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Insights into ammonia borane enabled green synthesis of *N*-substituted lactams from biomass-derived keto-acids and amines

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Abstract

The reductive amination/cyclization of biomass-based keto-acids and amines to lactams under mild condition with ammonia borane (NH_3-BH_3) as hydrogen donor in the absence of additives is reported herein for the first time, and is demonstrated with 22 examples affording lactams in moderate to excellent yield. A combination of *in situ* NMR and control experiments indicated that reductive amination occurs via imine formation and double hydrogen transfer from NH_3-BH_3 during the reaction.

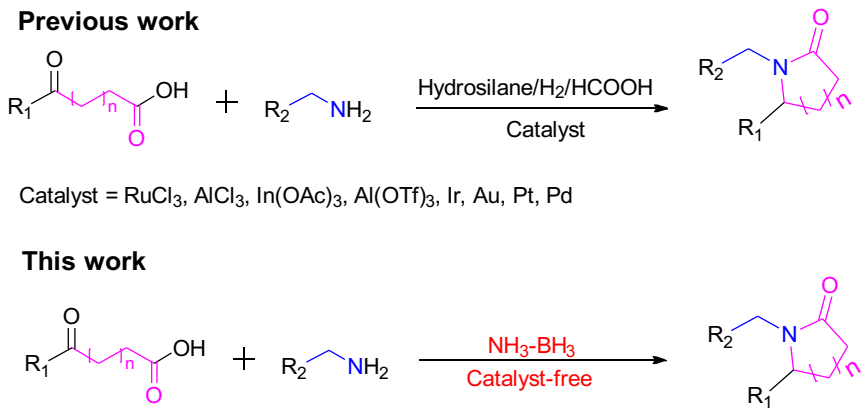
Keywords

Ammonia borane, reductive amination to lactam, biomass-derived keto-acids, *in situ* NMR, double hydrogen transfer mechanism

Introduction

N-substituted lactams are heterocyclic compounds that are widely employed in the synthesis of more complex molecular structures of pesticides, pharmaceuticals, and surfactants.[1-3] Lactam synthesis can employ γ-butyrolactone or butanediol as reactants.[4, 5] However, utilization of low-cost keto-acid feedstocks that are directly obtainable from lignocellulosic biomass, such as levulinic acid (LA), provides new opportunities for more sustainable and cost-effective processes.[6]

Strategies for the synthesis of *N*-substituted lactams from keto-acids and amines have earlier been devised using homogeneous catalysts, such as Ru- or Ir-complexes, $AlCl_3$, $RuCl_3$, $In(OAc)_3$, and ionic liquids.[7-13] Also heterogeneous catalysts have been used for the conversion of keto-acids to lactams, but only employing expensive noble metals, such as Pd, Pt, and Au.[14-16] Additionally, a few catalyst-free systems have been developed for lactam synthesis relying on a Leuckart-Wallach type mechanism using harsh reaction conditions[17,18]. Previous systems for the synthesis of *N*-substituted lactams rely on the use of formic acid, organic silanes or molecular hydrogen as reductant, as summarized in Table S1. Resultant drawbacks and concerns include high reaction temperature, excess usage of hydrogen donor, difficult product isolation or handling of hazardous pressurized gas (Scheme 1, top).



Scheme 1. Different strategies of the synthesis of lactams from keto-acids and amines.

Ammonia borane (AB) is an excellent hydrogen storage material with a high hydrogen content of 19.8 wt%. Compared with the previously used hydrogen-donors such as hydrosilane, H_2 and formic acid, AB appears to be the clearly more promising option for the synthesis of lactams under benign conditions. Advantages include that AB is a solid hydrogen source that is easy to use, AB by-products formed after reaction are water-soluble and the high hydrogen content and high activity result in an atom-efficient usage of AB. Therefore, AB has been successfully applied for the reduction of unsaturated bonds (C=N and C=O) in the presence of designed catalysts,[19-22] while its application in lactam synthesis has remained undeveloped. Herein, we report a novel and highly versatile strategy for the synthesis of *N*-substituted lactams via reductive amination/cyclization of LA and amines with AB as hydrogen donor, as shown in Scheme 1, bottom. To the best of our knowledge, this is the first catalyst-free system that facilitates conversion of keto-acids and amines into *N*-substituted lactams using AB as hydrogen donor. In the study, 22 different lactams were synthesized in up to 99% yield using various keto-acids and amines with as low as half equivalent AB dosage in neat solvent under mild conditions (80 ºC, 2 h). The reaction pathway of the reductive amination and the role of AB were elucidated using a combination of *in situ* NMR and control experiments.

Results and Discussion

In initial experiments, the reductive amination/cyclization of LA and benzylamine (BA) with AB was screened in common organic solvents as well as water (Figure 1a). The aprotic, unpolar solvent hexane afforded rather low conversion and *N*-benzyl-5-methylpyrrolidone (BMPD) selectivity because of limited AB solubility. In contrast, protic polar solvents like methanol and ethanol gave good BMPD yields (70-80%), while essentially only 4-hydroxypentanoic acid formed in water (Figure S1) due to the fast reduction of the carbonyl group of LA under the applied reaction conditions. In aprotic, polar solvents like CH_3CN, THF, DMSO and CH_2Cl_2, the BMPD yields were even better and the latter solvent

facilitated the highest yield of 90%. Notably, the biomass-derived, green solvent γ-valerolactone (GVL) also provided a good yield of 80%, but its relatively high boiling point (bp. 205 °C), which is almost identical to the boiling point of BMPD (202-204 °C), complicates product isolation. Hence, based on overall considerations including product isolation/purification, cost and accessibility, CH_2Cl_2 was chosen for the proceeding investigations.

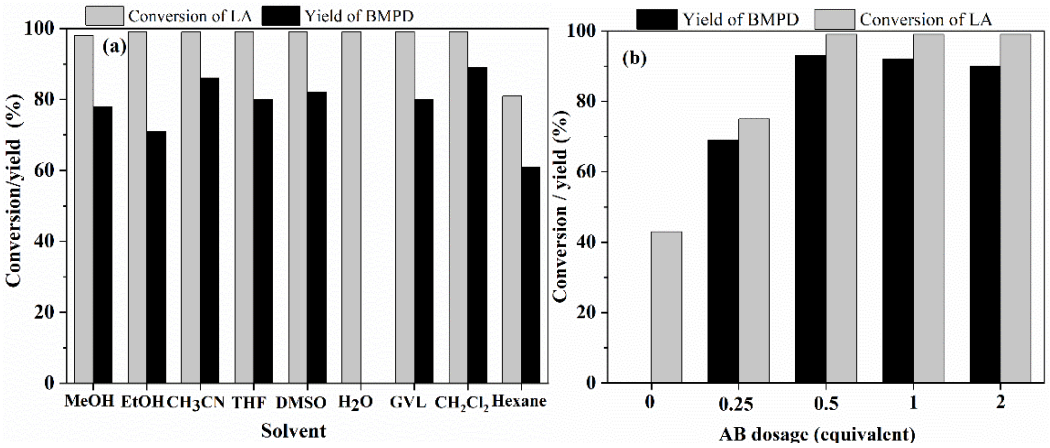


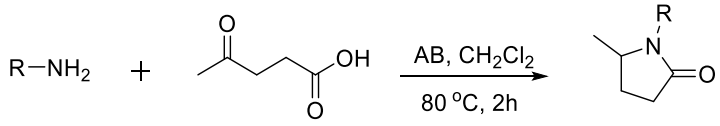
Figure 1. a) Effect of solvent on the formation of BMPD from LA and BA (reaction conditions: 1 mmol LA, 1.5 mmol BA, 0.5 mmol AB, 2.0 mL solvent, 120 °C, 2 h). (b) Effect of AB dosage on the formation of BMPD from LA and BA (reaction conditions: 1 mmol LA, 1.5 mmol BA, 2.0 mL CH_2Cl_2, 80 °C, 2 h).

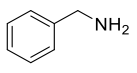
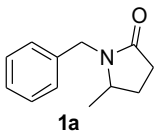
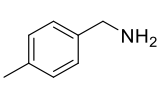
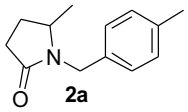
Optimization of the reaction temperature and reaction time in CH_2Cl_2 resulted in an improved yield of 92% BMPD at 80 °C after 2 h (Table S2), while lower temperature afforded the secondary amine 4-(benzylamino)pentanoic acid as the dominant product (Figure S2). AB dosage also had an apparent effect on the efficiency of the reaction, as only the corresponding imine product (i.e. 4-(benzylimino)pentanoic acid) was formed, while the targeted lactam was not formed in the absence of AB. However, a relatively low dosage of 0.5 equivalents of AB with respect to LA was found sufficient to obtain full LA conversion and the highest yield of BMPD (Figure 1b). Although a similar yield of BMPD

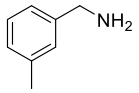
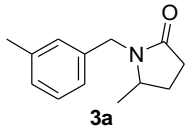
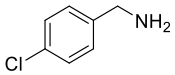
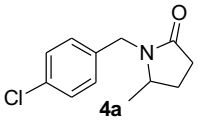
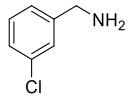
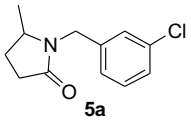
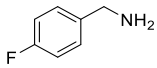
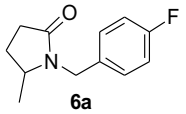
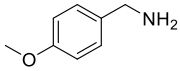
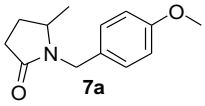
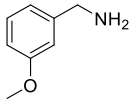
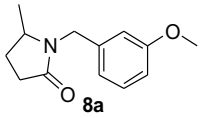
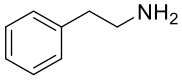
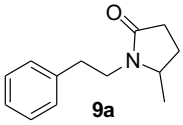
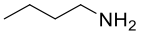
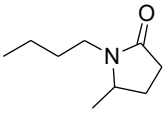
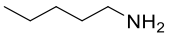
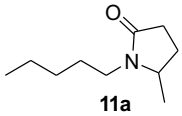
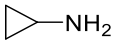
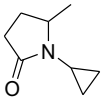
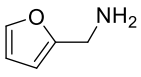
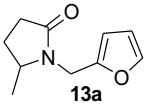
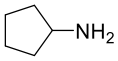
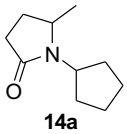
has been reported previously in a few other catalyst-free systems, the current AB reaction system with low hydrogen dosage is, as far as we are aware, the most benign reported until now (Table S3).

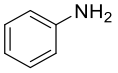
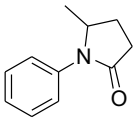
Using the optimal reaction conditions for BMPD formation, the applicability of the AB hydrogen donor system was demonstrated for the synthesis of alternative *N*-substituted-pyrrolidones in good to excellent yield by reaction of LA with various primary alkyl- and benzylamines (Table 1). For substituted benzylamines, para-substitution with electron-donating or electron-withdrawing groups (methyl, methoxy, fluoro and chloro) appeared to provide higher reactivity towards lactam formation than meta-positioned groups, suggesting a higher nucleophilicity of the former compounds (entries 2-8). Also, extension of the carbon chain of benzylamine to phenylmethanamine (entry 9), as well as aliphatic amines with different carbon chain lengths (n-butylamine, cyclopropylamine and n-hexylamine, entries 10-12), resulted in excellent yields (92-99%) of the corresponding lactams. Likewise, biomass-based heterocyclic furfuryl amine gave a high yield of 91% of lactam product (entry 13). In contrast, cyclopentanamine and aniline (entries 14 and 15) suffered from relatively low reactivity and yields (36-53%), possibly due to their lower nucleophilicity caused by steric effects and lower basicity, respectively.

Table 1. Reductive amination of LA with various amines using AB



Entry	Amine	Product	Yield (%)
1		 **1a**	92 (86)
2		 **2a**	97 (91)

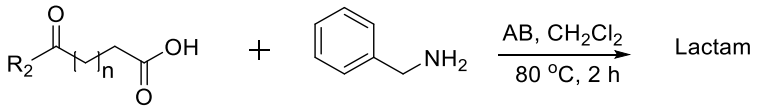
3		 **3a**	76 (72)
4		 **4a**	95 (88)
5		 **5a**	87 (81)
6		 **6a**	96 (90)
7		 **7a**	87 (83)
8		 **8a**	81 (77)
9		 **9a**	99 (94)
10		 **10a**	92 (86)
11		 **11a**	94 (86)
12		 **12a**	90 (88)
13		 **13a**	91 (88)
14		 **14a**	53 (49)

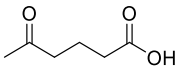
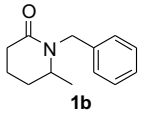
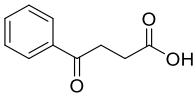
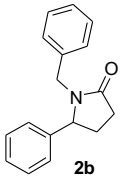
15		 **15a**	38 (30)

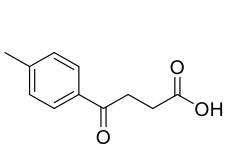
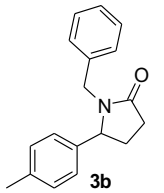
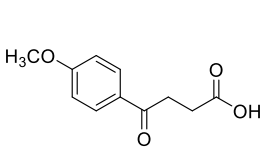
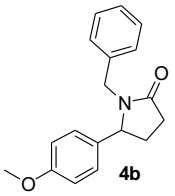
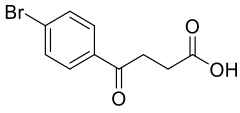
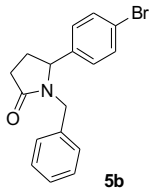
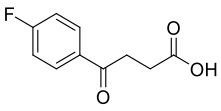
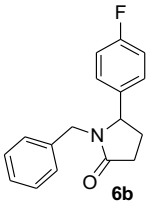
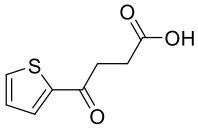
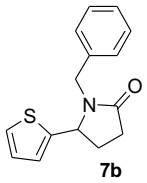
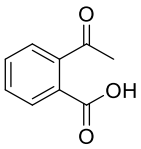
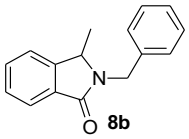
Reaction conditions: 1.5 mmol amine, 1 mmol LA, 0.5 mmol AB, 2.0 mL CH_2Cl_2, 80 ºC, 2 h. Yields were quantified by ^1H NMR using mesitylene as internal standard and after isolation (number in parenthesis).

The keto-acid 4-acetylbutyric acid, having a longer carbon chain than LA, was further examined for the reductive amination with BA, and was found to also afford the desired lactam product in excellent yield >99% (Table 2, entry 1). Moreover, a series of structurally diverse pyrrolidinones containing two aromatic substituents (Table 2, entries 2-8) were synthesized directly from the corresponding keto-acids with the AB system. However, using the optimized reaction conditions established for BMPD synthesis only moderate yields (24-45%) of these special lactams were obtained, primarily due to easy reduction of the ketone group next to the aromatic ring of the keto-acids to a hydroxyl compound, which did not undergo lactam formation.

Table 2. Reductive amination of various keto-acids with BA using AB



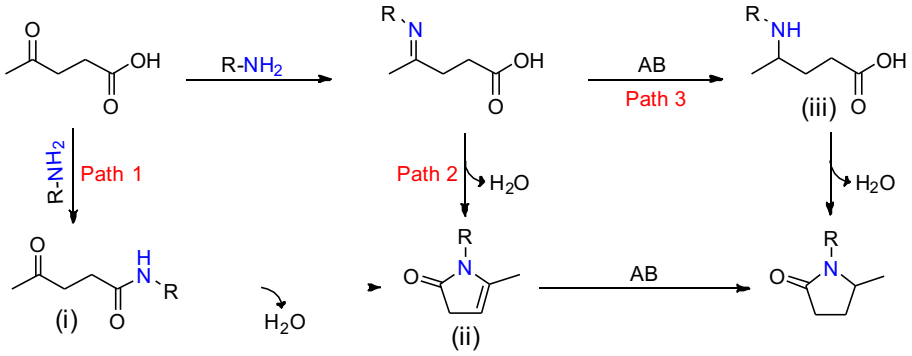
Entry	Keto-acid	Product	Yield (%)
1		 **1b**	>99 (96)
2		 **2b**	38 (31)

3		 **3b**	31 (26)
4		 **4b**	32 (28)
5		 **5b**	41 (37)
6		 **6b**	45 (42)
7		 **7b**	24 (21)
8		 **8b**	36 (33)

Reaction conditions: 1.5 mmol amine, 1 mmol keto-acid, 0.5 mmol AB, 2.0 mL CH_2Cl_2, 80 ºC, 2 h. Yields were quantified by ^{1}H NMR using mesitylene as internal standard and after isolation (number in parenthesis).

Levulinates, such as methyl levulinate, were also explored for BMPD formation under identical reaction conditions, but almost none of the desired products were detected. Instead, the by-products γ-valerolactone and methyl 5-hydroxypentanate were formed (Figure S3A). This observation indicated that the carboxyl group of the keto-acid promoted

the amination of the carbonyl group. Hence, based on the results and previous reports,[6,23] possible reaction routes of pyrrolidone synthesis from LA and amines involved three pathways as shown in Scheme 2; formation of amide (Path 1), amination/cyclization of imine (Path 2), and reductive amination/cyclization of imine (Path 3).



Scheme 2. Possible reaction pathways for the reductive amination/cyclization of LA and amines with AB as the hydrogen donor.

To verify the possible reaction mechanism a series of control and *in situ* NMR experiments were conducted. A specific amount of acetic acid was introduced into the reaction of methyl levulinate and BA under the same reaction conditions as above, which allowed an almost quantitative yield of BMPD to be obtained (Figure S3 and Scheme S1). This result demonstrated that the carboxylic acid of the keto-acid catalyzed the amination reaction, and amide (i) formed by acylation of the carboxylic acid with amine was most likely not an intermediate. An *in situ* ^{13}C NMR experiment (Figure 2a) carried out with LA, BA and AB in DMSO at 40 °C showed that LA was consumed completely within 30 min, while a non-negligible amount of imine was initially formed, but was consumed after an additional 30 min of reaction. The secondary amine (iii) was detected as the main product at this low temperature, and no intermediate (ii) was formed during the reaction. Furthermore, definite confirmation of the existence of the intermediate imine and the secondary amine (ii) was obtained by ^{1}H-^{13}C HSQC and HMBC NMR (Figure 2b), conclusively elucidating that the

reaction route for the formation of BMPD followed Path 3 of Scheme 1 via reductive amination/cyclization.

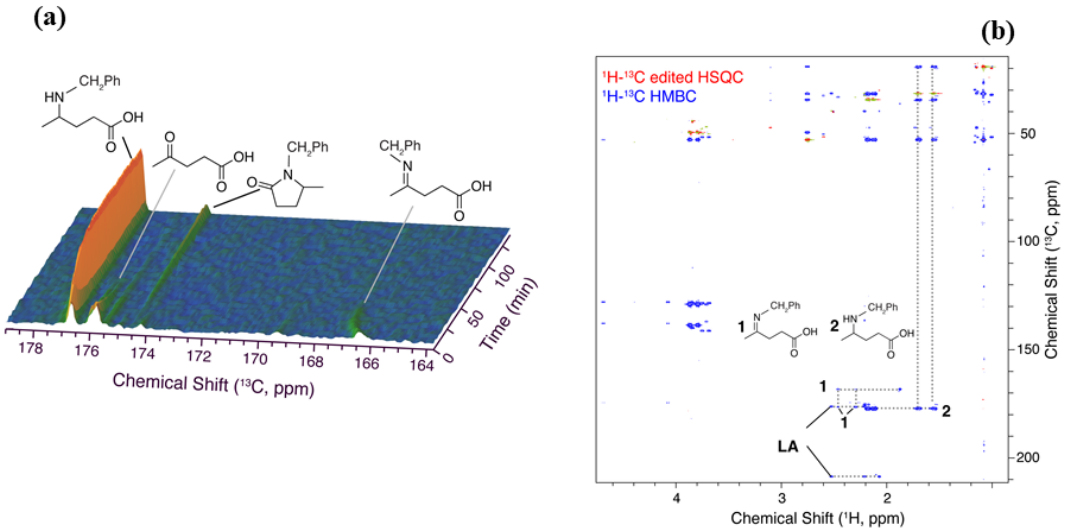


Figure 2. (a) *In situ* ^{13}C NMR spectra of the reductive amination/cyclization of LA and BA to BMPD (0.5 mmol LA, 1 mmol BA, 0.25 mmol AB, 1.0 mL DMSO, 40 ºC). (b) ^{1}H-^{13}C HSQC and ^{1}H-^{13}C HMBC NMR spectra of a representative reaction mixture during the reductive amination/cyclization of LA and BA to BMPD.

Recently, we showed that AB works as a reductant in the protic solvents methanol and water via decomposing into borane and ammonia.[24] However, no 4-aminopentanoic acid formed from decomposed ammonia and LA was detected herein using the aprotic solvent CH_2Cl_2, implying that the mode of action of AB was different from the mode of action in protic solvents. To confirm the action of AB in the aprotic solvent, *in situ* ^{11}B NMR was carried out on the reaction mixture of LA and BA in DMSO. As shown in Figure 3, AB was converted into polyiminoborane (PIB), polyaminoborane (PB), polyborazylene (PBZ) and cyclotriborazane (CTB) during the reaction.[25-28] CTB and PB were formed initially in the reaction, but disappeared rapidly within 5 and 20 min, respectively, thus indicating that they were intermediates in the conversion of AB into PIB and PBZ. Consistent with these results and with previous results,[26,28] a plausible reaction mechanism for the formation of

BMPD with 0.5 equivalents of AB is proposed in Scheme S2. In the mechanism, AB is initially reduced to an imine and converted into NH_2BH_2, which is further rapidly converted into PB and CTB, which reduced another equivalent of imine and formed the dehydrogenated products PBZ and PIB. Hence, by this pathway, AB generated two equivalents of hydrogen via double hydrogen transfer, consistent with the experimental results obtained during the AB dosage study (Figure 1b).

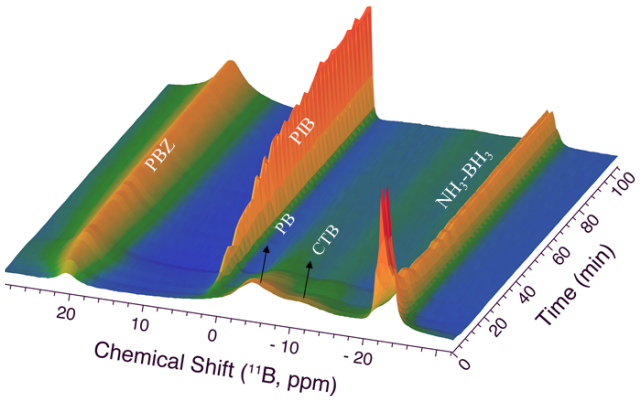


Figure 3. *In situ* ^{11}B NMR spectra of BMPD formation from LA and BA in DMSO (0.5 mmol LA, 1 mmol BA, 0.25 mmol AB, 1.0 mL DMSO, 2 h, 40 ºC).

To further support the results from the NMR experiments, deuterium labeling experiments were conducted with ND_3BH_3, NH_3BD_3 or ND_3BD_3 instead of AB at identical reaction conditions and the products were examined by mass spectroscopy. As shown in Figure S4, BMPD with a higher fraction of 190 amu m/z was generated when using NH_3BD_3 or ND_3BD_3 as the reductant. However, only the normal product with 189 amu m/z was detected when using ND_3BH_3, because the N-D of AB reacted with nitrogen of the imine to form a secondary amine, which does not contain deuterium in the final cyclization product after water removal. This result further illustrates that the mode of action for AB followed a double hydrogen transfer in the aprotic solvent.

Conclusion

An effective low-cost strategy for reductive amination/cyclization of keto-acids and amines with AB as the hydrogen donor under mild reaction conditions was developed. The reported system is versatile and applicable to a broad range of substrates using unprecedentedly low reductant dosage, as exemplified by the synthesis of 22 different lactams in moderate to excellent yield. A combination of *in situ* NMR spectroscopic investigations and control experiments including the use of deuterated AB allowed to conclusively elucidate a reaction mechanism for the reductive amination and the mode of action of AB. Notably, the introduced AB system has a higher atom economy and allows simpler product purification than commonly reported silane and formic acid systems, and may thus find broad applicability.

Associated Content

Supporting Information

Materials and methods, reaction results, reaction scheme and mechanism, and NMR and MS spectra and data (PDF).

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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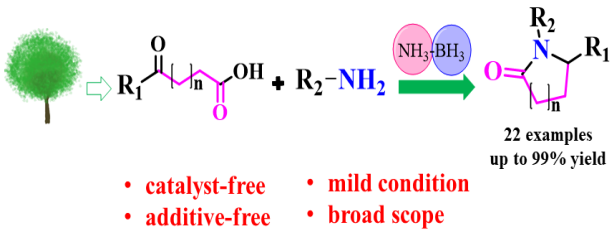

Synopsis

Ammonia borane facilitates the benign and efficient synthesis of *N*-substituted lactams from biomass-based keto-acids and amines.