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Organocatalytic decarboxylation of amino acids as a route to bio-based amines and amides

Laurens Claes, Michiel Janssen, and Dirk E. De Vos*[a]

Abstract: Amino acids obtained by fermentation or recovered from protein waste hydrolysates represent an excellent renewable resource for the production of bio-based chemicals. In an attempt to recycle both carbon and nitrogen, we report here on a chemocatalytic, metal-free approach for decarboxylation of amino acids, thereby providing a direct access to primary amines. In the presence of a carbonyl compound the amino acid is temporarily trapped into a Schiff base, from which the elimination of CO_2 may proceed more easily. After evaluating different types of aldehydes and ketones on their activity at low catalyst loadings (≤ 5 mol%), isophorone was identified as powerful organocatalyst under mild conditions. After optimisation many amino acids with a neutral side chain were converted in 28-99% yield in 2-propanol at 150 °C. When the reaction is performed in DMF, the amine is susceptible to *N*-formylation. This consecutive reaction is catalysed by the acidity of the amino acid reactant itself. In this way, many amino acids were efficiently transformed to the corresponding formamides in a one-pot catalytic system.

Introduction

Amino acids have nowadays major applications in human health and nutrition as well as in animal feed formulation. Bulk production processes based on fermentation and enzymatic catalysis have been developed to meet the global demand, which nowadays exceeds 5 million tons per year.[1],[2] Amino acids can also be obtained by hydrolysis of protein-rich biomass residuals from the agro-, food and biofuel industries, *e.g.* wheat dried distillers grains with solubles, sugar beet/cane vinasses or slaughterhouse waste.[3] However, protein waste has often poor nutritional quality and should therefore rather be considered as a renewable resource of both carbon and nitrogen for the chemical industry.[4]-[8]

Selective modification or elimination of the carboxylic acid moiety at the α-carbon of amino acids provides direct access to a range of value-added nitrogenous chemicals.[9]-[14] We showed earlier that the majority of the amino acids present in plant protein hydrolysates can be converted into amino alcohols by Rh-catalysed hydrogenation,[14] or into nitriles by electrochemical or transition metal-catalysed oxidative decarboxylation.[11] In this work we study the decarboxylation of amino acids to bio-based amines; the latter have applications in the synthesis of polymers, pharmaceuticals and agrochemicals.[15][16]

The non-oxidative decarboxylation of amino acids is catalysed by homogeneous transition metal complexes, such as Cu^{I}-phenanthroline.[17] However, this method involves high catalyst loadings (10 mol%) and proceeds at high temperature (> 180 °C). Moreover, the scope is limited to amino acids with aliphatic and aromatic side chains, from which the corresponding primary amines are isolated only in moderate yield (up to 68%). Wallentin and co-workers developed a photocatalytic approach, which is more promising in terms of scope, yield and conditions, but a protecting group is required on both the amine moiety and side chain functional groups to obtain high selectivity in the presence of radical species.[18] Decarboxylation is also a step in several photoredox-based carbon-carbon bond-forming reactions using protected amino acids as a coupling partner.[19]-[23]

Transition metal-free approaches for amino acid decarboxylation have been reported as well. For instance, the formation of biogenic amines in food and beverages is related either to the presence of carbohydrate- or lipid-derived reactive carbonyl compounds,[24],[25] or to the action of amino acid decarboxylases containing pyridoxal 5'-phosphate (PLP) or a pyruvoyl group as cofactor.[26],[27] In these systems the decarboxylation is facilitated by the formation of a Schiff base adduct between the amino acid and the carbonyl compound, which allows to stabilise charged intermediates by electron delocalisation in a conjugated system (Scheme 1). Moreover, these enzymes are able to tune the selectivity towards decarboxylation rather than to transamination or racemisation by exploiting stereo-electronic interactions between the Schiff base adduct and the surrounding protein matrix.[28]-[31] The decarboxylation of amino acids has been performed with isolated enzymes,[32]-[34] but the expensive PLP cofactor is slowly consumed by transamination and the long-term stability can also be an issue, even after immobilisation.[35]

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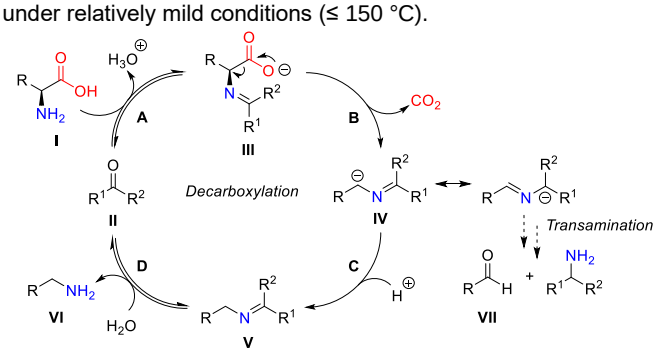
In an attempt to mimic the enzymatic approach, both aliphatic and aromatic carbonyl compounds have been proposed as suitable mediators for amino acid decarboxylation. Although these compounds have often been evaluated as stoichiometric reagents,[36]-[50] they are not consumed according to the mechanism (Scheme 1). However, their ability to act as a catalyst has only rarely been exploited before. Promising results were obtained for α,β-unsaturated ketones like 2-cyclohexen-1-one in certain case studies, but reactions were still applied with rather high catalyst loadings and at high temperature.[41]-[50] Therefore, this study aims to identify a performant organocatalyst for amino acid decarboxylation, which is active at low loadings (≤ 5 mol%) and under relatively mild conditions (≤ 150 °C).



Scheme 1. Mechanism of the organocatalytic decarboxylation of α-amino acids: [**A**] condensation between the α-amino acid (**I**) and the carbonyl compound (**II**); [**B**] decarboxylation of the Schiff base adduct (**III**); [**C**] protonation of the azomethine ylide intermediate (**IV**), and [**D**] hydrolysis of the Schiff base adduct (**V**), with release of an amine (**VI**) and regeneration of the catalyst. Transamination, where the carbonyl compound is consumed and the α-amino acid is converted to the corresponding aldehyde (**VII**), can be a competitive side reaction.

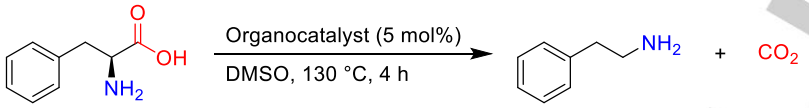
Results and Discussion

Decarboxylation of amino acids to amines

Catalyst screening. The decarboxylation of phenylalanine (**1a**) to 2-phenethylamine (**2a**) was studied as a model reaction to assess the intrinsic catalytic activity of different carbonyl compounds under relatively mild conditions (Table 1; additional examples in the Supporting Information (Table S1)). To that end, a catalyst loading of 5 mol% was applied, which is low in comparison with previous studies.[36]-[50] The thermal decarboxylation of **1a** at 130 °C – in the absence of any additional carbonyl compound – occurred only to a limited extent (entry 1). First, structural analogues of PLP and the pyruvoyl cofactor present in amino acid decarboxylases were selected as potential organocatalysts, but pyridine-4-carbaldehyde, 4-acetylpyridine and methyl pyruvate showed no activity (entries 2-4). These observations demonstrate clearly that the enzymatic approach benefits from interactions between the Schiff base adduct and the surrounding protein matrix in the active site. For instance, the pyridine moiety in PLP can be protonated and is then able to serve as a temporary electron sink which stabilises the azomethine ylide intermediate (Scheme 1, **IV**).[29] The range of nearly inactive carbonyl compounds further comprises dicarbonyl compounds (entry 5), aliphatic and aromatic aldehydes (entries 6-7), saturated cyclic ketones (entry 11) and aromatic ketones (entries 12-13). On the other hand, low but clear activities were observed for pyrrole- and indole-based aldehydes (entries 8-9) and aliphatic ketones (entry 10); the yield of **2a** was typically < 30%. Aryl aliphatic ketones with an electron-donating substituent at the *o*- or *p*-position of the aromatic ring produce **2a** in higher yields, even > 50% (entries 26-27 versus 25 and 28-29). However, acetophenone itself was partially consumed by transamination to 1-phenethylamine (entry 25). α,β-Unsaturated ketones (entries 14-24), in particular the derivatives of 2-cyclohexen-1-one (entries 18-21 and 23), are among the most active organocatalysts: for instance, **2a** was produced in > 85% yield within 4 h by using isophorone or 3-phenyl-2-cyclohexen-1-one. These catalysts increased the amine yield at least by a factor 10 compared to the thermal reaction. Also carvone seems to perform very well even at a relatively low temperature and at a low catalyst loading (entry 23). This terpenoid-based α,β-unsaturated ketone was recently applied by Morrison and co-workers in the decarboxylation of **1a**, though under more drastic conditions: they performed the reaction at 190 °C with two molar equivalents of carvone, and obtained **2a** in 78% yield within 5 min.[48] Here we show that a similar yield can be obtained by using isophorone under milder conditions and at much lower catalyst loadings. The latter is advantageous regarding catalyst efficiency and product purification.

The differences in reactivity between these carbonyl compounds can be rationalised in terms of the mechanism (Scheme 1). Performant organocatalysts, *viz.* aryl aliphatic ketones and α,β-unsaturated ketones, contain a molecular motif that enables electron delocalisation in a conjugated system and stabilises the azomethine ylide intermediate (**IV**) obtained by decarboxylation of the Schiff base adduct (**III**). A higher reactivity was observed for ketones that contain an electron-donating substituent on the aromatic ring (Table 1, entries 26-27 versus 25 and 28-29). However, ketones that contain two aromatic moieties were almost inactive (entries 12-13), probably because the extent of resonance stabilisation became too pronounced. A similar trend was observed for α,β-unsaturated cyclic ketones bearing a methyl or phenyl substituent at position C-3 (entries 17 versus 16; 19-21 versus 18). Although the catalytic activity clearly depends on resonance stabilisation, the electron density on the α-carbon atom of the substrate should remain sufficiently high to facilitate the protonation of intermediate **IV**. In addition, the sp^2-hybridised carbon atoms of both the carbon-nitrogen and carbon-carbon double bonds in **III** should be coplanar, preferably in a six-membered ring, to facilitate electron delocalisation.[29] For instance, a threefold increase in the yield of **2a** was achieved by using 3-methyl-2-cyclohexen-1-one instead of 3-methyl-2-cyclopenten-1-one (entries 19 versus 17), because the latter suffers from a higher ring strain. The difference in activity between 1-tetralone and 1-indanone can be explained in a similar manner (entries 30 versus 31). The high performance of isophorone can be attributed to the presence of these key features in its molecular motif, and therefore this ketone was selected for further investigation. Moreover, isophorone is commercially available and cheap, as it is produced by base-catalysed aldol condensation of acetone.

Table 1. Decarboxylation of phenylalanine (**1a**) to 2-phenethylamine (**2a**): catalyst screening.[a]



1a **2a**

Entry	Organocatalyst	Y_{2a} [%][b]	Entry	Organocatalyst	Y_{2a} [%][b]
1	–	6	17	3-Methyl-2-cyclopenten-1-one	26
2	Pyridine-4-carbaldehyde	6	18	2-Cyclohexen-1-one	47
3	4-Acetylpyridine	5	19	3-Methyl-2-cyclohexen-1-one	83
4	Methyl pyruvate	6	20	Isophorone	86
5	2,4-Pentanedione	13	21	3-Phenyl-2-cyclohexen-1-one	86
6	Butyraldehyde	13	22	3-Methoxycarbonyl-2-cyclohexen-1-one	18
7	Benzaldehyde	9	23	(*R*)-Carvone	77
8	Pyrrole-2-carbaldehyde	25	24	1-Acetyl-1-cyclohexene	57
9	Indole-3-carbaldehyde	32	25	Acetophenone	35
10	Acetone	32	26	2'-Methoxyacetophenone	55
11	Cyclohexanone	13	27	4'-Methoxyacetophenone	53
12	Benzophenone	14	28	2'-Bromoacetophenone	23
13	9-Fluorenone	10	29	4'-Bromoacetophenone	28
14	4-Methylpent-3-en-2-one	51	30	1-Tetralone	75
15	2,6-Dimethyl-2,5-heptadien-4-one	63	31	1-Indanone	44
16	2-Cyclopenten-1-one	16	32	2-Indanone	8

[a] Conditions: **1a** (0.25 mmol), organocatalyst (0.0125 mmol), DMSO (1 mL), 130 °C, 4 h. [b] The yield (*Y*) of **2a** was determined by GC analysis using benzonitrile as the internal standard.

Optimisation of reaction conditions. The influence of several parameters such as catalyst loading, time and solvent was studied for the isophorone-catalysed decarboxylation of **1a** (see also Supporting Information, Figures S1-S2). When the progress of the reaction under standard conditions was monitored in function of time, the yield of **2a** reached an optimum between 1 h and 4 h, and decreased upon prolonging the reaction time to 24 h (Figure 1). A similar trend was observed at reduced catalyst loadings, *e.g.* 2.5 and 1 mol% isophorone. Although both the initial rate and yield decreased by using only 1 mol% of isophorone, **2a** was still produced in about 70% yield within 4 h. On the other hand, when the reaction was performed under solvent-free conditions, **2a** was obtained in 80% yield after 4 h. Nevertheless, further experiments were conducted using a catalyst loading of 5 mol% isophorone.

The decarboxylation **1a** was also performed in other solvents than DMSO (Table 2). The selection was limited to polar solvents, both protic and aprotic, mainly for reasons of amino acid solubility and stabilisation of charged intermediates. The reaction did not proceed in water (entry 1) because Schiff base condensation, which is an essential step in the catalytic cycle, is inhibited. Moreover, isophorone has a limited solubility in water. Among the high-boiling solvents, DMSO remains the most appropriate choice and this solvent is also less harmful than for instance *N*,*N*-dimethylformamide (DMF), *N*,*N*-dimethylacetamide (DMAc) and *N*-methylpyrrolidone (NMP) (entries 11 versus 13-15).[51] Remarkably, *N*-(2-phenethyl)formamide and *N*-(2-phenethyl)acetamide were identified as the main products after 24 h in DMF or DMAc respectively, suggesting that **2a** is susceptible to a consecutive *N*-acylation thereby using the solvent as acyl donor (*vide infra*). Low-boiling solvents are however more attractive in terms of sustainability and product purification (entries 1-8, 10).

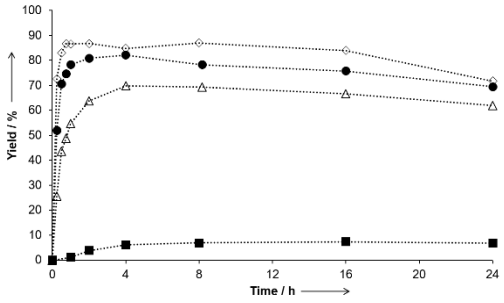
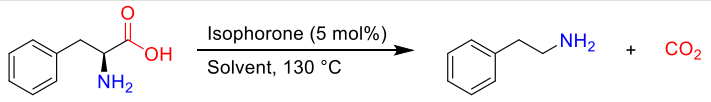


Figure 1. Variation of the catalyst loading in the decarboxylation of phenylalanine (**1a**) to 2-phenethylamine (**2a**). Conditions: **1a** (0.25 mmol), isophorone, DMSO (1 mL), 130 °C. The yield of **2a** was determined by GC analysis using benzonitrile as the internal standard. Legend: (■) no catalyst, (△) 1 mol%, (●) 2.5 mol%, and (◇) 5 mol% of isophorone.

Table 2. Isophorone-catalysed decarboxylation of phenylalanine (**1a**) to 2-phenethylamine (**2a**): solvent screening.[a]



1a **2a**

Entry	Solvent	T_{bp} [°C]	Conditions[a]	Y_{2a} [%][b]		
				2 h	4 h	24 h
1	Water	100	A	*n.r.*[c]	*n.r.*[c]	*n.r.*[c]
2[d]	Methanol	65	A	37	44	53
3[e]	Ethanol	78	A	53	82	89
4[e]	1-Propanol	97	A	40	81	89
5	2-Propanol	82	A	37	62	88 (83)[f]
6[e]	1-Butanol	118	A	44	64	88
7	2-Butanol	100	A	11	29	87
8	*tert*-Butanol	82	A	16	55	88
9	Ethylene glycol	198	B	23	18	10
10	Acetonitrile	82	A	16	33	42
11	Dimethyl sulfoxide	189	B	85	86	74
12	Formamide	210	B	*n.r.*[c]	*n.r.*[c]	*n.r.*[c]
13	*N*,*N*-Dimethylformamide	153	B	11	9	8
14	*N*,*N*-Dimethylacetamide	166	B	76	74	42
15	*N*-Methylpyrrolidone	202	B	72	70	63
16	Sulfolane	287	B	19	38	67

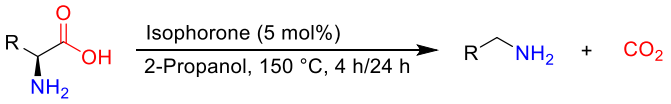
[a] Conditions A: **1a** (1.25 mmol), isophorone (0.0625 mmol), solvent (5 mL), 130 °C, stainless steel autoclave. Conditions B: **1a** (0.25 mmol), isophorone (0.0125 mmol), solvent (1 mL), 130 °C, glass reactor. [b] The yield (*Y*) of **2a** was determined by GC analysis using benzonitrile as the internal standard. [c] *n.r.* = no reaction. [d] Phenylalanine methyl ester was obtained in 15%, 20% and 26% yield after 2 h, 4 h and 24 h, respectively. [e] The yield of phenylalanine alkyl ester was always < 5%. [f] Isolated yield of the hydrochloride salt between brackets.

Whereas the yield of **2a** proceeds through an optimum in function of time in most polar aprotic solvents, such behaviour was not observed for most protic solvents. Moreover, **2a** was obtained in almost 90% yield after 24 h in C_2-C_4 alcohols (entries 3-8). A lower rate was observed in secondary alcohols (entries 5 versus 4; 7 versus 6) and **1a** was partially consumed by esterification when the reaction was carried out in methanol (entry 2). This side reaction should be avoided because the decarboxylation does not proceed from an amino acid ester. Therefore, 2-propanol was considered as the most suitable solvent for decarboxylation.[51]

By switching the solvent from DMSO to 2-propanol, longer reaction times were required to obtain **2a** in high yield at 130 °C (entry 5). The reaction time could be strongly reduced by increasing the temperature: **2a** was produced in 90% yield within 1 h at 150 °C (Supporting Information, Figure S3), whereas more than 4 h were required to obtain a similar result at 130 °C. Moreover, the high performance of isophorone can be maintained at catalyst loadings as low as 0.5 mol%: **2a** was produced in 87% yield within approximately 4.5 h, whereas the yield was nearly 40% in the absence of catalyst. The latter result is remarkably high in comparison with the thermal reaction in DMSO and can be explained by the presence of acetone in the reaction mixture, which may originate from solvent dehydrogenation under aerobic conditions. Nevertheless, the catalytic effect of isophorone was clearly demonstrated at short reaction times and therefore 150 °C was selected as the optimal temperature for amino acid decarboxylation in 2-propanol.

Substrate scope. The isophorone-based system was evaluated for other amino acids (Table 3). Intrinsic differences in reactivity among various substrates were demonstrated by performing the decarboxylation for 4 h and 24 h. Besides, the solubility of amino acids in the reaction medium should also be considered. Glycine (**1b**) and amino acids with an aliphatic side chain such as alanine (**1c**), valine (**1d**), leucine (**1e**), isoleucine (**1f**) and norleucine (**1g**) were converted to the corresponding primary amines **2b**-**2g** in

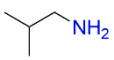
Table 3. Scope of the isophorone-catalysed decarboxylation of amino acids to amines.[a]



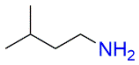
1b-1x **2b-2x**

2b: *Y* = 35% * / 99%

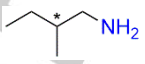
2c: *Y* = 59% * / 99% (99%)



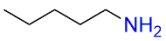
2d: *Y* = 96% / 98% (80%)



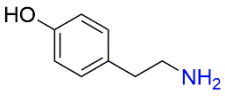
2e: *Y* = 98% / 98% (79%)



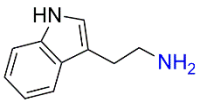
2f: *Y* = 98% / 98% (87%)



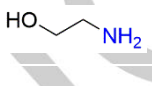
2g: *Y* = 99% / 99%



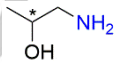
2h: *Y* = 2% * / 29%



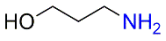
2i: *Y* = 89% / 91%



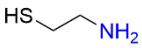
2j: *Y* = 53% * / 99% (88%)



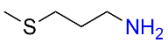
2k: *Y* = 30% * / 99% (94%)



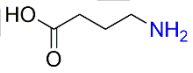
2l: *Y* = 44% / 45%



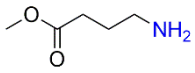
2m: *Y* < 1% / < 1%



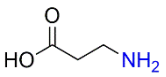
2n: *Y* = 90% * / 99% (91%)



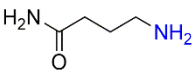
2o: *Y* < 1% * / < 1% [b]



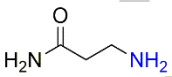
2p: *Y* < 1% / < 1% [c]



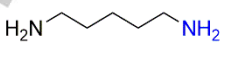
2q: *Y* < 1% * / < 1% * [d]



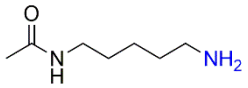
2r: *Y* = < 1% * / < 1% [e]



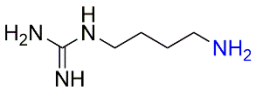
2s: *Y* = 7% * / 9% *



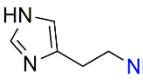
2t: *Y* = 8% * / 28% * [f]



2u: *Y* = 90% * / 99%



2v: *Y* < 1% * / < 1% *

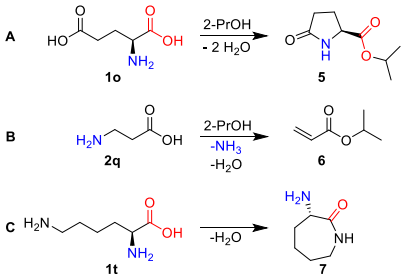


2w: *Y* = 7% * / 37% *

2x: *Y* =99% / 99% (97%)

[a] Conditions: amino acid (1.25 mmol), isophorone (0.0625 mmol), 2-propanol (5 mL), 150 °C, 4 h or 24 h, stainless steel autoclave. The yield (*Y*) of the amine was determined by GC analysis using benzonitrile as the internal standard; isolated yield of the hydrochloride salt obtained after 24 h between brackets. Reactions with incomplete substrate conversion are marked by an asterisk (*). [b] The yield of isopropyl pyroglutamate (**4o**) was 12% and 75% after 4 h and 24 h, respectively. [c] The combined yield of methyl and isopropyl pyroglutamate (**4o**) was 32% and 85% after 4 h and 24 h, respectively. [d] Isopropyl acrylate (**4q**) was obtained in 5% yield after 24 h. [e] The yield of 2-pyrrolidone was 7% and 11% after 4 h and 24 h, respectively. Isopropyl pyroglutamate was obtained in 32% and 64% yield after 4 h and 24 h, respectively. [f] The yield of α-amino-ε-caprolactam (**4t**) was 10% and 7% after 4 h and 24 h, respectively.

excellent yield (> 98%) after 24 h. Moreover, the reactivity of the substrate increases with the length of the alkyl side chain. These observations confirm that a higher electron density on the α-carbon in the substrate is beneficial regarding the protonation of the azomethine ylide intermediate **IV** (Scheme 1, step **C**). Proline (**1x**), which contains a secondary amine, shows an exceptionally high reactivity since pyrrolidine (**2x**) was produced in 99% yield within 4 h. In this case the decarboxylation proceeds through an iminium cation-type intermediate. Within the class of amino acids with an aromatic side chain, the reactivity of tryptophan (**1i**) is similar to that of **1a**, because tryptamine (**2i**) was obtained in 89% yield within 4 h. However, the decarboxylation of tyrosine (**1h**) and histidine (**1w**) was limited because of their low solubility in 2-propanol. Serine (**1j**) and threonine (**1k**) were converted successfully to ethanolamine (**2j**) and 1-amino-2-propanol (**2k**) respectively, but the ω-amino alcohol from homoserine (**1l**) was obtained in rather poor yield, even after 24 h. Methionine (**1n**) was efficiently converted with 90% yield within 4 h, showing that the thioether moiety was tolerated. Cysteine (**1m**), which contains a thiol group in the side chain, was degraded completely at 150 °C; GC-MS analysis revealed diethyl disulfide as major by-product. The decarboxylation of amino acids with acidic and basic groups in the side chain was unsuccessful. Both glutamic acid (**1o**) and glutamine (**1r**) were converted to isopropyl pyroglutamate rather than to γ-aminobutyric acid (**2o**) or γ-aminobutyramide (**2r**), even when the free carboxylic acid group at the γ-position of **1o** was protected by esterification (**1p**). The lactamisation of **1o**, **1p** and **1r** and subsequent esterification to alkyl pyroglutamates (**5**) proceeded fast in an alcohol solvent at 150 °C (Scheme 2, **A**). Although pyroglutamic acid is not able to form a Schiff base adduct with isophorone, it should not be considered as a waste product because it can be converted to 2-pyrrolidone by Pd-catalysed decarboxylation under more drastic conditions.[12]



Scheme 2. Side reactions observed during the isophorone-catalysed decarboxylation of certain amino acids: [**A**] lactamisation and esterification of glutamic acid (**1o**) to an alkyl pyroglutamate (**5**); [**B**] deamination and esterification of β-alanine (**2q**) to an alkyl acrylate (**6**), and [**C**] lactamisation of lysine (**1t**) to α-amino-ε-caprolactam (**7**).

Further, aspartic acid (**1q**) and asparagine (**1s**) were almost unreactive under these conditions, mainly for reasons of solubility. Isopropyl acrylate (**6**) was identified as the main product from **1q** instead of the expected β-alanine (**2q**), suggesting that a deamination step is involved (Scheme 2, **B**). Additional experiments showed that acrylate esters were not obtained by decarboxylation of fumaric acid under identical conditions, and therefore decarboxylation must precede deamination in the production of acrylates from **1q**. The reactivity of lysine (**1t**) was affected by the presence of an additional amino group in the side chain. Indeed, Schiff base condensation occurs to a much lesser extent under basic conditions and the ε-amino group is in competition with the α-amino group for Schiff base condensation with isophorone. Moreover, lactamisation of **1t** to α-amino-ε-caprolactam (**7**) was observed as a side reaction (Scheme 2, **C**). Isophorone loadings > 100 mol% might be beneficial for the production of 1,5-pentanediamine (**2t**) in higher yields. Alternatively, a protecting group on the ε-amino group of lysine, as in *N*-ε-acetyllysine (**1u**), allows to obtain the corresponding amine **2u** in 90% yield even within short reaction times. The lack of reactivity observed for arginine (**1v**) can be explained in a similar manner. Finally, this procedure for organocatalytic decarboxylation of amino acids can be applied on gram scale without loss in yield, which has been demonstrated for phenylalanine and leucine (Supporting Information).

Tandem decarboxylation – *N*-acylation of amino acids to amides

When the isophorone-catalysed decarboxylation of **1a** was performed in DMF, *N*-(2-phenethyl)formamide (**3a**) was obtained in 84% yield after 24 h, whereas the yield of **2a** was < 10% (Table 4, entry 2). A similar side reaction was observed in DMAc, but the yield of *N*-(2-phenethyl)acetamide (**4a**) was only 45% after 24 h (entry 3). In both cases, the amide was produced by a consecutive *N*-acylation (Figure 2), which proceeds by a nucleophilic attack of **2a** on the carbonyl group in DMF or DMAc. GC-MS analysis confirmed that dimethylamine remains as a co-product in solution. The extent of *N*-acylation is dependent on the accessibility and the electrophilic character of the carbonyl group in the acyl donor, and was therefore more pronounced in DMF than in DMAc. In contrast to the reaction in DMSO, the overall yield of amino acid decarboxylation in DMF, taking into account both the amine **2a** and the amide **3a**, remains nearly constant at longer reaction times (Figure 2). Because both the amino acid reactant and the corresponding amine are able to form Schiff base adducts with isophorone, *in situ* modification of nucleophilic amines to inert amides provides a strategy to perform the decarboxylation with higher efficiency under mild conditions.

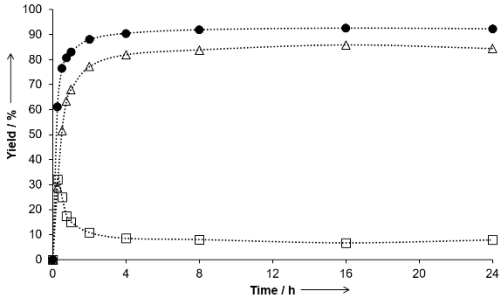
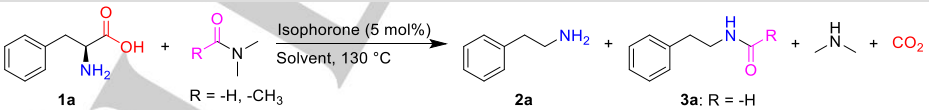


Figure 2. Time course plot for the tandem decarboxylation – *N*-formylation of phenylalanine (**1a**) to 2-phenethylamine (**2a**) and *N*-(2-phenethyl)formamide (**3a**). Conditions: **1a** (0.25 mmol), isophorone (0.0125 mmol), DMF (1 mL), 130 °C. The yield of **2a** and **3a** was determined by GC analysis using benzonitrile as the internal standard. Legend: (□) yield of **2a**, (△) yield of **3a**, and (●) overall yield.

Table 4. Isophorone-catalysed decarboxylation of phenylalanine (**1a**) in high-boiling solvents.[a]



Entry	Solvent	Y_{2a} [%][b]		$Y_{3a\ or\ 4a}$ [%][b]		$S_{3a\ or\ 4a}$ [%][b]	
		4 h	24 h	4 h	24 h	4 h	24 h
1	Dimethyl sulfoxide	86	74	< 1	< 1	–	–
2	*N*,*N*-Dimethylformamide (R = -H)	9	8	81	84 (75)	91	91
3	*N*,*N*-Dimethylacetamide (R = -CH_3)	74	42	12	45	14	52

[a] Conditions: **1a** (0.25 mmol), isophorone (0.0125 mmol), solvent (1 mL), 130 °C. [b] The yield (*Y*) of 2-phenethylamine (**2a**) and *N*-(2-phenethyl)formamide (**3a**) or *N*-(2-phenethyl)acetamide (**4a**) were determined by GC analysis using benzonitrile as the internal standard; isolated yield between brackets. The selectivity (*S*) to **3a** was expressed by the ratio $Y_{3a} / (Y_{2a} + Y_{3a})$, and analogously for **4a**.

Formamides are important intermediates in the synthesis of agrochemicals, pharmaceuticals and isocyanides. They are prepared from primary and secondary amines by organocatalysis, acid- or transition metal-mediated catalysis, thereby using CO, methanol, paraformaldehyde, formic acid or esters thereof as a precursor of the carbonyl group.[52] In an alternative manner, they can be produced by *N*-formylation of amines in DMF, which is for instance catalysed by CeO_2.[53] However, high metal loadings (40 mol%) and elevated temperatures (up to 180 °C) are generally required to produce formamides in high yield. The tandem decarboxylation – *N*-formylation of amino acids was observed here for the first time and is proposed as an alternative route towards functionalised formamides, because both reactions can be performed under mild conditions in a one-pot catalytic system, even in the absence of transition metals. This two-step reaction will therefore be studied in more detail.

Optimisation of reaction conditions. The tandem decarboxylation – *N*-formylation of **1a** was again selected as the model reaction to study the effect of parameters such as catalyst loading and temperature. Isophorone is the actual catalyst for the decarboxylation of **1a** in DMF: the conversion was negligible in the absence of isophorone, but even 1 mol% of the ketone was sufficient to increase the overall yield of **2a** and **3a** to 88% within 24 h (Supporting Information, Figure S4). A further increase in catalyst loading to 2.5 or 5 mol% was beneficial in terms of rate and overall yield, and may compensate for eventual catalyst degradation. Indeed, isophorone was partially consumed by transamination and subsequent *N*-formylation to *N*-(3,5,5-trimethyl-2-cyclohexen-1-yl)formamide; the extent of catalyst degradation can be as high as 20%. Further optimisation was therefore performed using 5 mol% of isophorone. Although the tandem reaction proceeds at 100 °C, the rate can be increased at higher temperatures: the overall yield of **2a** and **3a** was 93% after 4 h at 150 °C, whereas at least 24 h were required to obtain the same result at 100 °C (Figure S5). Product degradation at higher temperatures was however not observed in DMF. The optimal temperature was selected at 130 °C, because high overall yields were obtained within 8 h under mild conditions.

Acid-catalysed *N*-formylation of amines. When **1a** and **2a** were treated in the presence of isophorone in DMF under identical conditions, **3a** was produced with higher rate and in higher yield from **1a** than from **2a**, respectively in 84% and 59% yield after 24 h (Figure 3). These observations suggest that the *N*-formylation of **2a** in the tandem process is catalysed by the substrate **1a** itself. The carboxylic acid group has a key role, which was confirmed by additional experiments. First, when the decarboxylation of **1a** in DMF was performed in the presence of a strong, non-nucleophilic base like 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), the yield of **3a** was reduced from 81% to 43% after 4 h (Supporting Information, Table S2). However, in this case the decarboxylation step might also be influenced by the altered acid-base conditions. Secondly, acidic additives facilitate the *N*-formylation of **2a** in DMF: the yield of **3a** was increased from 19% to 86% within 4 h by the addition of only 5 mol% acetic acid to the reaction medium (Table S3).

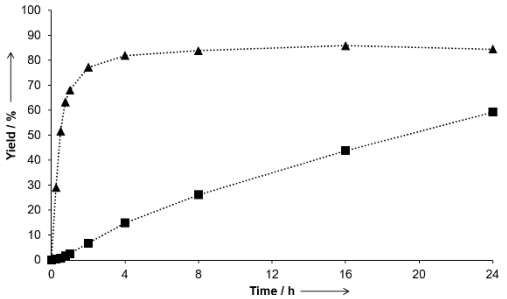
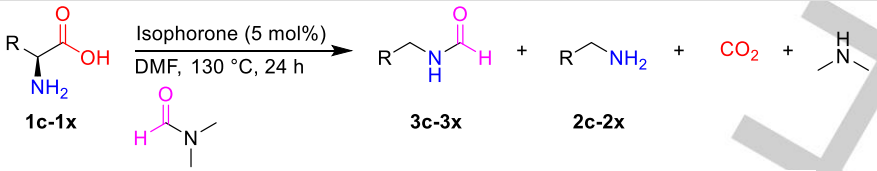
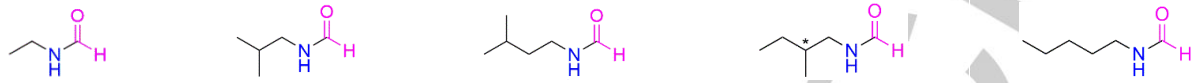


Figure 3. Tandem decarboxylation – *N*-formylation of phenylalanine (**1a**, ▲) versus *N*-formylation of 2-phenethylamine (**2a**, ■) in DMF. Conditions: **1a** or **2a** (0.25 mmol), isophorone (0.0125 mmol), DMF (1 mL), 130 °C. The yield of *N*-(2-phenethyl)formamide (**3a**) was determined by GC analysis using benzonitrile as the internal standard.

Substrate scope. The catalytic system that was optimised for the tandem decarboxylation – *N*-formylation of **1a** is also able to convert other amino acids to the corresponding formamides (Table 5). A catalyst loading of 5 mol% isophorone was applied and reactions were performed at 130 °C for 24 h to account for eventual differences in substrate reactivity, as was demonstrated earlier in Table 3. Formamides **3c-3g** were obtained in > 90% yield from alanine (**1c**), valine (**1d**), leucine (**1e**), isoleucine (**1f**) and norleucine (**1g**). The formamide **3x** derived from proline (**1x**) was also obtained in excellent yield. However, the decarboxylation of tryptophan (**1i**) proceeded to a lesser extent compared to the reaction in 2-propanol. Remarkably, whereas the decarboxylation of tyrosine (**1h**) and histidine (**1w**) was unsuccessful in 2-propanol, the tandem reaction in DMF produced the corresponding formamides **3h** and **3w** in 74% and 82% yield respectively. A similar result was obtained for aspartic acid (**1q**), although the effect was less pronounced. Reducing the concentration of nucleophilic primary amines in the reaction medium by *N*-formylation increases the tendency of unconverted amino acids towards Schiff base condensation with isophorone. *N*-Formylation thus allows to overcome the major bottleneck in Schiff base-mediated amino acid decarboxylation. Substrates with a functionalised side chain can be converted with a higher overall yield by the tandem process. The formamides **3j-3l** and **3n** derived from serine (**1j**), threonine (**1k**), homoserine (**1l**) and methionine (**1n**) were produced in good to excellent yield; however cysteine (**1m**) was again degraded completely under these conditions. Glutamic acid (**1o**), its 5-methyl ester derivative (**1p**) and glutamine (**1r**) were mainly converted to pyroglutamic acid (Scheme 2, **A**), which was subsequently formylated at its amide nitrogen to *N*-formylpyroglutamic acid. Finally, lysine (**1t**) was converted to a much higher extent in DMF than in 2-propanol, because the reactivity of the ε-amino group in the side chain was also diminished by *N*-formylation in DMF; *N*,*N'*-(pentane-1,5-diyl)diformamide (**3t**) was obtained in 69% yield. The decarboxylation proceeds even faster when the ε-amino group is already protected at the onset of the reaction, as in *N*-ε-acetyllysine (**1u**). Finally, asparagine (**1s**) and arginine (**1v**) were unreactive under these conditions.

Table 5. Scope of the tandem decarboxylation – *N*-formylation of amino acids to formamides.[a]





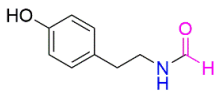
3c: *Y* = 99% (*S* > 99%)
2c: *Y* < 1%

3d: *Y* = 91% (*S* = 95%)
2d: *Y* = 5%

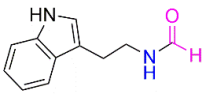
3e: *Y* = 93% (*S* = 96%)
2e: *Y* = 4%

3f: *Y* = 94% (*S* = 94%)
2f: *Y* = 6%

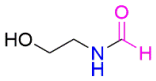
3g: *Y* = 96% (*S* = 96%)
2g: *Y* = 4%



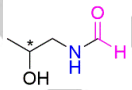
3h: *Y* = 74% (*S* = 92%)
2h: *Y* = 7%



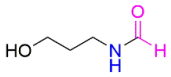
3i: *Y* = 35% (*S* = 78%)
2i: *Y* = 10%



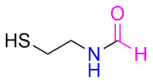
3j: *Y* = 98% (*S* = 98%)
2j: *Y* = 2%



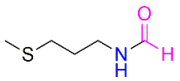
3k: *Y* = 98% (*S* = 98%)
2k: *Y* = 2%



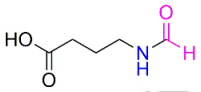
3l: *Y* = 76% (*S* > 99%)
2l: *Y* < 1%



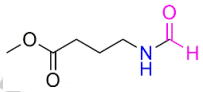
3m: *Y* < 1%
2m: *Y* < 1%



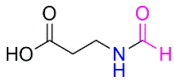
3n: *Y* = 96% (*S* = 96%)
2n: *Y* = 4%



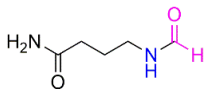
3o: *Y* < 1% [c]
2o: *Y* < 1%



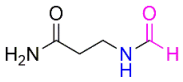
3p: *Y* < 1% [d]
2p: *Y* < 1%



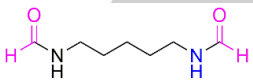
3q: *Y* = 21% (*S* = 53%)
2q: *Y* = 19%



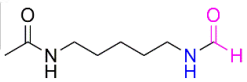
3r: *Y* < 1% [e]
2r: *Y* < 1%



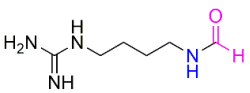
3s: *Y* = 3%
2s: *Y* = 2%



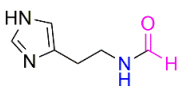
3t: *Y* = 69% (*S* = 88%)
2t: *Y* < 1%



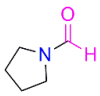
3u: *Y* = 88% (*S* = 90%)
2u: *Y* < 1%



3v: *Y* < 1%
2v: *Y* < 1%



3w: *Y* = 82% (*S* = 95%)
2w: *Y* = 4%



3x: *Y* = 97% (*S* = 97%)
2x: *Y* = 3%

[a] Conditions: amino acid (0.25 mmol), isophorone (0.0125 mmol), DMF (1 mL), 130 °C, 24 h. [b] The yields (*Y*) of the amine and the amide as well as the selectivity (*S*) to the amide were determined by GC analysis using benzonitrile as the internal standard. [c] The yields of pyroglutamic acid and *N*-formylpyroglutamic acid were 19% and 21% respectively. [d] The combined yield of pyroglutamic acid and methyl pyroglutamate was 47%, and the yield of *N*-formylpyroglutamic acid was 21%. [e] The yields of 2-pyrrolidone and *N*-formylpyroglutamic acid were respectively 21% and 75%.

Conclusions

Organocatalysis provides a powerful tool to perform the non-oxidative decarboxylation of amino acids under relatively mild conditions and in the absence of transition metals. Detailed insights have been gained in the remarkably high activity of α,β-unsaturated ketones and in particular isophorone at low catalyst loadings. The organocatalytic system allows to produce several bio-based nitrogenous chemicals by simply changing the solvent: many amino acids can be converted with good to excellent yields to the corresponding amines in 2-propanol, whereas formamides are obtained in DMF because the amines are susceptible to a consecutive acid-catalysed *N*-acylation. The chemocatalytic approach is especially useful in the valorisation of the neutral amino acid fraction, and therefore highly complementary to the enzymatic decarboxylation of acidic and basic amino acids. Although the mechanism relies on Schiff base formation between the amino acid and the ketone, the catalytic cycle may be inhibited by the accumulation of amines in the process medium at high conversion, because the ketone can be trapped in a Schiff base adduct with the product. *In situ* modification of amines, for example by *N*-acylation, can be a useful approach to achieve a higher overall yield in amino acid decarboxylation.

Experimental Section

General procedure for decarboxylation of amino acids. A 10 mL stainless steel reactor was charged with amino acid (1.25 mmol, 1 equiv.), isophorone (0.0625 mmol, 5 mol%), 2-propanol (5 mL) and a stirring bar, sealed and heated at 150 °C under magnetic stirring. After 4 h or 24 h the reactor was cooled to room temperature in an ice bath. Benzonitrile (1.25 mmol) was added afterwards as an internal standard for quantitative analysis of the product mixture by gas chromatography (GC).

General procedure for tandem decarboxylation – *N*-formylation of amino acids. A 2 mL glass vial was charged with amino acid (0.25 mmol, 1 equiv.), isophorone (0.0125 mmol, 5 mol%), DMF (1 mL) and a stirring bar, sealed and heated at 130 °C under magnetic stirring. After 24 h the vial was cooled to room temperature in an ice bath. Benzonitrile (0.25 mmol) was added afterwards as an internal standard for quantitative analysis of the product mixture by GC.

Other experimental procedures for the synthesis of 2-cyclohexene-1-one derivatives, isolation of amines and formamides out of process mixtures and larger scale reactions are available in the Supporting Information. Data on compound characterisation by GC-MS and NMR spectroscopy are provided as well.

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Keywords: amino acids • organocatalysis • Schiff base • amines • amides

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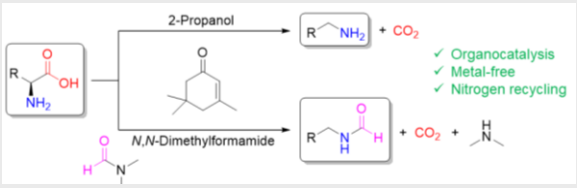

A catalytic system based on isophorone is able to convert a broad range of amino acids to the corresponding amines in the absence of transition metals under mild conditions. The decarboxylation can be coupled with the *N*-formylation of amines by performing the reaction in DMF, resulting in a one-pot process to obtain amino acid-derived formamides. Both methods provide opportunities for recycling nitrogen from protein-rich biomass waste.

*Dr. Laurens Claes, Michiel Janssen and Prof. dr. Dirk E. De Vos**

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Organocatalytic decarboxylation of amino acids as a route to bio-based amines and amides