Synthesis of *N*-Acetyl-α-aminobutyric Acid *via* Amidocarbonylation: A Case Study

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Abstract: The synthesis of *N*-acetyl-α-aminobutyric acid by amidocarbonylation of propionaldehyde with acetamide in the presence of palladium catalysts is studied in detail. The influence of various reaction conditions and compositions (e.g., the co-catalysts acid and bromide) on the yield of *N*-acetyl-α-aminobutyric acid is shown. For the first time it is demonstrated that the palladium-catalyzed amidocarbonylations of aldehydes can be run with significantly lower halide concentrations (<30 mol %) without a major yield decrease. While phosphine-free catalyst systems give best yields at low CO pressure, phosphine-ligated palladium catalysts lead to better yields at higher CO pressure. At low palladium loadings (<0.1 mol %), unwanted condensation reactions of propionaldehyde become increasingly competitive.

Keywords: *N*-acetyl-α-aminobutyric acid; amidocarbonylation; amino acids; catalysis; palladium

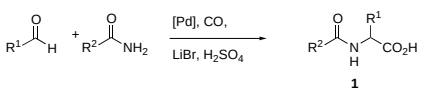
Introduction

The synthesis of *N*-acyl-α-amino acids has aroused continuous attention because of their exceptional biochemical importance as integral part of peptides and proteins.[1] In addition, *N*-acyl-α-amino acids constitute interesting building blocks for organic synthesis and are of commercial importance as industrial fine chemicals.[2] A wide spectrum of industrial applications of *N*-acyl-α-amino acids is based on their biological activity as small-molecule drugs. Here, captopril, a hypotensive proline derivative,[3] and *N*-acetylcysteine, an active mucolytic agent,[4] are two of the most prominent examples.

The paramount importance of various *N*-acylamino acids has attracted considerable interest in industrial-scale productions. Apart from fermentation of natural amino acids and subsequent acylation, a large number of elegant synthetic routes to non-natural amino acids have been developed in recent decades.[5] However, most of these reactions are not suited for an economic multi-kg preparation. Still, the classical Strecker and Bucherer–Bergs reactions in combination with subsequent hydrolysis are the benchmarks for the industrial synthesis of non-natural amino acids. The sequence of Strecker reaction and subsequent acylation is established on large scale by Tanabe and Degussa.[6] From a standpoint of sustainability, this three-step synthesis (Strecker, hydrolysis, acylation), which generates stoichiometric amounts of salts, requires a great deal of improvement.

A promising direct ("one-pot") route to racemic *N*-acyl-α-amino acids **1** is the so-called amidocarbonylation reaction, which comprises the reaction of an aldehyde, an amide, and carbon monoxide in the presence of cobalt or palladium catalysts (Scheme 1).[7] In view of modern economic and environmental concerns, the remarkable features of the amidocarbonylation are 100% atom efficiency and the utilization of ubiquitous and cheap starting materials.

The amidocarbonylation reaction was accidentally discovered by H. Wakamatsu at Ajinomoto Co. in 1970 while studying the oxo process of acrylonitrile with $Co_2(CO)_8$ as catalyst.[8] Some time ago, we developed highly efficient palladium catalyst systems for this reaction. Stimulated by a few initial experiments of Jägers,[9] we demonstrated for the first time that aliphatic and aromatic aldehydes smoothly react with various amides and CO in the presence of palladium/phosphine catalysts and acid co-catalyst to give a variety



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Scheme 1. Pd-catalyzed amidocarbonylation of aldehydes with amides.

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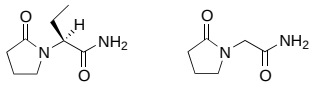


3 **4**

Figure 1. (−)-(*S*)-α-Ethyl-2-oxo-1-pyrrolidine-acetamide (Levetiracetam®) (**3**) and the structurally related Piracetam® (**4**).

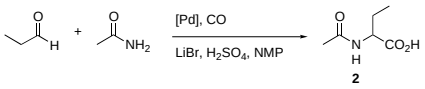
Figure 2. Six-fold parallel autoclave with aluminum insert and glass reaction tubes.

of *N*-acyl-α-amino acids.[10] In addition to carboxamides, ureas were also shown to undergo a similar reaction (ureidocarbonylation) to give the corresponding hydantoins.[11]

More recently, we became interested in the synthesis of *N*-acetyl-α-aminobutyric acid (**2**) which is used as an ingredient in skin disease drugs.[12] The amidocarbonylation of propionaldehyde and acetamide clearly represents the economically most attractive route to this target molecule with special regard to raw material costs and number of reaction steps. Apart from *N*-acetyl-α-aminobutyric acid (**2**) , the deacylated amino acid itself is even more important as it is a component of some proteins, albeit in extremely small amounts. The most significant pharmaceutical application for α-aminobutyric acid is the use for the preparation of Levetiracetam® (**3**) (Figure 1).[13]

Levetiracetam® (**3**) is a relatively new anti-epileptic drug,[14]] which was released in November 2000 and is structurally related to well-known Piracetam® (**4**).[15]

In this paper, we present an in-depth study of the palladium-catalyzed amidocarbonylation of propionaldehyde which is of general interest for the production of α-aminobutyric acid derivatives. We examined the influence of wide variations of the reaction conditions and compositions on the outcome of the amidocarbonylation of propionaldehyde with acetamide and CO. In order to cut down time- and cost-extensive solitary



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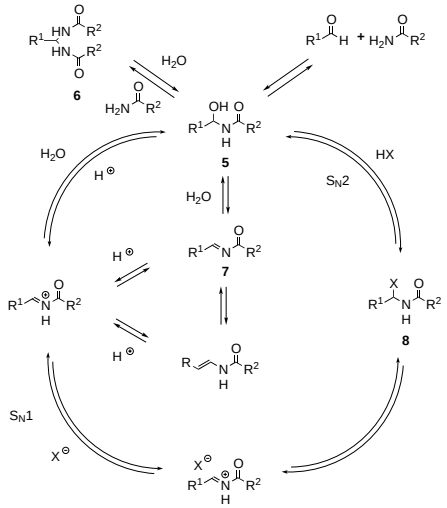
Scheme 2. Pd-catalyzed amidocarbonylation of propionaldehyde with acetamide.



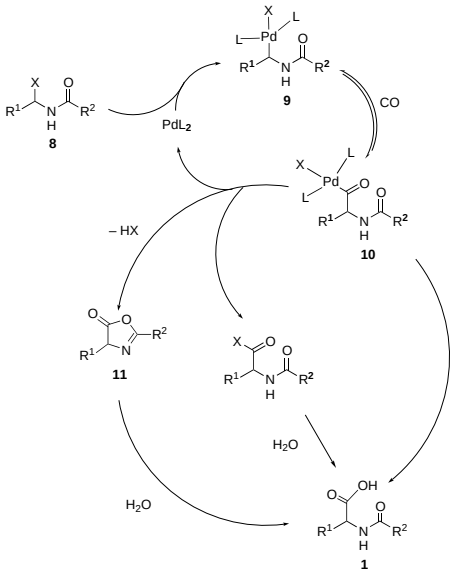
Scheme 3. Proposed pre-equilibria for the Pd-catalyzed amidocarbonylation.

reaction set-ups, we performed most of the reactions in a parallel manner to ensure identical reaction conditions and generally enhance the throughput (Figure 2).[16]

Results and Discussion

Initial experiments (Scheme 2) were run under the conditions previously optimized for other aliphatic aldehydes. Due to the increased reactivity of propionaldehyde in unwanted aldol reactions, a larger excess of the aldehyde (200 mol %) was used compared to the standard amidocarbonylation conditions (100 mol %).[17]

The proposed mechanism of the underlying domino condensation-carbonylation-hydrolysis sequence is shown in Schemes 3 and 4. Aldehyde and amide combine to give *N*-(α-hydroxyalkyl)amide **5**, which is in equilibrium with other condensation products, such as 1,1-bisamide **6**, *N*-acylimine **7**, and *N*-acylenamine species. In the presence of catalytic bromide ions, a small amount of the *N*-(α-bromoalkyl)amide **8** is formed. We assume that a catalytically active Pd(0) species, which arises from the employed Pd(II) precursor under the predominantly reductive reaction conditions (CO, aldehyde, phosphine), subsequently inserts into the alkyl C-Br bond *via* oxidative addition (Scheme 4). Similar palladium-catalyzed activation processes of alkyl bromides and chlorides have been recently reported by Knochel,[18] Fu,[19] and us.[20]



Scheme 4. Proposed mechanism for the palladium-catalyzed carbonylation.

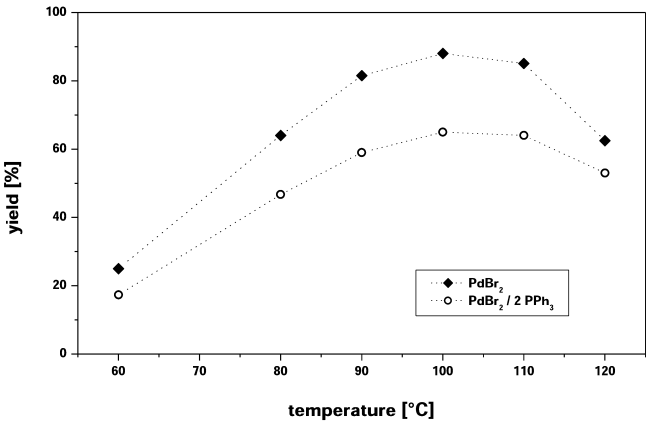


Figure 3. Influence of temperature: reactions were run for 12 h at 60 bar CO pressure using 50 mL NMP (1 M in acetamide and 2 M in propionaldehyde), 0.25 mol % catalyst, 35 mol % LiBr, 1.5 mol % H_2SO_4.

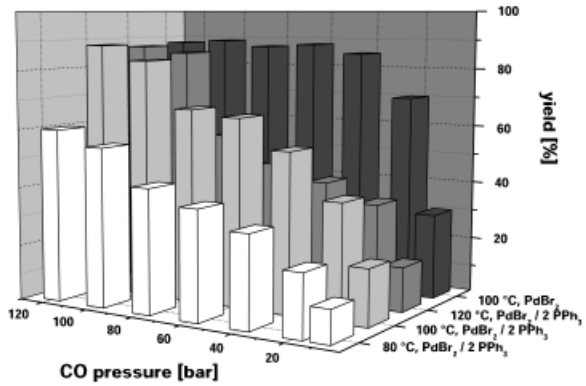


Figure 4. Influence of temperature and pressure: reactions were run for 12 h at 60 bar CO pressure using 50 mL NMP (1 M in acetamide and 2 M in propionaldehyde) and 0.25 mol % catalyst, 35 mol % LiBr, 1.5 mol % H_2SO_4.

The resultant palladium(II) alkyl complex **9** is transformed to the corresponding acyl complex **10** by intramolecular CO insertion. Upon hydrolytic cleavage, the desired *N*-acetyl-α-amino acid is released and the catalytically active Pd(0) species is recycled. Although the intermolecular attack by water might be the most likely cleavage pathway, the intermediacy of an oxazolone **11** cannot be excluded.

Initially, the influence of the crucial reaction parameters pressure and temperature using $PdBr_2/PPh_3$ and $PdBr_2$ as catalyst systems was studied in our test reaction. Under the standard conditions, the phosphine-free catalyst generally gave higher yields of *N*-acetyl-α-aminobutyric acid than the phosphine-ligated catalyst system (Figure 3). This demonstrates that phosphine ligands mainly have a stabilizing effect on the metal complex in this reaction but do not increase the activity. Amidocarbonylation reactions are usually associated with temperatures above 60 °C. At lower temperatures, the predominant formation of 1,1-bisamidopropane **12** and other unwanted aldol condensation products was observed. So far, the best results (>80%) were obtained at 100 °C in the presence of $PdBr_2$. At temperatures >120 °C, a significant decrease in the product yield was observed, mostly due to the rapid consumption of propionaldehyde in aldol reactions.

Studies of the influence of the CO pressure on the palladium-catalyzed amidocarbonylation of aldehydes have largely been neglected in the past. Generally, reactions were performed at (somewhat arbitrary) 60 bar CO pressure. In order to provide a concise study, the test system propionaldehyde/acetamide was subjected to wide variations of the CO pressure (10–120 bar, Figure 4). Reactions with the phosphine-free reference system ($PdBr_2$) were studied at 100 °C, whereas reactions with the $PdBr_2/PPh_3$ system were performed at 80, 100, and 120 °C. Surprisingly, the CO pressure revealed a major influence on the overall yield. As shown in Figure 4, only low yields (10–30%) were detected at 20 bar. With $PdBr_2$ as catalyst, the reaction proved rather independent of the applied pressure above 40 bar. However, in the presence of triphenylphosphine, the yield increased as the CO pressure was increased. Especially at elevated temperatures (100 and 120 °C), an increased CO pressure (80–120 bar) was observed to have a remarkably enhancing effect on the yield. Apparently, high-pressure conditions are needed to ensure rapid CO insertion in the presence of PPh_3 ligand. Hence, one could conclude that CO and the phosphine act as competing ligands. While the former drives the product formation, the latter somewhat inhibits product formation but is likely to exhibit a stabilizing effect on the active Pd(0) species.

The importance of bromide ions as co-catalysts has been shown in previous studies (Schemes 3 and 4). Standard palladium-catalyzed amidocarbonylation pro-

cedures used typically 35 mol % LiBr as halide source. Bromide salts constitute major byproducts of the reaction and are desirable to be reduced. Unfortunately, it has been shown earlier that the yield of the amino acid is significantly decreased at lower halide concentrations.[21] Apart from the halide co-catalyst, the presence of a Brønsted acid (e.g., H_2SO_4) has an enhancing effect on the palladium-catalyzed amidocarbonylation of aldehydes. Standard procedures utilized 1 mol % H_2SO_4, though no detailed investigations on the optimal composition have been performed so far. In order to carefully analyze the solitary effects of both co-catalysts, the employed concentrations of LiBr and H_2SO_4 were varied independently (Figures 5 and 6). As potential synergistic effects of both co-catalysts have been largely neglected in the past, they were also subject of our investigations. We especially aimed at lowering the required bromide concentration by fine tuning the employed H^+ concentration.

A study of the influence of the bromide concentration on the yield of *N*-acetyl-α-aminobutyric acid (**2**) demonstrated the superiority of the phosphine-ligated catalyst system over the phosphine-free catalyst at low bromide concentrations. For the first time, the palladium-catalyzed amidocarbonylation gave high product yields at low halide concentrations when CO pressures of $\geq$ 100 bar were applied. With as little as 5 – 10 mol % LiBr, the yield of *N*-acetyl-α-aminobutyric acid was still in the $>$ 80% region (Figure 5).

As shown in Figure 6, minor changes in the acid concentration resulted in major changes of the product yield. Hence, it seemed very important not only to add a "drop of sulfuric acid" (common lab practice), but to measure the actual amount of added acid co-catalyst accurately. The $PdBr_2$ and $(PPh_3)_2PdBr_2$ systems behaved quite differently. With $PdBr_2$, the product yield increased by roughly 52% (up to 88%) upon addition of 1.5 mol % H_2SO_4. A further increase of the acid content (up to 3 mol %) slightly decreased the target yield. The $PdBr_2/PPh_3$ catalyzed reactions were very sensitive to the acid concentration. However, best yield were obtained with 0.5 mol % H_2SO_4. A further increase of acid content significantly reduced the product yield. This major influence of the concentration of the acid co-catalyst might be assigned to the high reactivity of propionaldehyde in aldol condensation reactions.

Next, we looked for synergistic effects of the two co-catalysts (Br^-, H^+) under the optimized conditions. As shown in Figure 7, the concentration of H_2SO_4 has a less pronounced effect at high-pressure conditions. It appears that the required LiBr and H_2SO_4 concentrations affect the yield in an additive manner. This behavior might be explained by a Lewis acid catalysis effect of Li cations.

Due to the significant differences between the phosphine-ligated and phosphine-free catalyst systems, further investigations focused on optimizations of the

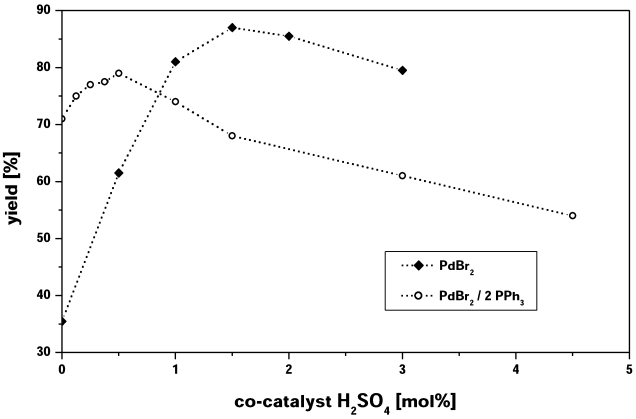


Figure 6. Influence of co-catalyst H_2SO_4: reactions were run for 12 h at 60 bar CO pressure and 100 °C using 50 mL NMP (1 M in acetamide and 2 M in propionaldehyde) and 0.25 mol % catalyst, 35 mol % LiBr.

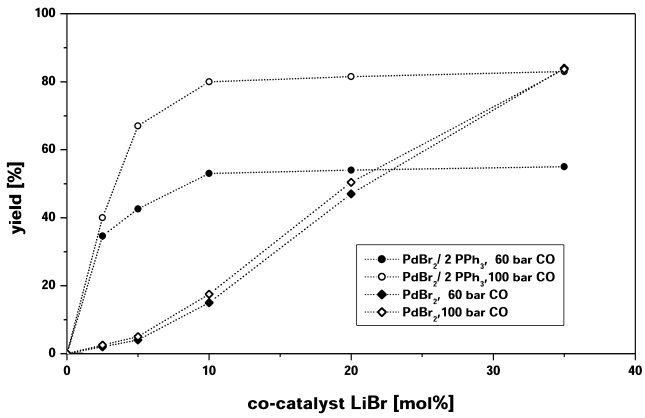


Figure 5. Influence of co-catalyst LiBr: reactions were run in the six-fold parallel autoclave for 12 h at 100 °C using 15 mL NMP (1 M in acetamide and 2 M in propionaldehyde) and 0.25 mol % catalyst, 1.5 mol % H_2SO_4.

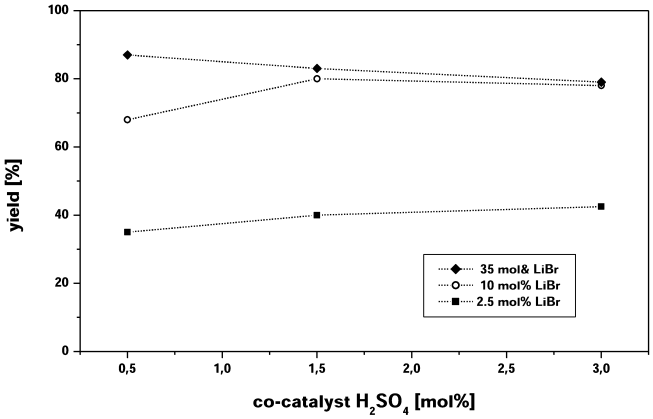


Figure 7. Determining synergistic effects of co-catalysts LiBr and H_2SO_4: reactions were run in the six-fold parallel autoclave for 12 h at 60 bar CO pressure using 15 mL NMP (1 M in acetamide and 2 M in propionaldehyde) and 0.25 mol % $PdBr_2$/2 PPh_3.

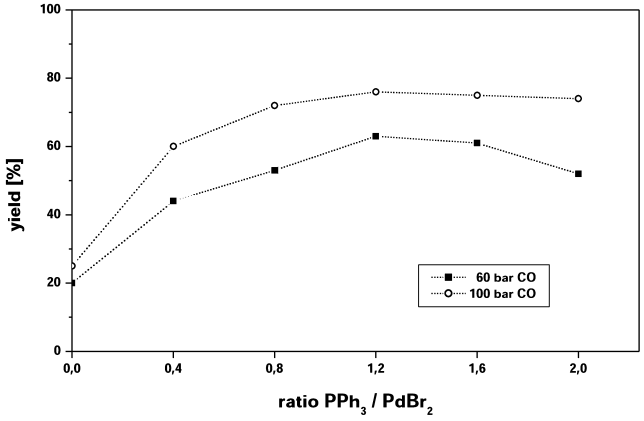
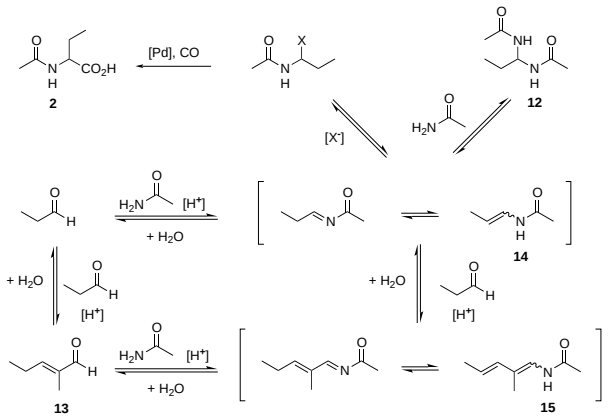


Figure 8. Influence of ligand to metal ratio: reactions were run in the six-fold parallel autoclave for 12 h at 100 °C using 15 mL NMP (1 M in acetamide and 2 M in propionaldehyde) and 0.25 mol % $PdBr_2$, PPh_3, 10 mol % LiBr, 1.5 mol % H_2SO_4.



Scheme 5. Major equilibrating species in propionaldehyde-acetamide condensation reactions and palladium-catalyzed amidocarbonylation reaction.

phosphine/palladium ratio. Interestingly, minor variations of the PPh_3 concentration had a major effect on the product yield, especially at lower CO pressures (Figure 8). The highest product yield was obtained with an equimolar Pd/P ratio.

Another issue that deserved further investigation was the reduction of the catalyst loading. While standard procedures employed 0.25 mol % palladium catalyst precursor, further screening reactions addressed the economic criteria associated with the high costs of palladium catalysts, and were thus performed with lower catalyst loading (Table 1).

From recent investigations into related alkoxycarbonylations we learned that it is sometimes necessary to increase the P/Pd ratio at low palladium concentrations to maintain optimal productivity.[22] Therefore, reactions with different P/Pd ratios were performed using 0.05 and 0.01 mol % Pd. While the catalyst turnover number (TON) could be increased up to 2700, the product yield dropped below a reasonable level. Consistently, analytical and preparative investigations of the reaction mixture revealed the presence of a variety of condensation products (Scheme 5).

Obviously, the decrease of the catalyst amount significantly favors non-metal catalyzed reactions toward various by-products. In addition to the simple condensation products of propionaldehyde and acetamide [1,1-bis(*N*-acetylamino)propane (**12**), 2-methyl-2-pentenal (**13**), 1-propenylacetamide (**14**)], we also detected and isolated two double bond isomers of the higher order condensation adduct *N*-(2-methyl-1,3-pentadienyl)acetamide (**15**). This formal Oppolzer – Overman type aminodiene is generated by *quasi* telomerization of two molecules propionaldehyde with one molecule acetamide. Successful implementation of these aminodiene building blocks in new multicomponent coupling reactions for the synthesis of various carbo- and heterocyclic compounds has recently been reported.[23]

Conclusion

The amidocarbonylation of propionaldehyde with acetamide to give *N*-acetyl-α-aminobutyric acid has been studied in detail. With regard to raw material costs and atom economy, this reaction constitutes the most

Table 1. Activity of Pd-catalysts in amidocarbonylation.[a]

ratio PPh_3/ $PdBr_2$	yield [%]		TON	
	0.05 mol % $PdBr_2$	0.01 mol % $PdBr_2$	0.05 mol % $PdBr_2$	0.01 mol % $PdBr_2$
2/1	48	15	960	1500
5/1	38	27	760	2700
10/1	9	25	180	2500
25/1	1	5	20	500

[a] Reactions were run in the six-fold parallel autoclave for 12 h at 60 bar CO pressure and 100 °C using 15 mL NMP (1 M in acetamide and 2 M in propionaldehyde), 10 mol % LiBr and 1.5 mol % H_2SO_4.

efficient approach to this amino acid derivative. Compared to standard amidocarbonylation conditions, the amount of halide co-catalyst could be significantly reduced, which is central to a desired low-waste approach. For the first time, an unexpected but significant increase of the yield of *N*-acylamino acids was observed when applying high-pressure conditions ($\geq$100 bar CO) in the palladium-catalyzed amidocarbonylation. This observation should also be of importance for amidocarbonylations of other reactive aldehydes.

Experimental Section

General Remarks

High pressure reactions were carried out in a 300-mL reactor (No. 4561 Parr Company) with a magnet-driven propeller stirrer or a 2000-mL reactor (No. 4522 Parr Company) equipped with a six-fold parallel insert. Product analysis of reaction mixtures was performed by HPLC analysis on a Hewlett Packard HP 1090 equipped with an Alphabond ® C18 column (Supelco Inc., 10 μm particle, 300 × 4.6 mm) using an eluent containing 93% (v/v) of an aqueous 0.225 M tetramethylammonium hydroxide solution, 4.85% (v/v) methanol, 2.0% (v/v) acetonitrile and 0.15% (v/v) acetic acid; benzoic acid as internal standard. All solvents and reagents were purchased from commercial sources and used without further purification.

NMR spectra were recorded on a Bruker ARX 400 in DMSO-d_6; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (*J*) in Hz. IR (KBr): Nicolet Magna 550, wavenumbers in cm^{-1}. MS (EI): AMD 402 (70 eV).

Typical Procedure for the Amidocarbonylation of Propionaldehyde with Acetamide

A 100-mL Schlenk flask was charged with $PdBr_2$ (0.125 mmol, 33.2 mg, 0.25 mol %), PPh_3 (0.25 mmol, 33 mg, 0.5 mol %), LiBr (17.5 mmol, 1.52 g, 35 mol %), and acetamide (0.05 mol, 2.96 g) under an inert gas atmosphere. Then, NMP (40 mL), propionaldehyde (0.1 mol, 7.4 mL), and a solution of H_2SO_4 (0.375 mmol, 37.5 mg, 1.5 mol %) in NMP (1 mL) were added. The solution was stirred until complete dissolution, and then cannula-transferred to a 300-mL autoclave. The reaction was pressurized to 40 bar CO, heated to 100 °C, and pressurized again to the actual reaction pressure of 60 bar CO. After 12 h, the gas was released and the reaction mixture was transferred to a 250-mL flask. The volatile compounds were removed under oil-pump vacuum (bp. of NMP ~207 °C!!), and the residue was taken up in methanol (10 mL) and the HPLC eluent (90 mL).

***d,l-N*-Acetyl-α-aminobutyric acid (2):** ^{1}H NMR: δ = 12.47 (bs, 1H, COO*H*), 8.06 (d, *J* = 7.5 Hz, 1H), 4.07 (dt, *J* = 5.2/7.9 Hz, 1H), 1.83 (s, 3H), 1.68 (m, 1H), 1.57 (m, 1H), 0.86 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR: δ = 173.7, 169.4, 53.2, 24.4, 22.3, 10.4; IR (KBr): ν = 3346, 2965, 2877, 1727, 1652, 1525, 1435, 1372, 1260, 1065, 1038 cm^{-1}. MS: *m/z* (rel. intensity) = 145 ([M^+], 3), 74 (100), 58 (100), 43 (47), 28 (22); anal. calcd. for $C_6H_{11}NO_3$ (145.16): C 49.65, H 7.64, N 9.65; found: C 49.58, H 7.60, N 9.72.

Acknowledgements

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References and Notes

[1] a) R. M. Williams, J. A. Hendrixs, *Chem. Rev.* **1992**, *92*, 889; b) R. O. Duthaler, *Tetrahedron* **1994**, *50*, 1539; c) H.-D. Jakubke, *Peptide: Chemie und Biologie*, Spektrum, Akad. Verl. Heidelberg, Berlin, Oxford, **1996**, p. 313.

[2] a) H. H. Szmant, *Organic Building Blocks for Chemical Industry*, Wiley, New York, **1989**; b) R. M. Williams, *Synthesis of Optically Active α-Amino Acids*, in *Organic Chemistry Series*, Vol. 7, (Eds.: J. E. Baldwin, P. D. Magnus), Pergamon, Oxford, **1989**; c) A. P. Mikhalkin, *Russ. Chem. Rev.* **1995**, *64*, 259.

[3] a) M. F. Czarniecki, L. S. Lehmann, (to Schering), *EP* 355,784, **1988**; b) J. C. Plaquevent et al., (to Societe Civile Bioprojet), *EP* 419,327, **1989**; c) N. G. Delaney (to Squipp and Sons), *EP* 361,365, **1988**.

[4] a) A. R. Hallberg, P. A. S. Tunek, (to Draco), *EP* 317,540, **1987**; b) *Drugs of the Future* **1996**, *23*, 1052.

[5] a) A. G. Myers, J. L. Gleason, T. Yoon, D. W. Kung, *J. Am. Chem. Soc.* **1997**, *119*, 656; b) M. J. O'Donnell, S. Wu, J. C. Huffman, *Tetrahedron* **1994**, *50*, 4507; c) E. J. Corey, M. C. Noe, F. Xu, *Tetrahedron Lett.* **1998**, *39*, 5347; d) M. J. O'Donnell, N. Chen, C. Zhou, A. Murray, C. P. Kubiak, F. Yang, G. G. Stanley, *J. Org. Chem*. **1997**, *62*, 3962; e) D. A. Evans, S. G. Nelson, *J. Am. Chem. Soc*. **1997**, *119*, 6452; f) N. Voyer, J. Roby, S. Chenard, C. Barberis, *Tetrahedron Lett*. **1997**, *38*, 6505; g) Y. S. Park, P. Beak, *J. Org. Chem*. **1997**, *62*, 1574; h) M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc*. **1998**, *120*, 4901; i) H. Ishitani, S. Komiyama, S. Kobayashi, *Angew. Chem.* **1998**, *110*, 3369; *Angew. Chem. Int. Ed.* **1998**, *37*, 3186; j) M. J. Burk, G. J. Allen, W. F. Kiesman, *J. Am. Chem. Soc*. **1998**, *120*, 657; k) C. A. Krueger, K. W. Kuntz, C. D. Dzierba, W. G. Wirschun, J. D. Gleason, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc*. **1999**, *121*, 4284.

[6] *d, l*-Methionine: T. Lüßling, K. Müller, G. Schreyer, F. Theissen, (to Degussa), *DE* 2,421,167, **1974**.

[7] a) M. Beller, M. Eckert, *Angew. Chem.* **2000**, *112*, 1027; *Angew. Chem. Int. Ed.* **2000**, *39*, 1010; b) M. Beller, *Med. Res. Rev*. **1999**, *19*, 357; c) F. Wang, Z. G. Zhang, *Chin. J. Org. Chem*. **2002**, 22, 536; d) J. F. Knifton, *Amidocarbonylation*, in *Applied Homogeneous Catalysis with Metal Complexes*, (Eds.: W. A. Herrmann, B. Cornils), VCH, Weinheim, **1996**, pp. 159.

[8] H. Wakamatsu, J. Uda, N. Yamakami, *J. Chem. Soc. Chem. Commun*. **1971**, 1540.

[9] E. Jägers, H.-P. Koll, (to Hoechst AG), *EP-B* 0.338.33. B1, **1989**; *Chem Abstr*. **1990**, *112*, 77951.
[10] a) M. Beller, M. Eckert, E. W. Holla, *J. Org. Chem*. **1998**, *63*, 5658; b) M. Beller, W. A. Moradi, M. Eckert, H. Neumann, *Tetrahedron Lett*. **1999**, *40*, 4523; c) M. Beller, M. Eckert, W. A. Moradi, *Synlett* **1999**, 108; d) D. A. Freed, M. C. Kozlowski, *Tetrahedron Lett*. **2001**, *42*, 3403.
[11] a) M. Beller, M. Eckert, W. A. Moradi, H. Neumann, *Angew. Chem*. **1999**, *111*, 1562; *Angew. Chem. Int. Ed.* **1999**, *38*, 1454; for a related reaction see: b) R. D. Dghaym, R. Dhawan, B. A. Arndtsen, *Angew. Chem. Int. Ed*. **2001**, *40*, 3228.
[12] Yugenic Ltd. Partnership, *US Patent* 1999-227213; *Chem Abstr*. **1978**, *77*, 114240.
[13] UCB; *BE Patent* 762728; *Chem Abstr*. **1978**, *77*, 114240; UCB, *DE Patent* 2106418; *Chem. Abstr*. **1971**, *75*, 140681.
[14] S. Calleja, J. Salas-Puik, *Neurologia* **2001**, *16*, 427.
[15] F. Gualtieri, D. Manetti, M. N. Romanelli, *Curr. Pharm. Design* **2002**, *8*, 125.
[16] Due to the differing gas entrainments caused by different reaction vessels, results from 50 mL and 15 mL reactions are not directly comparable. A comparison of tendencies is admissible.
[17] Conditions previously optimized for other aliphatic aldehydes: 25 ml NMP (1 M in acetamide, 1 M in propionaldehyde), 0.25 mol % $PdBr_2$, 0.5 mol % PPh_3, 35 mol % LiBr, 1.0 mol % H_2SO_4, 60 bar CO, 100 °C, 12 h.
[18] A. E. Jensen, P. Knochel, *J. Org. Chem*. **2002**, *67*, 79.
[19] R. Netherton, C. Dai, K. Neuschutz, G. C. Fu, *J. Am. Chem. Soc*. **2001**, *123*, 10099.
[20] A. C. Frisch, N. Shaikh, A. Zapf, M. Beller, *Angew. Chem*. **2002**, *114*, 4218; *Angew. Chem. Int. Ed.* **2002**, *41*, 4056.
[21] M. Beller, M. Eckert, F. Vollmüller, *J. Mol. Catal.* **1998**, *135*, 23.
[22] a) W. Mägerlein, A. F. Indolese, M. Beller, *J. Mol. Cat.* **2000**, *156*, 213; b) W. Mägerlein, A. F. Indolese, M. Beller, *J. Organomet. Chem*. **2002**, *641*, 30; c) W. Mägerlein, A. F. Indolese, M. Beller, *Angew. Chem*. **2001**, *113*, 2940; *Angew. Chem. Int. Ed*. **2001**, *40*, 2856.
[23] a) H. Neumann, A. Jacobi von Wangelin, D. Gördes, A. Spannenberg, M. Beller, *J. Am. Chem. Soc.* **2001**, *123*, 8389; b) A. Jacobi von Wangelin, H. Neumann, D. Gördes, A. Spannenberg, M. Beller, *Org. Lett*. **2001**, *3*, 2895; c) H. Neumann, A. Jacobi von Wangelin, D. Gördes, A. Spannenberg, W. Baumann, M. Beller, *Tetrahedron* **2002**, *58*, 2381.