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A new class of catalysts with superior activity and selectivity for amidocarbonylation reactions [1]

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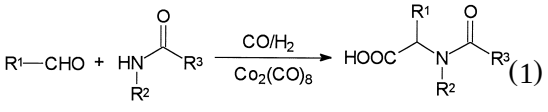
Abstract

For the first time, a detailed investigation of the newly developed palladium (Pd)-catalyzed amidocarbonylation for the synthesis of various *N*-acyl amino acids is described. A screening of important parameters led to a highly efficient process with the active catalyst system $PdBr_2/LiBr/H_2SO_4$. Based on our study of the influence of solvent, temperature, pressure, co-catalysts and substrates, we draw up a profile of the Pd-catalyzed amidocarbonylation and discuss the mechanism in detail. The successful employment of acetals and various aldehydes as starting materials demonstrates the synthetic potential of this atomeconomic process.

Keywords: Amidocarbonylation; Palladium; Catalysis; *N*-acyl amino acids; Multi-component reaction

1. Introduction

The amidocarbonylation, originally discovered by Wakamatsu et al. [2], is a remarkable and special case of the carbonylation of aldehydes. In the presence of amides and catalytic amounts of cobalt-complexes, aldehydes can be carbonylated directly to *N*-acyl amino acids (Eq. (1)).



(1)

As a matter of fact, amidocarbonylation procedures cannot compete commercially against cheap natural sources or fermentation. However, for non-natural amino acids, this atom economical process must be considered a superior alternative to the conventional Strecker reaction. As a three-component reaction, the amidocarbonylation employs ubiquitous feedstocks and with the maximum atom utilization and the avoidance of stoichiometric wasteful by-products, it fulfills the requirements demanded by ecological state of the art reactions. Because of the interest in *N*-acyl amino acids as chelating agents, detergents and products for enhanced oil recovery, the amidocarbonylation has high potential for future industrial realization [3,4].

Although the reaction has been investigated by several groups over the last 25 years, the reaction was limited to cobalt catalysis [5–7].

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[1] Part 4 of the series Palladium-Catalyzed Reactions for Fine Chemical Synthesis. For Part 3, see Ref. [1].

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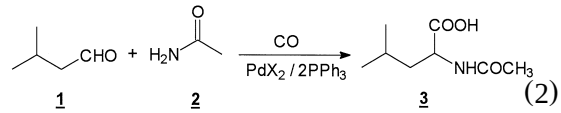
This limitation is relevant in that the cobalt catalyzed process shows poor catalyst activity (TON < 100), restriction in functional groups of the substrate and in general severe reaction conditions (150 bar CO/H_2). Thus, progress has mainly took place in widening the substrate spectrum by in situ generation of the aldehyde by various tandem processes like hydroformylation–amidocarbonylation or isomerization–amidocarbonylation [8]. So far, only few investigations concerning the mechanism of amidocarbonylations have been published [9,10]. Within these investigations, the most remarkable one by Ojima and Zhang [6] suggests that the limitation of the amidocarbonylation to cobalt catalysis could be due to the unique cobalt typical characteristic of forming stable aqua-complexes.

However, we recently described the first palladium (Pd)-catalyzed amidocarbonylation [11]. Here, we present this new reaction in detail and discuss its relevance to a likely mechanism. Moreover, we demonstrate that the transfer to Pd catalysis eradicates essential drawbacks of this reaction like poor catalyst activity and substrate limitation. Impressive catalyst turnover numbers (up to 25,000) and the synthesis of various functionalized *N*-acyl amino acids have been realized for the first time via amidocarbonylation [11]. Moreover, we describe the applicability of the Pd-catalyzed amidocarbonylation and report about newly synthesized important non-natural amino acids and the first application of acetals instead of aldehydes in this reaction.

2. Results and discussion

2.1. Evaluation of reaction conditions

In order to explore new catalyst systems for amidocarbonylations, we chose as test system the reaction of isovaleraldehyde with acetamide and CO in the presence of various metal complexes. In agreement with the patent literature, it turned out that Pd(II) halides in the presence of 2 equiv. triphenylphosphane can catalyze the reaction to *N*-acetyl leucine in principle (Eq. (2)) [12].



(2)

The following screening of characteristic reaction parameters revealed that the presence of halide anions as co-catalyst is essential. (For the need of halide co-catalyst in Pd-catalyzed carbonylation reactions of non-halides, see e.g., Ref. [13]). The influence of halide addition in the Pd-catalyzed amidocarbonylation of **1** and **2** is shown in Fig. 1.

The study shows that with increasing halide concentration, the isolated yield of the desired product increases ((+)-plot). The dependence follows an exponential function (exponent < 1) which suggests that at sufficient halide concentration, reaction steps which do not involve halide presence become rate affecting. A variation of different halide anions (Table 1) revealed the following: In the presence of high catalyst and low halide concentration, the use of iodide promoters lead to significant increase in yield (Table 1, entry 1 and 2). At higher halide and lower catalyst concentration, this effect is pushed into the background (different rate af-

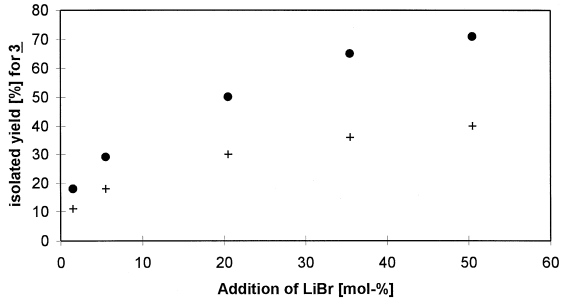


Fig. 1. Influence of halide addition on the isolated yield for **3**: (+)-curve: isolated yield (%) vs. addition of LiBr in (mol%). Reaction of 25.0 ml 1-M solution of isovaleraldehyde and acetamide in *N*-methylpyrrolidone (NMP) and 0.25 mol% $PdBr_2/2PPh_3$ with 60 bar CO at 80°C for 12 h; (·)-curve: isolated yield (%) vs. addition of LiBr (mol%), same reaction conditions with additional 1 mol% H_2SO_4.

Table 1
Examination of halide and acid co-catalysis in the Pd-catalyzed amidocarbonylation[a]

Entry	*p* (bar)	*t* (h)	Kat. (mol%)[b]	Halide	*X* (mol%)	Acid source	Acid (mol%)	Yield **3** (%)[c]
1	120	16	1	LiBr	5	–	–	33
2	120	16	1	Bu_4NI	5	–	–	67
3	60	12	0.25	LiBr	5	–	–	18
4	60	12	0.25	Bu_4NI	5	–	–	17
5	60	12	0.1	LiBr	35	H_2SO_4	1	80
6	60	12	0.1	Bu_4NI	35	H_2SO_4	1	82
7	60	12	0.1	LiCl	35	H_2SO_4	1	77
8	120	16	1	LiBr	5	H_2SO_4	1	68
9	60	12	0.25	LiBr	35	–	–	36
10	60	12	0.25	LiBr	35	H_2SO_4	1	92
11	60	12	0.25	LiBr	35	H_2SO_4	17.5	85
12	60	12	0.25	–	–	H_2SO_4	1	–
13	60	12	0.25	–	–	H_2SO_4	5	–
14	60	12	0.25	LiBr	35	TFA	1	70
15	60	12	0.25	LiBr	35	TsOH	1	68
16	60	16	1	HI	5	HI	5	58

[a]Reactions were run for 12 h at 80°C using 25.0 ml of a 1-M NMP (*N*-methylpyrrolidone) solution of isovaleraldehyde and acetamide.
[b]$PdBr_2/2PPh_3$.
[c]Isolated yield.

fecting step, for instance low catalyst concentration) (Table 1, entries 3–7). The observed grading of reactivity for different halides follows their nucleophilic characters (I > Br > Cl) [14]. The use of LiBr turned out to be convenient and was used as standard halide source throughout this study.

At low halide and/or low catalyst concentration, the yield of **3** can be significantly increased by addition of a strong acid as secondary co-catalyst, for instance sulfuric acid (Table 1, entries 1 and 8, 9 and 10). A general acid catalysis is observed. Addition of around 1 mol% of a strong acid is sufficient; higher acid concentrations are not beneficial (Table 1, entries 10 and 11). The presence of acid alone without halide anions does not lead to an efficient amidocarbonylation process (Table 1, entries 12 and 13). In general, strong acids ($pK_a < 3$) are suitable for successful acid co-catalysis in the amidocarbonylation reaction (Table 1, entries 14–16). Obviously, the use of halide hydrogen acids due to the double co-catalysis of halide and acid, is possible (Table 1, entry 16). However, due to the difference in required quantity of the two co-catalysts, the use of halide hydrogen acids seems not to be reasonable, especially when their corrosive nature is taken into account. The reaction profile with halide- and acid co-catalysis is illustrated in Fig. 1 ((•)-curve).

Among the various dipolar aprotic solvents tested, NMP turned out to be the best one for Pd-catalyzed amidocarbonylation. However, in dimethylformamide, dimethylacetamide and dioxane amidocarbonylation is possible too (Table 2).

In Pd-catalyzed reactions, like the Heck-, Suzuki- or carbonylation reactions, the presence of electron-rich ligands for the stabilization of

Table 2
Solvent screening for the Pd-catalyzed amidocarbonylation[a]

Entry	X	*X* (mol%)	Solvents	Yield of **3** (%)[b]
1	LiBr	35	NMP	80
2	LiBr	35	DMF	40
3	LiBr	35	DMAc	38
4	Bu_4NBr	35	Dioxan	32
5	LiBr	35	DMSO	< 5

[a]Reactions were run for 12 h at 80°C and 60 bar CO pressure using 25.0 ml of a 1-M solution of isovaleraldehyde and acetamide and 0.1 mol% $PdBr_2/2PPh_3$ as catalyst.
[b]Isolated yield.

the active catalyst species is discussed intensively [15]. Initial observations for the Pd-catalyzed amidocarbonylation show that a P/Pd ratio of 2:1 to 3:1 fits the optimum (Table 3, entries 1 to 3). At higher P/Pd ratios, the phosphine competes with CO for metal coordination leading to lower conversions. Experiments applying 1,4 bis(diphenylphosphino)-butane and (4*R*,5*R*)-(−)-4,5-bis(diphenylphosphinomethyl)-2,2,dimethyl-1,3-dioxolane (DIOP) show that chelating phosphine ligands are as suitable as monodentate phosphines in principle (Table 3, entries 4 to 6). Surprisingly, in the presence of ionic halides phosphine ligands are no longer necessary for catalyst stabilization (Table 3, entries 7 to 10). At 80°C, even in the absence of phosphine ligands, no Pd precipitation could be observed. In contrast, at 120°C even in the presence of 2 equiv. phosphine, precipitation was not avoided in all cases. Thus, in the absence of phosphine ligands, better results were obtained in experiments at a temperature of 80°C (Table 3, entries 9 and 10, 13 and 14), while at higher temperatures, the addition of phosphine ligands is beneficial.

Based on the numbers of equilibration and catalytic steps (see Section 2.2), the rate affecting influence of temperature is of utmost importance. Below a temperature of 60°C, no significant amidocarbonylation towards **3** takes place. In the interval from 60 to 140°C temperature represents a dominant reaction parameter as illustrated in Fig. 2. Admittedly, the illustrated examination reaches 100% yield at 140°C, but experiments at shorter reaction time confirm that no significant increase in rate could be obtained at temperatures higher than 140°C.

In contrast, the influence of pressure is of less importance for the Pd-catalyzed amidocarbonylation. It is found that in the absence of phosphine ligands, pressure reveals no rate affecting influence above 40 bar CO (Table 4, entries 1 and 2). Even at a pressure of 10 bar CO, excellent yields have been obtained. An amidocarbonylation at atmospheric pressure could not be realized till now (Table 4, entries 4 to 6).

In the presence of triphenylphosphine, CO pressure influences the reaction rate up to pressures of 60 bar of CO. In general, reaction rates are significantly lower with Pd phosphine catalyst systems (Fig. 3). Clearly, the inhibiting effect of phosphine ligands cannot be compensated by high CO pressure.

Under optimized conditions a turnover number of 25,000 (TOF > 400 h^{-1}) could be ob-

Table 3
Catalyst screening for the Pd-catalyzed amidocarbonylation[a]

Entry	*p* (bar)	*t* (h)	Catalyst	Pd (mol%)	Ligand	P (mol%)	LiBr (mol%)	H_2SO_4 (mol%)	Yield **3** (%)[b]
1	120	12	$PdBr_2$	1	–	–	–	–	9
2	120	12	$PdBr_2$	1	PPh_3	2	–	–	28
3	120	12	$PdBr_2$	1	PPh_3	16	–	–	5
4	60	12	$PdBr_2$	0.1	PPh_3	0.2	35	1	80
5	60	12	$PdBr_2$	0.1	bppb	0.2	35	1	80
6	60	12	$PdBr_2$	0.1	DIOP	0.2	35	1	70
7	60	12	$PdBr_2$	0.25	PPh_3	0.5	35	1	92
8	60	12	$PdBr_2$	0.25	–	–	35	1	89
9	60	12	$PdBr_2$	0.01	PPh_3	0.02	35	1	28
10	60	12	$PdBr_2$	0.01	–	–	35	1	37
11	60	12	$Pd_2(dba)_3$	0.25	PPh_3	0.5	35	1	60
12	60	12	$Pd(PPh_3)_4$	0.25	–	–	35	1	71
13	60	1	$PdBr_2$	0.25	PPh_3	0.5	35	1	37
14	60	1	$PdBr_2$	0.25	–	–	35	1	80

[a] Reactions were run for 12 h at 80°C and 60 bar CO pressure using 25.0 ml of a 1-M NMP solution of isovaleraldehyde and acetamide.
[b] Isolated yield.

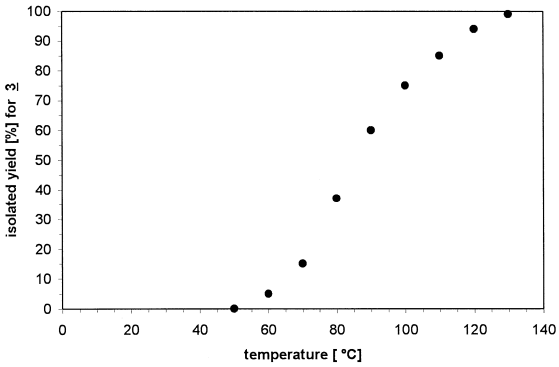


Fig. 2. Influence of temperature: reactions were run for 1 h at 60 bar CO pressure using 25.0 ml of a 1-M NMP solution of isovaleraldehyde and acetamide and 0.25 mol% $PdBr_2$ /2PPh_3, 35 mol% LiBr and 1 mol% H_2SO_4.

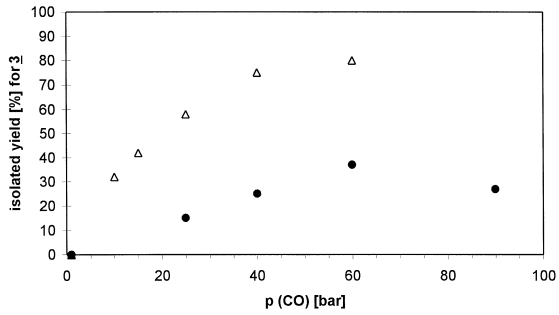


Fig. 3. Influence of CO pressure; reactions were run for 1 h at 80°C using 25.0 ml of a 1-M NMP solution of isovaleraldehyde and acetamide, 35 mol% LiBr and 1 mol% H_2SO_4 : Δ catalyst 0.25 mol% $PdBr_2$; ● catalyst 0.25 mol% $PdBr_2$ /2PPh_3.

tained for the synthesis of **3**. Thus, the Pd catalyst system exceeds all in literature known amidocarbonylation catalysts in activity by a factor of 10–100 (Table 5).

2.2. Postulated mechanism

For mechanistical discussions, it is worthwhile to look at the amidocarbonylation reaction from the point of a multi-component reaction. In this respect, one can regard the Wakamatsu reaction as a three-component reaction (Wakamatsu-3-component reaction: W-3-CR). One of the remarkable features of multi-component reactions is, that all starting compounds and intermediates are in equilibrium and only one subsequent reaction or sequence leads irreversibly to yield the product [16]. In case of the amidocarbonylation, we can divide the reaction in the preceding equilibria, the metal-catalyzed sequence and the irreversible cleavage of the acyl-complex yielding the *N*-acyl amino acid.

Table 4
Influence of CO pressure in the Pd-catalyzed amidocarbonylation[a]

Entry	*p* (bar)	*t* (h)	Yield **3** (%)[b]
1	60	1	80
2	40	1	78
3	25	1	58
4	25	12	99
5	10	12	85
6	1	12	–

[a]Reactions were run for 12 h at 80°C and 60 bar CO pressure using 25.0 ml of a 1-M NMP solution of isovaleraldehyde and acetamide and 0.25 mol% $PdBr_2$, 35 mol% LiBr and 1 mol% H_2SO_4.
[b]Isolated yield.

Based on our observations that the addition of both ionic halides and acid shows a synergistic effect in the Pd-catalyzed amidocarbonylation, we propose the following mechanism (Scheme 1).

The initial equilibrium step is the formation of the hemiamidal **I** by a nucleophilic attack of the amide to the aldehyde. In addition to side reactions, e.g., to corresponding bisamide, the hemiamidal **I** can react either via S_N1 or S_N2 substitution to give the α-halogenoamide **V**. Furthermore, hemiamidals containing N–H or α-C–H protons can eliminate water to the corresponding *N*-acyl imine **III** or the *N*-acylenamine **IV**. Clearly, the nucleophilic substitution of the hydroxyl groups is favored under acidic conditions.

It is assumed that a Pd(0) species **VII** subsequently inserts in an oxidative addition into the halide-carbon bond of the α-halogenoamide **V**. Due to the predominant reductive conditions (CO, aldehyde, phosphine), Pd(II) precursor complexes are reduced to the actually active Pd(0) complexes. In agreement with this assumption, Pd(0) complexes can also be used as a catalyst precursor (Table 3, entries 11 and 12).

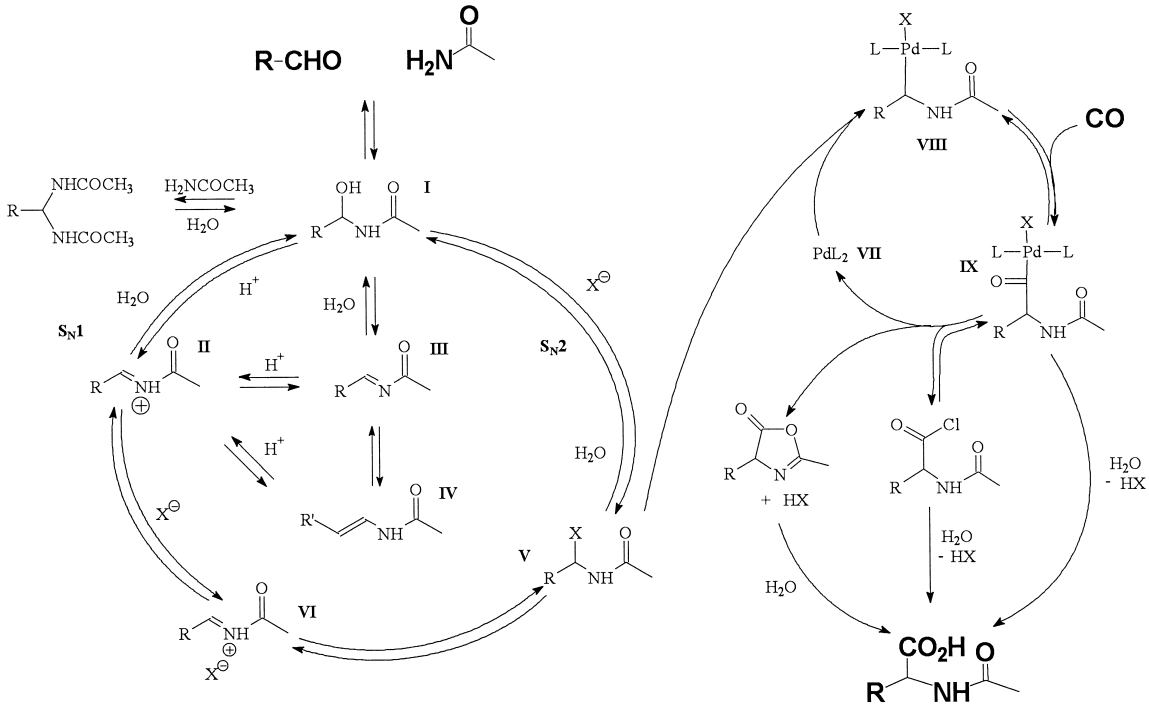
Table 5
Activity of Pd catalysts in amidocarbonylation[a]

Entry	*p* (bar)	*T* (°C)	*t* (h)	Pd (mol%)	P (mol%)	Yield **3** (%)[b]	TON	TOF (h^{-1})
1	60	120	60	$PdBr_2$, 0.01	PPh_3, 0.02	52	5 200	87
2	60	80	12	$PdBr_2$, 0.01		37	3 700	310
3	60	120	60	$PdBr_2$, 0.001	PPh_3, 0.002	25	25 000	417

[a]Reaction of 25.0 ml of a 1-M NMP solution of isovaleraldehyde and acetamide, 35 mol% LiBr and 1 mol% H_2SO_4.
[b]Isolated yield.

Apart from oxidative addition of Pd(0) to **V**, the formation of the 1-amidoalkyl-Pd(II)halogeno-complex **VIII** could be explained alternatively by the addition of the *N*-acyliminium-halide-ion pair **VI** to Pd(0). Although the importance of halide ions makes this reaction pathway less likely, it cannot be ruled out in principle.

CO insertion converts the alkyl-Pd species **VIII** to the corresponding acyl complex **IX**. For the cleavage of **IX** by reductive elimination, three pathways seem to be reasonable: (a) the intramolecular formation of an oxazolone derivative with subsequent hydrolysis, (b) the cleavage of an acid halide followed by hydrolysis, and (c) direct nucleophilic attack by water. Although the oxazolone formation cannot be excluded so far, it seems not the dominating reaction pathway to give the *N*-acyl amino acid because *N*-alkylated amides undergo Pd-catalyzed amidocarbonylation without problems. In this respect, it is important to note that *N*-alkylated amides would lead to less stable cationic oxazolones. The formation of acid halides has never been detected, but also cannot be ex-



Scheme 1. Proposed mechanism for the Pd-catalyzed amidocarbonylation

cluded at that time. Nevertheless, the intermolecular nucleophilic cleavage should be the major pathway.

The formation of the hemiamidal intermediate and its reactions is intensively examined in literature [17,18]. Typically, this first step of nucleophilic addition needs higher temperatures and base or acid catalysis. Therefore, we explain the beneficial effect of added acid by catalyzing preliminary equilibria steps. The essential co-catalysis by halide anions shows that the Pd catalyst is not able to carbonylate an intermediate of the preceding equilibrium, which exists in the absence of halide ions. This verifies the observation made in a number of Pd-catalyzed carbonylations that an oxidative insertion of a Pd(0) species into a C–X bond is indispensable either by applying a halide as substrate or by forming the halide intermediately, e.g., carbonylation of benzyl alcohol with the addition of halide ions [19].

The formation of **VIII** is dependent on the stabilization of the *N*-acyliminium cation (thus, the ion pair **VI** is also a likely precursor for the oxidative insertion) or the destabilization of the C–X bond, respectively. Thus, the nature of the nucleophile X plays a key role in the discussion of the nucleophilic substitution and the formation of **VIII**. The activity of tested halides in co-catalysis increases from chloride to iodide. This order correlates well with C–X bond energies indicating dissociation of this bond could have significant influence on the rate. Also, the order of reactivity of aryl halides in oxidative addition on $Pd(PPh_3)_4$ follows this trend [20,13].

On closer examination of successfully employed aldehydes, for instance benzaldehyde derivatives or pivalaldehyde, it reveals that the formation of an enamide intermediate (as discussed in the cobalt variant) is at least not necessary under Pd catalysis. In fact, one major difference in mechanism of the cobalt- and Pd-catalyzed amidocarbonylation is that the cobalt catalyst does a nucleophilic substitution on the hydroxy group while Pd catalysts do oxidative insertions in C–X bonds.

Two observations in the second (Pd-catalyzed) cycle are worthwhile to look at more detailed. After the oxidative addition of the α-halogenoamide **V**, the 1-amidoalkyl-Pd(II)halogeno-complex **VIII** still has a proton in β-position. In literature, only Pd-catalyzed carbonylations of aryl-, benzyl-, vinyl- and allyl halides are described in good yields, since these substrates cannot undergo β-H elimination. In case of the amidocarbonylation of primary amides, surprisingly the expected β-hydride elimination is suppressed. In agreement to other mechanistic studies, we propose a coordination of the acyl oxygen to Pd very much like in an investigation of the carbonylation of ethylene published by van Asselt et al. [21]. Therefore, the formation of an oxygen containing palladacycle could play a key role for suppressing β-hydride elimination.

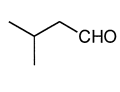
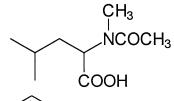
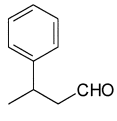
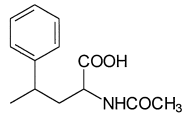
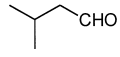
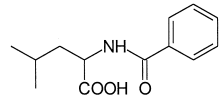
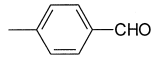
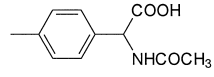
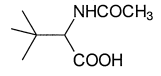
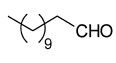
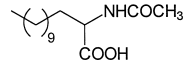
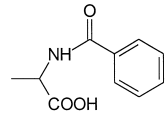
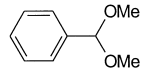
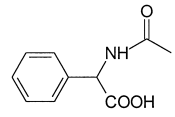
Secondly, the influence of carbon monoxide is of particular interest. As shown in Fig. 3, the reaction rate in the presence of triphenylphosphine ligands is significantly lower even at high pressures of CO. This reveals that the phosphine ligand could not be fully replaced by CO leading to the catalyst inhibitory effect of phosphine ligands, especially in the presence of high halide concentrations. Only at higher temperatures and minimal halide addition is the coordination of phosphine advantageous to stabilize the catalyst and prevent Pd precipitation. Similar inhibitory effects of phosphine ligands were observed for Pd-catalyzed cross coupling reactions with organic halides. Here, Beletskaya [22] introduced the concept of the so-called ligand free catalysis in which only solvent molecules function as weak donor ligands. Other examples of ligand free catalysis under mild conditions are known [23,24]. In general, the rise of reaction rate is about a factor of 2 to 3 compared to phosphine-assisted catalysis. This corresponds to the observed doubling of reaction rate observed in the Pd-catalyzed amidocarbonylation at 80°C. Nevertheless, to obtain not only high turnover frequencies but also high total turnover numbers, a catalyst stabilization for long term use is indis-

pensable. In addition to the stabilizing effect of NMP as weak donor ligand, we propose that additional halide ions have a positive influence on the Pd catalyst's stability and reactivity. The influence of halide anions on Pd catalysis has recently been investigated by Amatore et al. [25–27].

2.3. Synthetic applications of the Pd-catalyzed amidocarbonylation

In order to demonstrate the wide applicability of our Pd-based catalyst system, a host of various *N*-acyl amino acids have yet been synthesized, some of them published here for the first time (Table 6). Apart from the test system, *N*-acetyl leucine and other non-functionalized *N*-acetyl alkyl amino acids, the successful use of *N*-methyl amides in excellent yields is remarkable since these substrates are described in cobalt-catalyzed amidocarbonylation as difficult to react (Table 6, entry 1) [5]. The amidocarbonylation of other aliphatic amides and benzamide do not cause trouble, respectively (Table 6, entries 2 and 3). As a matter of fact, organic and medicinal chemistry have an increasing need

Table 6
N-acyl amino acids via Pd-catalyzed amidocarbonylation[a]

Entry	Starting compound	N-Acyl amino acid	Yield (%)[b]	TON
1			88	352 [11]
2			91	364
3			87	348 [11]
4			95	380 [3]
5			95	380
6			85	340
7			85	340
8			88	352

[a] Reactions were run for 12 h at 120°C and 60 bar CO pressure using 25.0 ml of a 1-M NMP solution of aldehyde or acetal and amide and 0.25 mol% $PdBr_2/2PPh_3$, 35 mol% LiBr and 1 mol% H_2SO_4.
[b] Isolated yield.

for non-proteinogenic amino acids because of their antimicrobial and enzyme inhibitory properties [28,29]. Here, arylglycines are of special interest since they are integral part of several important peptides like vancomycin or β-avoparcin [30,31]. The synthesis of *N*-acyl arylglycines via amidocarbonylation, not accessible by cobalt catalysis, turned out to give excellent yields with our Pd system (Table 6, entry 4). [2]

Herein, we report for the first time the synthesis of the widely used unnatural amino acid *N*-acyl *tert*-leucine, which is of special interest since it is implemented in several important drugs and chiral auxiliaries (Table 6, entry 5) [32]. The amidocarbonylation of long chain aliphatic aldehydes leads to surface active *N*-acyl amino acids used as biologically decomposable detergents in excellent yield (Table 6, entry 6).

In general, the applicability of amidocarbonylation can be widened by in situ generation of the aldehyde as shown with the cobalt-catalyzed variant intensively [5]. Frequently used precursors for aldehydes are acetals since they function as simple protection groups. Advantageously, in multi-step synthesis the protected aldehyde can be converted this way to the corresponding *N*-acyl amino acid in one single step. By few examples, we demonstrate here that acetals can be employed in Pd-catalyzed amidocarbonylation instead of aldehydes (Table 6, entries 7 and 8). As demonstrated by the synthesis of *N*-acetyl phenylglycine and *N*-benzoyl alanine the application of acetals does not involve decrease in yield or rate due to the acid co-catalysis.

3. Conclusion

The palladium-catalyzed amidocarbonylation, discussed in detail for the first time, is revealed as a powerful extension to the classical cobalt-catalyzed variant. A wide parameter screening lead to a high efficient process with the highly active catalyst system $PdBr_2/LiBr/H_2SO_4$ in NMP (TON 25,000). The wide applicability and tolerance of various substrates make this amidocarbonylation to a general and state-of-the-art method for the preparation of natural and non-natural *N*-acyl amino acids. Adding only one single catalytic step of enzymatic racemic resolution, the *N*-acyl amino acids can be converted to enantiomeric pure α-amino acids. [3] Moreover, with the Pd-catalyzed amidocarbonylation we have now catalysts in hand which should be controllable by ligand sphere offering the development of an asymmetric amidocarbonylation.

4. Experimental

A 300-ml stirred reactor with a magnet-driven propeller stirrer was used for the high pressure reactions.

General procedure: 25.0 ml of a 1-M solution of aldehyde and amide in NMP, 0.25 mol% $(PPh_3)_2PdBr_2$, 1 mol% H_2SO_4, and 35 mol% LiBr were allowed to react under 60 bar CO at 120°C for 12 h. The volatile components were removed in vacuo, 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 and extracted with ethyl acetate. Then the organic phases were combined and dried over magnesium sulfate, and the solvent was removed in vacuo. The product was recrystallized from a suitable solvent mixture, e.g., ethanol/ethyl acetate.

4.1. Characterization of the N-acyl amino acids *1–8*

(±)-*N*-acetyl-*N*-methyl-leucin (**1**): mp 112°C; ^{1}H NMR (DMSO-d_6) δ 12.8 (bs, 1H), 5.05 (80%) + 4.40 (20%) (dd, $J = 4.5$, 11.0 Hz bzw.

[2] From the work of M. Beller, M. Eckert, unpublished results (1997).

[3] From the work of M. Beller, M. Eckert, H. Geissler, W. Holla, unpublished results (1997).

J = 6.03, 8.54 Hz), 2.81 (80%) + 2.65 (20%) (s, 3H), 2.00 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 173.3 + 172.8, 170.7, 58.3 + 53.4, 37.5 + 36.9, 31.8 + 28.3, 24.6, 23.2, 21.8 21.3; FT-IR (KBr): ν = 2961m, 2875m, 2519m, 1716s, 1594s; CI-MS m/z 188 (M + H$^+$).

(±)-*N*-acetyl-(2-phenylpropyl)-glycin (**2**): mp 98°C; ^{1}H NMR (DMSO-d_6) δ 12.1 (bs, 1H), 8.13–8.17 (2d, J = 8.5 Hz, 1H), 7.1–7.3 (m, 5H), 4.18 (m, 0.5H), 3.72 (m, 0.5H), 2.80 (m, 1H), 1.93–1.85 (m, 2H), 1.88 (s, 1.5H), 1.86 (s, 1.5H), 1.21 (d, J = 7.03 Hz, 1.5H), 1.17 (d, J = 7.03 Hz, 1.5H); ^{13}C NMR (DMSO-d_6) δ 174.2 + 174.1, 169.43 + 169.35, 146.8 + 145.5, 128.5 + 128.4, 127.1 + 126.9, 126.3 + 126.1, 50.6 + 50.3, 36.1 + 35.5, 22.6 + 22.4, 20.7; FT-IR (KBr): ν = 3330m, 2959m, 1700s, 1623s, 1560s, 1494w, 1453w, 1248m; CI-MS m/z 236 (M + H$^+$, 100%).

(±)-*N*-benzoyl-leucin (**3**): mp 140°C; ^{1}H NMR (DMSO-d_6) δ 12.7 (bs, 1H), 8.62 (d, J = 7.8 Hz, 1H), 7.88 (d, 2H), 7.55 (m, 1H), 7.49 (m, 2H), 4.45 (m, 1H), 1.8 (m, 2H), 1.62 (m, 1H), 0.96 (d, 3H), 0.92 (d, 3H); ^{13}C NMR (DMSO-d_6) δ 174.4, 166.5, 134.1, 131.4, 128.3, 127.5, 51.0, 24.6, 23.1, 21.3; FT-IR (KBr): ν = 3279m, 3062m, 2962m, 1723s, 1636s, 1603s, 1579m, 1534s, 1492m, 1245s; CI-MS m/z 236 (M + H$^+$, 100%).

(±)-*N*-acetyl-α-(4-toluolyl) glycine (**4**): 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, 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$^+$).

(±)-*N*-acetyl-*tert*-leucin (**5**): mp 230°C; ^{1}H NMR (DMSO-d_6) δ 12.3 (bs, 1H), 7.94 (d, J = 7.5 Hz, 1H), 4.10 (d, 1H), 1.90 (s, 3H), 0.95 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 172.7, 169.5, 60.3, 33.4, 26.8, 22.4; FT-IR (KBr): ν = 3360s, 2981m, 2965m, 2937m, 1706s, 1617s, 1550s, 1374w; CI-MS m/z 174 (M + H$^+$).

(±)-2-*N*-acetyl-amino laurinacid (**6**): mp 110°C; ^{1}H NMR (DMSO-d_6) δ 12.4 (bs, 1H), 8.07 (d, J = 7.7 Hz, 1H), 4.11 (d, J = 7.7 Hz, 1H), 1.82 (s, 3H), 1.64–1.52 (m, 2H), 1.22 (m, 21H), 0.84 (t, J = 6.4 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 174.3, 169.7, 52.4, 31.8, 31.5, 29.5, 29.4, 29.3, 29.2, 29.0, 25.8, 22.8, 22.6, 14.4; FT-IR (KBr): ν = 3340s, 2919s, 2849m, 2441w, 1918m, 1717s, 1544s, 1380m, 1350m, 1157m; CI-MS m/z 272 (M + H$^+$, 93%), 226 (40%), 184 (100%).

(±)-*N*-benzoyl-alanin (**7**): mp 162°C; ^{1}H NMR (DMSO-d_6) δ 12.6 (bs, 1H), 8.71 (d, J = 7.5 Hz, 1H), 7.94 (d, J = 8.0 Hz, 2H), 7.54 (m, 3H), 7.49 (m, 2H), 4.48 (dt, 1H), 1.46 (d, J = 7.6 3H), ^{13}C NMR (DMSO-d_6) δ 174.3, 166.2, 134.0, 131.4, 128.3, 127.5, 48.2, 17.0; FT-IR (KBr): ν = 3369s, 1982m, 1725m, 1704s, 1629s, 1579m, 1547s, 1451m, 1213s; CI-MS m/z 194 (M + H$^+$).

(±)-*N*-acetyl-α-(phenyl) glycine (**8**): 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, 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.

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References

[1] M. Beller, T.H. Riermeier, Eur. J. Inorg. Chem. 1 (1998) 29.
[2] H. Wakamatsu, J. Uda, N. Yamakami, J. Chem. Soc. Chem. Commun., 1971, p. 1540.
[3] J.J. Lin, J.F. Knifton, CHEMTECH (1992) 248–252.
[4] J.F. Knifton, Amidocarbonylation, in: W.A. Herrmann, B. Cornils (Eds.), Applied Homogeneous Catalysis with Metal Complexes, VCH, Weinheim, 1996, pp. 159–168.

[5] K. Izawa, Yuki Gosei Kagaku Kyokaishi 46 (1988) 218–231.
[6] I. Ojima, Z. Zhang, Organometallics 9 (1990) 3122–3127.
[7] J.G. de Vries, R.P. de Boer, M. Hogeweg, E.E.C.G. Gielens, J. Organomet. Chem. 61 (1996) 1842–1846.
[8] I. Ojima, K. Hirai, M. Fujita, T. Fuchikami, J. Organomet. Chem. 279 (1985) 203–214.
[9] J.-J. Parnaud, G. Campari, P. Pino, J. Mol. Catal. 6 (1979) 341–350.
[10] P. Magnus, M. Slater, Tetrahedron Lett. 28 (1987) 2829–2832.
[11] M. Beller, M. Eckert, F. Vollmüller, S. Bogdanovic, H. Geissler, Angew. Chem. Int. Ed. Engl. 36 (1997) 1494–1496.
[12] E. Jägers, H.-P. Koll, DE 0338330, 1988.
[13] G. Cavinato, L. Toniolo, J. Mol. Catal. 78 (1993) 131–142.
[14] L. Cassar, M. Foa, J. Organomet. Chem. 51 (1973) 381.
[15] J. Tsuji, Palladium Reagents and Catalysts, Wiley, Chichester, 1995.
[16] I. Ugi, Proc. Estonian Acad. Sci. Chem. 44 (1995) 237–273.
[17] H. Hellmann, Angew. Chem. 69 (1957) 463–471.
[18] H. Hellmann, G. Opitz, α-Aminoalkylierungen, Verlag Chemie, Heidelberg, 1960.
[19] G. Cavinato, L. Toniolo, J. Mol. Catal. 58 (1990) 251.
[20] P. Fitton, E.A. Rick, J. Organomet. Chem. 28 (1971) 287–291.
[21] R. van Asselt, E.E.C.G. Gielens, R.E. Rülke, K. Vrieze, C.J. Elsevier, J. Am. Chem. Soc. 116 (1994) 977–985.
[22] I.P. Beletskaya, J. Organomet. Chem. 250 (1983) 551–564.
[23] V. Farina, B. Krishnan, J. Am. Chem. Soc. 113 (1991) 9585–9595.
[24] T.I. Wallow, B.M. Novak, J. Org. Chem. 59 (1994) 5034–5037.
[25] C. Amatore, M. Azzabi, A. Jutand, J. Organomet. Chem. 363 (1989) C41–C45.
[26] C. Amatore, M. Azzabi, A. Jutand, J. Am. Chem. Soc. 113 (1991) 8375–8384.
[27] C. Amatore, A. Jutand, A. Suarez, J. Am. Chem. Soc. 115 (1993) 9531–9541.
[28] J. Gante, Angew. Chem. Int. Ed. Engl. 33 (1994) 1699–1720.
[29] A. Giannis, T. Kolter, Angew. Chem. Int. Ed. Engl. 32 (1993) 1244–1267.
[30] D.L. Boger, R.M. Borzilleri, S. Nukui, J. Organomet. Chem. 61 (1996) 3561.
[31] K. Burgess, D. Lim, C.I. Martinez, Angew. Chem. Int. Ed. Engl. 35 (1996) 1077.
[32] A.S. Bommarius, M. Schwarm, K. Stingl, M. Kottenhahn, K. Huthmacher, K. Drauz, Tetrahedron Asymmetry 6 (1995) 2851–2888.