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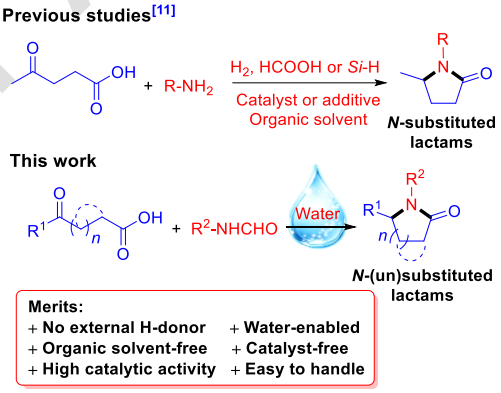
A facile direct route to *N*-(un)substituted lactams by cycloamination of oxocarboxylic acids without external hydrogen

Hu Li,[a,‡] Hongguo Wu,[a,‡] Heng Zhang,[a] Yaqiong Su,[b*] Song Yang[a*] and Emiel J. M. Hensen[b*]

Abstract: Lactams are privileged in bioactive natural products and pharmaceutical agents and widely featured in functional materials. This study presents a novel versatile approach to the direct synthesis of lactams from oxocarboxylic acids without catalyst and external hydrogen. The method involves the *in situ* release of formic acid from formamides induced by water to facilitate efficient cycloamination. Water also suppresses the formation of by-products. This unconventional pathway is elucidated by a combination of model experiments and density functional theory calculations, where cyclic imines (5-methyl-3,4-dihydro-2-pyrrolone and its tautomeric structures) are found to be favourable intermediates toward the lactam, different from the conventional approach encompassing cascade reductive amination and cyclization. This sustainable and simple protocol is broadly applicable for the efficient production of various *N*-unsubstituted and *N*-substituted lactams.

Lactams are cyclic amides, which form a class of core structural motifs privileged in a variety of bioactive natural products and pharmaceutical agents.[1] These heterocyclic scaffolds feature amongst others in functional materials and catalysts.[2] Pyrrolidones are an ubiquitous sub-group of lactams, which are of great and long-standing interest in the preparation of those five-membered nitrogen-containing heterocycles.[2a,3] The regioselective establishment of C-C and C-N bonds is a powerful strategy to build *N*-heterocyclic compounds. An attractive approach to secondary lactams is catalytic cyclization of primary amides with intramolecular alkenes in the presence of metal catalysts *via* aza-Heck or aza-Wacker mechanisms, in spite of the need to use, respectively, highly electrophilic or nucleophilic nitrogen species.[4] Lactams can also be obtained in other ways, such as by combining homoenolates with acid-activated imines,[5] intramolecular hydrocarbamoylation of allylic formamides,[6] Michael/proton transfer/enol lactonization of acyl chlorides with dicarbonyls,[7] intramolecular alkenylation of acyclic bromoalkenes,[8] and cycloamination of prenyl carbamates and ureas[9]. All of these approaches require specific catalysts and/or additives as well as organic solvents in order to obtain satisfactory yields. Therefore, it would be desirable to develop a catalyst- and solvent-free protocol for the construction of valuable lactam skeletons from sustainable and low-cost substrates.

Oxocarboxylic acids contain one or more aldehydic or keto groups in a carboxylic acid and are widely available compounds. A prime example is levulinic acid (LA), which can be easily obtained from renewable lignocellulosic biomass.[10] The keto-acid LA can be converted with primary amines to *N*-substituted lactams or pyrrolidones via cascade reductive amination and cyclization catalyzed by transition metals (Scheme 1).[11] In connection with this, various strategies have recently been proposed to design and prepare catalysts with unique functionalities for simplifying the overall process, such as the use of low-pressure hydrogen, or hydrogen-donating co-reactants such as formic acid (HCOOH) and hydrosilanes under mild conditions.[11-13] Significant progress has been made in the selective production of *N*-substituted lactams and pyrrolidones from LA (Table S1), but in all cases the use of an organic solvent, an external hydrogen source and/or additives are key to obtain good results.



Scheme 1. Cycloamination strategies for the synthesis of *N*-(un)substituted lactams.

Leuckart reductive amination is a well-known reaction for catalyst-free upgrading of aldehydes and ketones to formamides using HCOOH as a hydrogen donor, although it is hampered by a low selectivity and high required reaction temperatures (ca. 180 °C).[14] Efforts to improve the product selectivity and reaction rate include the use of basic additives (e.g., NEt_3) or microwave heating to activate HCOOH and minimize the negative effect of its acidity during reductive amination.[15] Herein, we propose a novel and generic strategy involving *in situ* controlled-release of HCOOH from *N*-formyl species with deionized water for cyclic diamination of LA and other keto-acids. Our synthesis protocol provides access to various *N*-(un)substituted lactams without catalyst and external hydrogen, and requires no organic solvent (Scheme 1).

We explored the use of formamide (H_2NCHO) and HCOOH as nitrogen and hydrogen sources, respectively, for the cycloamination of LA (without catalyst and solvent) and obtained a moderate 5-methyl-2-pyrrolidinone (MPD) yield of 83% after

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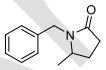
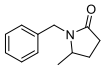
reaction for 1.5 h at 160 °C (Table 1, entry 1). From a green chemistry point of view, the 10-fold excess of HCOOH results in undesired waste with respect to process mass intensity (PMI = 8.7, entry 1) and E-factor (5.0, Table S2) parameters. Without HCOOH, the MPD yield decreased to 41% at 160 °C (entry 2), implying the possibility of *in situ* release of HCOOH from H_2NCHO or other *N*-formyl intermediates during the reaction. To explore this opportunity, several control experiments were conducted. First, LA can be directly cyclized to angelica lactones (ALs) by dehydration.[16] Second, H_2NCHO can be hydrolyzed in water with conversions up to ca. 70% after 1.5 h at 160 °C and were then constant upon prolonged reaction to 4 h. These findings demonstrate that water obtained by LA dehydration can in principle promote the hydrolysis of H_2NCHO and relevant *N*-formyl intermediates to release HCOOH. As expected, the addition of water (30 equiv.) into the reaction systems with and without HCOOH (entries 3 & 4) significantly accelerates the cycloamination reaction, providing comparable MPD yields of 92% and 94%. It is worth noting that the reaction without HCOOH exhibits superior green chemistry metrics including a high reaction mass efficiency (RME), a low E-factor, and good atom economy compared to the case with HCOOH (Table S2). The PMI of the present protocol that avoids the use of HCOOH is 8.5 (entry 4), much lower than values between 20 and 199 for other approaches reported in the literature (entries 5-11).[11,12d,13c,17] These features render our novel synthetic protocol highly promising for the sustainable production of lactams in good yield.

Table 1. Catalytic cycloamination of LA to lactams using different systems

Entry	Catalyst	Nitrogen source	Hydrogen source	Additive/ Solvent	Temp. (°C)	Time (h)	Lactam	Yield (%)	PMI[c]	Rate[d]	Ref.
1[a]	-	H_2NHCO	HCOOH	-	160	1.5		83	8.7	1107	
2[a]	-	H_2NHCO	-	-	160	4		41	6.2	205	This
3[b]	-	H_2NHCO	HCOOH	H_2O	160	1.5		92	13.7	1227	work
4[b]	-	H_2NHCO	-	H_2O	160	4		94	8.5	470	
5	-	Benzyl amine	HCOOH	NEt_3 / DMSO	100	12		87	199	73	13c
6	Pt-MoO_x/TiO_2	*n*-Octyl amine	3 bar H_2	-	100	20		99	66	50	12d
7	Ru-P complex	Benzyl amine	HCOOH	-	120	12		95	90	79	17
8	$In(OAc)_3$	R-NH_2	$PhSiH_3$	Toluene	120	1-24		49-97	>20	180	11b
9	Pt/P-TiO_2	Aqueous NH_3	1 bar H_2	MeOH	25	72		85	32	12	11a
10	Pt/P-TiO_2	5 bar NH_3 gas	15 bar H_2	MeOH	25	72		87	38	12	11a
11	Au/ZrO_2-VS	Aqueous NH_3	HCOOH	H_2O	130	16		85	45	53	11c

[a] Molar ratio of LA/H_2NHCO/HCOOH/H_2O 1:3:10:30
[b] Molar ratio of LA/H_2NHCO/H_2O 1:6:30
[c] Process mass intensity (PMI) is defined as (Mass of raw materials input) / (Mass of desired output)
[d] Reaction rate defined as mole of product / time (μmol h^{-1})

Table 1 shows that systems depending on metal catalysts require much longer reaction times (up to 72 h) to achieve moderate yields of either substituted or unsubstituted lactams (entries 8-11), despite relatively low reaction temperatures (25-130 °C).[11] Our protocol shows superior performance in terms of the reaction rate with and without HCOOH (1227 and 470 μmol h^{-1}, entries 3 & 4), while affording good lactam yield comparable to previously reported results (entries 3-11). The significant higher MPD formation rate with HCOOH indicates that hydrogen transfer may be the rate-determining step. Therefore, we hypothesized that optimizing the reaction conditions towards faster *in situ* release of HCOOH from H_2NCHO and involved N-formyl species assisted by water can improve the reaction performance without HCOOH. The use of 6 eqv. H_2NCHO and 30 eqv. water results in a satisfactory yield of ca. 90% MPD from LA at 160 °C after 2 h (Figures S1 & S2). The reaction temperature and time strongly impact the MPD formation rate and product distribution (Figure S3). Specifically, unreduced 5-methyl-3,4-dihydro-2-pyrrolone (MDPY) and nitrogen-free γ-valerolactone (GVL) were observed as by-products in the novel reaction system (Figures S4 & S5), besides previously reported 4-formamidopentanoic acid (FPAC) and 4-formamidopentanamide (FPAM) intermediates.[11b,12d,18] These findings suggest that the reducing and C-N coupling functionalities of the reaction system are responsible for the product distribution, which lies between typical catalyst-mediated reductive amination and our novel approach free from catalyst and external hydrogen.

As follows from Table 1, the thermal reaction system of LA and H_2NCHO with HCOOH (1107 μmol h^{-1}) instead of water (470 μmol h^{-1}) results in a superior MPD formation rate (entry 1 *vs* 4), highlighting the significance of hydrogen transfer in the overall cycloamination reaction. Although both types of reactions proceed via the key intermediates FPAC and FPAM, the reaction with excess HCOOH affords another cyclic compound *N*-formyl 5-methyl-2-pyrrolidinone (FMP) as a main by-product (Figure 1). We also observe that the presence of HCOOH substantially decreases the time to completely convert LA (20 min), in comparison with the water-assisted system (120 min). Notably, the formation of the relatively stable FMP results in a low MPD yield (Figure 1). Water suppresses the formation of FMP by hydrolysis, thus improving the MPD yield (Table 1, entry 1 *vs* 3). Thus, we can infer that water is not only favorable for *in situ* release of HCOOH by hydrolysis of H_2NCHO and *N*-formyl intermediates, but also avoids the formation of undesired

species like FMP that are chemically stable under anhydrous conditions.

The formation of GVL (Figures 1B & S3), which can be obtained from ALs via hydrogenation with HCOOH,[19] suggests that ALs can be the intermediates leading to the nitrogen-containing cyclics (*i.e.,* MDPY and MPD). To explore this possibility, α-AL was thermally treated with H_2NCHO in water or neat conditions, wherein respectively 44% and <6% MPD yields together with MDPY in ca. 8% and <1% yields were obtained after heating at 160 °C for 1 h. We can explain these differences by the reversibility of the reaction between LA and ALs,[16] with the presence of water shifting the equilibrium to the LA side. LA is the species that reacts to form MPD and MDPY. A kinetic study of the conversion of LA to MPD with normal and deuterated water reveals a secondary hydrogen isotope effect with k_H/k_D = 0.94 (Figure S6). The equilibrium deuterium isotope effect suggests reversible processes in the overall reaction of LA to MPD,[20] especially those participated with water.

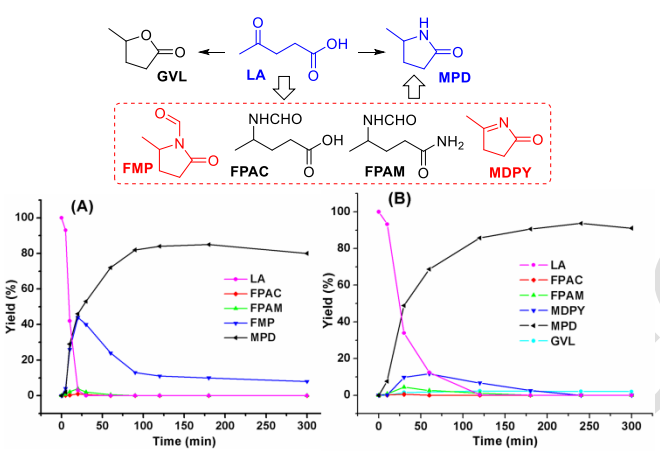


Figure 1. Product distribution in cycloamination of LA with H_2NCHO assisted by HCOOH (A) or water (B) heated at 160 °C for variable times.

Considering the possible activation role of acidic carboxyl group (-COOH) of LA in the synthesis of MPD via cycloamination, ethyl levulinate (EL) was used as a substrate instead of LA, yielding ca. 90% MPD (Figure S7). A kinetic study showed comparable reaction rate constant (k_{LA}/k_{EL} = 1.05) for cycloamination of LA (0.0519 min^{-1}) and EL (0.0493 min^{-1}; Figure S8), demonstrating that the acidity of the substrate has a minor effect on the reaction outcome. We also investigated the order of amination and amidation steps in the LA-to-MPD conversion by examining the reactivity of 2-pentanone and pentanoic acid under otherwise similar conditions (Figure S9). The results clearly show that amination is much faster than amidation independent of the presence of HCOOH. Another salient detail of this experiment was that the conversion of 2-pentanone and pentanoic acid were both lowered in water in comparison with the HCOOH-mediated reaction (Figure S9), further revealing that the rate-determining step in the cycloamination without external hydrogen source is likely the *in situ* release of HCOOH from H_2NCHO and involved *N*-formyl species assisted by water.

The hydrogen transfer process and the presence of ALs and MDPY tautomeric structures are illustrated by deuterium-labeled experiments (Figures S10-S12). The large body of reaction data allowed us to depict the reaction pathways for LA cycloamination with H_2NCHO and water in Figure 2A. Initially, H_2NCHO is reversibly hydrolyzed to NH_3 and HCOOH under hydrothermal conditions with a reported free energy of activation (ca. 146 kJ/mol),[21] while LA is able to undergo either C-N coupling with H_2NCHO to afford 4-(formylimino)pentanoic acid (IM-1) via IM-0 or intramolecular dehydration to give ALs with tautomeric structures, respectively, due to lack of enough HCOOH derived from H_2NCHO hydrolysis in the early stage. With the assistance of the *in situ* formed HCOOH, a limited amount of ALs is hydrogenated to GVL (Figure 2A). As the dominant reaction pathway, IM-1 is more prone to release HCOOH and undergo intramolecular cyclization, giving a favorable precursor MDPY with relevant tautomeric structures that are gradually transformed into MPD by hydrogen transfer during prolonged reaction. In parallel, IM-1 may undergo cascade transfer hydrogenation (FPAC), amidation (FPAM), and cyclization to afford the MPD product, despite the low rates of these reactions.

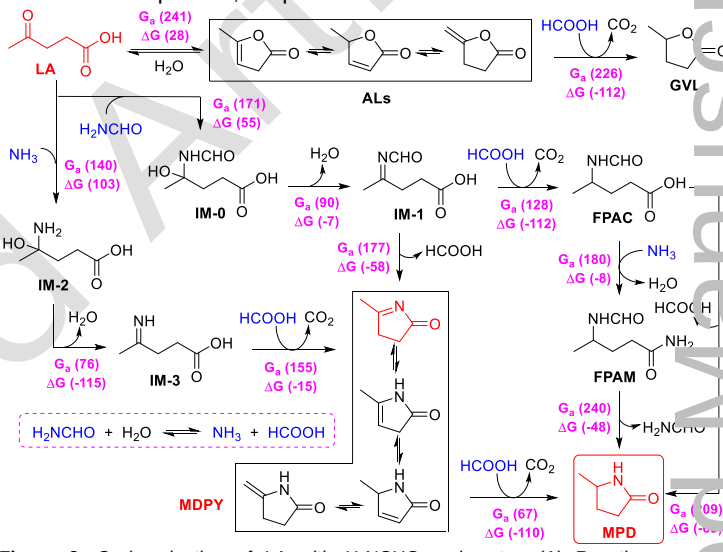


Figure 2. Cycloamination of LA with H_2NCHO and water: (A) Reaction pathways, and (B) Computed free energy profiles.
IM: intermediate; TS: transition state; Values in parentheses are free energies and enthalpies (kJ/mol).

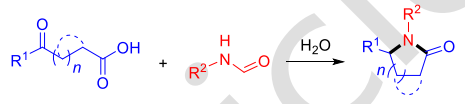
To examine whether LA-to-MPD conversion proceeding through MDPY is kinetically and thermodynamically favorable, density functional theory (DFT) calculations were performed at the B3LYP/6-311+G(2s,2p) level in conjunction with polarizable continuum model (PCM) to simulate the solvent effect (Figures 2 & S13). LA can react with H_2NCHO to obtain intermediate IM-0 by overcoming an activation free energy barrier (G_a) of 171 kJ/mol, followed by conversion to IM-1 through releasing one water molecule (G_a = 90 kJ/mol). From IM-1 to the product MPD via the precursor MDPY involving the release of HCOOH, the highest activation energy barrier is calculated to be 177 kJ/mol, in good agreement with the experimental activation energy of 162 kJ mol^{-1} (Figure S14). In contrast, the pathway via the precursor FPAC and FPAM toward MPD, respectively, requires a 32 kJ/mol and 63 kJ/mol higher activation energy, clearly demonstrating that the pathway involving MDPY is preferred. Notably, the FPAM formation requires a comparable activation energy of 180 kJ mol^{-1}, indicative of the possibility of resulting FPAM from IM-1 via FPAC, as identified by GC-MS (Figure S4),

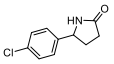
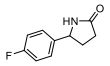
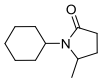
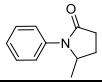
which is also consistent with the experimental results (Figures 1 & S3). In view of gaseous NH_3 and HCOOH being simultaneously formed in a certain amount from the thermal hydrolysis of H_2NCHO, the initial amination of LA with NH_3 instead of H_2NCHO was also taken into consideration (Figure 2). The energy barrier for the reaction between LA and NH_3 to afford MDPY successively via IM-2 and IM-3 was calculated to be 155 kJ/mol, which is slightly lower than the latter (177 kJ/mol). It is worth noting that the used reactants LA (b.p. ~245 ℃) and H_2NCHO (b.p. ~210 ℃) are both in liquid phase during the reaction process at a temperature of 160 ℃. Therefore, we may expect that amination occurs between these components as well as between liquid LA and NH_3 (gas), considering mass transfer limitations of gas-liquid phase reactions.[22] In addition, the ALs formation is disadvantageous by LA dehydration (Figure 2 & S13), as proved by the poor GVL yield. These results elaborate that cyclic imines (MDPY with its tautomeric structures) derived from LA by cycloamination are preferentially converted to the lactam via subsequent hydrogen transfer, which is totally different to the typical cascade reductive amination and cyclization process.

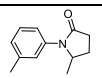
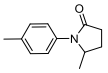
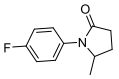
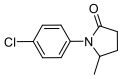
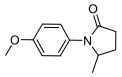
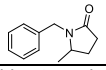
Encouraged by the prominent performance of the developed reaction system, the substrate scope with respect to functional group tolerance was further examined (Table 2). Apart from H_2NCHO (entry 1), ammonium formate ($HCOONH_4$) was found to exhibit much higher reactivity (entry 2), leading to shorter reaction (3 h) and higher MPD yield (97%). In comparison with H_2NCHO, the increasing hydrolysis ability of ammonium formate can contribute to the superior performance, also proving that the release of HCOOH from thermal treatment of H_2NCHO and involved *N*-formyl species is the rate-determining step. However, LA promoted by the mixture of equivalent HCOOH and NH_3 (aq.) only gave MPD in a low yield of ca. 70% under identical conditions, while increased amounts of GVL and formylated/condensed co-products were observed. Even worse, when primary amines (e.g., propylamine, cyclohexylamine, aniline, 3-methylaniline, 4-methylaniline, and benzylamine) and HCOOH were used as substrates for the cascade aqueous reaction processes, only 10-50% yields of *N*-substituted lactams were observed under optimized conditions. These results indicate that the *in situ* release of HCOOH from H_2NCHO, $HCOONH_4$ or other *N*-formyl species assisted by water is more favorable for suppressing the occurrence of side reactions to ensure relatively high selectivity toward MPD. When the 4-substituent of the oxocarboxylic acid substrate is changed from methyl to phenyl, 4-chlorophenyl, 4-fluorophenyl, and 2-thienyl groups, corresponding unsubstituted lactams in good yields (81-93%) are achieved (entries 3-6). All together with those 1,4-dicarbonyl substrates, a range of 1,5- and 1,6-dicarbonyl compounds can be also subjected to cycloamination, affording moderate to good yields (68-92%) of six- and seven-membered lactams, respectively (entries 7-10). Importantly, unsubstituted benzolactams (62-80%) can be obtained from *o*-phenyl dicarbonyl compounds with H_2NCHO assisted by water (entries 11 & 12). In addition to H_2NCHO, a series of other formamides that can be simply synthesized by catalyst-free *N*-formylation of amines with CO_2 [23] were also employed as both nitrogen and hydrogen sources, and relevant *N*-substituted lactams with satisfactory yields (75-98%) can be attained (entries 13-22).

In order to evaluate the potential of practical implementation of our new protocol, the efficiency of the catalyst- and external hydrogen-free system in the cycloamination of LA with H_2NCHO and water was examined in a continuous-flow microreactor. Under above-optimized reaction conditions (LA/H_2NCHO/H_2O molar ratio 1:6:30, reaction temperature 160 °C), a good MPD yield of 87% can be obtained with a residence time of 20 min. In comparison with the established batch procedure (Table 1, entry 4), the flow reactor shortens the reaction duration, with superior reaction rate and comparable lactam yield.

Table 2 Production of N-(un)substituted lactams from various oxocarboxylic acids and formamides



Entry	Oxocarboxylic acid R^1	*N*	Formamide R^2	Lactams	t(h)	Y(%)
1	CH_3	1	H		4	94
2[a]	CH_3	1	$HCOONH_4$		3	97
3		1	H		4	81
4		1	H		5	86
5		1	H		6	87
6		1	H		4	93
7	CH_3	2	H		5	92
8	CH_3	3	H		5	68
9		2	H		4	85
10		2	H		4	70
11			H		5	80
12			H		5	62
13	CH_3	1	CH_3		4	98
14	CH_3	1	CH_3CH_2		4	94
15	CH_3	1			4	80
16	CH_3	1			4	85

17	CH_3	1			4	83
18	CH_3	1			4	84
19	CH_3	1			5	75
20	CH_3	1			5	78
21	CH_3	1			4	89
22	CH_3	1			4	88

Reaction conditions: 2 mmol oxocarboxylic acids, 6 equiv. formamides, 30 equiv. water, 160 °C.
[a] $HCOONH_4$ instead of H_2NCHO was used as used nitrogen source.

In summary, a facile versatile approach to directly synthesize both *N*-unsubstituted and *N*-substituted lactams under catalyst- and external hydrogen-free conditions has been developed involving *in situ* release of HCOOH from formamides promoted by water for efficient cycloamination. Experimental and computational results show that cyclic imines are the key species toward the lactam by undergoing subsequent hydrogen transfer. This route is completely different to typical catalyzed reaction pathways, involving reductive amination followed by cyclization. The novel benign and versatile protocol exhibits good universality and applicability in lactam synthesis. We envision it to find broader application by giving access to various nitrogen-containing compounds, especially high-value *N*-heterocycles.

Experimental

Reaction procedures

All the experiments were carried out in a Teflon-lined stainless steel autoclave (inner volume 15 mL), placed in an oil-bath that was preheated to the desired reaction temperature (120-180 °C). In a typical reaction procedure, 2 mmol LA or keto acid, 12 mmol H_2NCHO or formamides (6 equiv.), and 60 mmol deionized water (30 equiv.) were added into the autoclave, and the reaction duration was recorded as the autoclave was placed into the oil-bath. After a specific reaction time, the autoclave was taken out of the oil bath and immediately cooled-down to ambient temperature with tap-water. Upon completion, the autoclave was opened and deionized water (or methanol) was added to the reacted mixture, which was subsequently analyzed by HPLC (or GC). Each experiment was separately conducted and repeated for 2-3 times. The obtained conversions and yields are average data of 2-3 individual experiments, with standard deviation (σ) in the range of 0.5-4.6%. Structures were confirmed by ^1H, ^{13}C NMR (JEOL-ECX 500 NMR spectrometer, $CDCl_3$), GC-MS, and HRMS.

For the product separation from the reaction mixture, CH_2Cl_2 or ethyl acetate can be used as an effective extractant. Typically, 3-5 mL deionized water was added into the mixture after the reaction, while the product lactam could be isolated by extraction with CH_2Cl_2 or ethyl acetate for 3 times (5 mL × 3). The resulting combined extractant was evaporated under reduced pressure to give the product lactam.

Regarding the continuous-flow reactions, a Labtrix®Start microreactor system (Chemtrix BV, NL) with a glass micro reactor (type 3227, volume: 19.5 µL) was utilized. Initially, LA, H_2NCHO, and deionized water in a molar ratio of 1:6:30 was evenly mixed and added into a flask. The resulting solution was pumped into the micro reactor (rate: 25 µL/min) under cooling until the reactor is full. Upon the reactor temperature was raised to 160 °C, the solution flow rate was set at 1.5 µL/min. After running for 1.5 h, sampling at timed intervals was conducted for GC analysis.

Computational methods

All DFT calculations were carried using the hybrid functional B3LYP [24] as implemented in Gaussian 09 D.01 software [25]. The all-electron 6-311+G(d,p) basis set was used for all atoms. The polarized continuum model (PCM) [26] with standard parameters for water solvent (ε = 78.3) was used to account for bulk solvent effects during geometry optimization and searching of transition states. Frequency analysis was performed to ensure that each transition state has only one imaginary frequency in the direction of the reaction coordinate. All relative energies discussed in this paper are referred to Gibbs free energies considered the zero point energy (ZPE) correction at 453 K.

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Keywords: cycloamination • hydrogen-free reduction • lactams • water • DFT

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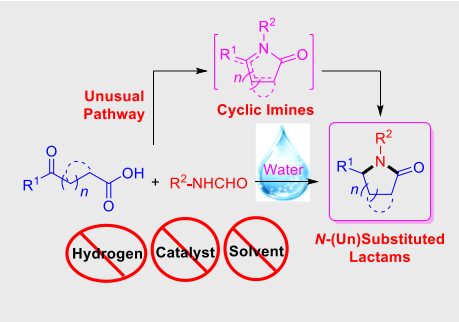
Entry for the Table of Contents

COMMUNICATION

Free to lactams: An external hydrogen and catalyst-free approach is developed to simply synthesize various *N*-(un)substituted lactams from bio-based levulinic acid and relevant keto acids by direct cycloamination with formamides, enabled by the co-added water to *in situ* release formic acid. An unconventional pathway encompassing cyclic imines as the key species toward the lactams is elaborated.



H. Li, H. Wu, H. Zhang, Y. Su, S. Yang,* E. J. M. Hensen**

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A facile direct route to *N*-(un)substituted lactams by cycloamination of oxocarboxylic acids without external hydrogen