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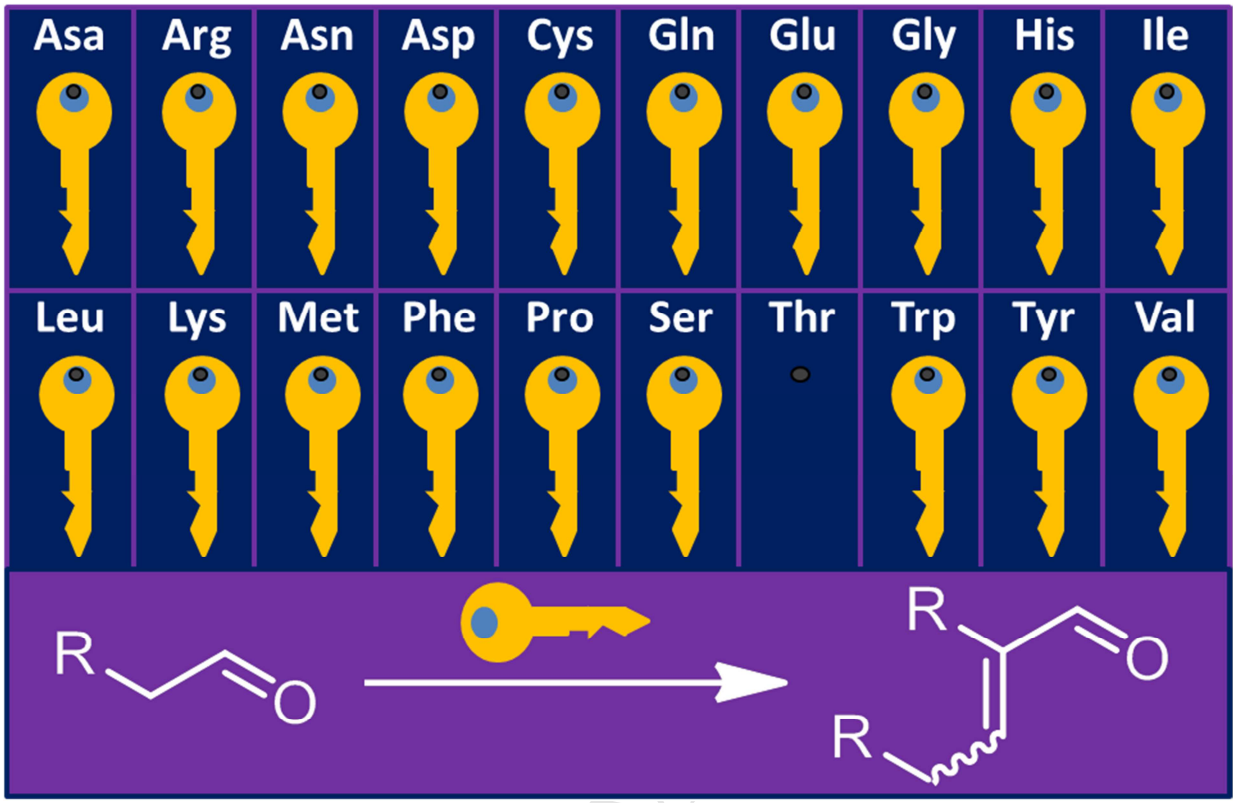
Graphical Abstract



20 proteinogenic amino acids were applied as organocatalysts in the homo aldol condensation of aldehydes. Basic amino acids were highly active at low catalyst concentrations and aromatic amino acids generated very good yields in short reaction times. The side chain groups have no catalytic activity, but they have a big impact on the catalytic activity. A general method was developed, being transferable to other substrates.

A Comprehensive Investigation and Optimisation on the Proteinogenic Amino Acid catalysed Homo Aldol Condensation

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Abstract

A systematic investigation regarding the application of catalytic amounts of all 20 proteinogenic amino acids in the homo aldol condensation of aldehydes is described obtaining excellent yields of the desired *α,β*-unsaturated aldehyde. These investigations proved the basic amino acids, lysine and arginine, are effective as organocatalysts, if comparably low concentrations are applied. Through the stepwise and systematic condition alteration, the reaction could be optimised and successfully transferred to other substrates with longer, branched or functionalised alkyl chains. The highest yields are observed with tryptophan as organocatalyst in only one hour reaction time with TONs of up to 27.

Keywords

Aldol Condensation; Aldehyde; Organocatalysis; Amino Acid

1. Introduction

The aldol reaction is a C-C bond forming reaction between aldehydes and/or ketones and was already described in the 19th century.[1] The aldol condensation of aldehydes is a very effective tool, gaining *α,β*-unsaturated aldehydes, which can be used in further organic reactions, especially in the dienamine catalysis[2] or in tandem catalyses[3].

In industry, the homo aldol condensation (HAC) is an essential reaction step to form the precursor 2-ethylhex-2-enal from butanal, which is used in the synthesis of different plasticisers, e.g. DEHP = bis(2-ethylhexyl)phthalate. The latter has the highest market share of 54% regarding the global plasticiser consumption.[4] Therein, butanal undergoes a base catalysed homo aldol condensation to 2-ethylhex-2-enal in a sodium hydroxide solution.

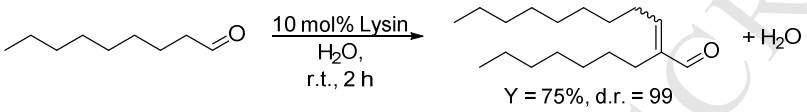
Besides the base catalysed homo aldol condensation of aldehydes in industry,[5] further investigations and catalyst developments were made with organic metal salts (2,4,6-trimethylphenoxymagnesium bromide)[6], transition metal complexes[7], electrolysis[8], acids[9], amines[10], amine/acid mixtures[11] and immobilised amines on silica[12].

Amino acids occupy a special position in organocatalysis having an amine and an acid function in their molecular structure. An advantage of applying amino acids is given by their ubiquitous existence being precursors of proteins.[13] They are easily accessible and have no GHS hazard statements. Therefore, they can be described as green reagents, if applied in chemical reactions.[14]

The first amino acid catalysed HAC was carried out with alanine as catalyst and acetaldehyde as substrate.[15] Later, only scattered examples were dealing with the amino acid catalysed HAC of aldehydes.[16] The multiple homo aldol condensation of acetaldehyde with proline led to 2,4-hexadienal, which was not investigated intensively and was

formed in 5% yield after two aldol condensation steps with 3 equivalents of acetaldehyde.[16a] A kinetic study with arginine, glycine, serine, alanine and proline[16b,c] revealed a complex kinetic behaviour, if arginine was used as catalyst in the HAC of acetaldehyde, which can form higher aldol condensation products. Therein, large rate constants were observed with a maximum at small catalyst concentrations, due to the transition from a first order reaction into a second order reaction. Therefore, the second order reaction is limiting the aldol condensation.

An environmentally friendly, green (water as solvent or no solvent) and transferable method to other substrates was established, wherein 10 mol% of lysine catalyses the HAC of aldehydes with unfunctionalised alkyl chains up to C_9-aldehydes in moderate to good yields of 46% - 75%. The application of arginine as catalyst was not pursued any further in this case, since only a yield of 24% was obtained. Therein, a turnover number (TON) up to 7.5 and a turnover frequency (TOF) up to 3.75 h^{-1} was achieved for unfunctionalised aldehydes.[16d] (Scheme 1)



Scheme 1. Established homo aldol condensation (HAC)[16d]

Amino acids can be used in the cross aldol condensation, which is described by an intermolecular aldol condensation between different substrates. With proline-triethylamine as catalyst, a ketone C-glycoside undergoes the aldol condensation with different ketones and aromatic aldehydes.[17]

Furthermore, an aldol condensation allows the generation of a stereo centre depending on the initial substrates. The application of enantiopure organocatalysts in an intramolecular aldol condensation enables asymmetric organocatalyses leading to products with high enantiomeric excesses. The first examples were given with stereoid cyclodione backbones as substrates and amino acids as catalysts. Therein, *L*-proline, *L*-alanine and *L*-phenylalanine were applied as organocatalysts and $HClO_4$ as additive simulating the dehydration.[18] Later, this reaction was extended to other product derivatives and up to 14 proteinogenic amino acids were compared with each other regarding their catalytic activities, reaction times, yields and enantiomeric excesses in the intramolecular aldol condensation. The "organocatalyst" was used equimolar to the substrate with $HClO_4$ as additive.[19]

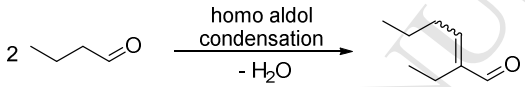
In the beginning of this millennium, first investigations towards the asymmetric cross aldol addition with amino acids have been made. The cross aldol addition of acetone with aldehydes is catalysed with 30 mol% *L*-proline[20] in DMSO achieving very high yields and enantiomeric excess. This protocol was extended to α-unsubstituted substrates as aldehydes.[21] The cross aldol addition between aldehydes in DMF with 10 mol% *L*-proline at low temperatures led to comparable results.[22] Therefore, proline has an exceptional position in organacatalysis, since a lot of organocatalysts are based on the five membered ring structure of proline.[23]

The cross aldol addition between ketones and aldehydes was extended to primary amino acids[24] using 20 mol% catalyst, e.g. isoleucine, with long reaction times of 7 d[25] or 30 mol% catalyst, e.g. valine, with very high yields and also long reaction times of 3 d.[26]

In this publication we fill the gap by giving a comprehensive overview on the reactivity of all 20 proteinogenic amino acids at same reaction conditions in the homo aldol condensation (HAC) of aldehydes. This systematic investigation enables a direct comparison between each amino acid, which was not possible yet, due to a scattered data set.[16] The model substrate butanal was chosen as linear alkyl aldehyde with an industrial background being an important precursor for plasticisers. From this data, we established a general method for the homo aldol condensation with different substrates using simple, green, mild and environmentally friendly conditions. Short reaction times (down to 1 h), amino acids as green catalysts with low catalyst loading (down to 3.33 mol%) and ethanol as a green solvent, which can be removed easily, were employed. Excellent yields, with high TONs and TOFs, were obtained if compared to other amino acid cataysed aldol reactions, which needed long reaction times in questionable solvents, e.g. DMF.[27]

2. Results & Discussion

We set our focus on the homo aldol condensation of unmodified aldehydes as starting material (Scheme 2). In all experiments the *trans* aldol condensate of butanal was the major product with a *trans/cis* ratio of > 20.



Scheme 2. Homo aldol condensation of butanal

For a better overview and a separate assessment we divide the investigated 20 proteinogenic amino acids in five groups, which are displayed in Figure 1. We used them as drawn, since their *L*-form is easily commercially available.

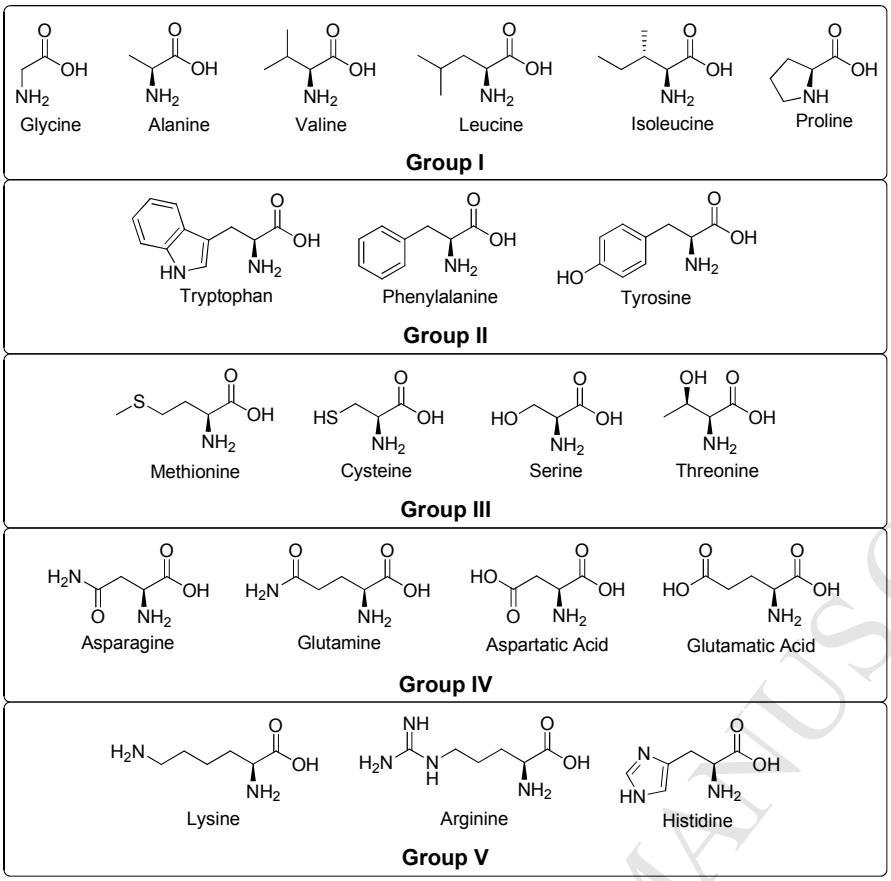


Figure 1. Amino acids divided in different groups

2.1 Systematic investigation of all 20 amino acids

We wanted to use simple conditions with only a few reagents, which can be easily removed and are non-toxic. The established reaction system should be transferable to other substrates, wherefore we used ethanol to ensure a homogenous solution of polar and non-polar reagents. Furthermore, we are already thinking about future developments using this homo aldol condensation as a tool for more complex conversions in e.g. tandem catalyses,[28] wherefore a simple reaction system is desirable for having more changing options.

In the first part of our investigation, different catalytic amounts between 1.67 mol% and 20 mol% of each amino acid were employed in the homo aldol condensation of butanal for a better comparability regarding their catalytic activity as organocatalysts by not using them in stoichiometric amounts.

Aromatic amino acids are characterised by aromatic groups in their side chain. The results of applying aromatic amino acids, Group II (Figure 1) is given in Figure 2 displaying observed yields over catalyst concentration. Tryptophan (indol side chain) and phenylalanine (phenyl side chain) already led to excellent yields, if only 3.33 mol% were used. This is a great catalyst amount, since other publications regarding the amino acid catalysed aldol reaction are dealing with higher catalyst concentrations of 20-30mol%. A quantitative yield was observed, if 20 mol% tryptophan were used. Nevertheless, it is quite astonishing why no conversion could be observed, if tyrosine was applied. The only

difference to phenylalanine is given by the phenol group. Presumably, tyrosine is active at higher concentrations (from approx. 30 mol%) needing higher reaction times. This is strengthened due to the investigation regarding the cross aldol addition of ketones with aldehydes. While 20 mol% tyrosine gave only traces of the product after 7 d,[25] a moderate yield of the cross aldol product was obtained after 53 h by applying 30 mol% of tyrosine.[26b]

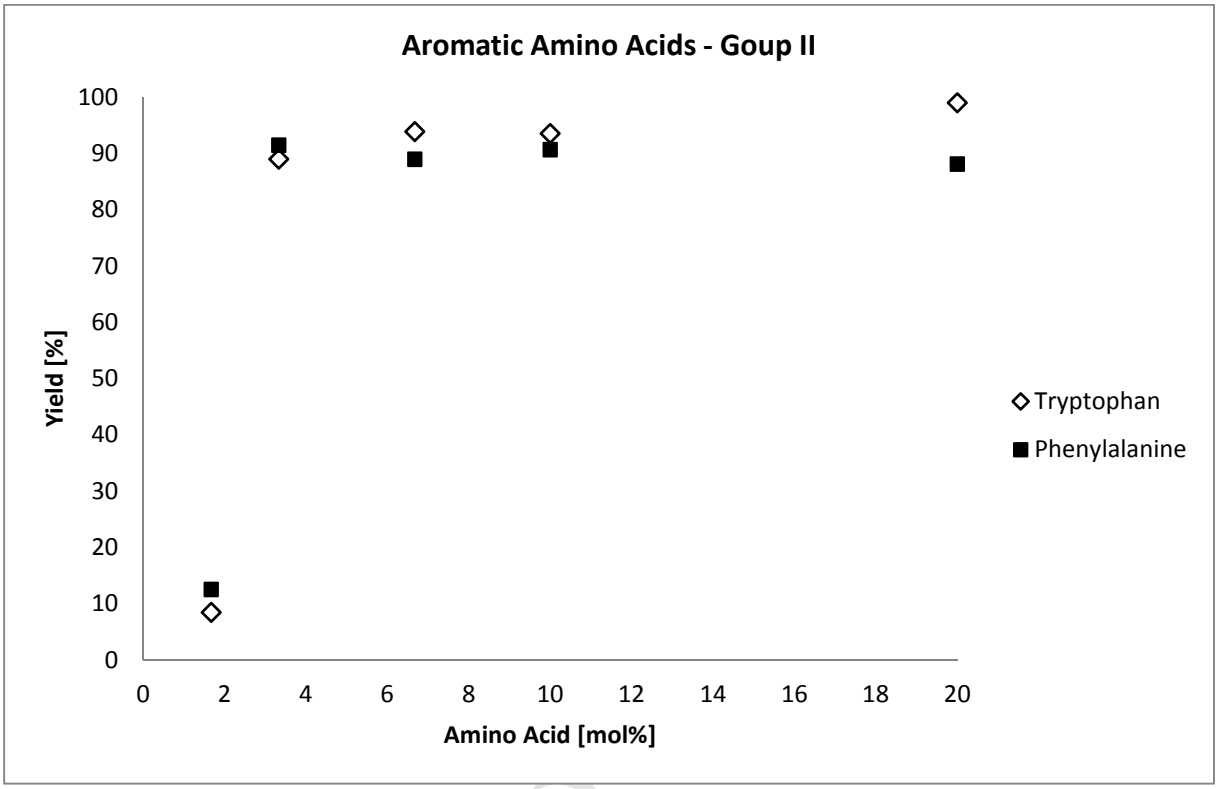


Figure 2. Yield over catalyst concentration plot of Group II; Conditions: 3 mmol butanal, amino acid, 1 mL EtOH, r.t., 16 h; tyrosine is not displayed due its inactivity at given catalyst concentrations.

An interesting trend is given in the aldol catalysed reaction with basic amino acids from Group V (Figure 1) displayed in Figure 3. These amino acids have further basic functionalities in their side chain. Experiments with histidine (imidazole side chain) as catalyst showed a general trend: the more catalyst is applied, the more yield can be observed with 29% yield at a concentration of 20 mol% catalyst. On the other hand, lysine (primary amino side chain) and arginine (guanidin side chain) as catalysts led to a maximum regarding the obtained yield, which resulted in high yields at low catalyst amounts. Lysine has its maximum at 3.33 mol% giving 82% yield and arginine at 6.67 mol% giving 85% yield. The results of arginine in the homo aldol condensation of butanal are in good agreement with the kinetic studies of Córdova and coworkers regarding the homo aldol condensation of acetaldehyde.[16b,c] Therein, the rate constants are varying with the concentration of the amino acid arginine. At low concentrations the rate constant is described by the first order, which is increasing linearly with the catalyst concentration and limited by the enamine formation. At higher concentrations, the reaction is described by the second order, which is limiting the overall reaction speed leading to lower yields controlled by the C-C bond formation. With arginine as catalyst, the transition from the first to the second order was reached at quite low catalyst amounts. In this publication, we could proof the same tendency with lysine as organocatalyst and with the application of longer chain aldehydes.

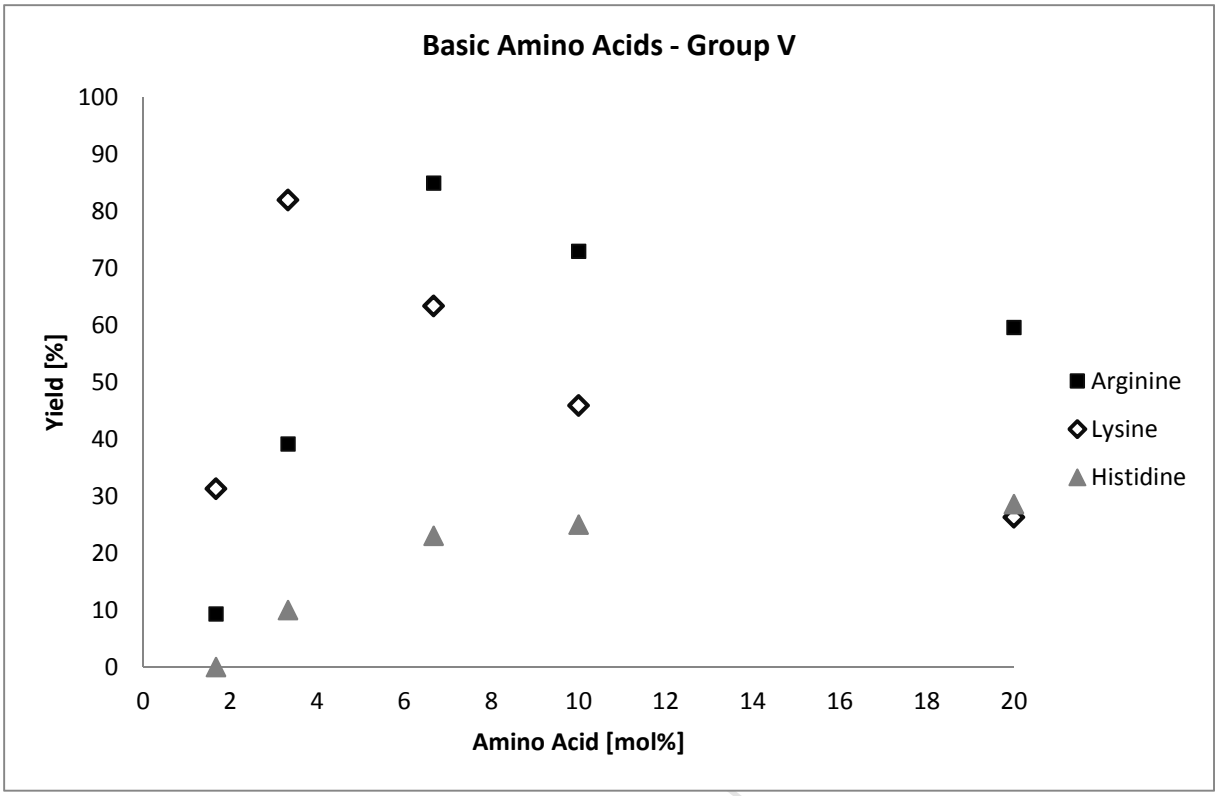


Figure 3. Yield over catalyst concentration plot of Group V; Conditions: 3 mmol butanal, amino acid, 1 mL EtOH, r.t., 16 h.

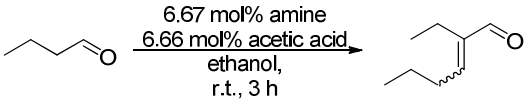
Results of group I, III and IV showed lower yields and can be found in the supporting information.

In summary, the systematic investigations revealed each activity of the 20 proteinogenic amino acids applied in catalytic amounts in the homo aldol condensation of the unfunctionalised aldehyde butanal in ethanol. Tryptophan, phenylalanine, arginine and lysine led to very good to excellent yields. In contrast to other publications in the field of amino acid catalysed aldol reactions, which often used about 30 mol% of amino acid, in here, low catalyst concentrations (3.33 mol% - 6.67 mol%) are sufficient furnishing 82% to 94% yield for the desired product.

2.2 Elaborating the catalytically active centre

There is no doubt that the α-amine in the amino acid is a catalytic active in the mechanism of the homo aldol condensation, since the amino acids in Group I are leading to the desired product if applied as organocatalysts. However, some amino acids are having further potential catalytically active centres by bearing other amine groups in their side chains. In order to shed some light into the catalytic activity of the side chain groups of the amino acid, we applied amines as surrogates of the side chains of lysine (*n*-butyl amine), arginine (guanidine) and tryptophan (indole). Additionally, these experiments were carried out with and without acetic acid simulating an amino acid muixture under same conditions as the experiments before.

Table 1: Applying model catalysts in the homo aldol condensation



No.	amine	acetic acid	Y
1.1	indole	-	<1
1.2		+	<1
1.3	n-butyl amine	-	<1
1.4		+	6
1.5	guanidine carbonate	-	<1
1.6		+	3
1.7	guanidine hydrochloride	-	<1
1.8		+	<1
1.9	---	+	---

Conditions: 3 mmol butanal, 6.67 mol% amine, 6.67 mol% acetic acid, 1 mL EtOH, r.t., 16 h. Results in %.

No significant catalytic activity was observed, if indole, *n*-butyl amine and guanidine were applied as organocatalysts in the homo aldol condensation (entries 1.1, 1.3 and 1.5). Guanidine was used as carbonate and hydrochloride salt, due to their easily availability. The addition of acetic acid is slightly increasing the yield to 6% (entry 1.4) and 3% (entry 1.6), if applied together with *n*-butyl amine or guanidine carbonate. Similar results with *n*-butyl amine and acetic acid (entry 1.4) are achieved if compared to the glycine catalysed homo aldol condensation (please see the Supporting Information), which is quiet well explainable, since both catalytic systems are having no substituents. Acetic acid has no catalytic activity (entry 1.9). These experiments proved, that the catalytically active centre is the α-amino group. The corresponding side groups are increasing or decreasing the catalytic activity of the α-amino group. Interactions with aromatic side groups within the mechanism are conceivable in the case of phenylalanine and tryptophan. These interactions are increasing the activity obtaining excellent yields. Lysine and arginine are the most basic applied amino acids with an unusual trend as seen in Figure 3. Therefore, the basicity should be responsible and determining the catalytically activity at low catalyst amounts, since at high catalyst amounts the reaction order is changing.

2.3 Reaction progress

For getting a better insight into the reaction, we investigated the reaction progress over time, simultaneously optimising the reaction to shorter reaction times. Tryptophan, phenylalanine, lysine and arginine were chosen for the detailed investigation, due to their high reactivity obtaining high yields.

First, the reaction progress of tryptophan and phenylalanine was investigated and the results are displayed in Figure 4. After 6 h comparable yields of 91% to 94% were obtained by either using tryptophan or phenylalanine. The superior advantage of the catalyst tryptophan is its high activity, wherefore an excellent yield of 95% was reached after only 1 h

with a TON of 14, if 6.67 mol% tryptophan was used. The addition of 3.33 mol% tryptophan is still leading to a very good yield of 90% after 1 h, with a higher TON of 27.

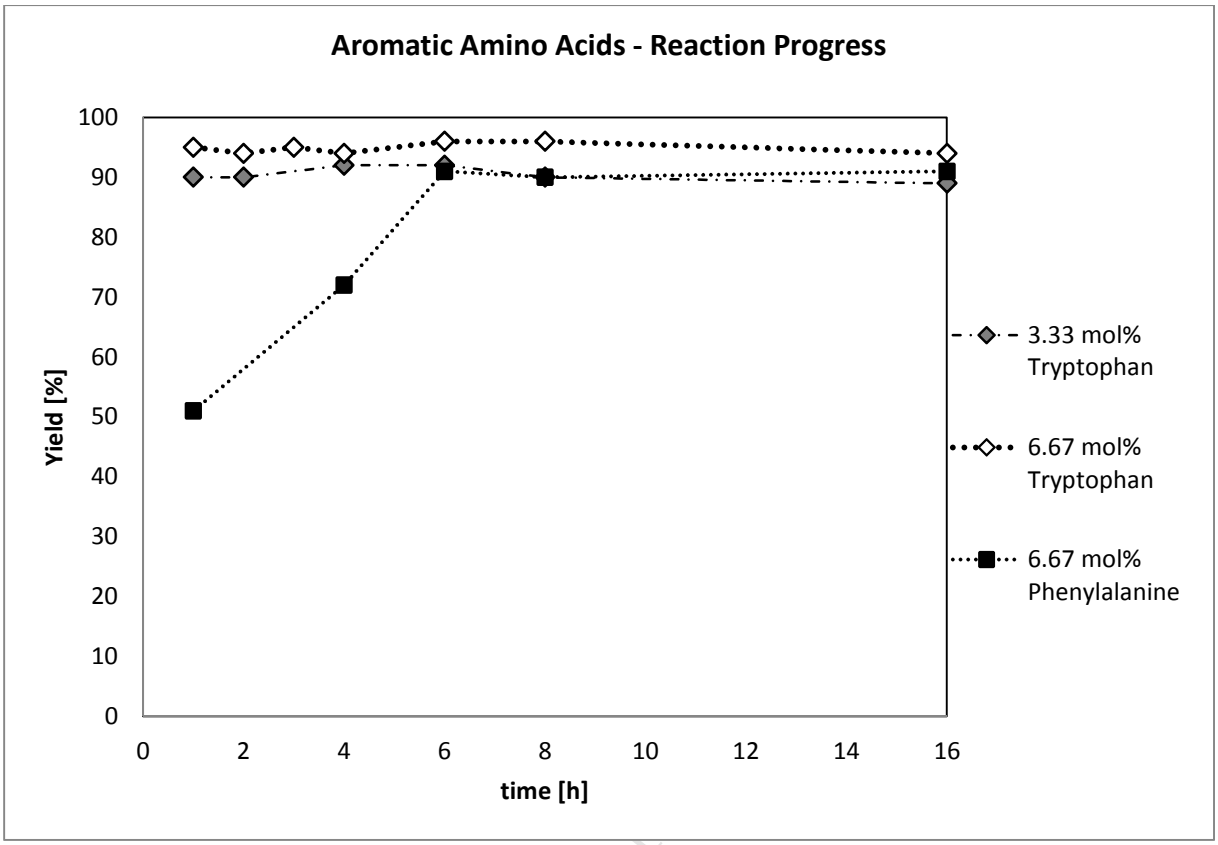


Figure 4. Yield over time plot; conditions: 3 mmol butanal, amino acid, 1 mL EtOH, r.t.

The same investigation of the reaction progress was made with lysine and arginine. (Figure 5) The reaction rate of arginine was lower resulting in a longer reaction time of 16 h yielding 85%. Lysine was applied in two different concentrations for a better insight regarding the kinetics. After only 45 min a maximum yield of 75% was obtained, if 5 mol% lysine was added. The reaction was slower with a lower amount of 3.33 mol% lysine. However, a higher maximum yield of 82% was achieved. These results validate the previous kinetic studies,[16c] wherein higher catalyst concentrations increase the reaction rate, but limit the overall reaction. This results in lower yields, as can be seen in these investigations.

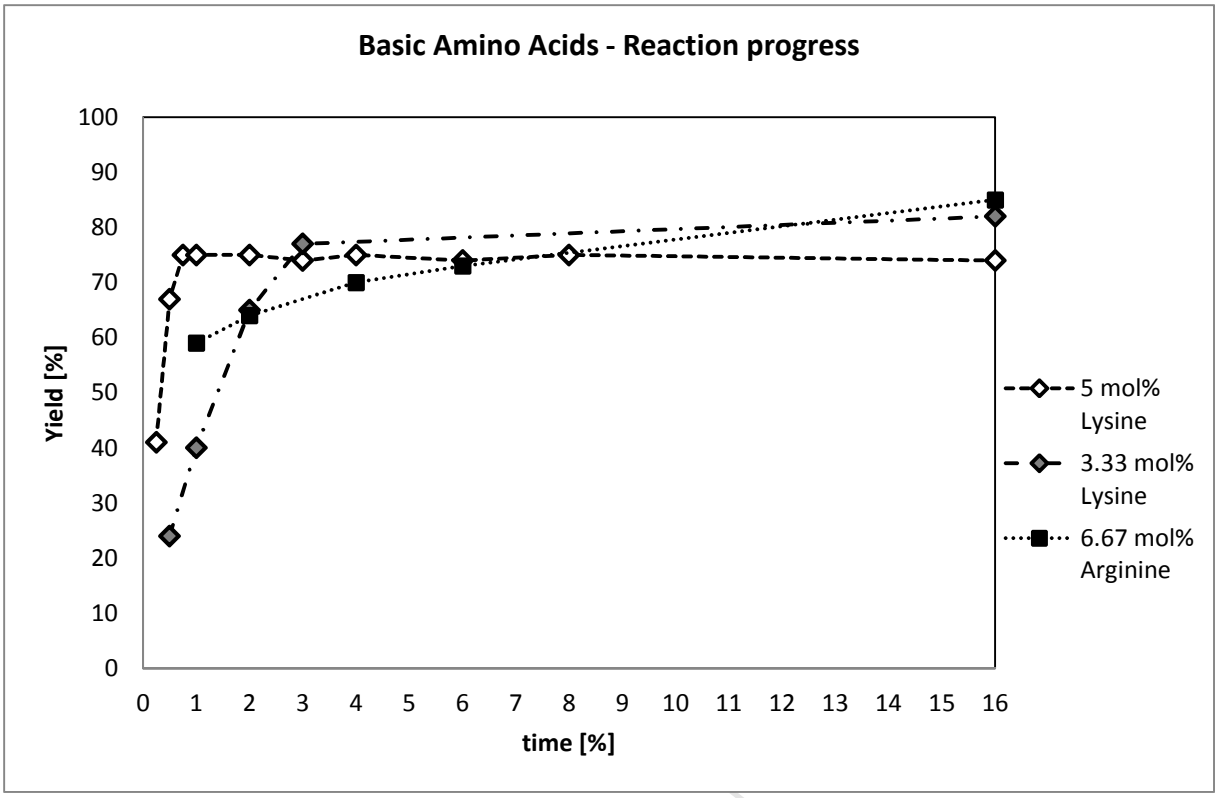


Figure 5. Yield over time plot; Conditions: 3 mmol butanal, amino acid, 1 mL EtOH, r.t.

A short summary of the achieved results with catalytic amounts of proteinogenic amino acids as organocatalysts in the homo aldol condensation of butanal is given in Figure 6.

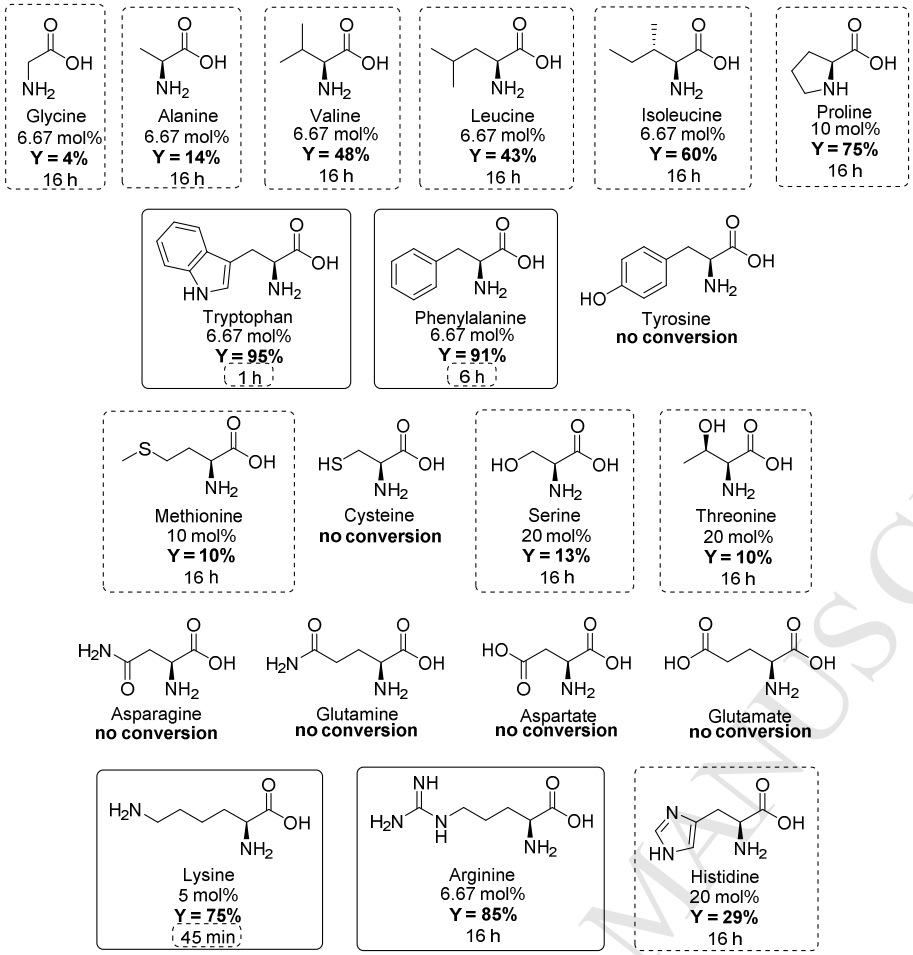


Figure 6. Summary of the results after the systematic investigation applying 20 proteinogenic amino acids; Conditions: 3 mmol butanal, amino acid, 1 mL EtOH, r.t.

2.4 Substrate scope

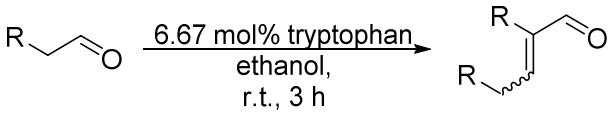
In the next step, the transferability of the optimised reaction conditions will be explored using other substrates with longer, branched and functionalised alkyl chains (Table). Tryptophan was chosen for the substrate scope due to its high activity obtaining excellent yields in a short time. The reaction was carried out in ethanol on the one hand and in water on the other hand, since the use of amino acids is usually associated to aqueous reaction media.

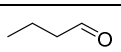
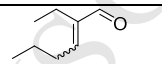
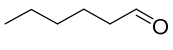
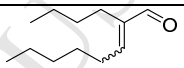
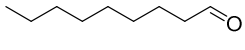
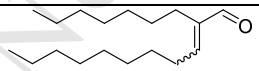
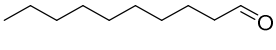
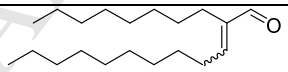
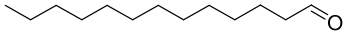
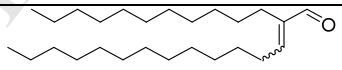
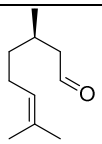
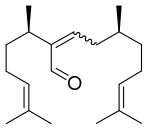
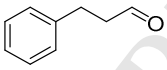
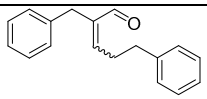
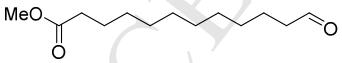
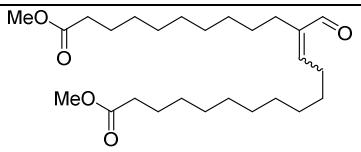
Consistently, very high yields have been observed for every applied substrate after only 3 h reaction time and 6.67 mol% organocatalyst tryptophan in ethanol. Very good yields of 77% - 87% were observed for the aldol condensation products from the entries in 2.2, 2.3 and 2.7. Excellent yields of 90% - 95% have been observed for the products displayed in 2.1, 2.4, 2.5 and 2.6. Methyl-12-oxododecanoate was converted almost quantitatively to its aldol condensation product (entry 1.8). These results are showing a successful established homo aldol condensation which is catalysed by an amino acid and transferable to other substrates as well. Performing the reactions in aqueous medium

led to phase transfer limitations, since all reaction mixtures showed a two phase system, which resulted in lower yields for the longer chain aldehydes (entry 2.3 – 2.9). A very poor yield of 9% was obtained by using citronellal.

Products from entries 2.2 – 2.5 are of high interest, since butanal is already being used as a plasticiser precursor (entry 2.1). The product from citronellal could represent a potential lubricant precursor, due its high branched structure[29] (entry 2.6). The product of the renewable methyl-12-oxododecanoate is a potential polymer precursor having an α,ω-bifuncionality (entry 2.8).

Table 2. Substrate screening with optimised conditions



No.	Substrate	Product	Y	Y[a]
2.1			95	96
2.2			77	78
2.3			84	77
2.4			90	77
2.5			94	71
2.6			94	9
2.7			87	99
2.8			99	--[b]

Conditions: 3 mmol substrate, 6.67 mol% tryptophan, 1 mL EtOH, rt, 3 h. Results in %; [a] reactions were performed in 1 mL H_2O instead of EtOH; [b] n.d. = not determined.

3. Conclusion

The homo aldol condensation of unfunctionalised aliphatic aldehydes was investigated in respect to the used amino acid, catalyst loading, side chain and reaction time. Therein, we applied every single proteinogenic amino acid in catalytic amounts and established a general method for the homo aldol condensation for different substrates with very good to excellent yields up to 99% in only 3 h. Tryptophan was the most effective amino acid catalyst regarding reaction time and yield with a TON and TOF of 27 or 27 h^{-1}. The catalytic activity depends on the respective side chain, which has an activating or deactivating effect. Therefore, the side chain groups have no catalytic activity, but they have a big impact on the catalytic activity. Furthermore, the investigations displayed, that arginine and lysine have their maximum rate constant at low catalyst concentrations of 6.67 mol% or 3.33 mol%, due to their unique behaviour. Obtained products are already used as plasticiser precursors in the industry or they represent potential lubricants or polymer precursors, if the renewables, citronellal or methyl-12-oxododecanoate, are applied as substrates. Based on these results, a combination of the homo aldol condensation with a further organocatalysed establishing a tandem catalysis would be an interesting development for future investigations.

4. Experimental

4.1 General techniques and materials

The solvent ethanol was purchased from VWR with a purity of 99.8%, all amino acids were purchased from Sigma Aldrich and all substrate were purchased from ABCR, Acros, Alfa Aesar and Sigma Aldrich. All reagents were used without further purification. For column chromatography technical quality solvents were used. Thin-layer chromatography (SiO_2, TLC) was performed on Merck TLC silica gel 60 F254. Column chromatography was performed on Merck silica gel 60 (0.040 – 0.063 nm). NMR spectra were recorded on Bruker DRX400 (400 MHz) spectrometers with TMS as internal standard. $CDCl_3$ was used as solvent and purchased from DEUTERO. Chemical shifts are reported in parts per million as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet, dt = doublet of triplet), coupling constant, and integration. Gas chromatography was performed on a HP 6890 (Hewlett-Packard, Waldbronn, Germany) using a FID at 325°C and a HP-5 column (30 m, diameter 0.32mm, film thickness 25mm) in connectionwith an auto sampler. The carrier gas was nitrogen (v = 1.2mL/min, 30 cm/s). The injection volume was 1µL and the split ratio 1:30.

4.2 General procedure for the aldol condensation

0.2 mmol tryptophan, 1mL ethanol and 3 mmol butanal were added into a screwed test tube. The reaction mixture was stirred at room temperature for one hour. The catalyst was removed by a short silica colomn. Afterwards, the sample for the gas chromatography was prepared with 0.0250 g dibutyl ether, 0.4750 g reaction mixture and 0.5000 g isopropanol. A yield of 95% for 2-ethylhex-2-enal was obtained.

4.3 Isolation of the aldol condensation product

1.1. Dimethyl 11-formyltricos-11-enedioate (Product from entry 2.8)

0.2 mmol tryptophan, 1mL ethanol and 3 mmol methyl-12-oxododecanoate were added into a screwed test tube. The reaction mixture was stirred at room temperature for three hours. Afterwards, the solvent was evaporated and the product was purified by column chromatography (cyclohexane/ethyl acetate 50:1 → 5:1) yielding 99% of dimethyl 11-formyltricos-11-enedioate. ^{1}H NMR (400 MHz, CDCl3) δ: 9.37 (s, 1H), 6.45 (t, J = 7.5 Hz, 1H), 3.68 (m, 6H), 2.31 (m, 6H), 2.23 (m, 2H), 1.62 (m, 4H), 1.50 (m, 2H), 1.30 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.5, 174.7 x 2, 155.8, 144.2, 51.9, 34.5, 30.1, 29.9, 29.8 x 5, 29.7, 29.6, 29.5 x 2, 29.4, 29.2, 29.1, 25.3 x 2, 24.4.

The characterisation data of the other aldol condensation products from table 2 were already determined and are matching with the analytical data from the literature[30]

Acknowledgments

We thank T. Seidensticker for synthesising methyl-12-oxododecanoate, which was applied in our substrate scope.

Supplementary data

Supplementary data with detailed experimental procedures and ^{1}H & ^{13}C NMR spectra of the compounds associated with this article are available in the Supporting Information.

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