticals, agrochemicals, even as fine chemicals such as chelating agents and specialty detergents.[3)] Although the synthesis of *N*-acyl α-amino acids has been a field of intensive research for years, the need for environmentally friendly and economically reasonable protocols for the preparation of many important non-natural amino acids remains. In general, recently developed elegant laboratory scale preparations are economically not attractive, while large scale processes, which use the combination of Strecker reaction and subsequent acylation, produce overstoichiometric amounts of salt by-products. Within our interest on catalytic reactions with potential industrial application, we developed the homogenous palladium-catalyzed amidocarbonylation[4)] as an attractive one step procedure for the synthesis of *N*-acyl α-amino acids from aldehydes, amides and CO.[5)] In order to make this method more useful for practical purposes, it is desirable to simplify recycling of the catalyst and purification of the product. In this paper we like to report for the first time a simplified version of the palladium-catalyzed amidocarbonylation, which proceeds efficiently with Pd/C in the absence of phosphine ligands. Moreover, we demonstrate the superiority of the Pd/C catalyst system in the synthesis of *N*-substituted non-natural amino acids which are of current interest as structural units of peptoids.[6)]

During a study on the up-scaling of the synthesis of *(R,S)*-*N*-acetyl-α-cyclohexylglycine, which is of actual importance as building block in new pharmaceuticals, an efficient recycling of the palladium catalyst and an easy purification of the product was needed. Therefore we became interested on the use of Pd/C as catalyst for amidocarbonylation reactions. Preliminary studies were performed with 1.0 mol% Pd/C and 35 mol% LiBr in the absence of phosphine ligands in *N*-methylpyrrolidone (NMP). Indeed, the reaction proceeds smoothly to give (R,S)-*N*-acetyl-α-cyclohexylglycine in 98% yield (Table 1, entry 1)!

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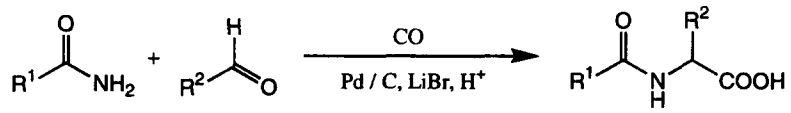
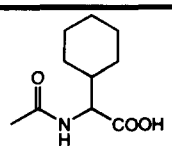
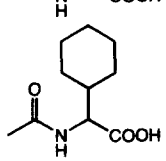
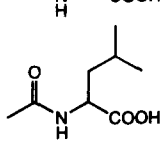
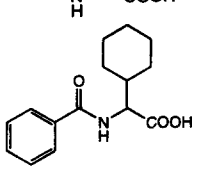
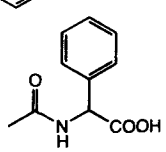
Table 1: Palladium-catalyzed amidocarbonylation with Pd/C as catalyst[a]



Entry	Product	Catalyst [mol-%]	Temp. [°C]	Yield [%] [b]	TON
1		1.0	120	98	98
2[c]		1.0	120	97	97
3		1.0	100	75	75
4[d]		1.0	120	70	70
5		1.0	120	74	74

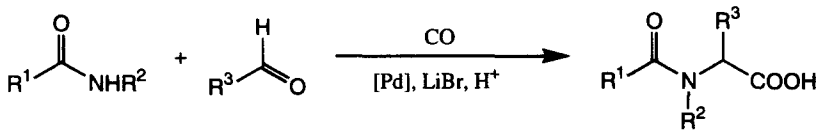
[a] Aldehyde and amide (25.0 ml each of 1 M solution in *N*-methylpyrrolidone), 1.0 mol% Pd / C, 1 mol% H_2SO_4 and 35 mol% LiBr were treated with 60 CO at 100 or 120 °C for 12 h. [b] Yield of isolated product. [c] Acetonitrile as solvent and 35 mol% Bu_4NBr instead of LiBr. [d] Benzonitrile [9].

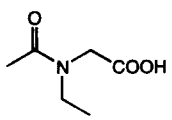
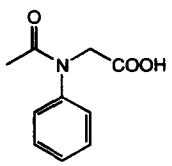
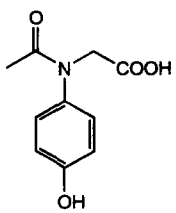
Apart from NMP, acetonitrile turned out to be suitable as solvent for the Pd/C-catalyzed amidocarbonylation (Table 1, entry 2). Regarding industrial applications acetonitrile as solvent is of special interest due to the fact that after hot filtration of the catalyst, the product crystallizes almost quantitatively from this solvent at room temperature. After recrystallization from ethyl acetate, the product was isolated in 97% yield (> 99% purity). This procedure enables an extremely easy up-scaling.

Apart from amides, inexpensive starting compounds like nitriles can also be used for the one pot synthesis of amino acids[7] with Pd/C. Here, the hydrolysis of benzonitrile with one equivalent sulfuric acid and water and subsequent amidocarbonylation with cyclohexancarbaldehyde generates *N*-benzoyl-cyclohexylglycine in 70 % yield (Table 1, entry 4). Arylglycines are of actual interest in organic and medicinal because of their antimicrobial and enzyme inhibitory properties.[8] Hence, it is interesting to note that *N*-acetyl-

phenylglycine is obtained in one step in 74% yield (Table 1, entry 5). To evaluate further advantages of the heterogeneous catalyst compared to the PdX_2/PR_3 catalyst precursor, a series of *N*-substituted amides was reacted with paraformaldehyde (Table 2, entry 1-8). The resulting products are of general interest as building blocks for peptoids.[6] A summary of the catalytic reactions is given in Table 2.[9]

Table 2: Amidocarbonylation of *N*-substituted amides[a]



Entry	Product	Catalyst	Temp. [°C]	Yield [%] [b]	TON
1		$PdBr_2$ / 2 PPh_3	130	27	54
2		Pd / C	130	78	156
3		$PdBr_2$ / 2 PPh_3	130	45	90
4		Pd / C	130	65	130
5		$PdBr_2$ / 2 PPh_3	120	55	110
6		Pd / C	120	72	144

[a] Paraformaldehyde and amide (25.0 ml each of 1 M solution in N-methylpyrrolidone), 0.50 mol% catalyst, 1 mol% H_2SO_4 and 35 mol% LiBr were treated with 60 CO at 120 or 130 °C for 60 h. [b] Yield of isolated product.

After optimization, it turned out that *N*-substituted-glycines were obtained in good yields at slightly higher reaction temperatures. The synthetic potential of the method is illustrated by the synthesis of *N*-ethyl, *N*-phenyl and *N*-aryl-substituted glycines. Here, especially interesting is the efficient amidocarbonylation of the anti-inflammatory drug 4-*N*-acetylaminophenol (paracetamol®) to *N*-acetyl-*N*-4-hydroxyphenylglycine (72%). In all cases the yield of the desired *N*-acyl-*N*-substituted amino acid was higher with Pd/C than with $PdBr_2$/2 PPh_3. We explain the superiority of Pd/C catalyst due to an easier deactivation of the $PdBr_2$/2 PPh_3 catalyst system at 120 – 130 °C compared to Pd/C.

In conclusion, we have developed an extremely easy to perform Pd/C-catalyzed amidocarbonylation. As demonstrated by the synthesis of several *N*-acetyl amino acids, the advantages of Pd/C as catalyst are: a)

simple product purification, b) no need of adding phosphine ligands, c) easy catalyst recycling, and d) thermally more robust catalyst system. Moreover, we have shown that selected *N*-substituted glycines can be synthesized in higher yields than with $PdBr_2$/2 PPh_3. In addition, this catalyst system is particularly attractive in combination with acetonitrile as solvent for industrial application.

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References and Notes

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9. **General procedure for amidocarbonylation:**
   25.0 ml of a 1-M solution of aldehyde and amide in NMP, 0.50 mol% catalyst, 1 mol% H_2SO_4, and 35 mol% LiBr were allowed to react under 60 bar CO at 120 °C for 60 h. The volatile components were removed in-vacuo, and the residuce was taken up in a saturated aqueous solution of $NaHCO_3$. After washing 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 in-vacuo. The product was recrystallized from a suitable solvent mixture. All isolated compounds were characterized by NMR, IR and mass spectroscopy. The purity of the products, as measured by HPLC, was > 99 %.
   N-Acetyl-*N*-(4-hydroxyphenyl)glycine: ^{1}H NMR (400 MHz, 25 °C, DMSO-d_6): δ = 12.5 (bs, 1H, COO*H*), 9.64 (bs, 1H, O*H*), 7.15 (d, *J*(H,H) = 8.7 Hz, 2H, *H*-aromat.), 6.77 (d, *J*(H,H) = 8.7 Hz, 2H, *H*-aromat.), 4.15 (s, 2H, CH_2), 1.75 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (100 MHz, 25 °C, DMSO-d_6): δ = 170.7 (*C*OOH), 169.9 (*C*O), 156.8, 134.7, 128.8, 115.9, 50.9 (CH_2), 21.8 ($COCH_3$); IR (KBr): ν[cm^{-1}] = 3367 m, 2943 w, 1767 w, 1745 s, 1614 s, 1578 s, 1509 s; MS (CI, 70 eV): *m/z* = 210 [M+H$^+$], 168, 151, 100, melting point: 195 °C.