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SHORT COMMUNICATION

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On the Michael Addition of Water to α,β-Unsaturated Ketones Using Amino Acids

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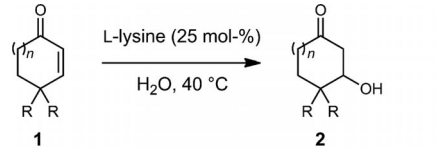
The use of water as a nucleophile for Michael additions is still a challenge in organic chemistry. In this report we describe the use of amino acids as catalysts for the Michael addition of water to α,β-unsaturated ketones. All 20 proteinogenic amino acids were screened and L-lysine was identified as the best candidate. To obtain a better insight and to determine the minimum requirements of the catalyst, several structurally related compounds were tested. The reaction was characterized in terms of conditions and equilibrium.

Introduction

The Michael addition of water to α,β-unsaturated ketones still seems to be a difficult task to achieve by using chemical methods. Although in nature this reaction is ubiquitous due to its presence in many metabolic cycles, only a few methods using non-enzymatic approaches have been reported. Apart from enzymatic methods using hydratases,[1] for example, fumarase, malease, citraconase and enoyl-CoA hydratase, which are used on an industrial scale, the only enantioselective direct catalytic example described so far was published recently and involved the use of a DNA-based catalyst for the hydration of enones in water.[2] The indirect asymmetric addition of water by hydroboration, that is a two-step approach, has also been described recently using a Taniaphos catalyst.[3] Another method involving the use of a palladium-wool complex to convert 2-cyclohexen-1-one into 3-hydroxycyclohexanone in a non-asymmetric fashion has been reported.[4] This method provides high conversions, however, earlier studies[5] and theoretical calculations[6] indicated that the reaction equilibrium lies on the substrate side. Furthermore, the use of acidic ion-exchange resins has been reported[7] and the use of phosphine catalysts has been described for the addition of water and other nucleophiles to α,β-unsaturated ketones.[8] However, most of the methods furnishing racemic products suffer from complex, cumbersome or expensive preparation of the catalysts.

In the last few years, amino acids have played an important role in organocatalysis. In particular, proline and its derivatives have been established as versatile catalysts for a variety of different reactions including Michael additions (for selected examples see ref.[9] and for reviews see ref.[10] and references cited therein). In some of these methods, the use of water or mixtures of water and organic solvent as reaction media was highlighted, but the addition of water was not reported. This gives an indication of the difficulty of using water as a nucleophile in Michael additions. Moreover, the use of an amino acid as catalyst and water as both solvent and nucleophile has so far not been reported.

We report herein the use of amino acids as catalysts for the Michael addition of water to α,β-unsaturated ketones (Scheme 1). As a result of its rigid character and its frequent use in earlier studies, 2-cyclohexen-1-one (**1a**) was chosen as the main test substrate. The study focused on L-lysine and L-histidine as the most promising catalysts. Furthermore, the reaction conditions and reaction equilibrium were evaluated and different α,β-unsaturated ketones were tested. To obtain more insight into this reaction, the



1

1a: *n* = 1, R = H
1b: *n* = 1, R = CH_3
1c: *n* = 2, R = H

2

2a: *n* = 1, R = H
2b: *n* = 1, R = CH_3
2c: *n* = 2, R = H

Scheme 1. Michael addition of water to α,β-unsaturated ketones catalysed by lysine.

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minimum requirements of the catalysts were determined by reducing the number of functional groups on both L-histidine and L-lysine.

Results and Discussion

We started our investigation by screening the 20 proteinogenic amino acids as potential catalysts for the Michael addition of water to 2-cyclohexen-1-one (**1a**) as the main test substrate. Because the reactions were carried out in water as the only solvent, the pH needs to be considered an important parameter. The dissolution of amino acids alone in water leads to a change in the pH of the reaction medium. Therefore all reactions were buffered to pH 7 by using sodium phosphate (250 mM). To avoid the presence of additional amines, no nitrogen-containing buffer systems or salts were used. To compare the rate of the reaction, the initial rates (reaction time 3 h) were measured well before the maximum yield was reached. Blank reactions containing only substrate and the corresponding buffer were performed in parallel.

As shown in Figure 1, most of the 20 amino acids catalyse the addition of water to 2-cyclohexen-1-one (**1a**), except for tyrosine, which shows no acceleration compared with the background reaction caused by buffer alone. This might be caused by the fact that tyrosine is barely soluble in water and therefore no homogeneous reaction system could be established.

The four fastest reactions were observed with L-histidine, L-lysine, L-glutamine and L-cysteine. The fastest reaction rate was achieved with L-cysteine, but taking the mass balance into account, this system is not competitive with, for example, L-lysine. Side-reactions such as polymerization cause the consumption of 2-cyclohexen-1-one without the formation of the desired Michael addition product leading to a slight decrease in the mass balance. L-Glutamine showed good activity, but again the mass balance was not as good as with L-lysine (90% compared with 97%). Based on these results, L-lysine[11] and L-histidine were further investigated as two structurally different amino acids. In general, however, it can be noted that the three basic amino acids, L-arginine, L-histidine and L-lysine, are among the best catalysts tested. Also, L-glutamine, an amino acid with a polar uncharged side-chain, showed good catalytic abilities. It should be emphasized that no changes in the pH of the buffer system were ensured after dissolution of the amino acids. Grouping the amino acids by their structural and electronic properties showed no clear trend. Also, a plot of the pK_a values of the α-amino groups against conversion showed no correlation between the reaction rate and pK_a (see the Supporting Information).

Because the reaction takes place in water, the pH of the reaction medium might have an influence on the reaction rate and should therefore be considered. To quantify this effect, the initial rates were measured at different pH values by using sodium phosphate buffer (pH 6–8) and borate buffer (pH 9 and 10) to control the pH of the reaction medium.

The results of pH screening clearly show the dependency of the reaction on the pH of the medium (pH axis, Figure 2). The conversion of 2-cyclohexen-1-one into 3-hydroxycyclohexanone increased with increasing pH. Because OH^- ions might be the active species attacking the Michael acceptor, the concentration of OH^- plays an important role in the reaction rate and therefore higher pH values lead to an acceleration of the reaction. In parallel, it can be noted

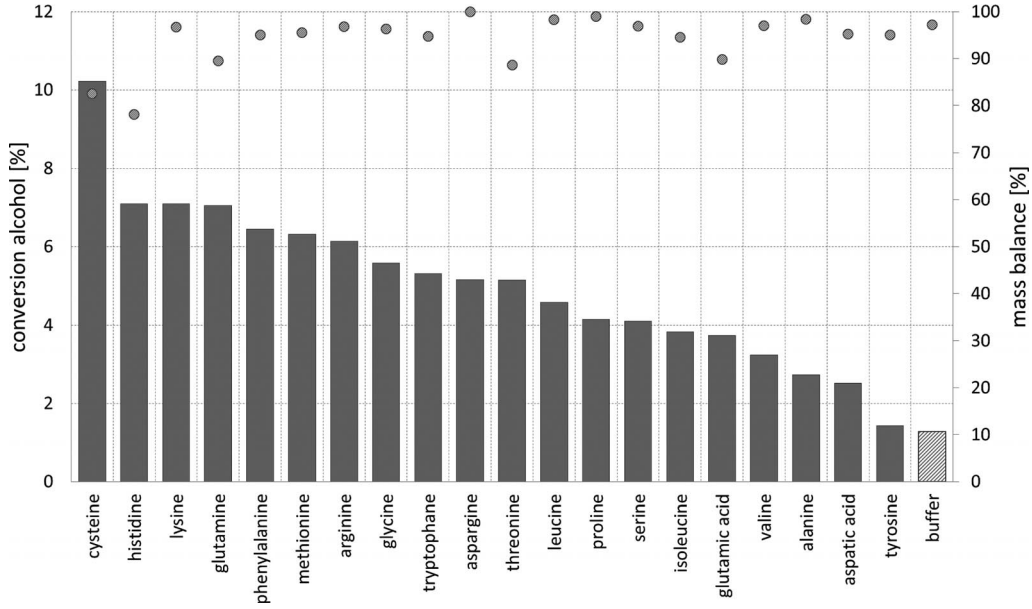


Figure 1. Screening of the 20 proteinogenic amino acids for their ability to catalyse the Michael addition of water to 2-cyclohexen-1-one (**1a**) yielding 3-hydroxycyclohexanone. The bars represent conversion. The blank reaction is represented by the striped bar. Dots represent the mass balance.

that by increasing the pH, the mass balance decreases and more side-reactions occur due to the harsher reaction conditions. Here again, polymerization products form, as is evident by the change in colour of the reaction mixture; the colourless reaction mixture turned yellowish over time at pH values higher than 8.

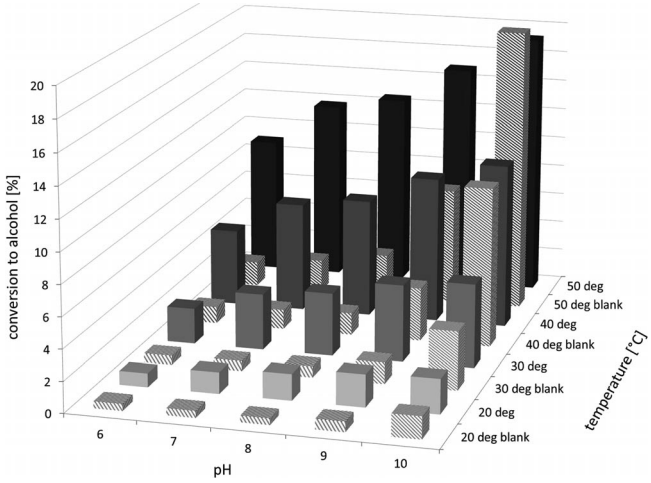


Figure 2. Temperature and pH profile for the addition of water to 2-cyclohexen-1-one (**1a**). Reactions were carried out at the given temperatures and pH values for a reaction time of 3 h (initial rates). Full bars represent reactions with L-lysine as catalyst, striped bars represent blank reactions (buffer only, no L-lysine added).

At pH values of around 10, no beneficial effect of the amino acid could be detected because the background reaction caused by the buffer is equally fast. An approximately neutral pH gave the best results in terms of reaction rate and mass balance, for example, at pH 7, the L-lysine-catalysed reaction is around six times faster than the background reaction mediated by buffer only.

The dependence on temperature was also evaluated between 20 and 50 °C. A clear trend towards a higher reaction rate was detected at higher temperatures. Experiments revealing the temperature dependence were also carried out as initial rate experiments (reaction time 3 h). All temperatures were tested at pH values from 6 to 10, including blank experiments with buffer only. It can be noted that at higher temperatures the reaction seems to be more prone to the polymerization side-reaction. This is again evident by the change in colour from colourless to yellowish and by the incomplete mass balance. Compromising between mass balance and reaction velocity, the best results were achieved at 40 °C.

After optimizing the reaction conditions, the minimal requirement of the catalyst was investigated. Contemplating the catalytically active moiety, amino acids have several potential reactive centres. On the one hand, the primary amine or the carboxylic acid group might play an important role, on the other hand, the imidazole moiety of L-histidine might be an important feature. In another scenario, both moieties may need to be present. As the reaction is base-catalysed (Figure 2), the focus was set on the primary amine group rather than on the carboxylic acid functionality. Several structurally reduced catalysts based on L-histidine and L-lysine were tested. Decreasing the number of functional groups should indicate which functionalities are involved in the catalysis. On this basis, cadaverine, butylamine, propylamine, ethylamine and methylamine were tested as possible truncated L-lysine analogues (Figure 3).

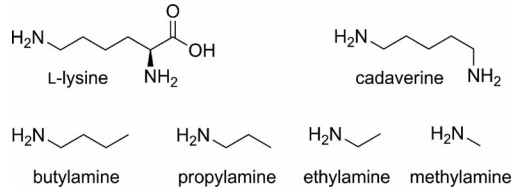


Figure 3. Study of the minimum requirement for the catalyst L-lysine: primary amines cadaverine, butylamine, propylamine, ethylamine and methylamine were used.

The same principle was applied to L-histidine. As possible catalysts, histamine, 4-methyl-1*H*-imidazole, imidazole and pyrrole were tested. The small amino acids glycine and L-alanine, representing catalysts in which both the primary amine and the carboxylic acid are retained but not the second primary amine or imidazole moiety, were included for comparison (Figure 4).

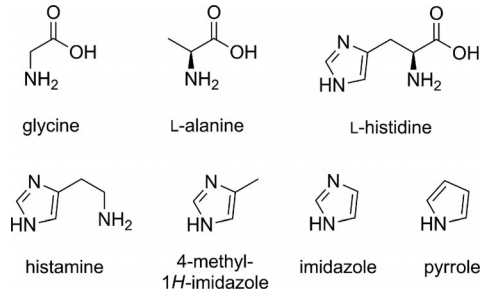


Figure 4. Study of the minimum requirement for the catalyst L-histidine: imidazole derivatives histamine, 4-methyl-1*H*-imidazole, imidazole and pyrrole were used. Glycine and L-alanine as catalysts with both the carboxylic acid moiety and the primary amine retained have also been studied.

The use of propylamine, ethylamine, 4-methyl-1*H*-imidazole, imidazole or pyrrole showed no significant effect over buffer alone. Note also that none of the reactions with the structurally reduced catalysts were as fast as with L-histidine or L-lysine. The same holds true for glycine, which can be seen as a structurally reduced version of L-leucine and L-histidine.

Comparison of the results obtained with the truncated catalysts and with L-lysine and L-histidine showed that in principle a primary amino group is essential (Figure 5). Nevertheless, when no carboxylic acid moiety is present, as for cadaverine or histamine, the rate of the reaction is almost reduced by half and no acceleration of the reaction rate was observed with ethylamine or propylamine. Thus it can be concluded that the carboxylic acid moiety also has an important influence on the reaction. This is supported

by the findings of Ramachary and Mondal, who used a nitrogen-containing base, in general, proline or pyrrolidine derivatives, in combination with an acid for the addition of methanol and longer-chain alcohols to a variety of different α,β-unsaturated ketones.[9d] Amino acids combine both of these features in one molecule and because the carboxylic acid moiety is deprotonated under neutral conditions, it might also serve as a proton acceptor and deprotonation of water might occur. Our findings support the assisting effect of the acid functionality, and based on the mechanism proposed by Ramachary and Mondal, the following mechanism can be assumed for the addition of water to 2-cyclohexen-1-one (**1a**; Scheme 2). Starting with the formation of aminal **3**, the iminium cation **4**, which is in equilibrium with **5**, is formed by the elimination of OH^-. The mechanism proceeds via the attack of the OH^- species at the 3-position. The formation of the OH^- ion from water is assisted by the deprotonated carboxylic acid moiety. Upon hydrolysis, the Michael product **2a** is released and the free amino acid is formed ready to enter the next catalytic cycle.

A closer look at how enzymes, and therefore nature, perform the addition of water reveals that the water molecule is often deprotonated and coordinated by a carboxylate residue in the active site. For example, in the case of enoyl-CoA hydratase, a hydratase that is involved in the degradation of fatty acids, the water is deprotonated/coordinated by two glutamic acid residues.[12] Furthermore, a very recent study of the dehydration of β-hydroxy ketones using small synthetic β-turn tetrapeptides as catalysts led to a similar mechanism in which again both the amino and carboxylic acid functionality are involved.[13]

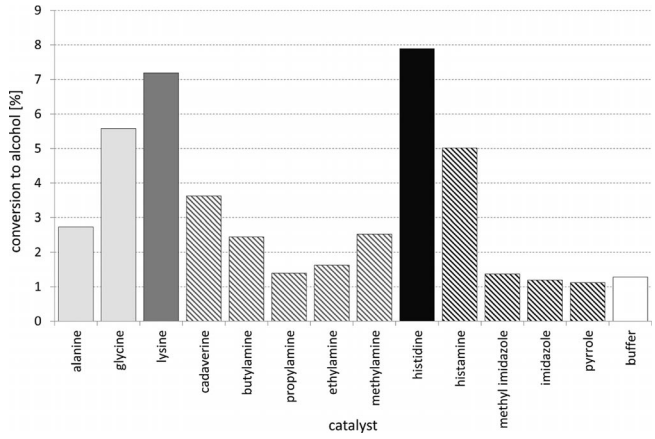
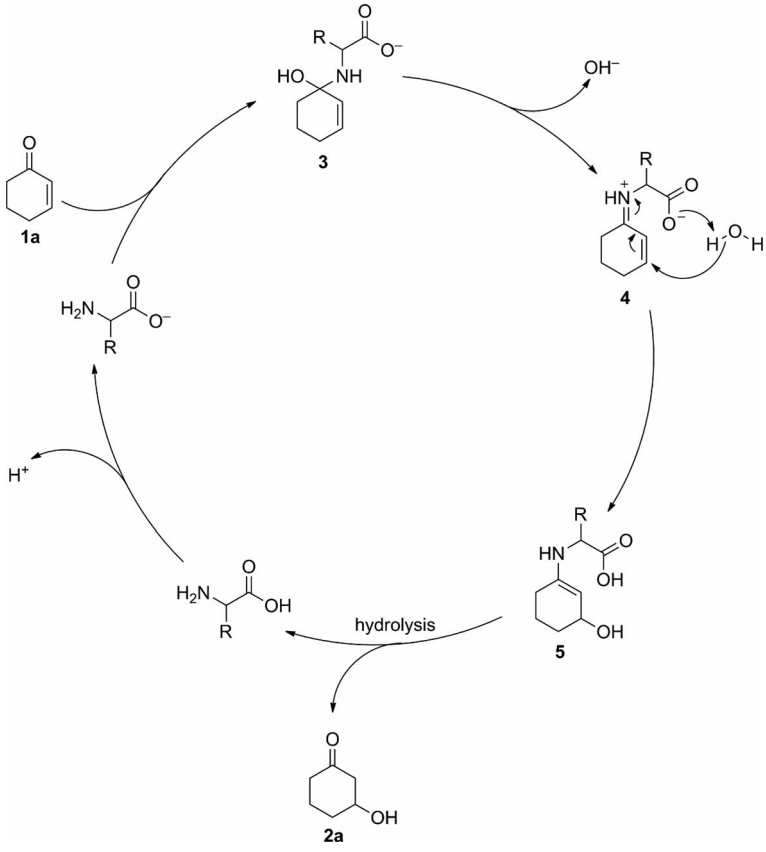


Figure 5. Conversions achieved with structurally different catalysts for the addition of water to 2-cyclohexen-1-one (**1a**). Non-amino acid catalysts are shown as striped bars, L-lysine as a grey bar, L-histidine as a black bar, and L-alanine and glycine as light-grey bars. Conversions were measured in the linear phase of the reaction. The conversion with buffer only (white bar) is shown for comparison.

The position of the equilibrium was investigated by following the reaction over time and the equilibrium constant was calculated from the final conversion. Given an equilib-



Scheme 2. Proposed catalytic cycle for the hydration reaction.

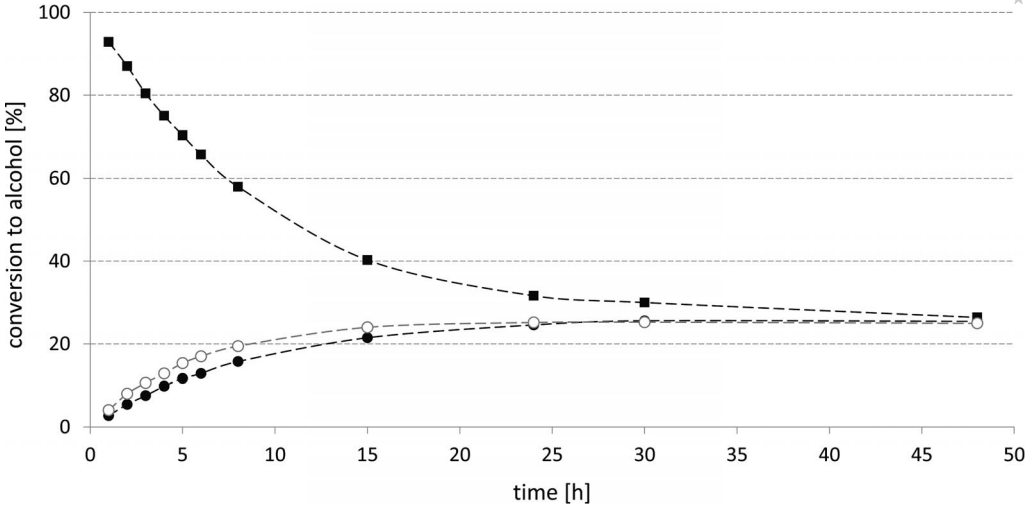


Figure 6. Time course of both the hydration and dehydration reaction catalysed by L-lysine. ●: hydration reaction of 2-cyclohexen-1-one with 25 mol-% catalyst; ○: hydration reaction with 50 mol-% catalyst; ■: dehydration reaction of 3-hydroxycyclohexanone with 25 mol-% catalyst.

rium constant of 0.36 ± 0.04, the reaction lies on the substrate side allowing a maximum conversion of 25%. Although water is present in huge excess, the substrate side is still preferred as a result of the conjugation of the double bond to the ketone.

Further proof of the equilibrium was evidenced by doubling the amount of catalyst, which still led to a conversion at 25% (Figure 6). The equilibrium constant calculated from our data is in accord with previous investigations,[5] however, our data does not support the results reported by Wang et al., who claimed yields of 92.0% by using a palladium–wool complex as catalyst for the addition of water to 2-cyclohexen-1-one.[4]

Attempts to obtain higher yields by employing a biphasic system using different organic solvents to achieve concurrent extraction of the product did not provide a solution to the problem. In fact, the opposite was the case. By using a biphasic system, the substrate immediately migrates into the organic phase and is therefore no longer available for the addition of water. Because the reaction proceeds very cleanly, both the product and the remaining substrate can be isolated in pure form after simple silica gel chromatography. This allows the reuse of the remaining substrate in additional reaction cycles and therefore an economically improved reaction system.

To elucidate the substrate scope, six further α,β-unsaturated ketones structurally closely related to the main test substrate **1a** were tested by using L-lysine as catalyst (Figure 7). The results are presented in Table 1.

Because the addition of water creates a new chiral centre, the *ee* of the product **2a** was determined after conversion to the corresponding acetate.[16b] Although optically pure amino acids were used, the addition of water did not proceed in an asymmetric fashion and no *ee* could be determined.

Given that water is considered to be a poor nucleophile, it is even more astonishing that simple compounds like amino acids can promote the hydration reaction. Because no *ee* was detected for product **2a**, and considering the simplicity of L-lysine, there is still room for improvement in terms of asymmetric induction. However, the small size of water might make the asymmetric Michael addition with low molecular weight catalysts challenging. For example, Ramachary and Mondal reported the asymmetric Michael addition of benzyl alcohol as a nucleophile to 3-nonen-2-one using L-proline as catalyst, which resulted in an *ee* of 11%.[9d] The low *ee* obtained in the reaction with a bulky nucleophile like benzyl alcohol shows the challenge of the asymmetric addition.

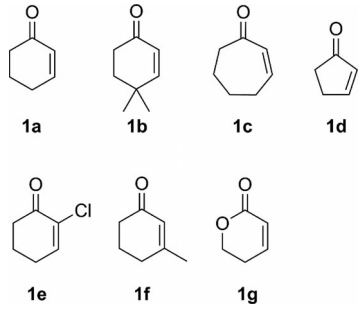


Figure 7. Substrates tested for the addition of water to 2-cyclohexen-1-one (**1a**) using L-lysine as catalyst.

Table 1. Isolated yields from preparative-scale hydration reactions.[a]

Substrate	Isolated yield [%][a]
1a	21.0
1b	9.8
1c	14.3
1d	n.c.
1e	n.c.
1f	n.c.
1g	n.c.

[a] n.c.: no conversion.

Conclusions

β-Hydroxy ketones are an important class of compounds often found as a common structural motif in natural products. Although the molecules themselves look rather simple, their synthesis can be challenging. One-step synthetic strategies commonly used for the preparation of β-hydroxy ketones structurally closely related to 3-hydroxycyclohexanone are, for example, the desymmetrization of the corresponding diol by using, for example, molecular oxygen, *N*-hydroxyphthalimide and $[Co(acac)_3]$,[14] dimethyldioxirane[15] or sodium dichromate.[16] Starting the desymmetrization from the diketone rather than from the diol by using a biocatalytic approach has also been described.[17] Another route involves the hydrogenolysis of β-epoxy ketones using, for example, Bu_3SnH/Bu_3SnI/phosphine oxide[18] or $[Cp_2TiCl]$.[19] Also, the pyridinium-assisted ring-opening of epoxide rings followed by $NaBH_4$ reduction has been described.[20] Although intramolecular aldolization of keto aldehydes is rarely employed, good results have been obtained by using triazabicyclo[4.4.0]dec-5-ene (TBD) as base.[21] However, a straightforward approach starting from the α,β-unsaturated ketone by the direct Michael addition of water to the conjugated double bond still had not been described.

Thus, we have investigated the use of amino acids, in particular, L-lysine, as novel catalysts for the Michael addition of water to α,β-unsaturated ketones by using 2-cyclohexen-1-one (**1a**) as the main test substrate. The reaction proceeds under mild conditions by using water both as substrate and green solvent following the principle of "the best solvent is no solvent".[22] Furthermore, L-lysine represents a cheap, readily available and sustainable catalyst.

Experimental Section

General Methods: ^1H and ^{13}C NMR spectra were recorded with a 400 MHz spectrometer (^1H: 400 MHz, ^{13}C: 100 MHz) and chemical shifts (δ) are given in ppm. Column chromatography was performed by using silica gel 60 (particle size 0.063–0.2 mm). Ethyl acetate and petroleum ether used for column chromatography were distilled before use. Silica gel plates 60 F_{254} were used for TLC. The conversion from 2-cyclohexen-1-one (**1a**) to 3-hydroxycyclohexanone (**2a**) was determined by GC (column: Varian CP-Wax 52 CB, 50 × 0.53 × 2.0 μm) using an internal standard (dodecane) and calibration lines for both substrate (2-cyclohexen-1-one) and product (3-hydroxycyclohexanone) with the following specifications and temperature program: start 80 °C hold for 5 min, to 140 °C at 50 °C/min, hold for 3 min, to 200 °C at 50 °C/min, hold for 3 min, to 250 °C at 50 °C/min, hold for 1 min; injector temperature: 250 °C, detector temperature: 270 °C, total nitrogen flow: 20 mL/min; retention times: 2-cyclohexen-1-one: 7.22 min, 3-hydroxycyclohexanone: 12.90 min, dodecane: 3.89 min. GC–MS analysis was performed with a mass-selective detector using He as carrier gas and a Varian FactorFour VF-1ms column (25 m × 0.25 mm × 0.4 μm). The *ee* of 3-oxocyclohexyl acetate was measured by GC with a chiral stationary phase (Chiradex GTA) using the following temperature program: injector temperature: 200 °C, detector temperature: 220 °C, split 60, start 150 °C, hold for 10 min, to 170 °C at 25 °C/min, hold 1.2 min. Retention times for racemic acetylated alcohol: 6.2 min and 6.7 min (*R* and *S*; in accordance with literature[16b]). Electrospray Ionization (ESI) high-resolution mass spectrometry was performed with a Bruker micrOTOF-Q instrument in positive ion mode (capillary potential of 4500 V).

General Procedure for Initial Rate Measurements: Reactions were carried out in 1.5 mL screw-capped glass vials to prevent evaporation of substrate/product. Shaking was performed in a heated table-top shaker at the given temperature. Buffers in the range pH 6–8 were prepared as sodium phosphate buffers, buffers at pH 9 and 10 were prepared as borate buffers (all at a buffer strength of 250 mM). L-Histidine or L-lysine monohydrochloride (0.05 mmol) was dissolved in the required buffer (1 mL) and 2-cyclohexen-1-one (20 mg, 0.21 mmol) was added. For blank reactions the set-up was the same but without the addition of the amino acid. Reactions were allowed to proceed at the given temperature for 3 h. For work-up, the aqueous reaction mixtures were saturated with NaCl and extracted with ethyl acetate (2× 0.5 mL). The combined organic layers were dried with Na_2SO_4 and analysed by GC (for method see General Methods).

General Procedure for Catalyst Screening: The reaction set-up for the catalyst screening was the same as used to determine the initial rates. L-Arginine, L-histidine, L-lysine monohydrochloride, L-aspartic acid, L-glutamic acid, L-serine, L-threonine, L-aspargine, L-glutamine, L-cysteine, glycine, L-proline, D-alanine, L-isoleucine, L-leucine, L-methionine, L-phenylalanine, L-tryptophan, L-tyrosine, L-valine, histamine, 4-methyl-1*H*-imidazole, imidazole, pyrrole, cadaverine dihydrochloride, butylamine, propylamine, ethylamine and methylamine (0.05 mmol) were dissolved in sodium phosphate buffer (pH 7, 1 mL, 250 mM). After the addition of 2-cyclohexen-1-one (**1a**; 20 mg, 0.21 mmol), the reaction was allowed to proceed for 3 h at 40 °C. Work-up and analysis were performed as described above.

Time Study and Equilibrium Reaction: Samples for the time study were prepared and analysed as described above in General Procedure for Initial Rate Measurements. Reactions were performed at 40 °C and sodium phosphate buffer (pH 7, 250 mM) was used.

General Procedure for Substrate Screening: Reactions were carried out as described in the General Procedure for Initial Rate Measurements. Whenever the substrate was not soluble in buffer, acetonitrile was used as co-solvent. After extraction with ethyl acetate, the samples were dried with Na_2SO_4 and crude samples were analysed by GC–MS (Varian FactorFour VF-1ms column, 25 m × 0.25 mm × 0.4 μm, with He as carrier gas).

Preparative-Scale Synthesis of 3-Hydroxycyclohexanone (2a): For isolation and characterization of the Michael addition product, the reaction was carried out on a preparative scale. 2-Cyclohexen-1-one (**1a**; 3.02 g, 31.3 mmol) was dissolved in sodium phosphate buffer (pH 7, 150 mL, 250 mM). L-Lysine monohydrochloride (1.37 g, 7.5 mmol) was added and the reaction was stirred for 24 h at 40 °C. Work-up was performed by continuous liquid–liquid extraction overnight (200 mL of ethyl acetate was continuously bubbled through the aqueous phase). The organic phase was dried with Na_2SO_4 and evaporated under reduced pressure. The crude product mixture was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether, 1:1) to yield 0.74 g (21%) of a colourless oil. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.64–1.80 (m, 2 H), 1.96–2.11 (m, 2 H), 2.29 (t, J = 6.6 Hz, 2 H), 2.39 (dd, J = 7.5, 14.1 Hz, 1 H), 2.46 (s, 1 H), 2.63 (dd, J = 4.1, 14.1 Hz, 1 H), 4.14–4.21 (m, 1 H) ppm (in accord with the literature[16b]). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.5, 32.4, 40.7, 50.1, 69.3, 210.8 ppm (in accord with the literature[16b]). MS: *m*/*z* (%) = 114 (24) $[M]^+$, 73

(13), 71 (33), 69 (13), 68 (45), 60 (46), 58 (30), 57 (19), 55 (66), 54 (15), 44 (99), 43 (100), 42 (94), 41 (48), 40 (13).

Preparative-Scale Synthesis of 3-Hydroxy-4,4-dimethylcyclohexanone (2b): For isolation and characterization of the Michael addition product, the reaction was carried out on a preparative scale. 4,4-Dimethylcyclohexanone (**1b**; 0.97 g, 7.69 mmol) was dissolved in sodium phosphate buffer (pH 7, 35 mL, 250 mM) and acetonitrile (15 mL). L-Lysine monohydrochloride (0.45 g, 2.5 mmol) was added and the reaction mixture was stirred for 24 h at 40 °C. Work-up was performed by continuous extraction with ethyl acetate (200 mL) overnight. The organic phase was dried with Na_2SO_4 and evaporated under reduced pressure. The crude product mixture was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether, 1:1) to yield 0.11 g (9.8%) of a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.07 (s, 3 H), 1.12 (s, 3 H), 1.44–1.52 (ddd, J = 6.7, 7.9, 14.2 Hz, 1 H), 1.86 (ddd, J = 6.6, 7.0, 13.6 Hz, 1 H), 1.94 (s,1 H), 2.31–2.43 (m, 2 H), 2.40 (dd, J = 8.1, 14.6 Hz, 1 H), 2.64 (dd, J = 4.2, 14.8 Hz, 1 H), 3.69 (dd, J = 4.3, 8.1 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.0, 26.1, 34.1, 34.7, 37.7, 46.4, 50.4, 210.1. ppm. MS: m/z (%) = 142 (13) $[M]^+$, 86 (86), 82 (12), 72 (11), 71 (25), 70 (55), 69 (28), 67 (12), 58 (40), 57 (54), 56 (100), 55 (59), 53 (13), 44 (22), 43 (97), 42 (24), 41 (80).

Preparative-Scale Synthesis of 3-Hydroxycycloheptanone (2c): For isolation and characterization of the Michael addition product, the reaction was carried out on a preparative scale. Cyclohept-2-enone (**1c**; 1.03 g, 9.41 mmol) was dissolved in sodium phosphate buffer (pH 7, 35 mL, 250 mM) and acetonitrile (15 mL). L-Lysine monohydrochloride (0.45 g, 2.5 mmol) was added and the reaction mixture was stirred for 24 h at 40 °C. Work-up was performed by continuous extraction with ethyl acetate (200 mL) overnight. The organic phase was dried with Na_2SO_4 and evaporated under reduced pressure. The crude product mixture was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether, 1:1) to yield 0.17 g (14.3%) of a yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.44–1.51 (m, 1 H), 1.62–1.78 (m, 5 H), 2.09 (s, 1 H), 2.27–2.42 (m, 2 H), 2.62–2.70 (m, 2 H), 3.96 (ddd, J = 3.9, 7.3, 10.8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.7, 24.2, 38.7, 44.3, 51.6, 67.4, 212.2 ppm. MS: m/z (%) = 128 (7) $[M]^+$, 110 (12), 86 (25), 82 (14), 71 (45), 70 (14), 69 (39), 68 (56), 67 (32), 60 (14), 58 (29), 57 (78), 56 (29), 55 (84), 54 (14), 53 (11), 45 (14), 44 (38), 43 (100), 42 (39), 41 (72), 40 (10). HRMS (ESI): calcd. for $C_7H_{12}NaO_2$ $[M + Na]^+$ 151.0735; found 151.0733.

Determination of the *ee* of 3-Oxocyclohexyl Acetate:[16b] 3-Hydroxycyclohexanone (**2a**; 300 mg, 2.63 mmol) obtained by the preparative-scale reaction using L-lysine was dissolved in pyridine (3 mL) and acetic anhydride (0.81 g, 8.92 mmol) was added. The reaction was allowed to proceed overnight at room temperature and then stopped by extraction with acidified water (3 mL) and Et_2O (3 × 10 mL). The combined organic layers were washed with water and brine, dried with Na_2SO_4, and evaporated under reduced pressure. The crude product mixture was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether, 1:2) to yield 0.38 g (92%) of a colourless oil. The *ee* was measured by GC (for the method, see General Methods). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.74–1.98 (m, 4 H), 2.08 (s, 3 H), 2.37 (t, J = 6.5 Hz, 2 H), 2.48 (dd, J = 6.3, 14.8 Hz, 1 H), 2.61 (dd, J = 4.3, 14.8 Hz, 1 H), 5.20–5.25 (m, 1 H) ppm (in accord with the literature[16b]). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.6, 21.1, 29.2, 40.9, 46.5, 71.5, 170.1, 208.3 ppm (in accord with the literature[16b]). MS: m/z (%) = 156 (<1) $[M]^+$, 114 (4), 113 (2), 97 (5), 96 (27), 95 (1), 86 (7), 85 (3), 81 (2), 73 (3), 71 (4), 70 (2), 69 (7), 68 (33), 67 (5), 60 (3), 58 (5), 57 (2), 55 (13), 54 (5), 53 (2), 45 (1), 44 (4), 43 (100), 42 (15), 41 (20), 40 (5).

2-Chlorocyclohex-2-enone (1e):[23] 2-Cyclohexen-1-one (1 g, 10.40 mmol) was dissolved in DMF/c.HCl (15 mL, 1:1) followed by the addition of *m*-CPBA (2.68 g, 15.54 mmol). The reaction was allowed to proceed for 30 min at room temperature and was then quenched with 1 N $NaHCO_3$ (10 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic layers were dried with Na_2SO_4. The organic solvent was evaporated under reduced pressure and the crude reaction product purified by flash chromatography on silica gel (ethyl acetate/petroleum ether, 1:8) to yield 0.73 g (54%) of a pale-rosy solid (m.p. 69–72 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.03–2.09 (m, 2 H), 2.48 (dt, J = 5.0, 5.4 Hz, 2 H), 2.59 (t, J = 6.6 Hz, 2 H), 7.14 (t, J = 4.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.6, 27.0, 38.5, 132.2, 146.5, 191.4 ppm (in accord with the literature[23]). MS: m/z (%) = 130 (68) $[M]^+$, 132 (23) $[M]^+$, 104 (26), 102 (75), 91 (14), 89 (46), 88 (18), 76 (19), 74 (58), 67 (98), 65 (23), 63 (11), 61 (16), 55 (100), 53 (23), 51 (18), 50 (12), 42 (17), 41 (27), 40 (10).

Supporting Information (see footnote on the first page of this article): The plot of pK_a against conversion from amino acid screening, ^{1}H and ^{13}C NMR spectra and HRMS spectrum.

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