

RESEARCH ARTICLE

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Combination of the structural components of amino acids with fatty acids: access to an unknown class of “fatty” α -amino acids by palladium-catalyzed amidocarbonylation†

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A new class of amino acids, so-called fatty amino acids, which integrate the typical structural motif of another important class of natural products, fatty acids, is presented. By applying palladium-catalyzed amidocarbonylation, diverse new *N*-acyl fatty amino acids are synthesized in one step in a 100% atom-efficient manner. Utilizing a small amount (0.5 mol%) of simple commercial Pd(OAc)₂, the desired products can be synthesized in good to high yields, up to multi-g-scale. The shown products represent a combination of two essential classes of natural products and provide new bio-based building blocks with potential for many applications.

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Introduction

α -Amino acids and their derivatives are a prerequisite for life on Earth.^{1–10} Apart from their manifold biological functions in humans, animals, and plants, they find numerous applications in diverse fields ranging from nutrition and pharmaceuticals to cosmetics. Another class of essential biomolecules are fatty acids, which are aliphatic monocarboxylic acids with longer, linear, and partially unsaturated carbon chains. Esters of fatty acids with glycerol are found in all natural fats and oils and represent an important renewable feedstock highly relevant for the chemical industry.^{11–14}

Due to their importance, α -amino acids and fatty acids have been studied in detail by chemists, biologists, and many other scientists for more than a hundred years, and a large number of derivatives have been synthesized for numerous applications.^{15–23} Although both biochemically essential classes of compounds occur in all living organisms, surprisingly there are no “hybrid” molecules in nature, *e.g.* amino acids with longer (unsaturated) aliphatic chains in the α -position. Clearly, such extended alkyl

groups will determine the hydrophobicity of the respective amino acid. In fact, hydrophobic interactions play a dominant role in stabilizing protein structures. Why has evolution avoided such chemical compounds? To answer this and to study the properties of “fatty” amino acids, it is important to provide synthetic methodologies, which allow a convenient and general preparation of such compounds. Very surprisingly, such derivatives (with alkyl chains >C9) have not been synthesized to the best of our knowledge (Fig. 1). Therefore, we set out to develop an efficient and environmentally friendly protocol to make such molecules conveniently available on a g-scale for further studies. A straightforward route to synthesize natural and unnatural *N*-acyl amino acids is the so-called amidocarbonylation of aldehydes (Fig. 2a).²⁴ This one-pot, three-component reaction makes use of aldehydes, amides, and carbon monoxide in the presence of a suitable metal catalyst. Amidocarbonylations are generally catalyzed by cobalt and palladium complexes. As they are 100% atom-economical and use readily available substrates, they are also interesting from ecological and economic points of view.

Originally in 1971, Wakamatsu reported the use of cobalt carbonyl complexes for this transformation.²⁵ Later, researchers at Hoechst developed a palladium-catalysed variant, which works under milder reaction conditions.²⁶ Interestingly, homogeneous^{27–30} and heterogeneous^{31–34} palladium catalysts have been applied in the latter and related cases.

The carbonylation of fatty aldehydes with CO in the presence of amides should in principle lead to unnatural long-chain amino acids, which also exhibit interesting amphiphilic (surface-active) properties.^{35–37} At this point, it is worth men-

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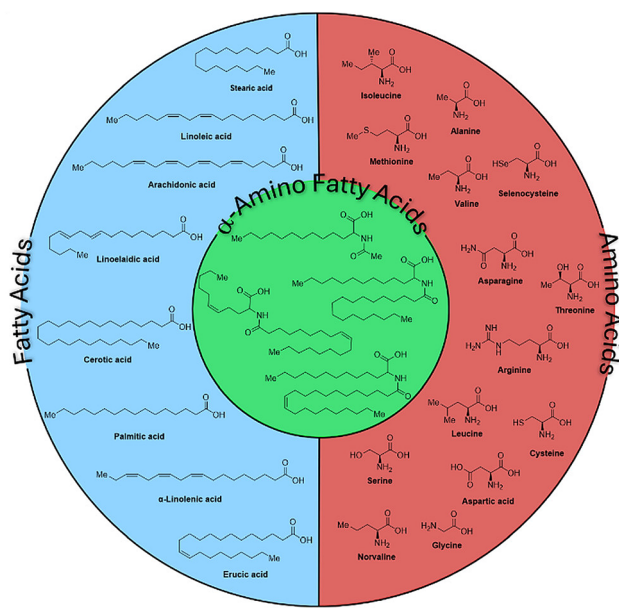


Fig. 1 "Fatty" α -amino acids: a new class of compounds.

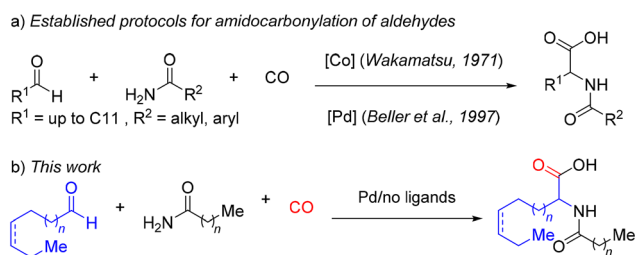


Fig. 2 Amidocarbonylation of aldehydes and amides.

tioning that the synthesis of new (bio-)surfactants with a hydrophilic head and a hydrophobic tail gained increasing attention in recent years,^{38–40} e.g. as part of modern vaccines.⁴¹

Against this background, we report here the first synthesis of a new class of unnatural amino acids. More specifically, we show that a variety of α -fatty amino acid derivatives are readily accessible by a palladium-catalysed amidocarbonylation reaction of the corresponding aldehydes in very good yields and selectively (Fig. 2b).

Results and discussion

We commenced our studies using commercially available dodecanal **1a** and acetamide **2a** as model substrates in the presence of 1 mol% Pd(OAc)₂, 1 mol% H₂SO₄, and 35 mol% LiBr in *N*-methyl-2-pyrrolidone (NMP) as solvent at 100 °C under 60 bars of CO. Similar reaction conditions have been reported by some of us in the developmental studies of palladium-catalysed amidocarbonylation.²⁴ Gratifyingly, the desired product was obtained in quantitative yield under these conditions.

To identify crucial reaction parameters, some variations of the metal precursor, temperature, pressure, additives, and solvent were made (Fig. 3). Notably, in all these experiments, a 1 : 1 ratio of amide and aldehyde was used, which is the most economical and avoids additional waste formation. Among the different palladium precursors, Pd(acac)₂ and Pd(OAc)₂ provided **3a** in quantitative yield, while Pd₂dba₃ and PdBr₂ gave lower product yield. Utilizing different solvents in the reaction furnished the product **3a** in lower yield compared to NMP. In general, high product yields were obtained at lower CO pressure (20 bar) and lower temperature (60 °C). Decreasing the amount of catalyst proved to be viable and with only 0.1 mol% Pd(OAc)₂, 80% yield of **3a** was achieved. Furthermore, high catalyst turnover numbers (TON > 2000) in this transformation could be realized. From a mechanistic point of view, it is interesting that the reaction is quite sensitive to the amount of LiBr (35 mol%). As discussed below (see Fig. 5), the formation of α -bromo-*N*-alkylamide seems to be crucial for the product formation. In agreement with this assumption, the replacement of LiBr with LiCl resulted in a lower yield of **3a**. To better understand the amidocarbonylation of dodecanal, a kinetic profile of the model system was created under the optimized conditions. For this purpose, reactions were interrupted at precise moments and the crude reaction mixture was analysed. The first hour of the reaction time, 60% of product **3a** was formed in addition to 40% of unreacted aldehyde **1a** (Fig. 4 and Table S1, entry 2[†]), showing the rapid nature of the process. Interestingly, after 6 hours, neither aldehyde **1a** nor amide **2a** was observed, but the product yield still increased in the following 10 h until a nearly quantitative yield of **3a** was obtained (Table S1, entry 5[†]). It is worth mentioning that the aldehyde and amide showed the same rate of consumption in the reaction and no intermediates could be observed. Adding new substrates and co-catalysts after 16 hours led to the formation of an additional 40% of **3a**, indicating that the catalyst was still "alive".

Performing the model reaction under standard conditions but without CO showed significant conversion of dodecanal and acetamide; however, apart from an aldol condensation by-product, no other product was observed by GC-MS (see the ESI for details[†]). All these control experiments agree with the previously postulated mechanism for the Pd-catalysed amidocarbonylation of aldehydes (Fig. 5).²⁶ The process starts with the condensation between the aldehyde **1a** and the amide **2a**, resulting in the intermediate **4**. Then, due to acidic conditions, protonation of the hydroxy group and further replacement by a bromide anion lead to intermediate **5**, which is in equilibrium with **4**. Then, oxidative addition of Pd⁰ species to intermediate **5** starts the catalytic cycle and leads to **6**. Next, CO coordinates to the stabilized Pd⁺² intermediate, furnishing **7**. After ligand exchange, the desired product is formed by reductive elimination and the active Pd⁰ species is restored to start again the catalytic cycle.

To showcase the possibility to provide multi-gram-scale amounts of this novel class of compounds, e.g. for biological studies, we carried out upscaling experiments. As expected,



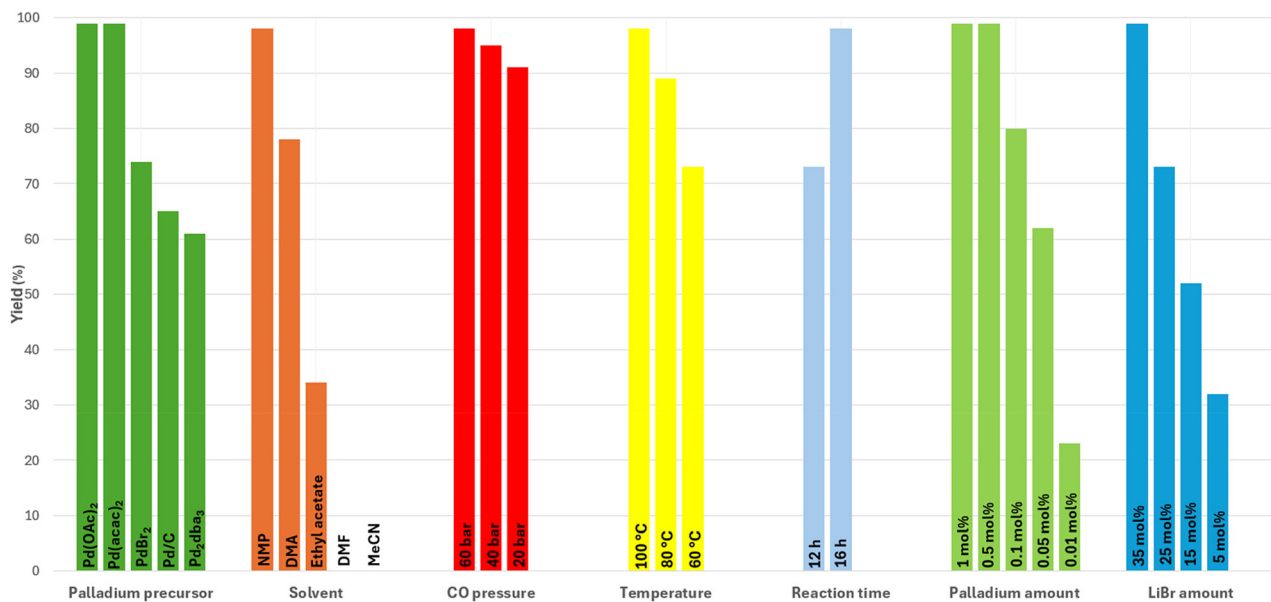


Fig. 3 Palladium-catalysed amidocarbonylation of dodecanal with acetamide: variation of reaction conditions. Reactions were conducted on a 0.5 mmol scale and yields were determined by ¹H-NMR analysis using 3,5-bis(trifluoromethyl)bromobenzene as an internal standard.

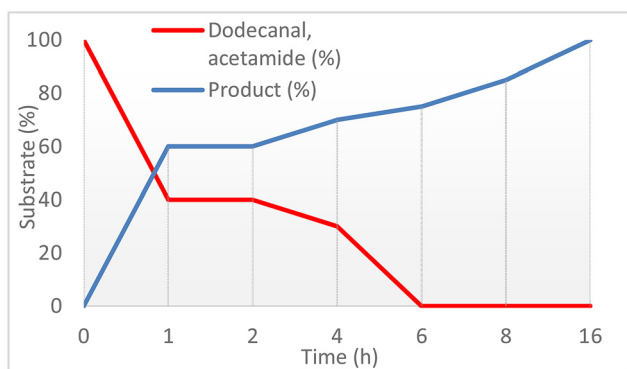


Fig. 4 Consumption of dodecanal and acetamide, and formation of product **3a** hour by hour.

product **3a** could be easily isolated in around 8 g after filtration, solvent removal, and extraction without the necessity of column chromatography. Then, we started to prepare a variety of *N*-acyl amino acids with longer alkyl chains and investigated the scope of the reaction (Fig. 7). First, we performed reactions of the model aldehyde dodecanal **1a** with different amides. Applying *N*-alkyl amides, such as acetamide **2a**, butanamide **2b**, and stearamide **2c**, provided the corresponding products **3a**, **3b**, and **3c** in good to high yields (84%, 90% and 78%, respectively). Similarly, cyclohexanecarboxamide **2g** led to the desired product **3g** in 75% yield. In humans, it is well known that saturated fatty acids have undesired biological properties. In contrast, unsaturated fatty acids have several health benefits, including potentially reducing the risk of heart disease. Hence, we tested unsaturated amides containing isolated double bonds in the alkyl chain, like oleamide **2d** and erucamide **2e**. To our delight, the reaction

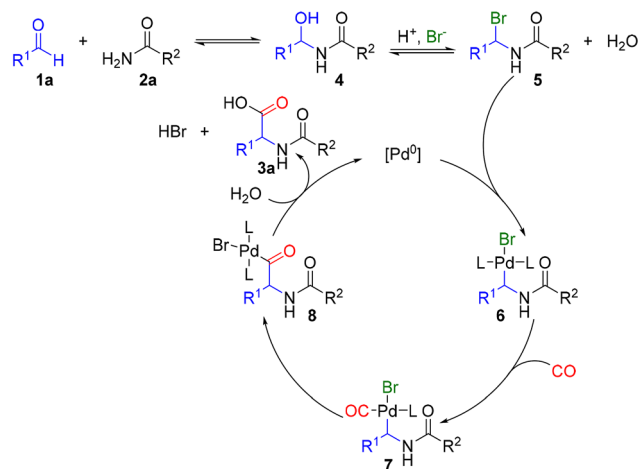


Fig. 5 Proposed mechanism for the Pd-catalyzed amidocarbonylation of aldehydes.

system is well tolerant towards olefins and the respective products **3d–e** were furnished in good yields (68% and 71%). These latter results are noteworthy, as Pd-catalysed double bond isomerization or olefin carbonylation reactions could be expected. We also performed the reaction with industrially relevant methacrylamide containing a conjugated double bond, and the product **3f** was obtained in 55% yield. For the first time, this substrate has been applied in amidocarbonylations and it was also possible to obtain suitable crystals for SC-XRD and its structure could be confirmed (Fig. 6, see the ESI for details[†]).⁴²

Next, we turned our attention to the reaction of dodecanal with aromatic amides bearing different substituents. The parent benzamide **2h** gave the respective *N*-aryl-fatty amino



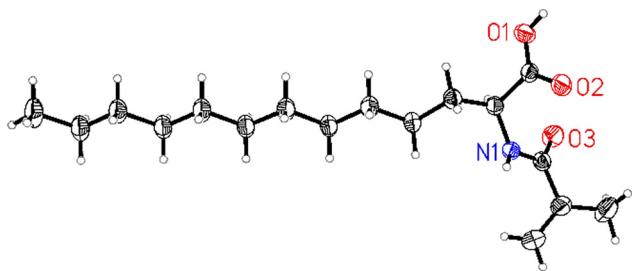


Fig. 6 Molecular structure of **3f**. Displacement ellipsoids correspond to 50% probability.

acid **3h** in 75% yield, while more electron-rich 4-methoxybenzamide **2i** provided the desired product **3i** in 63%. Amides containing other functional groups, such as carboxylic acid and cyclic amide, were also tolerated, and the respective **3j** and **3k** products were isolated in 34% and 77% yields. However, *N*-methyl acetamide **2l** showed only low reactivity under these optimized conditions. As expected, aromatic aldehydes furnished the desired products **3p–m** in 38–83% yields.

Furthermore, other unsaturated aldehydes can be utilized to provide novel amino acids in one step. As an example, (*Z*)-dec-4-enal **1r** reacted smoothly with acetamide **2r** to afford product **3r** in 85% yield, while the product **3s** from the reaction with oleamide **2d** was obtained in 57%. In addition, cyclohexanecarboxamide and 4-methoxybenzamide furnished the respective products **3t** and **3u** in 69% and 85% yields, respectively. Applying 2,6-dimethylhept-5-enal, a fragrance aldehyde also known as melonal **1q** was obtained in 35% yield.

Apart from all these examples, other functionalized aldehydes including geranial, vanillin, 5-hydroxymethylfurfural (HMF), furfural, and syringaldehyde were tested. Unfortunately, under the standard reaction conditions in these cases no desired product was formed and unwanted side reactions such as oligomerization occurred.

Procedure and characterization

An 8 mL vial equipped with a stir bar was charged with Pd(OAc)₂ (0.5 mol%), aldehyde (0.5 mmol, 1 equiv.), amide

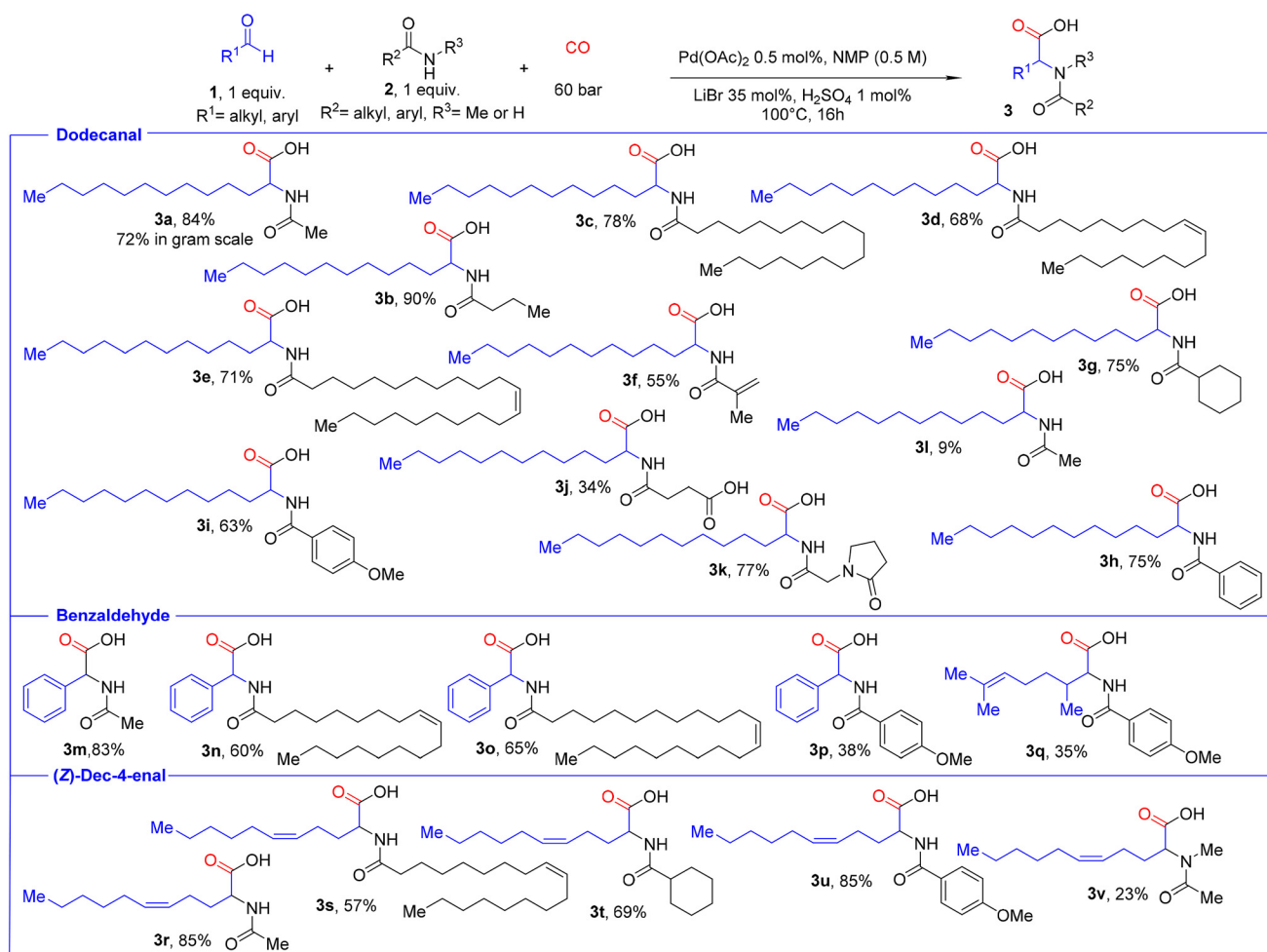


Fig. 7 Synthesis of diverse *N*-acyl fatty α -amino acids. Reaction conditions: Pd(OAc)₂ (0.5 mol%), aldehyde (0.5 mmol, 1 equiv.), amide (0.5 mmol, 1 equiv.), LiBr (35 mol%) and H₂SO₄ (1 mol%) in NMP (1 mL), CO (60 bar), 100 °C, and 16 h. Isolated yields from 0.5 mmol scale reactions.



(0.5 mmol, 1 equiv.), LiBr (35 mol%) and H₂SO₄ (1 mol%) in NMP (1 mL). The reaction mixture was stirred under 60 bar CO at 100 °C for 16 h. After this time, the crude product was filtered through a small pad of Celite® with EtOAc and it was concentrated under reduced pressure. Then, NMP was removed from the crude product with distillation (1 mbar, 68 °C) and extraction methods or column chromatography were performed.

Conclusions

In summary, we have developed a protocol for the synthesis of an overlooked class of α -amino acid derivatives. It is very surprising that amino acids with long (unsaturated) alkyl chains in the α -position have never been described or found in living organisms or plants, although another important class of biomolecules, fatty acids, contain such structural units. We believe that it will be interesting to study the biological function of such amino acids and modified peptides or proteins. Therefore, it is necessary to provide synthetic protocols for their synthesis. We show that the known palladium-catalysed amidocarbonylation can be easily utilized to prepare a variety of so-called fatty amino acids in a 100% atom-efficient manner in the presence of low catalyst amounts.

All the obtained products have previously not been synthesized and present an interesting class of compounds, which combine two essential classes of natural products. Integrating such novel amino acids allows for the preparation of peptides and proteins with many potentially biological functions, as hydrophobic residues from amino acids contribute significantly to receptor activation, G protein coupling, and oligomerization processes. In addition, their physical properties as surfactants make this synthetic protocol interesting for several applications in chemistry and biology. Finally, it is worth mentioning that the developed procedure can be combined with subsequent enzyme-catalysed kinetic resolution, which should allow for a straightforward two-step synthesis of the respective amino acid enantiomers.^{42,43}

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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