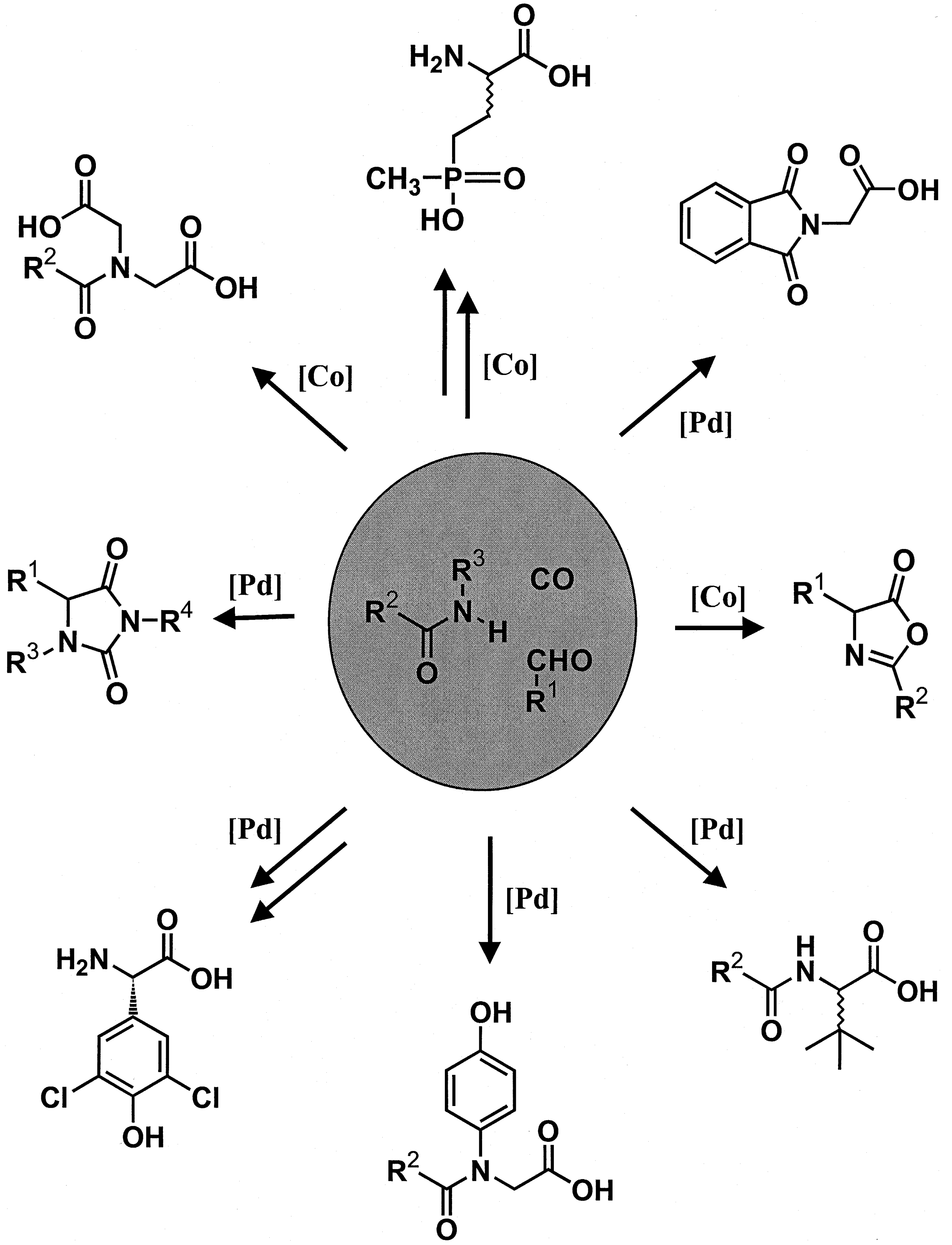
An Atom-Economic Route to Amino Acid Derivatives through Amidocarbonylation



Through these cobalt- and palladium-catalyzed three-component reactions of aldehydes, amides, and carbon monoxide, *N*-acyl-α-amino acid derivatives can be obtained very efficiently

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Amidocarbonylation—An Efficient Route to Amino Acid Derivatives

Matthias Beller* and Markus Eckert*

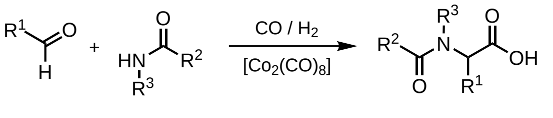
Dedicated to Dr. H. Wakamatsu on the occasion of his 70th birthday

Atom efficient, multicomponent reactions that lead to high-value products from inexpensive starting materials are of both economic and ecological interest for industrial organic synthesis. α-Amino acids are amongst the most important compounds in chemistry and biology. As well as their biochemical significance as building blocks of peptides and proteins, α-amino acids are also becoming increasingly interesting as fine chemicals. Possibly one of the key reactions in the preparation of these compounds is transition metal catalyzed amidocarbonylation, where the α-amino acid framework is constructed in a single step from an aldehyde, an amide, and carbon monoxide. This article gives a current overview of transition metal catalyzed amidocarbonylation reactions used in the synthesis of α-amino acids derivatives. A classification and summary of the significant features of this three component reaction is first presented together, with an historical introduction. This section is followed by two sections on cobalt- and palladium-catalyzed amidocarbonylation. A discussion of the mechanism of each of the different amidocarbonylation variants form an introduction. Overviews on further synthetic development of the methodology, such as the domino reaction with an amidocarbonylation step and the expansion of the range of starting materials, form the main topics of both variants. The potential of the method is demonstrated with the help of examples of special synthetic utility (for example, the preparation of arylglycines). Finally, possibilities for future developments in transition metal catalyzed amidocarbonylation reactions are proposed on the basis of the current state of knowledge.

Keywords: amidocarbonylation • amino acids • cobalt • homogeneous catalysis • palladium

1. Introduction

Amidocarbonylation has great potential for the industrial synthesis of racemic *N*-acylamino acids because of its atom economy and range of application. *N*-acyl-α-amino acids are formed in one step from the reaction of an aldehyde, an amide, and carbon monoxide in the presence of cobalt or palladium catalysts [Eq. (1)].



(1)

Amidocarbonylation is the only transition metal catalyzed multicomponent reaction that constructs the amino acid framework directly from simple, inexpensive starting materials. In the past the reaction has undergone many new developments, principally in the area of in situ aldehyde generation. Several review articles on cobalt-catalyzed amidocarbonylation have appeared over the last decade either as book contributions or in journals.[1] In addition to a description of the historical aspects and a comparison with related methods, this contribution presents a review of the more recent developments in cobalt-catalyzed amidocarbonylations and, for the first time, in palladium-catalyzed amidocarbonylations.

The newly awakened interest in this reaction reflects the fact that C_1 chemistry (here with CO), which in the past has mainly made its appearance in the synthesis of bulk chemicals, is receiving greater attention in the area of fine and specialty chemicals for a number of economic and ecological reasons.[2]

The structural motif of the *N*-acyl-α-amino acids is found in a large number of compounds from the most diverse areas of applications. Examples include the pharmaceuticals captopril

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and N-acetylcysteine, the herbicide Flamprop-isopropyl, the anionic sarcosinate tensides, and simple dipeptides such as the sweetener aspartame (Figure 1).

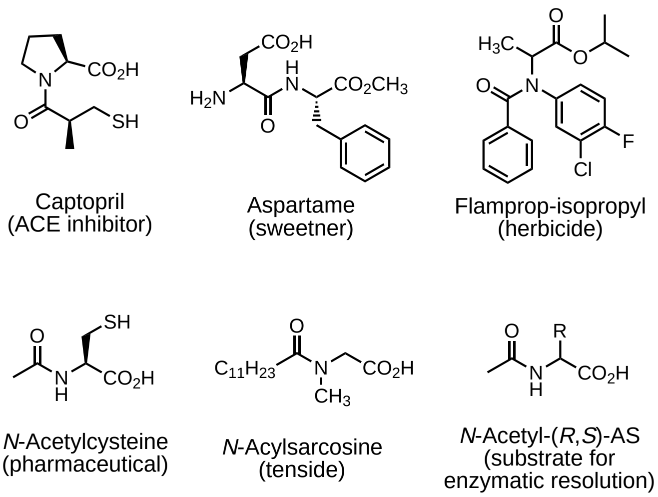

Figure 1. Examples of the applications of N-acyl-α-amino acids

Increasing environmental awareness and cost pressures make it necessary[3] to question and rethink existing chemical procedures used for the synthesis of N-acylamino acids, such as the acylation of free amino acids by the Schotten–Baumann method or cascade reactions involving an initial Strecker reaction followed by hydrolysis and subsequent acylation with anhydrides.[4]

Racemic N-acylamino acids are of considerable importance for the preparation of both natural and unnatural, enantiomerically pure amino acids. The development of synthetic chemical routes to optically active amino acids remains even now one of the great challenges in amino acid chemistry, as is demonstrated by numerous publications in recent years.[5] The trend is shifting in a consequent manner from diastereoselective variants to the use of asymmetric catalytic methods. The target of enantioselectivity, which has been the focus in the past, is only one factor of many that have to be considered in respect of industrial processes. Thus, enzymatic separation of racemic N-acetylamino acids (for example, N-acetylvaline or N-acetylmethionine) is still currently the method of choice if amino acids are to be prepared on a large scale, despite many known asymmetric catalytic procedures.

With the background of an increasing demand for different amino acids, this review article aims to demonstrate the potential of amidocarbonylation to utilizate readily accessible raw material sources and generate a wealth of useful compounds, as well as highlight future development possibilities.

1.1. Historical Background

At the beginning of the 1970s, two routes were discovered, starting at the same time from quite different directions, for the formation of N-acylamino acids by the reaction of an aldehyde, an amide, and carbon monoxide. Whereas Wakamatsu et al. at Ajinomoto first discovered cobalt-catalyzed

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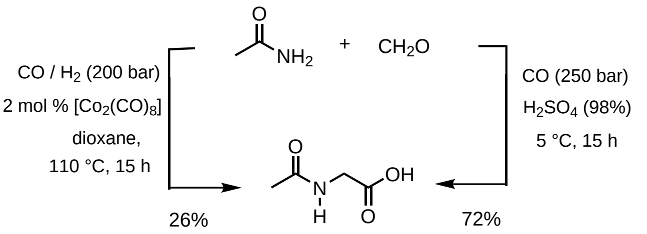
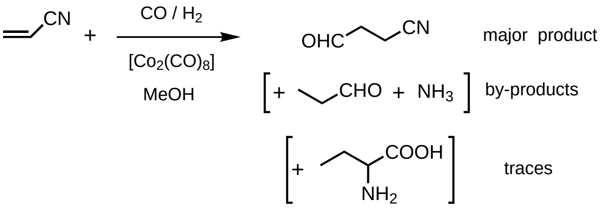
amidocarbonylation in 1970 during investigations into the oxo process of acrylonitrile,[6] Witte and Seeliger developed a corresponding Koch carbonylation in sulfuric acid (Scheme 1) in 1971 at Hüls.[7]



Scheme 1. The discovery of amidocarbonylation.

1.1.1. *The Wakamatsu Reaction*

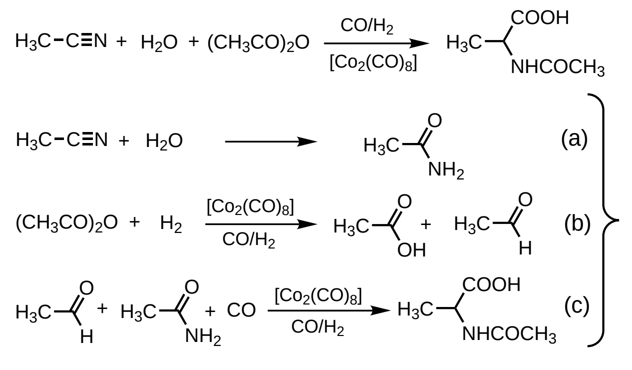
The development of the oxo process for the preparation of 3-cyanopropionaldehyde from acrylonitrile in the central research laboratories of Ajinomto was the essential step in the discovery of today's well-known amidocarbonylation reaction. As early as 1962 the hydroformylation of acrylonitrile with methanol as the solvent had been used successfully on a commercial scale.[8] Closer investigations into the formation of propionaldehyde as a by-product in the industrial process showed small amounts (2.5 %) of α-aminobutyric acid were present in stoichiometric reactions of acrylonitrile with $[HCo(CO)_4]$ in addition to propionaldehyde and ammonia [Eq. 2].



(2)

It was first assumed that an insertion reaction of CO into acrylonitrile was involved, and it became clear that an investigation of the reaction of acetonitrile, synthesis gas, water, and acetic anhydride under cobalt catalysis was necessary, however, no formation of alanine was observed. Surprisingly this reaction was first made possible by an additional hydrolysis of the reaction solution with hydrochloric acid, albeit in low yield. Wakamatsu concluded that the reaction did not proceed through CO insertion into the nitrile, but occured by prior hydrolysis of the nitrile to the amide (Scheme 2a) and the known reduction of acetic anhydride[9] to acetaldehyde and acetic acid (Scheme 2b), therefore, in the final instance, a reaction of acetaldehyde, acetamide, and carbon monoxide occurred (Scheme 2c).

The reaction of acetaldehyde and acetamide with synthesis gas under cobalt catalysis led consequentially to N-acetylalanine in high yield. Today this reaction is generally known under the name of amidocarbonylation. At the time Wakamatsu published only a short communication,[6] and it was Pino et al. who first confirmed in 1979 that the reaction was of general applicability and led to N-acyl-α-amino acids in high yields.[10]



Scheme 2. Historical aspects of the discovery of amidocarbonylation.

1.1.2. *The Amidomethylation of Carbon Monoxide*

The reaction of cationic α-amidoalkyl compounds with nucleophilic carbon atoms of aromatics, olefins, acetylenes, and active methylene groups is well known. In 1971 Witte and Seeliger at the Chemische Werk Hüls Troisdorf GmbH (now Degussa–Hüls AG) were successful in using the weak nucleophile carbon monoxide in such reactions for the first time.[7, 11] The N-acyliminium ion, formed in situ by reaction of an amide and paraformaldehyde, is converted into N-acylglycine derivatives with carbon monoxide (250 bar) in concentrated sulfuric acid at 5 °C. Methylols, bisamides, and methoxymethylene compounds are also suitable precursors of N-acyliminium ions in this reaction, and since the carbonylation of a functionalized carbenium ion occurs in sulfuric acid to form the carboxylic acid, it can in principle also be considered as a Koch carbonylation.[12] This amidocarbonylation variant has hitherto found no further application because of the severe reaction conditions and the structural limitation of glycine derivatives.

1.1.3. *Palladium-Catalyzed Amidocarbonylation*

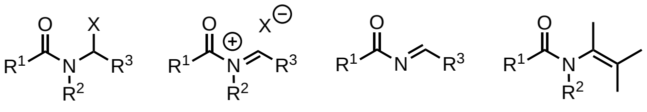
In contrast to other carbonylation reactions it is surprising that for almost two decades cobalt carbonyls have been used exclusively as catalysts in amidocarbonylations. It was only in 1987 during a search for patent-free catalyst systems for amidocarbonylation[13] that Jägers et al. at Hoechst AG discovered that palladium halides could function as precatalysts and catalyze the reaction. A closer reading of the first amidocarbonylation patent[6b] would have enabled this discovery to have been made much sooner! As early as 1970 the admittedly over-stoichiometric reaction of acetaldehyde with acetamide and synthesis gas in the presence of 1.67 equivalents of palladium dichloride to form alanine (2.5 % yield relative to Pd) was described in a patent example. In a comprehensive examination of amidocarbonylation by palladium catalysis we were able to develop this method further and to establish it as a method for the synthesis of numerous N-acylamino acid derivatives.[14]

1.2. Reactions Related to Amidocarbonylation

For both a better understanding of the amidocarbonylation variants and for future developments it is useful to consider reactions that are mechanistically related to amidocarbonylation. On the basis of the initial equilibria, the method represents a reaction of an *N*-acyliminium ion (or *N*-acyliminium ion precursor) with a nucleophile, here carbon monoxide. Thus a relationship with the classical α-amidoalkylation procedures is established. If only the key metal-catalyzed step is considered, the amidocarbonylation can be classified as a transition metal catalyzed carbonylation (Scheme 3).

Since amidocarbonylation represents a carbonylation of a C–X compound (with X = OH, OMe, hal, etc.), general conclusions can be drawn from methanol carbonylation (Monsanto process)[16] or benzoic acid synthesis from chlorobenzene.[17] However, there is also a relationship with transition metal catalyzed carbonylation of aldehydes. There are surprisingly few examples of this type of reaction. In addition to the nickel-catalyzed carbonylation of formaldehyde to glycolic acid[18] mentioned in Scheme 3, the palladium-catalyzed carbonylation of an electron-rich benzaldehyde derivative to form the phenylacetate ester is of interest.[19]

If amidocarbonylation is regarded as an amidoalkylation of carbon monoxide,[12, 20] the emphasis lies in the formation of electrophilic species of general structure **1**, wherein X represents a leaving group (Figure 2).[11, 20, 21] If the residue R^2 is hydrogen, HX elimination to the acylimine **2** frequently occurs, although enamides **3** can also function as α-amidoalkylation reagents,[22] usually after a corresponding protonation at the terminal C atom.



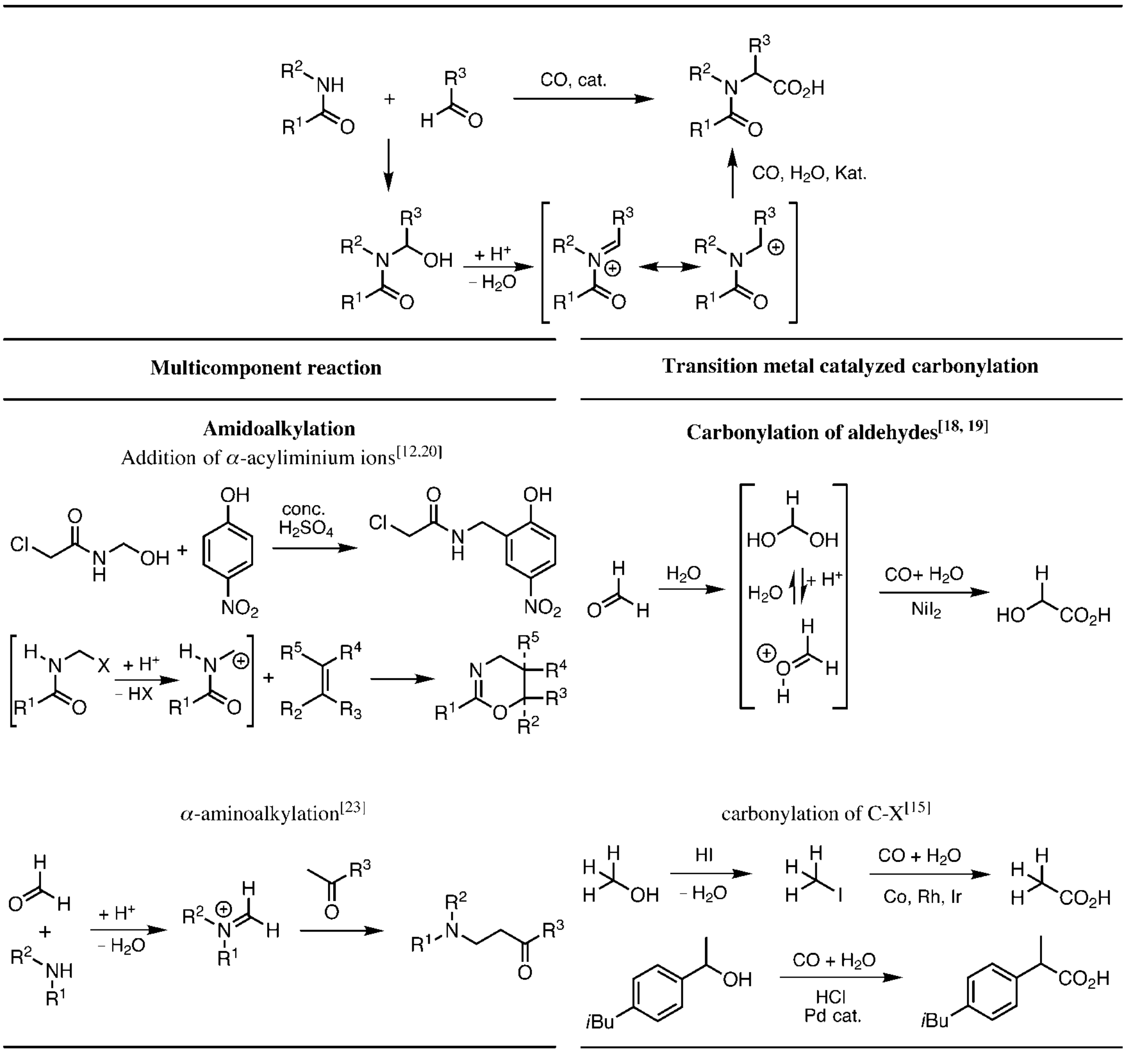
1 **2** **3**

X = OH, OR, hal, NHCOR, NR_2

Figure 2. Intermediates in α-amidoalkylations.

The most well known nucleophiles in such α-amidoalkylations are aromatics and olefins.[12] Electron rich arenes are converted into benzylamides and alkenes into dihydrooxazines in a cycloaddition reaction (Scheme 3).

Since the reactive α-amidoalkyl species are generally formed in situ from an aldehyde and an amide amidocarbon-



Scheme 3. Classification of amidocarbonylation.

ylation counts amongst the three component reactions (3-CR).[23] Familiar reactions are the Mannich and Biginelli reactions as well as the Strecker or Asinger reactions. Common to all is the reaction of an initially formed α-aminoalkyl species with a nucleophile. Within this context the cobalt-catalyzed amidocarbonylation can with some justification be called the "Wakakatsu 3-component reaction" (W-3CR).

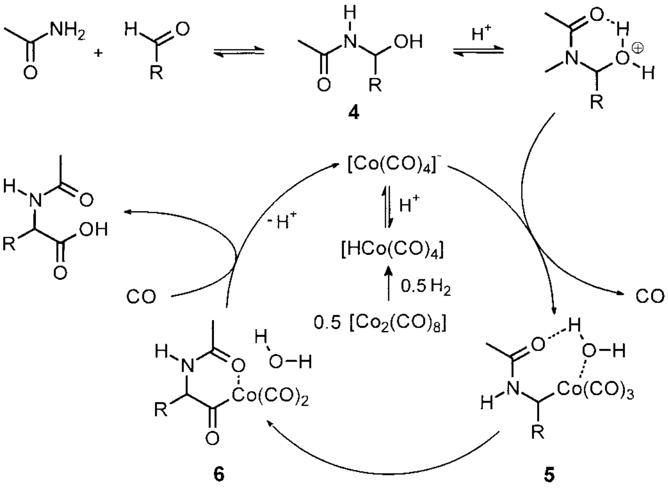
This different categorization of amidocarbonylation as a multicomponent reaction on the one hand and a carbonylation reaction on the other merges once again on the basis of the usual mechanistic classification; for the success of such a reaction the initial equilibria must be followed by an irreversible final step, which is the (usualy transition metal catalyzed) carbonylation step in the case of amidocarbonylation.

2. Cobalt-Catalyzed Amidocarbonylation

Cobalt-catalyzed amidocarbonylation is generally carried out at 70–160 °C, with synthesis gas pressures of 50–200 bar in solvents such as dioxane, THF, 1,2-dimethoxyethane (DME), ethyl acetate, acetone, or benzene. Dicobalt octacarbonyl $[Co_2(CO)_8]$ in amounts of 1–5 mol % usually functions as the catalyst precursor. The CO/H_2 ratio varies between 1/1 and 4/1, the concentration of the starting materials in the solutions is usually 0.1–3 mol/L^{-1}, and the amide may be used in excess.

2.1. The Mechanism of Cobalt-Catalyzed Amidocarbonylation

In the first step of the amidocarbonylation reaction a nucleophilic addition of the amide to the aldehyde occurs with formation of an N-α-hydroxyalkyl amide **4**,[10, 24] which can react with another amide molecule to form the bisamide in an equilibrium reaction or, depending upon the substitution pattern, can eliminate HX (X = OH, NRCOR) to form the corresponding N-acylimine or N-acylenamine (Scheme 4).[23–25]



Scheme 4. Postulated mechanism of cobalt-catalyzed amidocarbonylation.

In the cobalt-catalyzed carbonylation step it is assumed that the active catalyst species, the tetracarbonylcobaltate $[Co(CO)_4]^-$, forms the corresponding cobalt alkyl complex **5** with the protonated N-hydroxyalkyl amide in a nucleophilic substitution. The water formed possibly remains within the ligand sphere of the cobalt catalyst.[26] The actual generation of the cobaltate anion from $[Co_2(CO)_8]$ can take place in a number of ways, for example, a) in a reduction with hydrogen when $[HCo(CO)_4]$, a strong acid, is formed, or b) in the absence of hydrogen by a disproportionation with a base (amide) to $[CoB_6][Co(CO)_4]_2$,[27] where, however, the addition of an acid, for example, sulfuric acid, is necessary for the protonation.

The cobalt alkyl complex **5** is transformed into the cobalt acyl complex **6** by CO insertion. This product can be opened to the oxazolonium salt by intramolecular nucleophilic attack of the carbonyl oxygen atom of the amide group on the acyl–cobalt bond[28] or by intermolecular nucleophilic attack of water on the acyl bond with formation of the carboxylic acid.[26] In both cases the active catalyst species $[Co(CO)_4]^-$ or $[HCo(CO)_4]$ is regenerated and is then available for the next cycle.

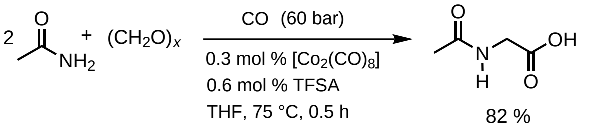
2.2 Method Developments in Cobalt-Catalyzed Amidocarbonylation

The emphasis of investigations to establish amidocarbonylation in the area of organic chemistry has without doubt hitherto laid in the exploitation of new starting materials by means of the in situ generation of the aldehyde component. In addition to aldehydes it is now possible to use olefins, acetals, epoxides, and allyl alcohols as well as alcohols and benzyl chloride as starting materials and treat them with amides and CO to form N-acylamino acids by amidocarbonylation.

2.2.1. Aldehydes

Aldehydes are the most important starting materials for amidocarbonylation. Numerous aldehydes have been used successfully in amidocarbonylation for the synthesis of natural and unnatural amino acid derivatives. However, cobalt catalysts are only capable of converting formaldehyde and aldehydes that possess at least one α-hydrogen atom. In the former case diamidocarbonylation is known, which leads, for example, to N-acylamino diacetic acids from a primary amide and two equivalents of formaldehyde.[29] Such reactions have a potential use in the industrial production of glufosinate intermediates. It is only with formaldehyde that cyclic amides such as 2-pyrrolidinone may be amidocarbonylated in moderate yield.[30]

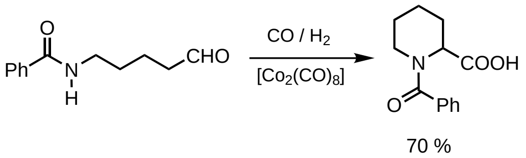
In order to carry out amidocarbonylation under mild conditions and in high yield the ligands were varied, acid co-catalysts were used, and a two-stage reaction procedure was developed. Lin et al. investigated the effect of different ligands in the synthesis of N-acetylglycine. This study showed that basic ligands such as PBu_3 allowed amidocarbonylation to be carried out at a lower pressure (55 bar). Ligands such as Ph_2SO or succinonitrile held the catalyst in solution such that the selectivity of the reaction and the recovery of the cobalt catalyst could be improved.[31] Thus, in the presence of succinonitrile the yield of N-acetylglycine could be increased from 63 to 78%, and the Co recovery from <10 to 80%. A successful reaction procedure at lower temperature (60–90°C) and with a higher rate of reaction was achieved by the addition of a strong acid ($pK_a < 3$) as co-catalyst. Moreover, under these conditions Drent et al. succeeded in carrying out amidocarbonylation with carbon monoxide instead of synthesis gas [Eq. (3); TFSA = trifluorosulfonic acid].[32]



(3)

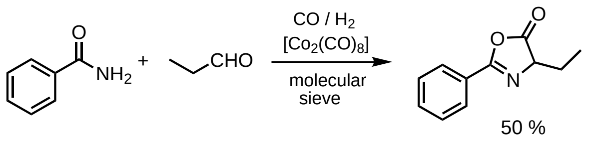
In 1994 a two-stage process was developed at Hoechst AG for the reaction of paraformaldehyde with N-methyl amides, which allowed the reaction to be carried out under very mild conditions. In the first stage methylol was formed by acid catalysis (80°C), which was carbonylated in the second stage by cobalt catalysis at 50–70°C and 10–50 bar (see sarcosinate preparation, Scheme 9) to afford the glycine derivative.[33] The success of this reaction procedure is explained by the first stage of methylol formation having a higher activation energy than the carbonylation stage, and the cobalt catalyst is considerably more stable at the lower temperatures of the acidic conditions.[1b] In addition, carbonylation at the lower temperatures leads to a conversion with significantly higher selectivity such that the yield of the industrially interesting fatty acid sarcosinates increases from 87[31] to 98%.

The preparation of ^{13}C-labeled N-acylamino acids[34] and the intramolecular amidocarbonylation of aldehydes demonstrates the preparative usefulness of the reaction. For example, it was possible to synthesize N-benzoylpipecolinic acid in 70% yield from the aldehyde in this way [Eq. (4)].[28]



(4)

Another variant that should be mentioned here is the amidocarbonylation of aldehydes in the presence of dehydrating agents such as molecular sieves. In this way oxazolones can be obtained directly in moderate yield, as Izawa et al. demonstrated with the preparation of 2-phenyl-5-ethyloxazolone [Eq. (5)].[28]



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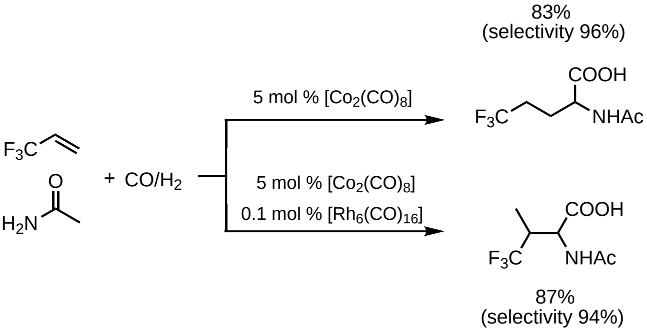
2.2.2. Olefins

Olefins are usually suitable as raw materials and are available commercially in a wide variety so that the combination of hydroformylation and amidocarbonylations with in situ aldehyde formation is of considerable importance. The hydroformylation stage can be catalyzed by cobalt carbonyl, rhodium carbonyl, or bimetallic Co-Rh complexes.

Although Wakamatsu et al. had suggested the use of olefines as early as 1974,[35] it was Stern et al. who first described this domino reaction.[36] 2-(Acetylamino)tetradecanoic acid was obtained from dodecene and acetamide in 73% yield on a greater than 100-g scale (conditions: 672 g dodecene, 256 g acetamide, 1.6 L dioxane, 1.05 g $[Co_2(CO)_8]$, 10 g $Co(OAc)_2$, 100 bar CO/H_2 (1/1), 100°C, 5 h). The question of *n*/*iso* regioselectivity was studied by Ojima et al. in investigations into the amidocarbonylation of trifluoropropene in which they synthesized N-acetyltrifluoronorvaline in the presence of 5 mol% $[Co_2(CO)_8]$ (yield 83%, selectivity 96%).[37] The addition of 0.1 mol% $[Rh_6(CO)_{16}]$ to the cobalt catalyst system achieved a selectivity reversal to N-acetyltrifluorovaline (yield 87%, selectivity 94%), which showed that the regioselectivity was determined at the hydroformylation stage (Scheme 5). IR studies of the reaction showed that the bimetallic complex $[CoRh(CO)_7]$ represented the active catalyst species.[38]



Scheme 5. Effect of rhodium carbonyl complexes on the amidocarbonylation of 3,3,3-trifluoropropene.

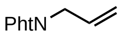
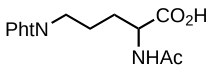
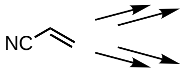
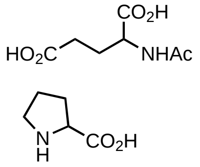
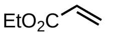
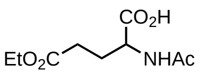
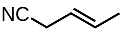
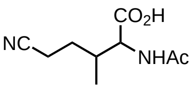
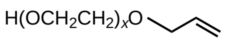
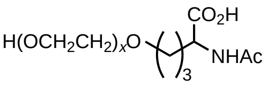
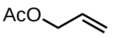
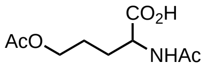
The positive effect of chelating phosphane ligands on the yield of domino hydroformylation–amidocarbonylation was demonstrated by Lin and Knifton in the reaction of tetradecene. The addition of 1 mol% of 1,3-bis(diphenylphosphanyl)propane (dppp) to 2 mol% of $[Co_2(CO)_8]$ enabled an increase in the yield of N-acetyl-α-aminohexadecanoic acid from 68 to 95% to be achieved.[31]

The use of functionalized olefins leads in many cases to interesting N-acylamino acid derivatives (Table 1). In addition to the proteinogenic amino acids lysine, glutaminic acid, and proline, cyano, polyoxyethylene, and O-acetyl-functionalized derivatives are accessible by amidocarbonylation. Diamidocarbonylation products may also be synthesized in moderate yields from terminal diolefins.[31]

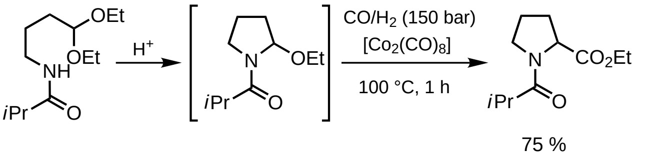
2.2.3. Acetals, Epoxides, and Allyl Alcohols

Acetals as simple protected aldehyde equivalents are either hydrolyzed in situ under the reaction conditions and react in

Table 1. Amidocarbonylation of functionalized olefins.

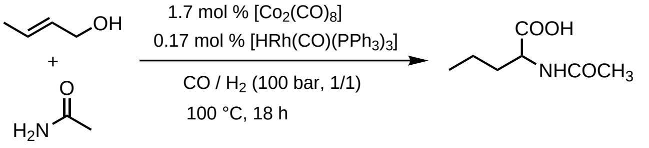
Entry	Functionalized olefin	Main product	Yield	Application
1			76 %	lysine[39]
2			n.a. 69 %	glutaminic acid[28] proline[28]
3			85 %	glutamate precursor[40]
4			85 %	polyamide[31a]
5			n.b.	tenside[31a]
6			85 %	polyamide esters[31a]

an analogous manner to the aldehydes, or they lead to the corresponding N-acylamino acid esters by water removal.[41] Mechanistically this variant of amidocarbonylation proceeds via N-acyl-α-alkoxy amines. The use of acetals is of particular advantage if other functional groups in the starting material make a protective group necessary as, for example in intramolecular amidocarbonylations, or if the respective ester is the desired product (however, a certain amount of the free acid is also formed) [Eq. (6)].[28]



(6)

The in situ generation of the aldehyde can be achieved by a preceding rearrangement reaction as is the case in the use of epoxides and allyl alcohols. Epoxides, such as styrene oxide or propene oxide, may be rearranged into aldehydes by Lewis acid catalysis and then amidocarbonylated as demonstrate successfully by Ojima et al. with [Ti(OiPr)$_4$] or [Al(OiPr)$_3$] as co-catalysts (see also phenylalanine preparation; Section 2.3).[37] Transition metal complexes such as [HRh(CO)(PPh$_3$)$_3$], [Fe$_2$(CO)$_9$], [RuCl$_2$(PPh$_3$)$_3$], and [PdCl$_2$(PPh$_3$)$_2$] have proved to be suitable for the in situ isomerization of allyl alcohols to enols, which then tautomerize to aldehydes [Eq. (7)].[42]

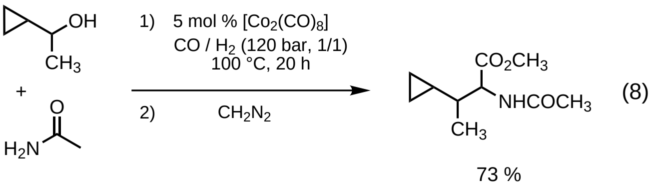


(7)

2.2.4. Alcohols and Benzyl Chloride as Substrates in Amidocarbonylation

Alcohols that form stable carbenium ions may be hydrocarbonylated to the corresponding aldehyde under oxo conditions and then amidocarbonylated. Yukawa et al. demonstrated the preparation of N-acetyl-O-methyltyrosine in 50 % yield from 4-methoxybenzyl alcohol.[43] Similarly, 1-cyclopropanylmethanol was converted into N-acetyl-3-cyclopropylanaline by a carbonylation – amidocarbonylation sequence [Eq (8).[44]

A new variant of amidocarbonylation uses benzyl chloride as the starting material to afford N-acetylphenylalanine in a domino hydrocarbonylation – amidocarbonylation sequence. By the shrewd selection of the individual reaction parameters de Vries et al. succeeded in achieving good yields (up to 79 %) of N-acylarylalanines, although high catalyst concentrations (12.5 mol % [Co$_2$(CO)$_8$)], high pressures (275 bar), and the addition of NaHCO$_3$ are necessary.[45] Critical factors here include the chloride ions that are formed in the first stage and which deactivate the catalyst.

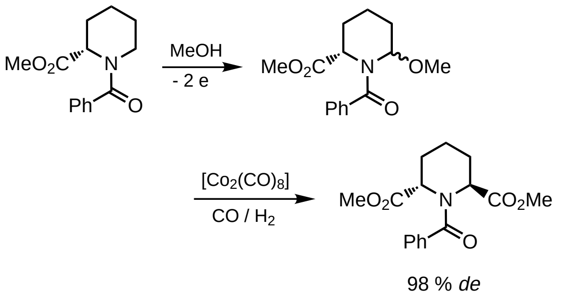


(8)

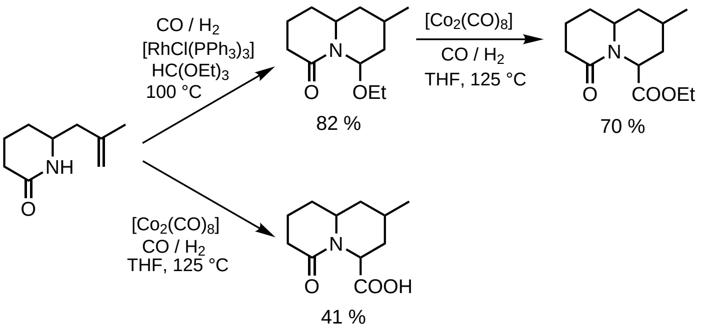
2.2.5. Carbonylation of N-α-alkoxyamides

N-α-Alkoxyamides are intermediates in the amidocarbonylation of acetals, which can be isolated or separately synthesized. They may be carbonylated in good yields to a number of interesting N-acylamino acids. Different methyl esters of N-acylamino acids were prepared in good yields by Izawa by the two-stage synthesis involving the anodic oxidation of cyclic amides to α-methoxyamides and subsequent cobalt-catalyzed carbonylation.[28] Particularly interesting is the high diastereoselectivity that was observed in the preparation of dimethyl *trans*-piperidine-2,6-dicarboxylate from optically active pipecolinic acid by this route (Scheme 6). This reaction currently represents the only example of an amidocarbonylation which takes place with high diastereoselectivity.

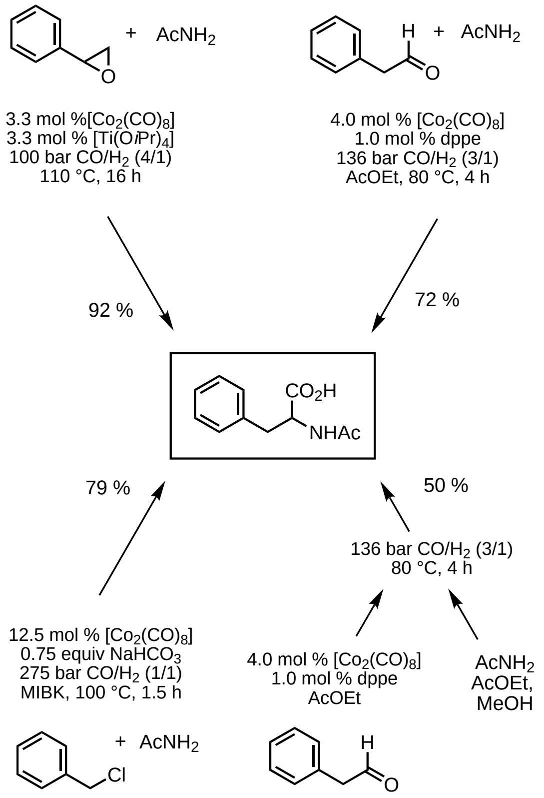
Ojima et al. prepared bicyclic N-α-ethoxyamides for mechanistic investigation by rhodium-catalyzed hydroformylation in the presence of triethyl orthoformate, which they were able to carbonylate to the corresponding ethyl esters in good or moderate yields by cobalt catalysis (Scheme 7).[26] The corresponding N-acylamino carboxylic acids could also be obtained directly in a cobalt-catalyzed domino hydroformylation – amidocarbonylation reaction.



Scheme 6. Preparation of *trans*-piperidine-2,6-dicarboxylic acid.



Scheme 7. Synthesis of cyclic quinolizidine derivatives.



Scheme 8. Cobalt-catalyzed amidocarbonylation to *N*-acetyl-D,L-phenylalanine. dppe = 1,2-bis(diphenylphosphanyl)ethane, MIBK = methyl isobutyl ketone.

2.3. Synthetic Applications of Cobalt-Catalyzed Amidocarbonylation

2.3.1. *N*-Acetyl-D,L-phenylalanine

N-Acetyl-D,L-phenylalanine is a precursor of L-phenylalanine, the key intermediate in the synthesis of aspartame (the methyl ester of L-aspartyl-L-phenylalanine) a sweetener developed by Ajinomto and Searle which is 140 times sweeter than saccharose.[46] Currently L-phenylalanine is produced by tyrosine fermentation. However, in an enzymatic aspartame process developed by the Holland Sweetener Company D,L-phenylalanine, which can be prepared advantageously by chemical means, can also be used as the starting material.[47] More recently, procedures starting from phenylacetaldehyde, benzyl chloride, and styrene have been proposed as alternative chemical synthetic methods for the amidocarbonylation step. The product may be obtained in 92% yield by a Lewis acid catalyzed rearrangement of styrene oxide to phenylacetaldehyde followed by amidocarbonylation.[37] The use of benzyl chloride in a domino hydrocarbonylation–amidocarbonylation sequence has given *N*-acetylphenylalanine in 79% yield after optimization of the conditions by the addition of $NaHCO_3$, although greater catalyst amounts and higher pressure were needed (Scheme 8).[45]

At the forefront of investigations into batch and continuous processes based on phenylacetaldehyde is the question of how to keep the cobalt catalyst in solution. Dppe has emerged as the ligand of choice, and yields of 50–72% have been achieved.[49] If the different amidocarbonylation methods for the preparation of phenylalanine are compared from an economic standpoint, it is clear that only those processes that start from benzyl chloride (< 1 US $ per kg) or styrene oxide (> 3 US $ per kg) have any chance of realization. Phenylacetaldehyde, at a price of about 14 US $ per kg, is clearly too expensive to be used industrially as a starting material. Styrene oxide is preferred to benzyl chloride as the starting material because of the lower incidence of side products. The disadvantages of the cobalt-catalyzed process are currently the low catalyst productivity and the space–time yields. These problems must be overcome by process improvements for a technical synthesis to be realized.

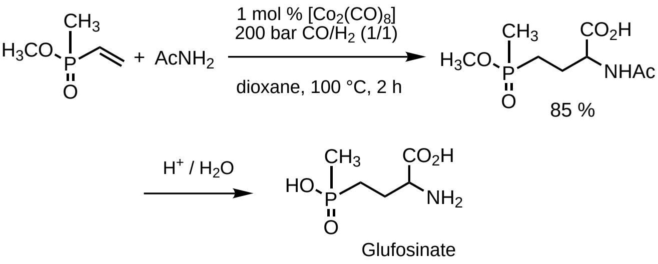
2.3.2. *Sarcosinates*

The long-chain *N*-acyl derivatives of sarcosine (*N*-methylglycine) belong to the group of anionic tensides that are used as components of surfactants, soaps, and emulsifiers because of their low hardening sensitivity and good dermatological compatibility.[46] Hitherto, sarcosinates were prepared industrially on a scale in excess of 10000 tonnes per year by a Schotten–Baumann reaction of a fatty acid chloride with the sodium salt of sarcosine.[4]

Although secondary amides generally give poorer results in amidocarbonylation, it has been possible to prepare sarcosinates successfully in a number of processes by the reaction of a fatty acid *N*-methylamide with paraformaldehyde. Lin and Knifton were able to produce *N*-methyllauroylglycine in two hours in 87% yield under severe conditions (200 bar CO/H_2 (3/1), 120°C with 3 mol% $[Co_2(CO)_8]$)].[31e] As already mentioned, Hoechst AG has developed an improved, two-stage process for the preparation of a number of *N*-acylsarcosines (Scheme 9) in which yields in excess of 98 % of the target product have been achieved under very mild conditions (see Section 2.2.1).[33] In particular, a method was developed to recover the cobalt catalyst used. The water-soluble cobalt salt was precipitated as cobalt hydroxide and then converted into a cobalt-containing melt with the *N*-acylsarcosine. The cobalt carbonyl catalyst was regenerated from the melt with synthesis gas (120 bar) at 90 °C and then reused.[33b] The process outlined here was used successfully in a 1-L to a 250-L scale, and as a result sarcosinates have been prepared on a ton scale in a pilot plant.

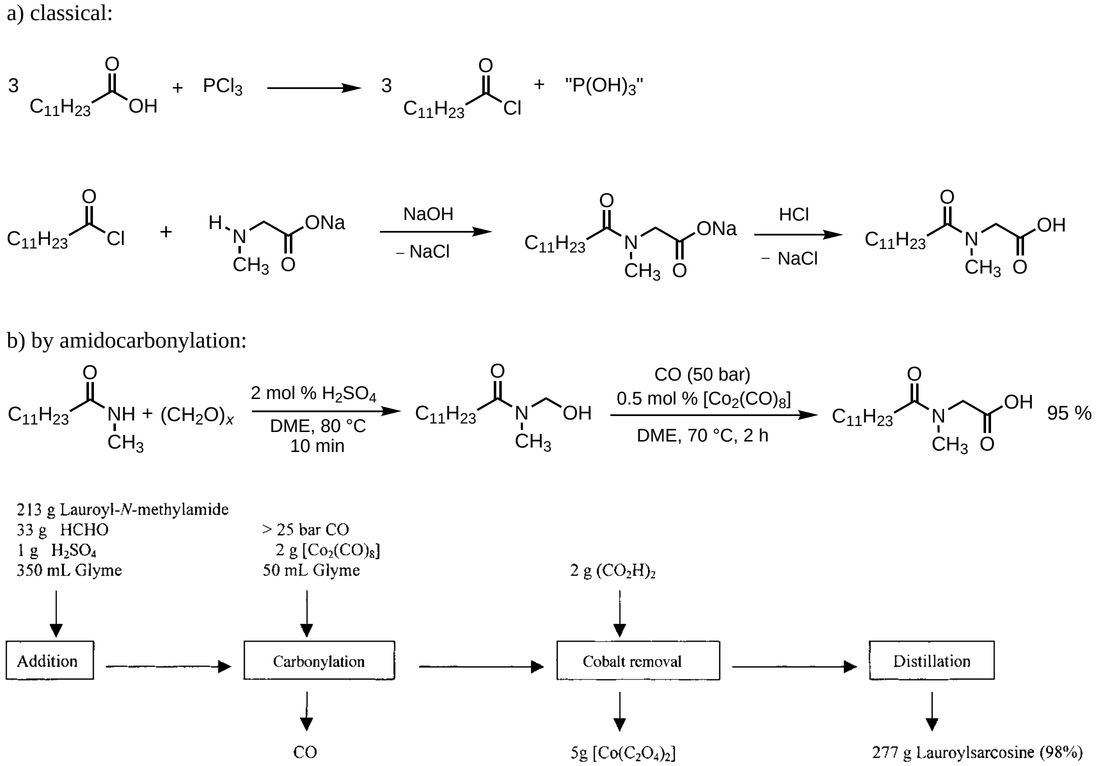
2.3.3. Glufosinate

Glufosinate is a naturally occurring hydroxyphosphorylamino acid with herbicidal and antibiotic properties and is marketed as a nonselective herbicide under the name BASTA. An above average growth in the product is expected in the coming years because of the development of genetically modified, BASTA-resistant plants. Consequently new and efficient methods for the synthesis of glufosinate are of considerable interest. Syntheses starting from the respective olefins, aldehydes, or acetals of the methyl phosphinate are known for the production of BASTA by amidocarbonylation. Jägers et al. (Hoechst AG) were successful with the conversion of 3-[butoxy(methyl)phosphoryl]propylaldehyde diethylacetal into the *N*-acetylamino acid in 79 % yield (1.8 mol % $[Co_2(CO)_8]$, 120 bar CO/H_2 (1/1), 120 °C) in one hour.[50] Glufosinate may also be obtained in an overall yield of 80 % by a domino hydroformylation–amidocarbonylation sequence with subsequent hydrolysis (Scheme 10).[51]



Scheme 10. Glufosinate preparation by amidocarbonylation.

In spite of numerous synthetically interesting possibilities for the use of amidocarbonylation in the production of *N*-acylamino acids, as far as we are aware sarcosinates have only been synthesized on a pilot plant scale. This observation is attributable in part to inadequate catalytic activity (turnover number (TON) < 100) as well as in most cases to the very high pressures (100–200 bar), which make the reaction economically unattractive. However, the realization of an adaptation of the Strecker synthesis, with subsequent Schotten–Baumann acylation to complete the amidocarbonylation, as an atom-efficient process (theoretically 100 %) for the preparation of a number of *N*-acylamino acids is worthwhile from an ecological viewpoint. In principle, two routes for the further improvement and investigation of amidocarbonylation, and thus a better utilization of the great potential of this method in the future, are conceivable. Firstly, the development of the



Scheme 9. Two-stage amidocarbonylation in the synthesis of *N*-acylsarcosines. DME = 1,2-dimethoxyethane.

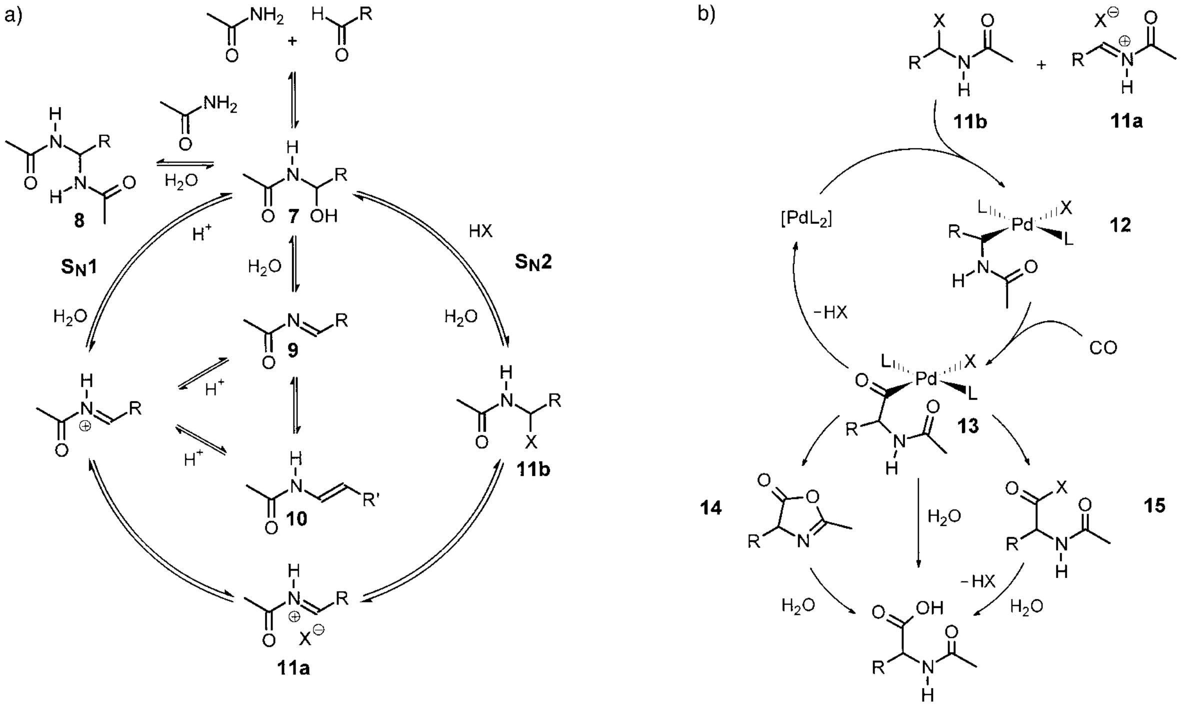
two-stage N-acylsarcosine process has illustrated that the scope for further optimization of the cobalt-catalyzed route is far from being exhausted. Secondly, the search for alternative catalyst systems has hitherto been greatly neglected, and the development of new transition metal catalyst systems for amidocarbonylation will reveal new pathways for further synthetic applications.

3. Palladium-Catalyzed Amidocarbonylation

In comparison to the cobalt catalyst variants, milder reaction conditions are generally used for amidocarbonylation in the presence of a palladium catalyst. Temperatures of 70–130 °C and carbon monoxide pressures of 10–60 bar are used. The presence of halide ions as co-catalysts have proved to be essential, and typically 10–35 mol% of LiBr or $n\mathrm{Bu_4NBr}$ are used. A synergistic effect, in which a doubling in the reaction rate without loss of specificity, is achieved by the addition of catalytic amounts of strong acids, for example 1 mol% H_2SO_4. Of the many different dipolar, aprotic solvents N-methylpyrrolidone (NMP) has proved to be particularly suitable. DMF, DMAc, or acetonitrile may also be used as solvents. The use of both palladium(0) (for example, $[Pd_2(dba)_3]$, $[Pd(PPh_3)_4)]$, and palladium(II) compounds (for example, $PdBr_2$, $Pd(OAc)_2$) as catalyst precursors is also possible. Under optimal conditions catalyst turnover numbers of 60000 (turnover frequency (TOF) > 1000 h^{-1}) may be achieved in the synthesis of N-acetylleucine by palladium-catalyzed amidocarbonylation. Thus, palladium catalysts have an activity greater than the cobalt systems by a factor of 10–100.[14, 52]

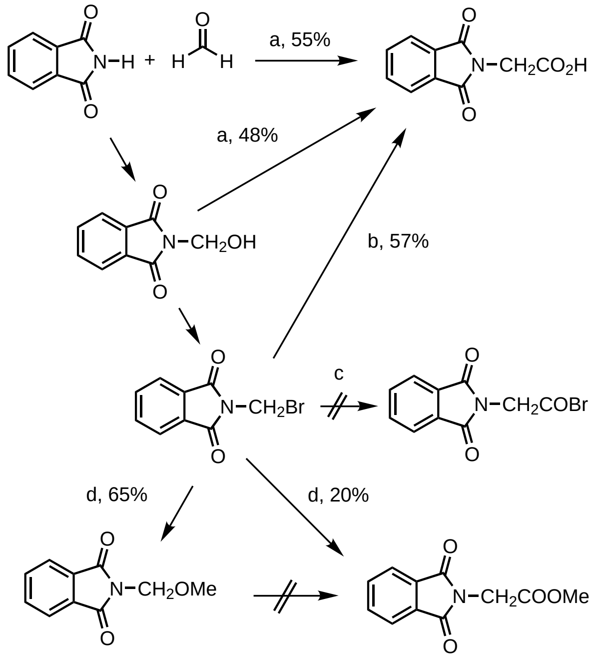
3.1. The Mechanism of Palladium-Catalyzed Amidocarbonylation

For a mechanistic discussion of palladium-catalyzed amidocarbonylation it is useful here to take as a basis the classification of amidocarbonylation into a multicomponent reaction and transition metal catalyzed carbonylation (Scheme 3), as described in Section 1.2. The initial equilibria, in which the starting materials and intermediates are in equilibrium, do not differ fundamentally from those of cobalt-catalyzed amidocarbonylation. However, additional critical intermediates are formed here through the involvement of halide ions (Scheme 11 a). After the initial step involving the formation of a α-hydroxyamide **7** by the nucleophilic attack of the amide on the carbonyl group followed by the generation of a bisamide **8**, an N-acylimine **9**, or enamide **10**, there is the possibility of forming a α-haloamide **11b** or the corresponding ion pair **11a**.[53] This intermediate probably plays a critical role in palladium-catalyzed amidocarbonylation since active palladium(0) species can insert into these halogen–carbon bonds in an oxidative addition. This assumption finds support in that the presence of halide ions are essential for successful conversion. Because of the predominantly reductive conditions (CO, aldehyde, phosphane), the Pd^{II} precursors are readily converted into the active Pd^0 species. Palladium(0) complexes such as $[Pd(PPh_3)_4]$ or $[Pd_2(dba)_3]$ are also ideally suitable as catalyst precursors for amidocarbonylation. The resulting Pd^{II}-alkyl complex **12** is subsequently transformed into the corresponding acyl complex **13** by a CO insertion. The cleavage of this compound probably occurs through the direct nucleophilic intermolecular opening of the complex by water. However, an intramolecular formation of an oxazolone derivative with subsequent hydrolysis cannot be ruled out in all cases.



Scheme 11. Postulated mechanism of palladium-catalyzed amidocarbonylation: a) initial equilibria; b) palladium-catalyzed carbonylation step.

The use of stable reaction intermediates has been studied in the mechanistic investigation of the amidocarbonylation of phthalimide with formaldehyde to give *N*-phthaloylglycine by palladium catalysis. Particularly rewarding was the carbonylation of the α-haloamide intermediate *N*-(bromomethyl)-phthalimide, which led to the carboxylic acid or the methyl ester only in the presence of a nucleophile such as water or methanol, respectively, through which it was possible to confirm that an intermolecular opening of the acyl complex had occurred (Scheme 12).



Scheme 12. Mechanistic investigations of palladium-catalyzed amidocarbonylation with the phthalimide–formaldehyde system. a) 0.25 mol% PdBr$_2$/2 PPh$_3$, 35 mol% LiBr, 1 mol% H_2SO_4, 60 bar CO, 12 h; b) 1 mol% PdBr$_2$/2 PPh$_3$, 1 mol % H_2SO_4, 1 equiv H_2O, 60 bar CO, 12 h; c) 0.25 mol% PdBr$_2$/2 PPh$_3$, 1 mol% H_2SO_4, 60 bar CO, 12 h; d) 1 mol% PdBr$_2$/2 PPh$_3$, 1 mol% H_2SO_4, 1 equiv MeOH, 60 bar CO, 12 h.

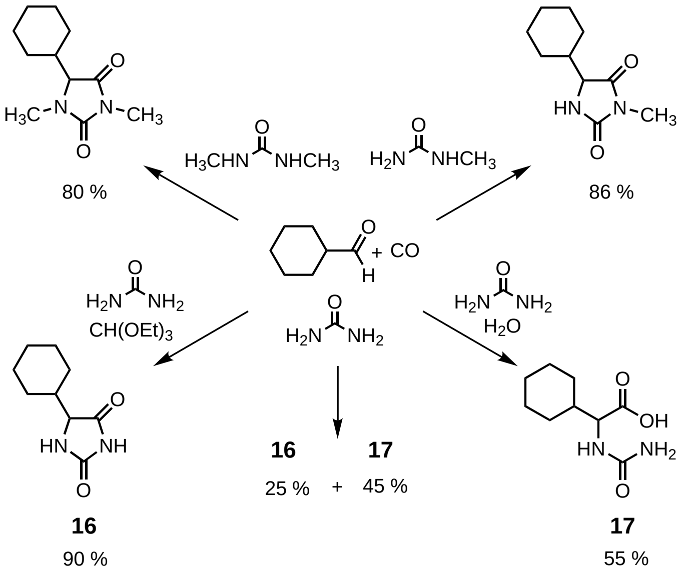
It was possible to isolate the palladium(II) alkyl complex and the corresponding acyl complex by the oxidative addition of the *N*-(bromomethyl)phthalimide to [Pd(PPh$_3$)$_4$].[54] Both complexes may be used successfully as a catalyst. In a high pressure NMR study it was also possible to follow the critical step of CO insertion leading to the formation of the acyl complex. Thus all critical steps of the palladium-catalyzed carbonylation cycle were now fully understood for the example of the amidocarbonylation of phthalimide with formaldehyde, and it was possible for the intermediates to be isolated so that the mechanism proposed in Scheme 11 could be underpinned.

3.2. Developments in the Methodology of Palladium-Catalyzed Amidocarbonylation

Whereas in cobalt-catalyzed amidocarbonylations the implementation of in situ aldehyde generation stands almost without exception in the foreground, in amidocarbonylation by palladium catalysis important developments in amide variation have been undertaken, the main highlights of which are described in the following section.

3.2.1. Ureidocarbonylation to Substituted Hydantoins

Depending on the nature of the starting material, the use of urea derivatives as amide components has made it possible to isolate the actual amidocarbonylation products, the *N*-ureidoamino acids. However, the substituted hydantoin is usually obtained with high selectivity.[55] Hydantoins are very important in both production of amino acids and in research of pharmaceutically active, low molecular weight heterocycles.[56] Until recently only 1,3-unsubstituted hydantoins were accessible in an efficient multi-component synthesis, the Bucherer–Bergs reaction.[57] Not only were 1,3-unsubstituted hydantoins accessible in ureidocarbonylation, but for the first time hydantoins varyingly substituted by a wide range of substituents (H, alkyl, aryl) in the 1-, 3-, and 5-position were also available in good yield and selectivity.[55] In conversions with free urea, control of selectivity leads to the hydantoin by the addition of a dehydration agent, or to the *N*-ureidoamino acid in the presence of an equivalent of water (Scheme 13).

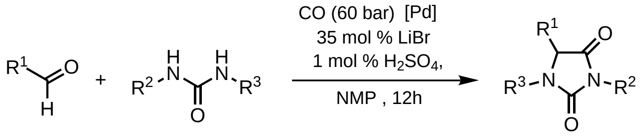


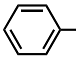
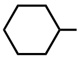
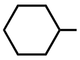
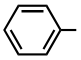
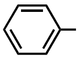
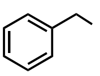
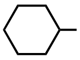
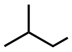
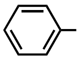
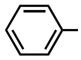
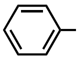
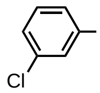
Scheme 13. Palladium-catalyzed ureidocarbonylation.

When monosubstituted ureas are used, 3-substituted hydantoins are obtained selectively, while with *N*,*N*′-disubstituted ureas the 1,3-substituted hydantoins are obtained (Table 2).[58] The acylpalladium(II) complex formed by CO insertion can first react intermolecularly with water to form the *N*-ureidocarboxylic acid, which then cyclizes,[59] or it can be opened directly with the intramolecular formation of the hydantoin.[60]

One important advantage of ureidocarbonylation lies in the practicability of the reaction, thus, for example 47 g (89%) of 5-cyclohexyl-1,3-dimethylhydantoin can be formed without complications in a 300-mL autoclave from 29 g of cyclo-

Table 2. Palladium-catalyzed ureidocarbonylation to substituted hydantoins.[a]



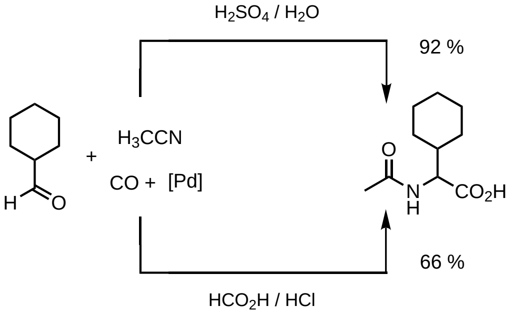
Entry	R^1	R^2	R^3	T [°C]	Yield [%][b]	TON
1		CH_3	H	80	75	300
2		C_2H_5	H	100	51	204
3			H	100	64	256
4			H	100	50	200
5		C_2H_5	C_2H_5	100	89	356
6		CH_3	CH_3	120	61	244
7[c]	H			130	93	372
8	H	CH_3	CH_3	100	73	292
9		CH_3	CH_3	100	85	340
10		CH_3	CH_3	100	79	316

[a] In each case a 25.0 mL solution of the urea (1.0 M) and the aldehyde (1.0 M) in *N*-methylpyyolidinone (NMP), 0.25 mol% $[PdBr_2(PPh_3)_2]$ prepared in situ, 35 mol% LiBr, and 1 mol% H_2SO_4 were treated with 60 bar carbon monoxide for 12 h. [b] Yield of the isolated product. [c] Reaction time 48 h.

hexanal, 22 g of dimethylurea, and carbon monoxide (60 bar, 0.16 g $PdBr_2$, 0.32 g PPh_3, 4.5 g LiBr, 0.25 g H_2SO_4, 100 °C, 24 h).

3.2.2 *Amidocarbonylation of Nitriles*

The use of acetamide currently stands in the way of the use of amidocarbonylation in the production of high tonnage *N*-acetylamino acids such as *N*-acetyl-D,L-valine or methionine. Unlike the raw material costs of various aldehydes and amines, it is clear that the amide components are frequently the cost-determining factor in the raw material costs. The corresponding nitriles may be regarded as economically interesting amide equivalents. For this reason the amidocarbonylation of nitriles was developed in which the amide is generated in situ.[61] A one-pot process with selective hydrolysis of the nitriles to the amides, and subsequent palladium-catalyzed amidocarbonylation has been carried out successfully by a number of routes. The dropwise addition of the nitrile to a concentrated sulfuric acid/water mixture[62] gave different *N*-acylamino acids in very good yields after amidocarbonylation (Scheme 14).



Scheme 14. Amidocarbonylation of nitriles.

In addition, *N*-acylamino acids may be prepared conveniently by passing a stream of HCl through a nitrile/formic acid solution[63] followed by carbonylation of the aldehydes formed.[64]

3.2.3. *Miscellaneous*

The special significance of halide ions as co-catalysts for palladium-catalyzed amidocarbonylation suggests that low-melting halide salts could be used as a reaction medium. The use of salt melts is known in the literature for hydrogenation, hydroformylation, olefin dimerization, and the Heck reaction.[65] Investigations have shown that the use of quaternary ammonium or phosphonium salts, such as $n\text{Bu}_4\text{NBr}$ or $n\text{Bu}_4\text{PBr}$, as the solvent give activities and selectivities as high as NMP in palladium-catalyzed amidocarbonylation.[66] The use of halide-free 1-ethyl-3-methylimidazolium hexafluorophosphate as the solvent has demonstrated that the presence of halide ions cannot be omitted, even in ionic liquids. In the reaction of cyclohexanal with acetamide in $n\text{Bu}_4\text{NBr}$, a catalyst turnover number of 20000 (TOF 330 h^{-1}) can be achieved with 0.001 mol% of $[PdBr_2(PPh_3)_2]$.

For a process-orientated palladium-catalyzed amidocarbonylation reaction it is important that the salt and solvent waste is kept as low as possible for each product. This may be achieved by, for example, the successful multiple use of the same product-saturated mother liquor from which the product crystallizes on cooling after the reaction.

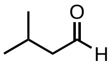
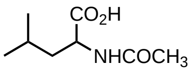
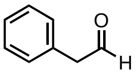
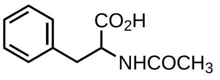
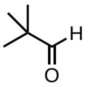
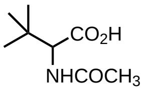
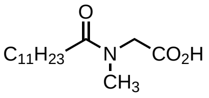
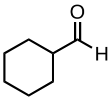
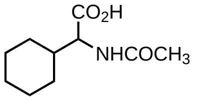
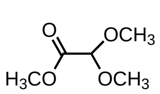
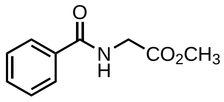
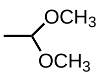
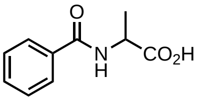
With the use of palladium on active carbon as the active catalyst it was possible to carry out amidocarbonylation in the presence of heterogeneous catalysts for the first time.[67] The otherwise system-inherent disadvantage of problematic catalyst separation in homogeneous catalytic reactions could be solved simply and efficiently in this heterogenization. The possibility of continuous process control in which the active catalyst remains constantly in the reaction is opened up by this variant. Almost quantitative conversions in palladium-catalyzed amidocarbonylation at only 10 bar CO pressure are not only of great interest for technical realization, but for the first time also permits a broad preparative utilization of amidocarbonylation in glass autoclaves, which are available in many laboratories.[68]

3.3. Synthetic Applications of Palladium-Catalyzed Amidocarbonylation

Amongst the synthetic applications of palladium-catalyzed amidocarbonylation, the examples discussed in greater detail here are those that are not amenable to cobalt catalysis, or have not otherwise been described. These include amidocarbonylation of aldehydes without α-H atoms, investigations into chemoenzymatic, two-stage processes for optically pure amino acids, and the preparation of N-substituted amino acids. In addition to these special applications (see below), numerous substrates have been used successfully in palladium-catalyzed amidocarbonylation, a few of which are listed in Table 3.

Of these, the high-yielding reaction to give *N*-acetyl-*tert*-leucine, which when enantiomerically pure is employed as a chiral auxiliary and as a building block in pharmaceutically active molecules,[69] is of special interest. The *N*-acetyl derivative of cyclohexylglycine, also an important unnatural amino acid, was obtained almost quantitatively with the palladium on active carbon catalyst (entry 5).[68] Acetals in the presence of one equivalent of water can also be used in place of the aldehyde in palladium-catalyzed amidocarbonylation (entries 6 and 7), and when methylglyoxalate dimethylacetal was used a concomitant decarboxylation afforded methyl glycinate.[68]

Table 3. Palladium-catalyzed amidocarbonylation of aldehydes and acetals.[a]

Entry	Aldehyde/acetal	*N*-Acyl-α-amino acid	Yield [%][b]
1			99
2[c]			78
3			95
4	CH_2O		85
5[d]			98
6[e]			42
7[e]			86

[a] In each case a 25.0 mL solution of the urea (1.0 M) and the aldehyde (1.0 M) in *N*-methylpyrrolidinone (NMP), 0.25 mol% $[PdBr_2(PPh_3)_2]$ prepared in situ, 35 mol% LiBr, and 1 mol% H_2SO_4 were treated with 60 bar carbon monoxide for 12 h. [b] Yield of isolated product. [c] 2 equiv aldehyde. [d] With 1 equiv H_2O. [e] Catalyst: 0.5 mol% Pd/C.

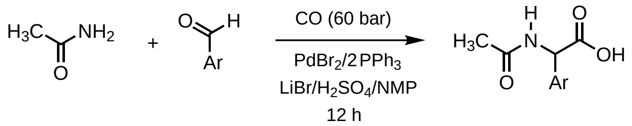
3.3.1. Functionalized Arylglycines

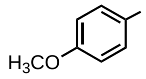
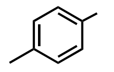
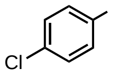
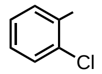
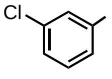
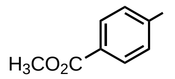
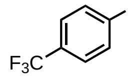
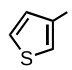
The products of amidocarbonylation of benzaldehydes, *N*-acyl-α-arylglycines, occur as substructures in many different pharmacologically active compounds.[70] Owing mainly to its occurrence in a group of highly effective glycopeptides, such as vancomycin, β-avoparcin, and chloropeptin I,[71] it has been one of the synthetically most investigated series of amino acids over the last two years.[72]

An atom-efficient synthesis by transition metal catalyzed amidocarbonylation has until now proved elusive since the classical cobalt catalysts cannot be extended to the carbonylation of aldehydes without an α-H atom. Instead benzylamides are formed as the product. Systematic studies have shown that amidocarbonylation of benzaldehydes in the presence of palladium catalysts allows the synthesis of many functionalized, racemic *N*-acetyl-α-arylglycines in very good yields (Table 4).[73]

It has also been found that substituents exert a significant electronic influence on the reactivity of the aldehyde.[74] Derivatives with electron-donating substituents react faster than those with electron-withdrawing substituents, although satisfactory yields could be achieved synthetically by an increase in the reaction temperature and reaction time. Further investigations with heteroaromatic aldehydes have

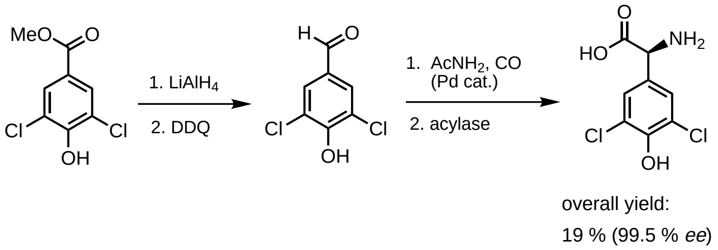
Table 4. Palladium-catalyzed amidocarbonylation of aromatic aldehydes.



Entry	Ar	σ_p[a]	(100 °C, 12 h)		(120 °C, 15 h)	
			yield [%][b]	TON[c]	yield [%][b]	TON[c]
1		−0.27	75	300	–	–
2		−0.17	86	344	95	380
3		0.30	65	260	–	–
4		–	56	224	–	–
5		–	63	252	–	–
6		0.39	52	208	89	356
7		0.54	42	168	82	328
8		–	–	–	42[d]	168

[a] Hammett constants for *para*-substituents. [b] Yield of isolated product. [c] TON [mol product/(mol cat.)]. [d] 60 h, 125 °C.

also given interesting heteroaryl glycines by this preparative route. The relevance of the palladium-catalyzed amidocarbonylation of benzaldehyde to the synthesis of natural products has also been demonstrated by the preparation in good to very good yields of 4-hydroxyarylglycines, which occur in cyclic glycopeptide antibiotics. In the case of the exemplary synthesis of the central amino acid of chloropeptin I,[75] (*S*)-3,5-dichloro-4-hydroxyphenylglycine, it was also possible to confirm the advantage of the two-stage combination of palladium-catalyzed amidocarbonylation and enantioselective, enzymatic hydrolysis by the acylase *Aspergillus spp.* in the synthesis of enantiomerically pure α-arylglycines. This synthesis is three steps shorter than the known literature method for similar derivatives, but with the same yield (Scheme 15).[76]



Scheme 15. Synthesis of the central amino acid of chloropeptin I by palladium-catalyzed amidocarbonylation.

3.3.2. *Chemoenzymatic Two-stage Processes for Optically Active Amino Acids*

In the past many elegant procedures have been developed for the preparation of enantiomerically pure α-amino acids.[5, 77] In spite of broad applicability and selectivity, many procedures have proved to be problematic when the methods have been applied to the 100-g scale or above. Furthermore, simple estimates of raw material costs show that even the most recent catalytic procedures are a factor of 10–100 more expensive than the route composed of a combination of multicomponent reaction (Strecker reaction/acetylation or amidocarbonylation) with enzymatic separation of the racemate. The sequence of chemical preparation of racemic *N*-acetylamino acids followed by enantioselective enzymatic hydrolysis is therefore one of the most versatile and industrially used methods for the preparation of optically active amino acids.[78] In this context the recent, more detailed description of the two-stage, chemoenzymatic process composed of amidocarbonylation and acylase-catalyzed racemate separation is of interest.[79]

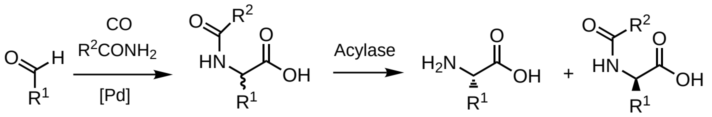
Different types of acylase differ not only in their activity and acceptance of the amino acid residue but are also to a large extent dependent upon the nature of the acyl residue.[80] Thus, in addition to acetyl derivatives, phenacetyl, methoxyacetyl, and formyl derivatives have been synthesized by palladium-catalyzed amidocarbonylation and hydrolyzed enantiospecifically with different acylases (AA, PKA, PA; Table 5).[80]

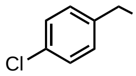
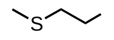
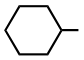
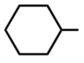
In this chemoenzymatic, two-stage synthesis it was possible to adapt the amidocarbonylation step for the use of different acylases. Thus, depending upon the derivative, it is possible to optimize the reaction for the best possible rate of hydrolysis and substrate tolerance by the selective coordination of the acyl residue with the acylase, which makes this method more attractive for the synthesis of enantiomerically pure amino acids. In this way it was also possible to prepare novel, *N*-acyl-functionalized amino acids by means of amidocarbonylation and to show that palladium-catalyzed amidocarbonylation is doubly convergent, that is, not only is an enormous breadth of substrate diversity tolerated in the aldehyde and hence in the amino acid residue, but equally a useful permutation in the amide moiety was accepted.

3.3.3. *N*-Substituted Glycines

As already mentioned, the amidocarbonylation of secondary amides—especially those with sterically demanding

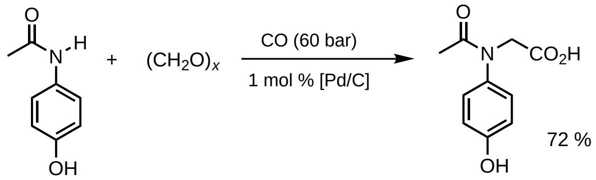
Table 5. Synthesis of enantiomerically pure α-amino acids by palladium-catalyzed amidocarbonylation and enzymatic hydrolysis.



	Amidocarbonylation[a]			Enzymatic hydrolysis		
entry	yield [%][b] (TON)	(*R*,*S*)-*N*-acyl-AS R¹	R²	enzyme[c]	(*S*)-AS yield [%] (*ee* [%])	(*R*)-*N*-acyl-AS yield [%] (*ee* [%])
1	75 (300)		CH_3	AA	40.4 (≥99.5)	45.6 (94.4)
2	75 (300)		CH_3	PKA	32 (≥99.5)	40 (85.6)
3	83 (332)		Bz	PA	38 (≥99.5)	49 (≥94)
4	83 (332)		CH_2OCH_3	PKA	43.9 (98.8)	47.2 (96.8)

[a] Conditions: 25 mL NMP (1M in aldehyde and acetamide), 0.25 mol% $[PdBr_2(PPh_3)_2]$, 35 mol% LiBr, 1 mol% H_2SO_4, 60 bar CO, 120 °C, 12 h. [b] Yield of isolated product. [c] AA = *Aspergillus spp.* acylase, PKA = pig liver acylase.

residues—are significantly more difficult to carry out than the corresponding reactions of primary amides. However, it has been possible to prepare a series of interesting N-substituted *N*-acetylglycines by reaction with formaldehyde.[67] Particularly good results have been achieved with a catalyst of palladium on activated carbon at 130°C and extended reaction times (60 h). For example, the respective reaction of paracetamol gave a 70% yield of *N*-acetyl-*N*-(4-hydroxyphenyl)glycine [Eq. (9)], the analogue of *N*-acetyl-4-hydroxyphenylglycine, which may also be prepared in very good yields by palladium-catalyzed amidocarbonylation.



(9)

N-Substituted glycines are building blocks of an important class of peptide mimics, the peptoids.[81] By the synthesis of different alkyl- and aryl-substituted glycines it was possible to show that palladium-catalyzed amidocarbonylation offers a simple route to the monomers of this medically important group of active compounds

4. Summary and Prospects

Since its discovery in 1971 cobalt-catalyzed amidocarbonylation has experienced numerous developments. Of particular importance here are the development of domino sequences such as the domino hydroformylation–amidocarbonylation reaction to give *N*-acylamino acids directly from olefins. Such reactions are prime examples of the increasingly discussed development of "sustainable" synthetic methods ("green chemistry"),[82] since more complex, industrially interesting products are formed in a 100% atom economic manner from simple building blocks.

With the establishment of palladium-catalyzed amidocarbonylation, critical advances have been made in the recent years with the attainment of higher catalyst activities under milder conditions. With respect to functional-group tolerance too, palladium-catalyzed variants are currently superior to the cobalt-catalyzed reaction. Synthetically, the spectrum could thus be widened by the preparation of functionalized arylglycines and hydantoins as well as the amidocarbonylation of nitriles. Today, standardized reactions with a catalyst of palladium on activated carbon and a carbon monoxide pressure of 10 bar simplifies the applicability of the methodology.

Although numerous elegant new synthetic methods are available for the preparation of enantiomerically pure amino acids, the development of economically practicable procedures on a scale in excess of 100 g are still a challenge. With this background, chemoenzymatic two-stage procedures of amidocarbonylation with subsequent enzymatic separation of the racemate offers an interesting route to enantiomerically pure, natural and unnatural amino acids on a multi-gram scale.

What are the future challenges in the area of amidocarbonylation procedures? Without doubt these include the development of asymmetric amidocarbonylation. We have succeeded in making the first step in this direction by the use of chiral phosphane ligands such as 1-diphenylphosphanylethylbenzene in the palladium-catalyzed amidocarbonylation of isovaleraldehyde to *N*-acetylleucine with 10% *ee*.[83] Other research groups have also recently observed enantiomeric excesses in palladium-[84] and cobalt-catalyzed amidocarbonylations,[85] although they are still unsatisfactory. The search for "efficient" ligands has only just begun. Although amidocarbonylation has been known for almost 30 years, another area of stereoselective methodology has been neglected. With one exception no diastereoselective conversions have been described. In the area of diastereoselective reactions, di- and oligopeptide preparations appear to us to be of particular interest for the future. Such reactions are fundamentally possible, but here too the task still remains to explore the applicability of the method systematically.

Although a large number of *N*-acylamino acids are easy to synthesize with palladium and cobalt catalysts, there are still aldehydes that are not amenable to amidocarbonylation, or are only unsatisfactorily so (for example, carbohydrate aldehydes, indole aldehydes, iodo- and bromo-substituted aldehydes, a few arylacetaldehydes). The use of ketones as carbonyl components would also be very interesting for the preparation of α-quarternary *N*-acylamino acids. Perhaps totally new catalyst systems will have to be used for these "problem cases". When it is considered that carbonylation reactions related to amidocarbonylation can be catalyzed not only by metal complexes of Co and Pd, but also, for example by Rh and Ir complexes, it should be fundamentally possible to develop alternative catalysts for amidocarbonylation.

A larger, industrial scale cobalt- or palladium-catalyzed amidocarbonylation is still awaited. Whereas the cobalt-catalyzed variant has been able to prove its industrial feasibility on a pilot plant scale, to our knowledge the more recent palladium-catalyzed variant has been only developed to a 2-L scale. Technical questions and the problem of the co-catalyst remain to be solved in the future.

In conclusion it remains to be said that amidocarbonylation, a three-component reaction with a terminal carbonylation step, is but one example of a transition metal catalyzed multicomponent reaction. In the development of such multicomponent reactions with the participation of a transition metal catalyzed step we see great potential for the development of totally new reactions, which will lead to greater creation of wealth by the formation of interesting products from simple starting materials.

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[1] Review article and book contributions: a) K. Kühlein, H. Geissler in *Transition Metals for Organic Synthesis* (Eds.: M. Beller, C. Bolm), WILEY-VCH, Weinheim, **1998**, p. 79; b) J. F. Knifton in *Applied Homogeneous Catalysis with Organometallic Compounds* (Eds.: B. Cornils, W. A. Herrmann), VCH, Weinheim, **1996**, p. 159; c) I. Ojima, *Chem. Rev.* **1988**, *88*, 1011; d) I. Ojima, *J. Mol. Catal.* **1986**, *37*, 25.

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