



Cite this: *Green Chem.*, 2024, **26**, 5253

## Weak-coordination-auxiliary aminocatalysis enables directed [3 + 2] cyclization for 2-acylindolizines†

Kui Zeng,  <sup>‡a</sup> Neeraj Kumar Pandit,  <sup>b</sup> João C. A. Oliveira, <sup>b</sup> Sebastian Dechert,  <sup>c</sup> Lutz Ackermann  <sup>\*b,d,e</sup> and Kai Zhang  <sup>\*a</sup>

The synthesis of 2-acylindolizines, possessing a readily modifiable ketone group, is of significant importance as it provides versatile precursors for the preparation of various indolizines. However, due to the electronically less active and more sterically demanding nature of  $\alpha,\beta$ -unsaturated ketones toward iminium formation with an aminocatalyst, the efficient one-pot transformation of  $\alpha,\beta$ -unsaturated ketones for distinct 2-acylindolizines bearing sensitive groups represents a challenge for synthetic chemists. Herein, we report a weak-coordination-auxiliary amino-catalyzed approach that enables directed [3 + 2] cyclization of  $\alpha,\beta$ -unsaturated ketones and N-heteroaryl ketones for the desired 2-acylindolizines *via* an iminium ion/enamine tandem sequence. A highly broad range of commercially available  $\alpha,\beta$ -unsaturated ketones (internal, terminal, and cyclic enones) can act as coupling partners for readily accessible 2-acylindolizines relative to the existing state-of-the-art methods. Control experiments and in-depth DFT calculations highlight the importance of weakly coordinated glycine's carboxylic group in promoting the intramolecular cyclization and 1,5-proton transfer processes.

Received 20th September 2023,  
Accepted 6th December 2023

DOI: 10.1039/d3gc03552b

[rsc.li/greenchem](https://rsc.li/greenchem)

## Introduction

Indolizines are an important group of N-heterocyclic motifs that are widely used for pharmaceuticals (Scheme 1a),<sup>1–3</sup> materials science<sup>4</sup> and chemical feedstocks.<sup>5–7</sup> Four representative traditional strategies, including Scholtz reaction,<sup>8,9</sup> the use of pyridinium N-methylides,<sup>10,11</sup> Tschitschibabin reaction<sup>12,13</sup> and cyclization of alkynes with heteroaromatic feedstocks,<sup>14–16</sup> are known for the preparation of indolizines. Efficient transformation methods that utilize readily available substrates for the one-pot synthesis of diverse indolizines, particularly those containing an electron-withdrawing group

at the C-2 position, are in high demand.<sup>17,18</sup> 2-Acylindolizines, with a readily modifiable ketone group at the C-2 position, provide versatile precursors for the preparation of various indolizines. In 2012, 2-acylindolizines were prepared *via* a palladium-catalyzed three component carbonylative cyclization/arylation cascade.<sup>19</sup> It not only relies on the precious metal palladium and toxic CO as the carbonyl source, the requirement of a pivaloyl (–OPiv) group on 2-propargylpyridine restricts the substitution pattern of the product. Wang *et al.* developed a cycloaddition reaction between 1-cyanocyclopropane 1-ester and pyridine or benzo-pyridine for synthesizing 1-cyano,2-acylindolizine.<sup>20</sup> Although this protocol is accessible to 2-acylindolizine with a cyano group, multiple steps are required to pre-construct complex 1-cyanocyclopropane 1-ester substrates. Alternatively, the [3 + 2] cyclization of readily available pyridine ketone with  $\alpha,\beta$ -unsaturated ketones provides another viable route to form the 2-acylindolizine core. As an example, 2-acylindolizines can be prepared *via* one-pot two component Baylis–Hillman reactions (Scheme 1b).<sup>21,22</sup> Their  $\alpha,\beta$ -unsaturated ketones can be activated with a Lewis-acid/Brønsted acid. However, an efficient catalyzed approach to a highly expanded range of commercially available versatile internal, terminal and cyclic enone substrates for broader scope of 2-acylindolizine with even higher efficiency *via* [3 + 2] cyclization is still highly desired.

<sup>a</sup>Sustainable Materials and Chemistry, Dept. Wood Technology and Wood-Based Composites, University of Göttingen, Göttingen, Germany.

E-mail: [kai.zhang@uni-goettingen.de](mailto:kai.zhang@uni-goettingen.de)

<sup>b</sup>Institute of Organic and Biomolecular Chemistry, University of Göttingen, Göttingen, Germany

<sup>c</sup>Institute of Inorganic Chemistry, University of Göttingen, Göttingen, Germany

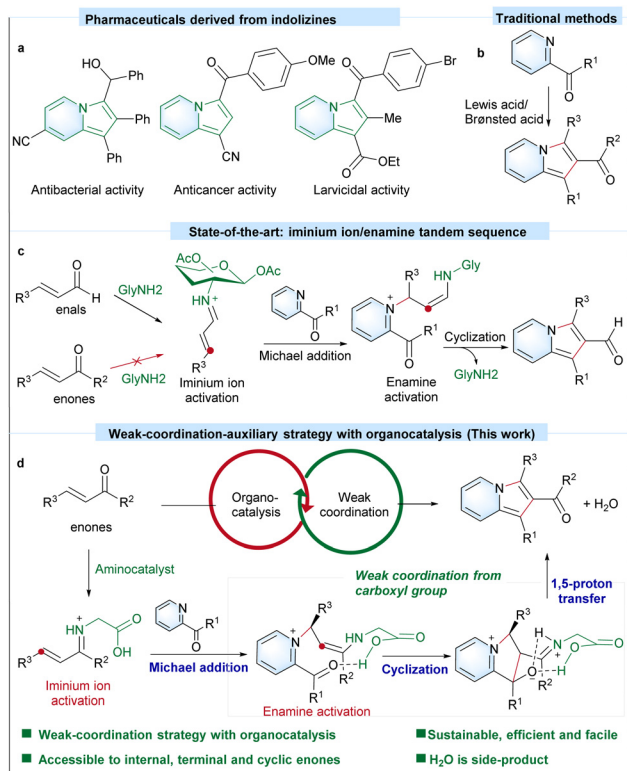
<sup>d</sup>Wöhler Research Institute for Sustainable Chemistry (WISCh), University of Göttingen, Göttingen, Germany

<sup>e</sup>DZHK (German Centre for Cardiovascular Research), Potsdamer Straße 58, 10785 Berlin, Germany

†Electronic supplementary information (ESI) available. CCDC 2115159 and 2115160. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d3gc03552b>

‡Current address: School of Pharmacy, University of Wisconsin–Madison, Madison, US.





**Scheme 1** Design of a weak-coordination-auxiliary strategy with a collaborative amino-catalyzed iminium ion/enamine tandem sequence for the preparation of 1,2,3-trisubstituted indolizine-2-ketones via one-pot reaction.

Inspired by the strategies of using an iminium ion and enamine mechanism to activate the carbonyl group with aminocatalysts,<sup>23–26</sup> our previous glucosamine-catalyzed strategy via a stereoauxiliary-iminium ion/enamine tandem sequence demonstrated the efficient preparation of a rich library of indolizine-2-aldehydes with one-pot [3 + 2] cyclization of 2-acetylpyridine and  $\alpha,\beta$ -unsaturated aldehydes (Scheme 1c).<sup>27</sup> As demonstrated,<sup>27</sup> Lewis-acid mediated Baylis-Hillman reaction (Scheme 1b)<sup>22</sup> cannot tolerate a group of sensitive functional groups (such as the hydroxyl group, *N,N*-dimethyl group, heterocyclic group, cyclic enone group *etc.*), but highlights the ability of the amino-catalyzed method to gain successful access to these  $\alpha,\beta$ -unsaturated aldehydes.<sup>27</sup> However, due to less electronic activity and more sterically demanding nature of  $\alpha,\beta$ -unsaturated ketones toward iminium formation with aminocatalysts,<sup>28–30</sup> the glucosamine-catalyzed strategy cannot efficiently access  $\alpha,\beta$ -unsaturated ketones for the preparation of 2-acylindolizines. We propose herewith that a weak-coordination-auxiliary strategy involving an aminocatalyst would help overcome the challenges, especially the energy barrier in the intramolecular cyclization step. With our ongoing interest in the carboxylate assisted activation strategy<sup>31–34</sup> and the preparation of *N*-heterocyclic compounds by sustainable organic synthesis methods,<sup>27,35,36</sup> herein, we report for the first time glycine-catalyzed [3 + 2] cyclization of

$\alpha,\beta$ -unsaturated ketones and *N*-heteroaryl ketones for various 2-acylindolizines by a weak-coordination-auxiliary strategy (Scheme 1d).

We initiated our studies using benzalacetone (**1a**) and 2-acetylpyridine (**2a**) for the preparation of 2-acylindolizine (**4**) via the aminocatalyzed [3 + 2] cyclization reaction (Table 1 and Table S1†). In the absence of catalyst **3**, only a low yield of **4** (13%) was obtained using LiBF<sub>4</sub> and propionic acid in CF<sub>3</sub>CH<sub>2</sub>OH solvent at 140 °C for 18 h under an Ar gas atmosphere (Table 1a). To promote the reaction activity with a higher yield of **4**, diverse aminocatalysts (**3a–3k**) were tested under the same conditions. The results revealed that amino acids, *e.g.* glycine **3i** (56%)<sup>37</sup> and (*tert*-butoxycarbonyl)-*L*-valine **3h** (57%),<sup>38</sup> were noticeably superior to *D*-glucosamine **3a** (27%),<sup>36</sup> 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy- $\beta$ -*D*-glucosamine **3b** (35%),<sup>27</sup> 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy- $\alpha$ -*D*-glucosamine **3c** (25%),<sup>27</sup> (*S*)-diphenyl(pyrrolidin-2-yl)methanol **3d** (21%),<sup>39</sup> (*S*)-2-(diphenyl(trimethylsilyl)oxy)methylpyrrolidine **3e** (30%),<sup>39</sup> *L*-proline **3f** (32%),<sup>23</sup> and (5*S*)-(-)-5-benzyl-2,2,3-trimethylimidazolidin-4-one **3g** (45%).<sup>24</sup> Besides, leucine with *D*/*L*-*tert*-butyl bulk steric hindrance did not obviously affect the reaction activity, such as that of **3j** (58%) and **3k** (53%). Based on the results presented in Table 1a, glycine was chosen as the optimal aminocatalyst, given the similar catalytic activity among these amino acid catalysts and its low price of 0.0837 £ per gram. After considerable experimentation (Table 1b and Table S1†), benzalacetone (**1a**, 0.2 mmol), 2-acetylpyridine (**2a**, 0.5 mmol), glycine (**3g**, 0.04 mmol), LiBF<sub>4</sub> (0.6 mmol) and pro-

**Table 1** Optimization of the aminocatalyzed [3 + 2] cyclization for 2-acylindolizine<sup>a</sup>

a. Optimization of aminocatalysts		
None	13%	
3a, Ac=H	27%	
3b, $\beta$ -anomer	35%	
3c, $\alpha$ -anomer	25%	
3d, X=H	21%	
3e, X=TMS	30%	
3f	32%	
3g	45%	
3h	57%	
3i	56%	
3j	58%	
3k	53%	
b. Standard conditions		
3i (20%), LiBF <sub>4</sub> (3.0 equiv.), propionic acid (2 equiv.), CF <sub>3</sub> CH <sub>2</sub> OH (0.9 mL), 140 °C, 18 h, Ar		
Entry	Deviation from standard conditions	Yield of <b>4</b> (%)
1	None	56
2	AcOH/CF <sub>3</sub> COOH replacing propionic acid	42/16
3	LiSO <sub>3</sub> CF <sub>3</sub> /LiCl replacing LiBF <sub>4</sub>	25/18
4	HFIP/CH <sub>3</sub> CN/toluene replacing CF <sub>3</sub> CH <sub>2</sub> OH	31/13/0

<sup>a</sup> **1a** (0.2 mmol), **2a** (2.5 equiv.), aminocatalyst (20 mol%), LiBF<sub>4</sub> (3.0 equiv.), propionic acid (2.0 equiv.), CF<sub>3</sub>CH<sub>2</sub>OH (0.9 mL), Ar, 18 h, and 140 °C. Yields were determined by <sup>1</sup>H-NMR analysis with CH<sub>2</sub>Br<sub>2</sub> as an internal standard.



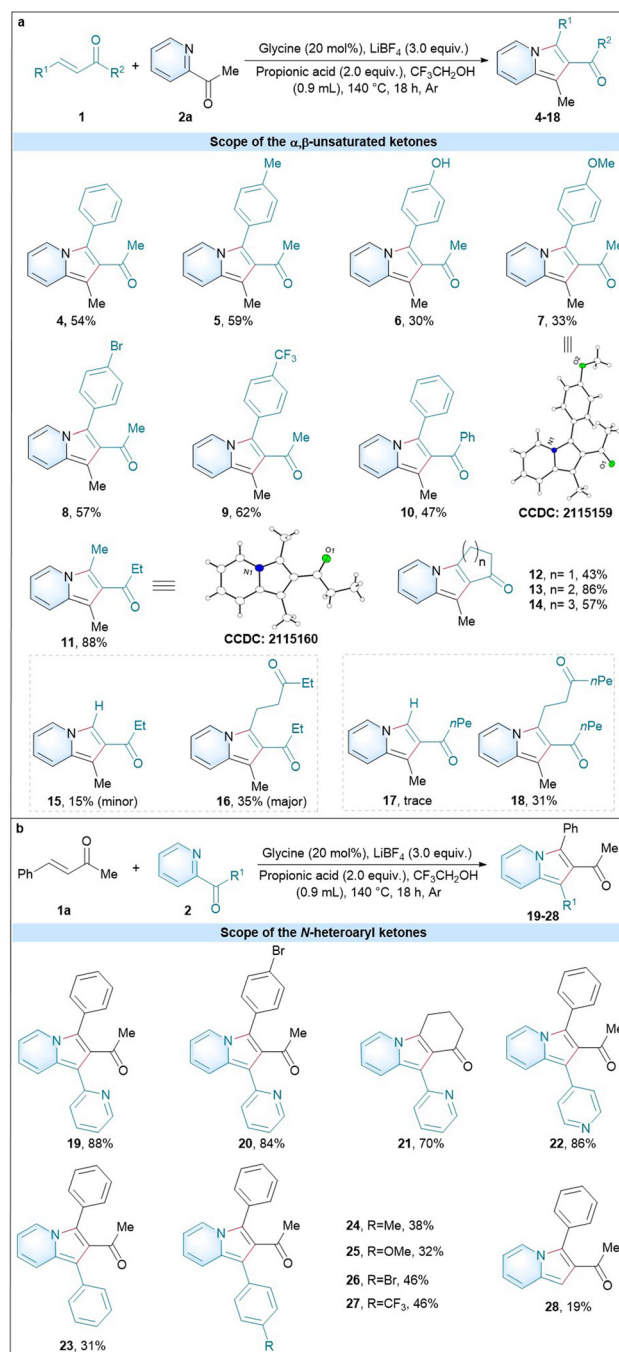
ponic acid (0.4 mmol) in  $\text{CF}_3\text{CH}_2\text{OH}$  solvent (0.9 mL) at 140 °C for 18 h under an Ar atmosphere were taken as optimal conditions.

With the established optimal glycine-catalyzed conditions in hand, we proceeded towards examining the scope with a variety of  $\alpha,\beta$ -unsaturated ketones **1** and N-heteroaryl ketones **2** under the standard conditions (Table 2). A group of internal aromatic  $\alpha,\beta$ -unsaturated ketones with electron-donating and -withdrawing groups were compatible with the reaction, such as **4** (54%), **5** (59%), **6** (30%), **7** (33%), **8** (57%), **9** (62%), and **10** (47%). It is worth noting that the internal aromatic  $\alpha,\beta$ -unsaturated ketone (**10**) with a bulk steric hindrance at the ketone position was also tolerant to the reaction conditions. Besides, the internal aliphatic  $\alpha,\beta$ -unsaturated ketone was also compatible with the standard conditions (**11**, 88%). In particular, a group of aliphatic cyclic  $\alpha,\beta$ -unsaturated ketones gave good to excellent yields (**12**, 43%; **13**, 86%; and **14**, 57%). The ring size of cyclic enones could affect the reaction steps like Michael addition and cyclization.<sup>27</sup> In addition to the internal  $\alpha,\beta$ -unsaturated ketones, the terminal  $\alpha,\beta$ -unsaturated ketone (pent-1-en-3-one) was also compatible with the standard conditions to give the two products **15** : **16** (15% : 35%). Even the terminal  $\alpha,\beta$ -unsaturated ketone (oct-1-en-3-one) could afford the corresponding product **18** (31%). The structures of **7** and **11** were determined by X-ray crystallographic analysis, and those of the other products in Table 2 were assigned by analogy.

The scope of the N-heteroaryl ketones was next studied using 4-phenylbut-3-en-2-one (**1a**) as a model substrate (Scheme 2b). As a result, di(pyridin-2-yl)methanone can well tolerate the optimal conditions with substrates 4-phenylbut-3-en-2-one, (*E*)-4-(4-bromophenyl)but-3-en-2-one and cyclohex-2-en-1-one to give the corresponding products **19** (88%), **20** (84%) and **21** (70%). Also the substrate pyridin-2-yl(pyridin-4-yl)methanone was also compatible with the conditions to yield **22** (86%). Moreover, a group of aromatic N-heteroaryl ketones with electron-donating and -withdrawing groups were found to give the corresponding products **23–27**. Beyond the substrates N-heteroaryl ketones, we also successfully expanded the glycine-catalysed strategy to different substrates, such as picolinaldehyde (**28**, 19%).

Large-scale synthesis of 1-(3-(4-bromophenyl)-1-(pyridin-2-yl)indolizin-2-yl)ethan-1-one (**20**) was achieved with 53% yield under optimal conditions (Scheme 2a). Azaheterocycles are the basic skeletons of many natural compounds and synthetic drugs with important biological activities.<sup>40</sup> The ability to prepare and achieve late-stage diversification of azaheterocycles is highly desired.<sup>41–43</sup> A group of late-stage transformations was applicable to prepare various 2-acylindolizines, in order to expand their potential applications. As an example, 1-(3-(4-bromophenyl)-1-(pyridin-2-yl)indolizin-2-yl)ethan-1-one (**20**) was chosen as the substrate for further modifications to synthesize distinct 2-acylindolizine derivatives (Scheme 2b). Starting from **20**, 3-(4-bromophenyl)-1-methylindolizine-2-carbaldehyde (**29**) was unexpectedly synthesized with the  $\text{Ph}_3\text{P}^+\text{CH}_3\text{Br}^-$  reagent. 1-(3-([1,1'-Biphenyl]-4-yl)-1-(pyridin-2-yl)

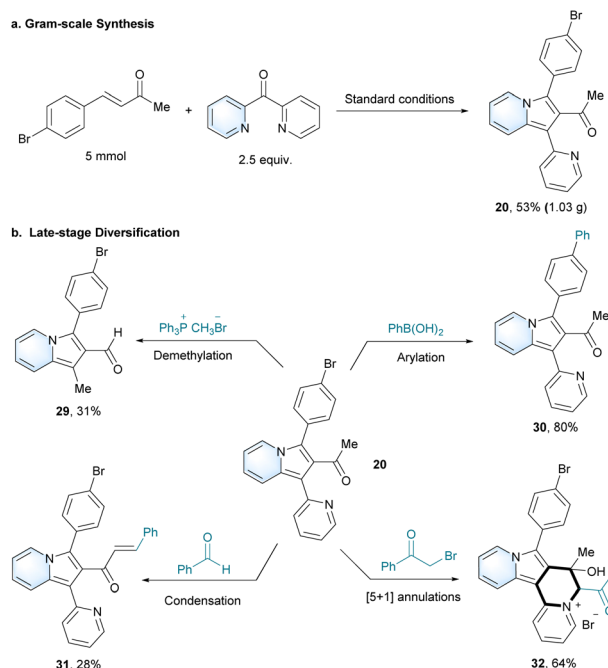
**Table 2** Aminocatalysis [3 + 2] annulation strategy for indolizine<sup>a</sup>



<sup>a</sup> **1** (0.2 mmol), **2** (2.5 equiv.), glycine (20 mol%), LiBF<sub>4</sub> (3.0 equiv.), propionic acid (2.0 equiv.), CF<sub>3</sub>CH<sub>2</sub>OH (0.9 mL), Ar, 18 h, and 140 °C. Yields were determined by <sup>1</sup>H-NMR analysis with CH<sub>2</sub>Br<sub>2</sub> as an internal standard.

indolizin-2-yl)ethan-1-one (**30**) was synthesized by the Suzuki–Miyaura coupling reaction. Notably, 3-(5-bromo-[1,1'-biphenyl]-2-yl)-1-(pyridin-2-yl)indolizine-2-carbaldehyde (**31**) was successfully synthesized *via* the dehydration coupling of **20** and benzaldehyde. Moreover, a one-pot synthesis of (6*S*)-6-benzoyl-8-(4-bromophenyl)-7-hydroxy-7-methyl-6,7-dihydroindolizino



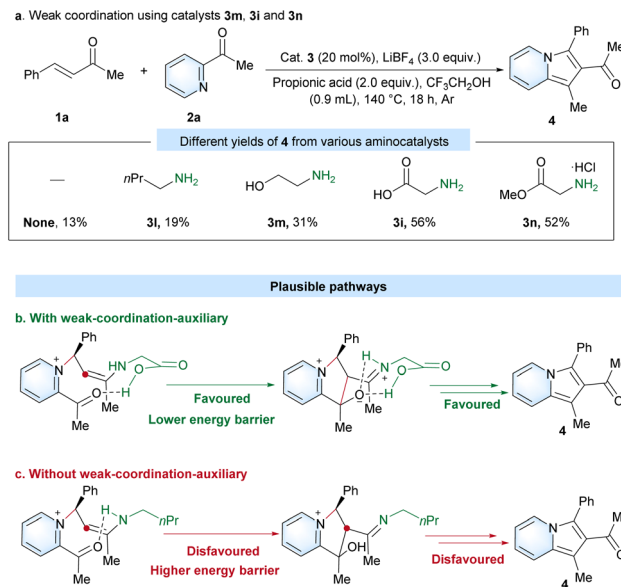


**Scheme 2** Large-scale synthesis (a) and late-stage diversifications (b).

[1,2-*a*]quinolizin-5-ium bromide (**32**) was also realized by the catalyst-free [5 + 1] annulation.

Amino acids such as **3h–3k** showed significantly better catalytic activity than **3a–3g** for amino-catalyzed preparation of 2-acylindolizine by directed [3 + 2] cyclization under the standard conditions (Table 1). These higher catalytic activities of amino acids could be derived from a weak cooperation effect of the carboxyl group of amino acids. Therefore, to investigate the proposed weak-coordination-auxiliary effect, a series of aminocatalysts (**3l**, **3m**, **3i** and **3n**) with different moieties (e.g. alkyl, hydroxyl, carboxyl and ester groups) at the  $\beta$  position were tested under the standard conditions (Scheme 3a). As a result, aminocatalyst **3l** gave only a low yield of **4** (19%), which showed almost the same reactivity as in the case without a catalyst (13%). Compared with catalyst **3l**, catalyst **3m** with a hydroxyl group could achieve a higher yield (31%). In particular, catalyst **3i** (56%) with a carboxyl group and catalyst **3n** (52%) with an ester group can obviously generate a better yield than **3l** (19%) and **3m** (31%). Therefore, the carboxyl group of glycine should have significantly promoted the efficiency of the reaction *via* a weak-coordination-auxiliary strategy, which results in a lower energy barrier in the intramolecular cyclization step (Scheme 3b and c).

To gain further insights into the details of the reaction mechanism, the DFT calculations for Michael addition and cyclization steps were performed at the PW6B95-D4/def2-TZVPP+SMD(2,2,2-trifluoroethanol)//TPSS-D3(BJ)/def2-SVP level of theory (Scheme 4) for three plausible pathways. Pathway A proceeds with a *syn*-conformed iminium ion, whereas pathways B and C proceed with an *anti*-conformed iminium ion in the absence and presence of a weak cooperation effect of the car-

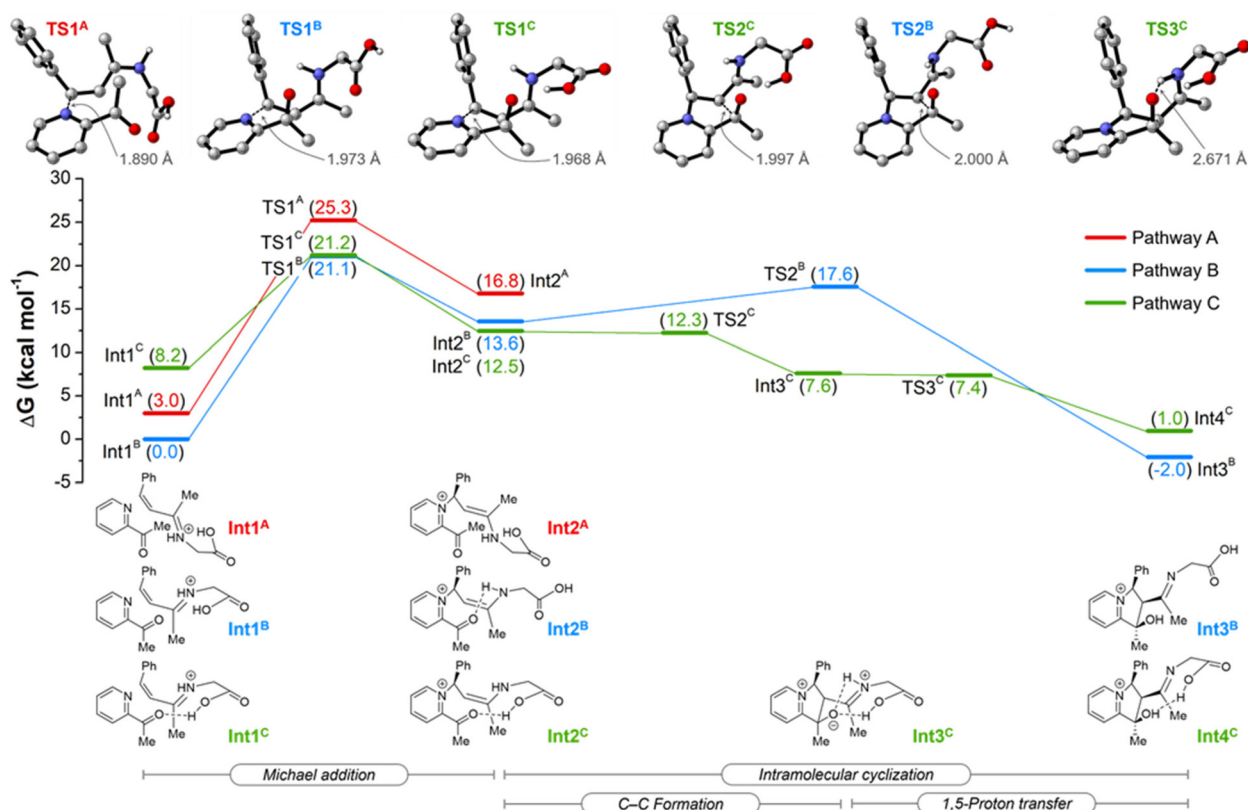


**Scheme 3** Control experiments for mechanistic study.

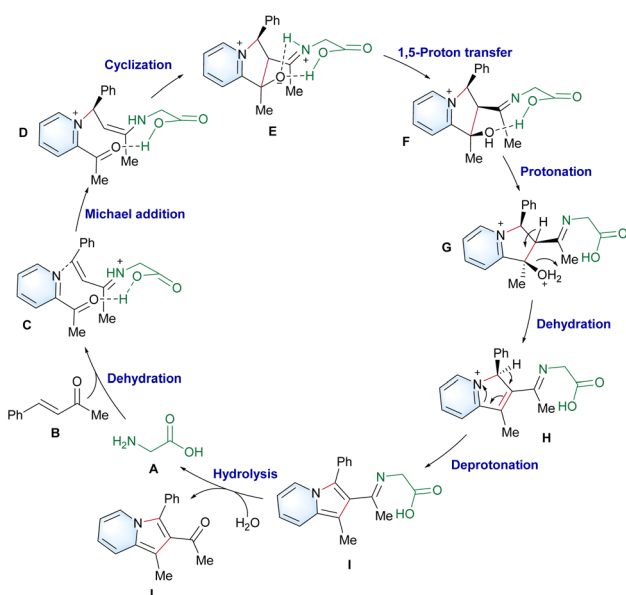
boxyl group of amino acid, respectively. All pathways commence with the attack of 2-acetylpyridine on the iminium ion *via* Michael addition **TS1** to generate the enamine intermediate **Int1**. The pathways B and C were found to be more energetically favorable than pathway A by approximately 4.1 kcal mol<sup>−1</sup> for the transition state **TS1**. Unfortunately, on proceeding further, the transition state for pathway A could not be located, which may be due to the larger distance between the H and O (4.9 Å) in the intermediate **Int2<sup>A</sup>** (Fig. S4†). This provides support for such a pathway not being involved. Calculations indicate that pathway C is kinetically favorable over pathway B, given the negligible and extremely facile energy barriers for the C–C formation and 1,5-proton transfer steps. The weak cooperation effect of the carboxyl group of the amino acid appears to promote the cyclization step and the formation of intermediate **Int4<sup>C</sup>**. Thus, DFT calculations highlight the role of the glycine's carboxyl group in the reaction mechanism, strongly supporting the outcome of control experiments (Scheme 3).

On the basis of our experimental and computational findings, a plausible catalytic cycle is proposed (Scheme 5). First, a more stable *anti*-conformed iminium ion **C** forms following the dehydration step. The carboxyl group of glycine cooperates with 2-acetylpyridine,<sup>44</sup> and enamine **D** is generated *via* Michael addition. Next, **E** forms after the intramolecular cyclization due to the lower energy barriers of C–C formation promoted by the weak-coordination-auxiliary effect of the carboxylic group. This was strongly verified by an energy difference of 5.3 kcal mol<sup>−1</sup> between **TS2<sup>C</sup>** (12.3 kcal mol<sup>−1</sup>) and **TS2<sup>B</sup>** (17.6 kcal mol<sup>−1</sup>) in Scheme 4. The weak-coordination-auxiliary effect further promotes the 1,5-proton transfer to form **F**. Then, intermediate **I** forms after the dehydration of **G** and deprotonation reaction of **H**. Finally, product **J** is generated from hydrolyzed **I** and the catalyst **A** regenerates to enter the next catalytic cycle.





**Scheme 4** Computed relative Gibbs free energies ( $\Delta G_{413.15}$ ) in  $\text{kcal mol}^{-1}$  for the amino-catalyzed 2-acylindolizine formation for the three considered plausible pathways. Calculations were performed at the PW6B95-D4/def2-TZVPP+SMD(2,2,2-trifluoroethanol)//TPSS-D3(BJ)/def2-SVP level of theory. Non-relevant hydrogens in the transition state structures were omitted for clarity.



**Scheme 5** The proposed mechanism.

**Table 3** The calculations of process mass intensity

Ref.	Yield of 13	PMI <sub>RRC</sub> , g g <sup>-1</sup>	PMI <sub>solv</sub> , g g <sup>-1</sup>	PMI, g g <sup>-1</sup>
21	8%	54.9	823.6	878.5
22	60%	3.6	13.2	16.8
27	22%	85.0	143.0	228.0
This work	86%	15.3	36.6	51.9

representative approaches is shown comparatively using product 13 as an example (Table 3). In addition to the highest yield of 13 (83%) achieved in our current work, the PMI<sub>RRC</sub> (expressed as the amount of reagents, reactants and catalyst) and PMI<sub>solv</sub> (solvent relative to the amount of isolated product) of our current approach and the work from the Badsara group<sup>22</sup> are obviously lower than those in the state-of-the-art works.<sup>21,27</sup> It should be noted that PMI<sub>solv</sub> does not take into account any solvent consumed during purification processes since the reference values for the comparative works are not available.

## Conclusions

We have shown how a combination of organocatalysis and the weak-coordination-auxiliary strategy can be used to address

Process mass intensity (PMI) is a key mass-based metric to evaluate the green credentials of reactions during process and chemical development.<sup>45</sup> The PMI of our current work and



the problem of activating enones in the one-pot [3 + 2] cyclization of  $\alpha,\beta$ -unsaturated ketones (internal, terminal, and cyclic enones) and N-heteroaryl ketones for the one-pot preparation of valuable 2-acylindolizine molecules. Glycine acts as a representative aminocatalyst to favor the reaction through an iminium ion/enamine tandem sequence, and it also provides a weak-coordination-auxiliary effect from its carboxyl group to overcome the energy barrier in intramolecular cyclization and 1,5-proton transfer processes. These were demonstrated by control experiments and DFT calculations. This novel glycine-catalyzed strategy with a weak-coordination-auxiliary effect is versatile enough to enable the development of other functionalization processes with an iminium ion/enamine tandem sequence.

## Experimental

### Preparation of 2-acylindolizines

A mixture of  $\alpha,\beta$ -unsaturated ketones (0.2 mmol), heteroaryl ketones (2.5 equiv.), catalyst **3g** (0.04 mmol), propionic acid (2.0 equiv.) and  $\text{LiBF}_4$  (3.0 equiv.) in  $\text{CF}_3\text{CH}_2\text{OH}$  (0.9 mL) was stirred at 140 °C under an Ar atmosphere for 18 h. The reactions were conducted in a sealed Schlenk tube and heated with an IKA magnetic heating agitator with a heating block. The reaction temperature was directly read from the temperature detector of the IKA apparatus and was calibrated with a thermometer. After cooling to room temperature, the reaction mixture was basified up to pH 7 using saturated  $\text{Na}_2\text{CO}_3$  aqueous solution, before extracting with diether ( $3 \times 3$  mL) and drying over anhydrous  $\text{Na}_2\text{SO}_4$ . After filtration and concentration in a rotary evaporator, the crude product was purified by flash chromatography on a silica gel (ethyl acetate:*n*-hexane) to give the products. More experimental details and characterization are available in the ESI.†

## Author contributions

K. Zh. conceived the concept. L. A. and K. Zh. supervised the project. K. Z. undertook all of the experimental work, analytical characterization, and spectroscopic analysis. N. K. P. and J. C. A. O. performed the DFT analysis. S. D. performed X-ray crystallography. K. Z., L. A., and K. Zh. analyzed the data and wrote the manuscript.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

Kai Zhang thanks German Research Foundation (DFG) for the financial support for the project with the grant number ZH546/8-1 and the University of Göttingen for the Department

Start-up funding. Kui Zeng thanks China Scholarship Council for the PhD grant. The generous support from the DZHK, the ERC advanced grant no. 101021358, the DFG Gottfried-Wilhelm-Leibniz-Preis and SPP 2363 to Lutz Ackermann is gratefully acknowledged.

## References

- 1 V. R. Vemula, S. Vurukonda and C. K. Bairi, *Int. J. Pharm. Sci. Rev. Res.*, 2011, **11**, 159–163.
- 2 G. S. Singh and E. E. Mmatli, *Eur. J. Med. Chem.*, 2011, **46**, 5237–5257.
- 3 V. Sharma and V. Kumar, *Med. Chem. Res.*, 2014, **23**, 3593–3606.
- 4 E. Kim, Y. Lee, S. Lee and S. B. Park, *Acc. Chem. Res.*, 2015, **48**, 538–547.
- 5 J. T. M. Correia, B. List and F. Coelho, *Angew. Chem., Int. Ed.*, 2017, **56**, 7967–7970.
- 6 D. Zhang, H. Song and Y. Qin, *Acc. Chem. Res.*, 2011, **44**, 447–457.
- 7 J. Hui, Y. Ma, J. Zhao and H. Cao, *Org. Biomol. Chem.*, 2021, **19**, 10245–10258.
- 8 V. Boekelheide and R. Windgassen Jr., *J. Am. Chem. Soc.*, 1959, **81**, 1456–1459.
- 9 M. Scholtz, *Ber. Dtsch. Chem. Ges.*, 1912, **45**, 734–746.
- 10 G. Poissonnet, M.-H. Th  ret-Bettiol and R. H. Dodd, *J. Org. Chem.*, 1996, **61**, 2273–2282.
- 11 A. R. Katritzky, G. Qiu, B. Yang and H.-Y. He, *J. Org. Chem.*, 1999, **64**, 7618–7621.
- 12 A. Tschitschibabin, *Ber. Dtsch. Chem. Ges. A and B*, 1927, **60**, 1607–1617.
- 13 U. Bora, A. Saikia and R. C. Boruah, *Org. Lett.*, 2003, **5**, 435–438.
- 14 S. Chuprakov, F. W. Hwang and V. Gevorgyan, *Angew. Chem., Int. Ed.*, 2007, **46**, 4757–4759.
- 15 A. V. Kel'in, A. W. Sromek and V. Gevorgyan, *J. Am. Chem. Soc.*, 2001, **123**, 2074–2075.
- 16 I. V. Seregin and V. Gevorgyan, *J. Am. Chem. Soc.*, 2006, **128**, 12050–12051.
- 17 D. A. Burnett and J. P. Vacca, *International patent No*, WO2018/195075A1, 2018.
- 18 M. Biagetti, A. Accetta, A. M. Capelli, M. Guala and M. Retini, *US patent No*, US2015/0361100A1, 2015.
- 19 Z. Li, D. Chernyak and V. Gevorgyan, *Org. Lett.*, 2012, **14**, 6056–6059.
- 20 J. Liu, L. Zhou, W. Ye and C. Wang, *Chem. Commun.*, 2014, **50**, 9068–9071.
- 21 Y.-C. Yuan, T.-Z. Liu and B.-X. Zhao, *J. Org. Chem.*, 2021, **86**, 12737–12744.
- 22 D. Basavaiah, G. Veeraraghavaiah and S. S. Badsara, *Org. Biomol. Chem.*, 2014, **12**, 1551–1555.
- 23 B. List, R. A. Lerner and C. F. Barbas, *J. Am. Chem. Soc.*, 2000, **122**, 2395–2396.
- 24 K. A. Ahrendt, C. J. Borths and D. W. MacMillan, *J. Am. Chem. Soc.*, 2000, **122**, 4243–4244.



- 25 A. Erkkilä, I. Majander and P. M. Pihko, *Chem. Rev.*, 2007, **107**, 5416–5470.
- 26 P. Chauhan, S. Mahajan and D. Enders, *Acc. Chem. Res.*, 2017, **50**, 2809–2821.
- 27 K. Zeng, R. Mei, S. Dechert, L. Ackermann and K. Zhang, *Commun. Chem.*, 2023, **6**, 40.
- 28 Q. Li, W. Y. Wong, W. H. Chan and A. W. Lee, *Adv. Synth. Catal.*, 2010, **352**, 2142–2146.
- 29 C. Brenninger, J. D. Jolliffe and T. Bach, *Angew. Chem., Int. Ed.*, 2018, **57**, 14338–14349.
- 30 X. Lu and L. Deng, *Angew. Chem., Int. Ed.*, 2008, **47**, 7710–7713.
- 31 J. Li, S. Warratz, D. Zell, S. De Sarkar, E. E. Ishikawa and L. Ackermann, *J. Am. Chem. Soc.*, 2015, **137**, 13894–13901.
- 32 J. Hubrich, T. Himmler, L. Rodefeld and L. Ackermann, *ACS Catal.*, 2015, **5**, 4089–4093.
- 33 S. Warratz, C. Kornhaass, A. Cajaraville, B. Niepoetter, D. Stalke and L. Ackermann, *Angew. Chem., Int. Ed.*, 2015, **54**, 5513–5517.
- 34 L. Ackermann, *Org. Process Res. Dev.*, 2015, **19**, 260–269.
- 35 K. Zeng, R. Mei, X. C. Zhang, L. B. Andreas and K. Zhang, *Chem. Commun.*, 2022, **58**, 6068–6071.
- 36 K. Zeng, J. Ye, X. Meng, S. Dechert, M. Simon, S. Gong, R. A. Mata and K. Zhang, *Chem. – Eur. J.*, 2022, **28**, e202200648.
- 37 F.-L. Zhang, K. Hong, T.-J. Li, H. Park and J.-Q. Yu, *Science*, 2016, **351**, 252–256.
- 38 M. Wasa, K. M. Engle and J. Q. Yu, *Isr. J. Chem.*, 2010, **50**, 605–616.
- 39 L. Klier, F. Tur, P. H. Poulsen and K. A. Jørgensen, *Chem. Soc. Rev.*, 2017, **46**, 1080–1102.
- 40 B. Wang, X. Hu, F. Sun, Z. Yang and W. Huang, *Interdiscip. Med.*, 2023, **1**, e20220010.
- 41 C.-C. Zhang, H.-L. Wu, X.-C. Yu, L.-T. Wang, Y. Zhou, Y.-B. Sun and W.-T. Wei, *Org. Lett.*, 2023, **25**, 5862–5868.
- 42 X.-S. Zhou, Z. Zhang, W.-Y. Qu, X.-P. Liu, W.-J. Xiao, M. Jiang and J.-R. Chen, *J. Am. Chem. Soc.*, 2023, **145**, 12233–12243.
- 43 K. Sun, D. Zhao, Q. Li, S. Ni, G. Zheng and Q. Zhang, *Sci. China: Chem.*, 2023, **66**, 2309–2316.
- 44 B. List, *J. Am. Chem. Soc.*, 2000, **122**, 9336–9337.
- 45 E. R. Monteith, P. Mampuy, L. Summerton, J. H. Clark, B. U. Maes and C. R. McElroy, *Green Chem.*, 2020, **22**, 123–135.

