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One-pot organocatalyzed synthesis of tricyclic indolizines†

Lucas A. Zeoly, [a] Lais V. Acconcia, [a] Manoel T. Rodrigues, Jr., [a] Hugo Santos, [a] Rodrigo A. Cormanich, [a] Juan C. Paniagua, [b,c] Albert Moyano *[d] and Fernando Coelho*[a]

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Indolizines and their saturated derivatives are important structural motifs present in several biologically active compounds of both natural and synthetic origin. We describe herein a one-pot approach for the synthesis of tricyclic indolizines catalyzed by a bicyclic imidazole-alcohol. The protocol is based on an aqueous Morita–Baylis–Hillman reaction between pyridine-2-carboxaldehydes and six- or seven-membered cyclic enones, followed by sequential intramolecular cyclization and dehydration. So, in a single operational step two new bonds (C–C and C–N) are formed in an organocatalyzed process that takes place in simple conditions (stirring in water at 60 °C for 12 h) and with great atom economy (water as the sole byproduct), affording the purified compounds in yields ranging from 19 to 70%. The facility of the cyclization strongly depends on the size of the cycloalkenone ring: while MBH adducts derived from six-, seven- or eight-membered cycloenones are readily transformed into the corresponding indolizines, cyclopentenone-derived MBH adducts do not cyclize. A competition experiment revealed that cycloheptenone-derived MBH adducts cyclize faster than cyclohexenone-derived adducts. Model DFT calculations have been performed to rationalize these reactivity trends.

Introduction

Nitrogenated heterocycles play an important role in several segments of the chemical and pharmaceutical industry.[1] Indolizines are unsaturated nitrogen heterocycles resulting from the fusion of two heterocyclic nuclei: a pyridine and a pyrrole, in which the nitrogen atom is shared by both rings. This structural motif is present in biologically active products of both natural and synthetic origin,[2] as well as in materials with other applications. Although the occurrence of the indolizine nucleus in natural products is rather scarce, their hydrogenated derivatives (either tetrahydroindolizines or indolizidines) are present in a variety of biologically important natural products, the best known of them being the so-called indolizidine alkaloids.[3] The structural resemblance of indolizines with indoles has stimulated the incorporation of this heterocycle in the design of synthetic compounds with different biological activities, such as, anti-cancer drugs,[4] anti-microbials,[5] anti-inflammatory compounds,[6] phosphatase inhibitors,[7] and drugs to treat schizophrenia,[8] among others.[9] Moreover, several polycyclic indolizines are fluorescent, with applications as biological probes[10] and in electronic devices[11] (Fig. 1).

Classically, indolizines have been prepared through Scholtz[12] or Chichibabin reactions.[13] However, the biological effects associated to the indolizine core and the interest for their photophysical properties have stimulated the development of a plethora of approaches to obtain this heterocyclic scaffold.[8,14,15] Recently, due to the same reasons, different methods to prepare polycyclic indolizines have been developed.[16]

The Morita–Baylis–Hillman (MBH) reaction[17] is a sustainable chemical transformation that provides access to small, functionalized molecules, and which has proven to be an efficient platform for the synthesis of the indolizine framework.[18] Polycyclic indolizines have also been synthesized by exploring the synthetic versatility of MBH adducts. However, in most instances it is necessary to use an acetylated[18a,b,f,h,j,k] or a

[a]*Laboratório de Síntese de Produtos Naturais e Fármacos, Department of Organic Chemistry, Institute of Chemistry, University of Campinas, PO Box 6154-13083-970, Campinas, SP, Brazil. E-mail: facoelho@unicamp.br*
[b]*Departament de Ciència de Materials i Química Física, Universitat de Barcelona, Facultat de Química, C. Martí i Franquès 1-11-08028, Barcelona, Spain*
[c]*Institut de Química Teòrica i Computacional, Universitat de Barcelona, Spain*
[d]*Departament de Química Inorgànica i Orgànica, Universitat de Barcelona, Facultat de Química, C. Martí i Franquès 1-11-08028, Barcelona, Spain*

†Electronic supplementary information (ESI) available: NMR (^{1}H, ^{13}C, ^{19}F) spectra for compounds **4ab**, **4eb**, **4gb**, **4ja**, **5aa–5ic**, **6ag**, **6eb**, **7**, **8**, **10** and **11**; HPLC chromatograms of compounds *rac*-**11** and (*R*)-**11**; cartesian coordinates, Gibbs free energies and lowest harmonic vibrational frequencies (LHVFs) computed for each species at the ωB97xD/aug-cc-pVTZ level in water using the IEFPCM implicit solvent model; relative energies of two transition states calculated for different DFT functionals. See DOI: https://doi.org/10.1039/d3ob00346a

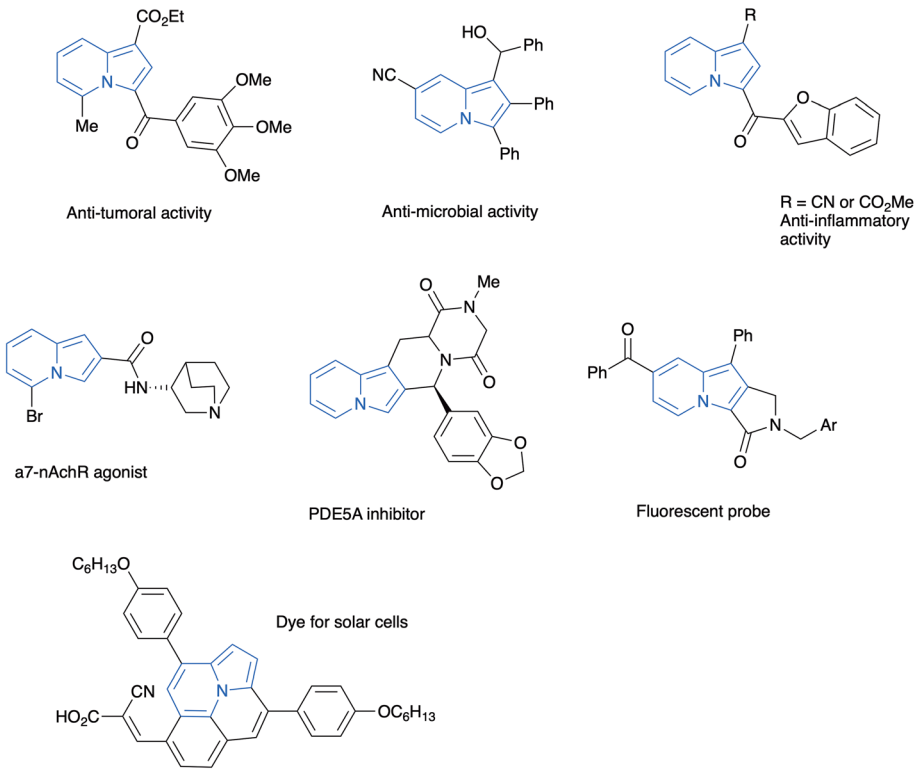
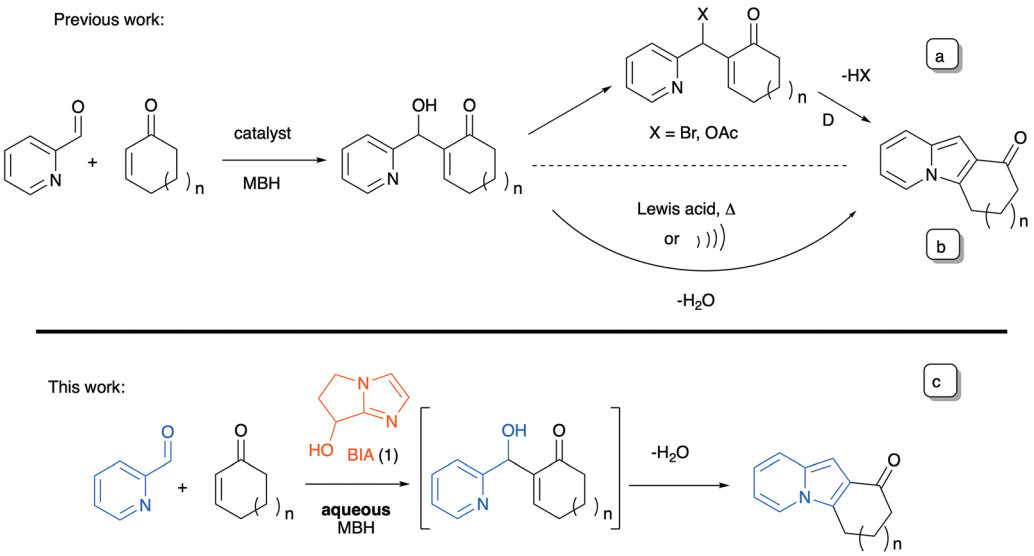


Fig. 1 Some representative examples of biologically active and of fluorescent indolizines.

brominated derivative (Scheme 1a).[18f,g] In the few cases where the adducts are used directly, they must usually be activated *in situ* by means of a Lewis acid[18c,i] or by using special reaction conditions, such as microwave irradiation (Scheme 1b).[18d] On the other hand, the MBH reaction has very seldom been used in a one-step, two-component synthesis of indolizines in a purely organocatalyzed process.[19] Batra and co-workers[18f] reported that without previous conversion to a bromide, the MBH adducts of cycloenones with *N*-substituted 1-formyl-β-carbolines cyclized very slowly (4 days in 1 : 1 THF–H_2O at rt) to the corresponding indolizino-indole derivatives. A single example was reported, with an isolated yield of 58%. We wish to disclose presently that the bicyclic imidazolyl alcohol (BIA) **1**, an extremely convenient catalyst for the aqueous MBH reac-



Scheme 1 Research background.

tions of conjugated cycloalkenones,[20,21] can be advantageously put to use in the direct organocatalyzed synthesis of a variety of tricyclic indolizines *via* a MBH/aza-Michael/dehydration cascade (Scheme 1c).

Results and discussion

Our research began with the observation that the BIA-catalyzed aqueous MBH reaction between 2-pyridinecarbaldehyde (**2a**) and 2-cyclohexenone (**3a**) consistently afforded mixtures of the expected MBH adduct **4aa**[18k,22] and of the tricyclic indolizine **5aa**, even at ambient temperature and with short reaction times (Table 1, entry 1). It is worth noting here that the reaction of **2a** and **3a** in the conditions described by Batra (0.5 equiv. DMAP, 1 : 1 THF–H_2O, rt)[18f] required 4 days for completion and afforded **5aa** in 40% yield.[18b]

Among the catalysts classically employed in MBH reactions, only BIA (Table 1, entry 1), 3-quinuclidinol (entry 2), triethylamine (entry 3), and imidazole (entry 4) were able to form indolizine **5aa** in good yield after 48 h at rt. Tetramethyl-1,3-propanediamine (TMPDA, entry 6) gave almost exclusively the MBH adduct, although in poor conversion. Both DBU (entry 5) and NaOMe in MeOH (entry 7) were not catalytically active at rt. BIA (entry 1) and 3-quinuclidinol (entry 1) exhibited the best ratios of conversion and yield. In the case of BIA, essentially complete conversion of the aldehyde **2a** was reached in less than 3 h. Interestingly, both catalysts have a hydroxyl group in the proximity of the nucleophilic nitrogen atom, which has been shown to play a relevant role in the catalysis of the MBH reaction.[23] This observation is also in accordance with the increase commonly observed in the MBH reaction rate when hydroxylic solvents are employed.[24]

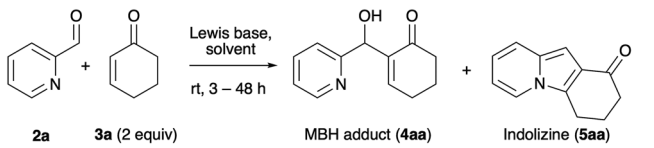
We chose the conditions of entry 1 (0.65 equiv. BIA, 10% mol of sodium dodecyl sulfate, SDS in water) as the starting point from which to optimize the yield of the indolizine product. Our choice was based on the observation that BIA gave a better indolizine/MBH adduct ratio than quinuclidinol. Additionally, this bifunctional Lewis base is easily prepared in large scale using cheap starting materials.[21,25] Thus, starting from these standard conditions (which had been previously optimized for the aqueous MBH additions of aryl aldehydes to cycloalkenones)[20] we evaluated different solvents, temperatures, and equivalents of surfactant (SDS). The reactions were run both in protic and in aprotic solvents, such as ^{i}PrOH, AcOH, MTBE, $CHCl_3$, HMPA and fluorobenzene. We were not able to detect indolizine formation in any of these. Note that attempts to promote the reaction with sodium methoxide in methanol (Table 1, entry 7) were also unsuccessful. So, we kept water as the solvent and evaluated the effect of the reaction temperature in the conversion. We ran reactions at 40 °C (67% of yield of **5aa** after 24 h), 60 °C (70% yield after 12 h) and 100 °C (52% after 12 h). Based on these results, 60 °C was established as the best temperature. The amount (20 mol% or 30 mol%) and type (CTAB, Triton-X100) of surfactant were also changed, however no modification in yield was observed, so that we kept the concentration of SDS at 10 mol%.

With the optimal condition in hands, we started the evaluation of the reaction scope, using a set of 2-cycloalkenones of different ring size and substitution degree (Fig. 2). 2-Cyclohexenone (**3a**), 2-cyclopentenone (**3b**), and 2-cycloheptenone (**3c**) were commercially available; the remaining enones (5,5-dimethyl-cyclohexenone (**3d**), 5-phenyl-cyclohexenone (**3e**), 5-piperonyl-cyclohexenone (**3f**), and 2-cyclooctenone (**3g**)) were prepared according to previously described protocols.[26,27]

A set of commercial 2-pyridinecarboxaldehydes with different substitution patterns (**2a–2i**; Scheme 2) were treated with 2 mol equiv. of cycloalkenones in the presence of BIA (1; 0.65 mol equiv.) in water and SDS (0.1 mol equiv.), at 60 °C during 12 h.

The reaction worked nicely with cyclohexenones **3a**, **3e**, **3f** and with cycloheptenone **3c** to afford the corresponding tri-

Table 1 Outcome of the MBH reaction between 2-pyridinecarboxaldehyde (**2a**) and 2-cyclohexenone (**3a**) catalyzed by Lewis bases



Entry	Lewis base (equiv./solvent)	Ratio **4aa**/**5aa**[a] 3 h	24 h	48 h	Yield[b] (%)
1	BIA (0.65/H_2O-10 mol% SDS[c])	58 : 42[d]	22 : 78	6 : 94	68
2	3-Quinuclidinol (0.65/H_2O)	74 : 26	26 : 74	8 : 92	68
3	Triethylamine (1.0/H_2O)	58 : 42	36 : 64	11 : 89	51
4	Imidazole (1.0/aq. sat. $NaHCO_3$)	—[e]	51 : 49	49 : 51[f]	42
5	DBU (1.0/H_2O)	—[e]	—[e]	—[e]	—[g]
6	TMPDA (1.0/H_2O)	—[e]	94 : 6	94 : 6	—[g]
7	NaOMe (1.0/MeOH)	—[e]	—[e]	—[e]	—[g]

[a] Ratio between the peaks corresponding to MBH adduct (**4aa**) and to indolizine (**5aa**), measured by analysis of relative areas (GC-MS). [b] Yield of **5aa** after 48 h, calculated by ^{1}H-NMR, using 1,2,4,5-tetrachloro-3-nitrobenzene as internal standard. [c] SDS = sodium dodecyl sulfate. [d] Conversion of **2a** was already complete at this point. [e] The conversion was too low to calculate the area ratio. [f] Total conversion of **2a** was achieved at this point. [g] Not determined.

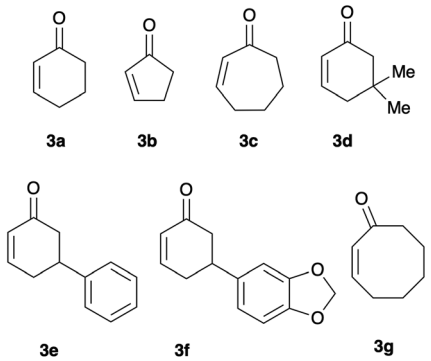
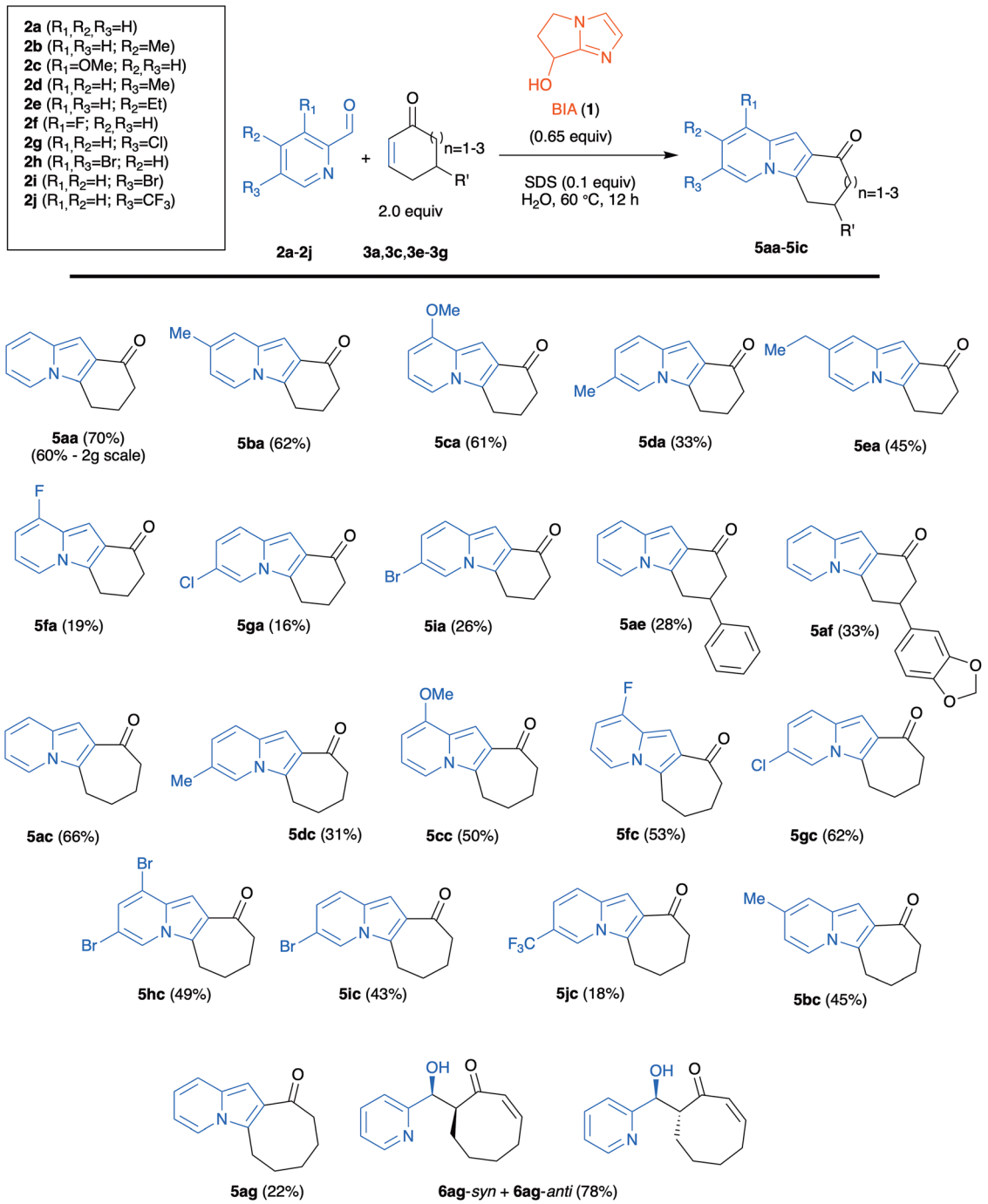


Fig. 2 Cycloalkenones **3a–g** chosen to evaluate the scope of the reaction.



Scheme 2 One-pot organocatalyzed synthesis of tricyclic indolizines. % Yields refer to isolated products after chromatographic purification.

cyclic indolizines **5** in one step and in moderate to good yields (Scheme 2). The yields with cycloheptenone **3c** (ranging from 31% up to 66%) were in several instances higher than those obtained with cyclohexenones (ranging from 16% to up 70%), especially for reactions with halogen-substituted 2-pyridinecarboxaldehydes (compare **5fa** with **5fc**, **5ga** with **5gc**, and **5ia** with **5ic**). The introduction of a substituent in the 5-position of **3a** gave rise to diminished yields (compare **5ae** and **5af** with **5aa**). The reactions with 5,5-dimethyl-2-cyclohexenone **3d** failed, as we did not detect the initial formation of the MBH adducts (probably due to the steric hindrance to the initial Michael addition of the nucleophilic catalyst).[23] A single example with 2-cyclooctenone **3g** was also examined. The low yield (22%) of the 2-cyclooctenone derivative **5ag** was due to the low MBH reactivity of **3g**, that led to the competitive formation (in 78% global yield) of aldol adducts **6ag**-*syn* and **6ag**-*anti* (which obviously cannot cyclize to the indolizine). It is worth noting therefore that the initially

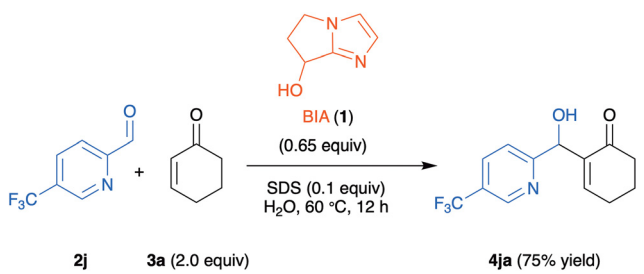
formed MBH adduct was converted quantitatively to the tricyclic indolizine **5ag**.

4-Methyl-substituted aldehyde **2b** gave, both for reactions with 2-cyclohexenone **3a** and with 2-cycloheptenone **3c**, better yields than the 5-methyl-substituted isomer **2d** (compare **5ba** with **5da**, and **5bc** with **5dc** in Scheme 2). In the case of aldehyde **2j**, with a strongly electron-withdrawing trifluoromethyl substituent at C-5, the reaction with **3c** gave the tricyclic indolizine **5jc** in very low yield (18%), while the reaction with **3a** exclusively afforded the MBH adduct **4ja** in 75% yield (Scheme 3).

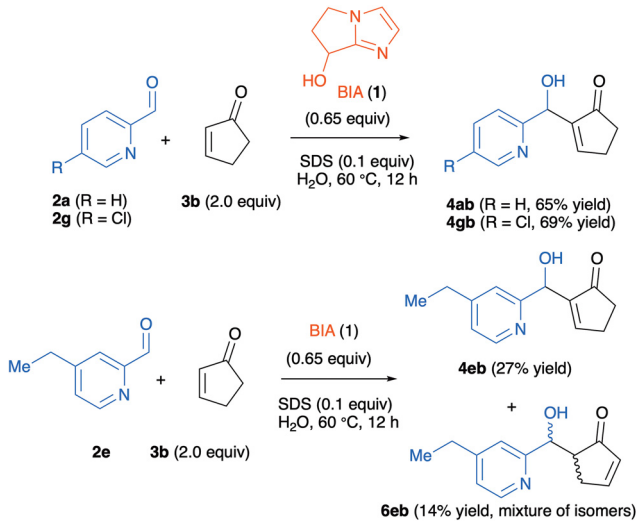
Even if in some instances (particularly in the reaction of 2-pyridinecarboxaldehydes bearing electron-attracting substituents with 2-cyclohexenones) yields are lower than 40%, this operationally simple, one-step process meets a series of green chemistry requirements, such as the use of water as solvent, high atom economy, the use of a cheap organic compound as the catalyst, and the possibility of recycling the reagents used in excess and the Lewis base, if necessary. It is also worth noting that the reaction can be used for the gram-scale synthesis of indolizines, as exemplified by the preparation of **5aa** (2 g) in 60% yield (see Scheme 2).

On the other hand, the cyclization to the indolizine did not take place when 2-cyclopentenone **3b** was employed as the Michael acceptor, independently of the nature of the pyridine-2-carboxaldehyde partner. For these reactions, we could only isolate the corresponding MBH adducts **4** mixed in some instances with the aldol products **6**. Three representative examples are shown in Scheme 4. We were unable to detect the formation of the corresponding indolizines **5**. Attempts to circumvent this issue, either by heating the reactions or by increasing the catalyst loading, failed. This indicates that MBH adducts derived from **3b** do not cyclize to the corresponding indolizines in aqueous solution, a behavior with strongly contrasts with that of the other enones with six, seven or eight-membered rings.

Having established the scope of the reaction, we devoted our attention to the mechanism of this transformation. An important fact revealed by the data gathered in Table 1 is that the **4aa**/**5aa** ratio is dependent on the nature of the promoter of the MBH reaction, raising the question of the eventual catalysis of *the cyclization/dehydration step* by the same compound. To ascertain this issue, we checked if the rate of the cyclization



Scheme 3 MBH adduct **4ja** obtained in the reaction of 5-trifluoromethyl-2-pyridinecarboxaldehyde **2j** with 2-cyclohexenone **3a**.

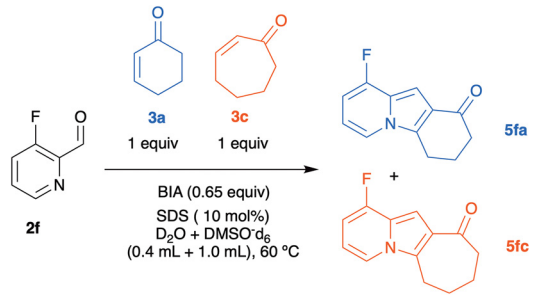


Scheme 4 MBH and aldol adducts obtained from the reactions of 2-pyridinecarboxaldehydes **2a**, **2e** and **2g** with 2-cyclopentenone **3b**.

of pure **4aa** (that could be obtained by stopping the BIA-catalyzed reaction after 1 h, followed by fast chromatographic purification of the product mixture in silica gel) in water was affected by the presence of the Lewis base catalyst. In fact, when a 0.1 M aqueous solution of MBH adduct **4aa** was stirred at 25 °C, and the evolution of the system was monitored by ^{1}H NMR spectroscopy, a similar conversion to **5aa** (*ca.* 32% after 2 h) was observed with: (a) 0.65 equiv. of BIA, (b) 0.65 equiv. of 3-quinuclidinol, and (c) in the absence of a Lewis base. No further conversion of **4aa** to **5aa** took place in $CDCl_3$ solution. This shows therefore that the role of the BIA catalyst **1** is restricted to promoting the MBH addition,[28] and that the cyclization/dehydration of the MBH adducts in water is much faster than in other solvents (including THF/H_2O mixtures).

Particularly in the case of electron-deficient 2-pyridinecarboxaldehydes, 2-cycloheptenone-derived MBH adducts appear to cyclize more efficiently than those obtained from 2-cyclohexenone. To collect more evidence about the reactivity of the cycloalkenones in the cyclization step, we decided to carry out a competition experiment. We selected for this purpose the reaction between 3-fluoro-2-pyridinecarboxaldehyde (**2f**) and a 1 : 1 mixture of 2-cyclohexenone **3a** and 2-cycloheptenone **3c** in water/DMSO (Scheme 5), for the following reasons: (a) the possibility of following the reaction by ^{19}F NMR, (b) electron-poor aldehydes give good yields of MBH adducts, and (c) the clear difference in yields observed between **5fa** and **5fc** in Scheme 2 suggested that the rates of formation of both adducts would also be very different.

The reaction was monitored using a pseudo-2D experiment directly in the NMR tube. Both enones were added at the same time and the tube was then brought to the spectrometer with the probe temperature already set at 60 °C. The spectra were collected for 6 h with a 10-minute interval between each acquisition and the result obtained for the formation of indolizines and the consumption of 3-fluoro-2-pyridinecarboxaldehyde are



Scheme 5 Competition experiment between **3a**, **3c** and the fluorinated pyridinecarboxaldehyde **2f**.

shown below (Fig. 3). We opted for monitoring the reaction by ^{19}F NMR, due to the high sensibility of this nucleus to small structural changes. Even though the fluorine atom is in the aromatic ring, the ^{19}F chemical shift in the indolizine **5fa** prepared from cyclohexenone (−125.5 ppm) is different from that of **5fc**, arising from cycloheptenone (−125.0 ppm). Analysis of Fig. 3 shows that the concentration of the pyridinecarboxaldehyde **2f** decreases continuously during the first 6 h of the reaction, and that the cycloheptenone-derived indolizine **5fc** is formed faster than the cyclohexanone-derived indolizine **5fb** (whose concentration does not change after 3 h from the beginning of the reaction). *This shows that as we had anticipated in this case the rate of the cyclization step is therefore determining the overall rate of the process*. Therefore, the reactivity order for the cyclization of the MBH adducts **4** to the indolizines **5** with respect the ring size of the enones is:

cycloheptenone > cyclohexenone ≫ cyclopentenone

On the other hand, the fact that the cyclooctenone-derived indolizine **5ag** is formed in essentially quantitative yield from the corresponding MBH adduct **4ag** (see data in Scheme 2) suggests that MBH adducts of cyclooctenone cyclize even faster than those of cycloheptenone.

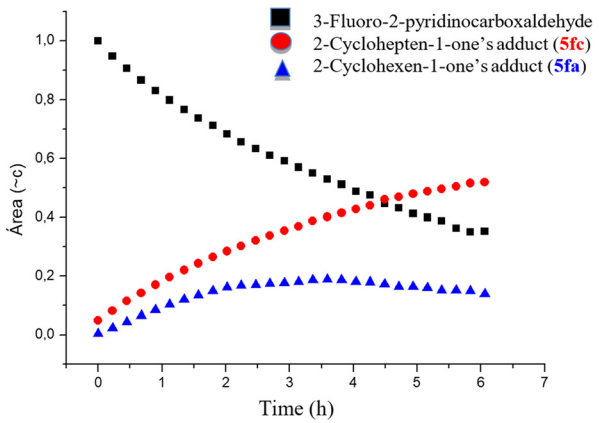


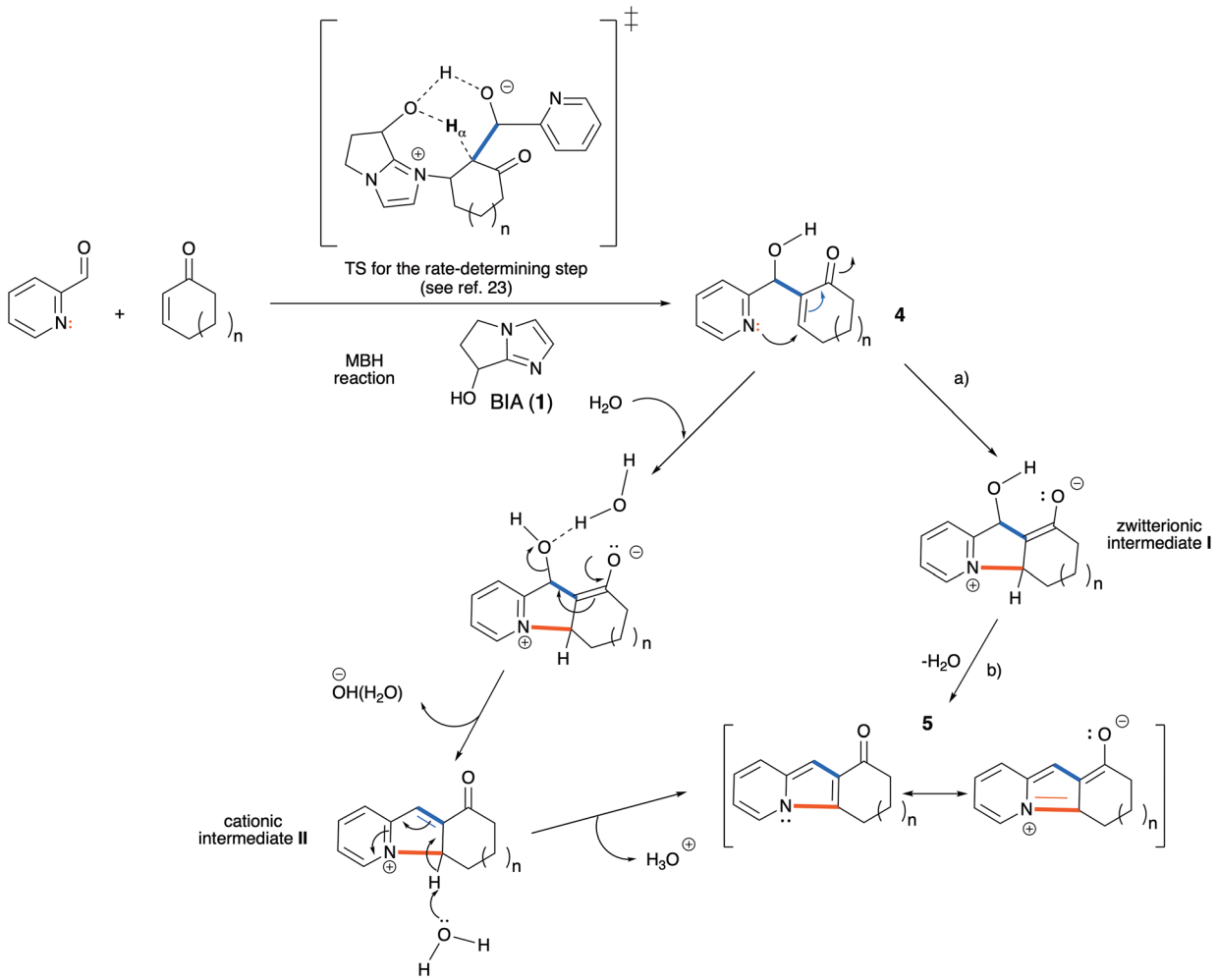
Fig. 3 Evaluating the relative rate of cyclization reaction using six and seven-membered enones (graph area *vs.* time obtained from analysis of the ^{19}F NMR spectra).

In summary, experimental evidence suggests that the efficiency of the bifunctional catalyst **1** in promoting the direct conversion of 2-pyridinecarbaldehydes and cyclic enones into the indolizine derivatives comes from the fact that the cyclization of the initially formed MBH adducts takes place in aqueous solution without the need of previous activation of the hydroxyl group or of acid catalysis and is accelerated by heating. The rate of the cyclization does not depend appreciably on the nature of the pyridinecarbaldehyde component but varies strongly with the ring size of the cycloenones.

A plausible mechanistic proposal for the conversion of the MBH adducts **4** into the indolizines **5** is that this key transformation takes place in two stages: (a) intramolecular Michael attack of the pyridine nitrogen to the enone moiety, leading to a cyclized zwitterionic intermediate (**I**), and (b) dehydration of **I** to afford the final product (Scheme 6). It is worth noting here that step (a) is a 5-*endo-trig* cyclization, a disfavored process according to Baldwin's rules for ring closure.[29] This step should therefore be highly endothermic, and its rate should be controlled both by the strain energy of the tricyclic intermediate **I** and by the polarity of the solvent. On the other hand, the dehydration step (b), although strongly exothermic due to the formation of water and of the resonance stabilization energy of the aromatic indolizinic ketone, should have a high activation energy for a concerted pathway, and is a likely candidate for catalytic assistance by a protic polar solvent. We propose that a water molecule, upon hydrogen-bonding to the hydroxyl group of **I**, provides a relatively low-energy pathway for the elimination of hydroxide anion, leading to the cationic intermediate **II** that can easily lose a proton to give the tricyclic indolizine.

We have performed theoretical calculations that give initial support to this hypothesis, at the DFT level of theory and both in water solution (implicit solvent model) and in the gas phase (gp). We have located and characterized the transition states (TS) for step (a) (intramolecular aza-Michael addition) of the cyclization/dehydration with 2-cyclopentenone, 2-cyclohexenone and 2-cycloheptenone, respectively. The results are summarized below (Fig. 4). See the ESI† for additional details about the calculations.

In agreement with our hypothesis, the calculations show that in water solution step (a) is endoergic in all instances, and that the activation free energies can be clearly correlated with the difference in free energy between the MBH adduct and the zwitterionic intermediate **I**. As can be seen from Fig. 4A, the energy barrier for the formation of the 5-membered tricyclic indolizine is 2.7 kcal mol^{-1} higher than that for the formation of the 6-membered one, which in turn is 1.2 kcal mol^{-1} higher than that for the formation of the 7-membered one. According to these data, the cyclization of the five-membered MBH product **4ab** is 1000 times slower than that of the seven-membered adduct **4ac**, that in turn is only ten times faster than the cyclization of **4aa**. These theoretical results corroborate our previous observations regarding *the very poor reactivity of the 5-membered ring analogues, which hinders indolizine formation during the surveyed reaction time*, and the higher reactivity of



Scheme 6 Plausible mechanism for the direct conversion of MBH adducts **4** into indolizines **5** in water. The two bonds formed in the overall process are showcased in blue (MBH step) and in red (aza-Michael/dehydration step).

the 7-membered adduct when compared to the 6-membered adduct in the cyclization reaction.

To assess the effect of the aqueous solvent in the process, we also computed the activation free energies for the cyclization step in the gas phase, at the same theoretical level (Fig. 4B). When comparing the relative energies of the transition states, we found that the energy barriers associated to **TS1**, **TS2** and **TS3** were respectively 4.1, 5.9 and 4.9 kcal mol^{-1} *lower* in water solution than in the gas phase. For the zwitterionic intermediates the effect of the solvent is even more pronounced, since in the gas phase their energies are systematically 10 kcal mol^{-1} higher than in water solution. The differential stabilization of the zwitterionic intermediates and of the corresponding transition states with respect to the starting MBH adducts upon solvation by a highly polar solvent is in accordance with the experimental observation that in non-aqueous media the direct cyclization of the MBH alcohols is very difficult and requires either the previous conversion of the hydroxyl moiety to a good leaving group or activation by means of a Lewis acid.[18]

At this point, we were also interested in evaluating the synthetic usefulness of these new polycyclic indolizines. Thus, indolizine **5aa** was taken as a platform for some chemical transformations. Our aim was to explore the reactivity of the different parts of the structure of this heterocycle, *i.e.*, the aromatic system, the benzylic position, the carbonyl group, and the alpha-carbonyl hydrogens. Initially, we treated indolizine **5aa** with NBS in acetonitrile, and we obtained a mixture from which the major isolated product was **7** (resulting from bromination of the cyclohexane moiety at the benzylic position), in 32% yield. Other attempts to brominate the indolizine core were unsuccessful. When **5aa** was submitted to classical Vilsmeier–Haack formylation conditions, the stable chloro dialdehyde **8** [30] was obtained in 70% yield after chromatographic purification. We also decided to evaluate the ability of tricyclic indolizine ketone **5aa** to participate in a condensation reaction. Thus, a methanolic solution of **5aa** was treated with KOH and with 2-amino-3-pyridinecarbaldehyde **9** at rt to give the new polycyclic 1,8-naphthiridine **10** in 62% yield after chromatographic purification (Scheme 7).

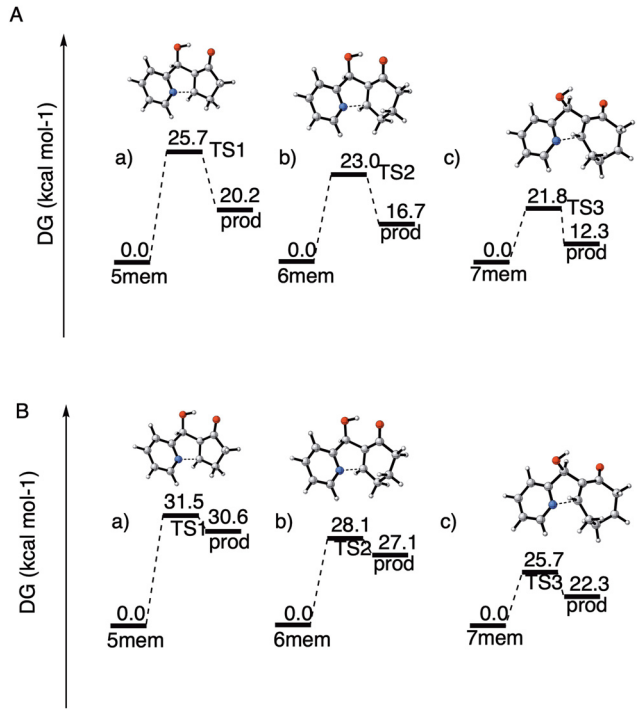
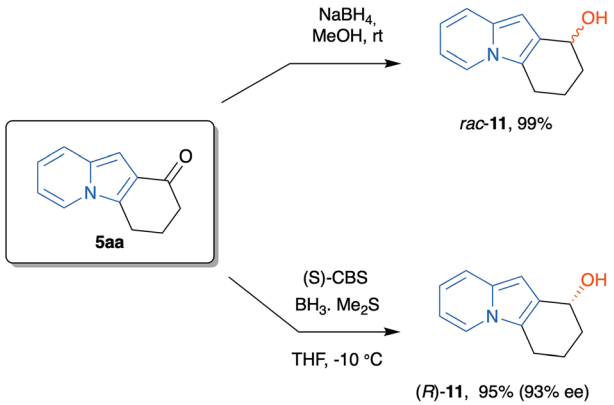


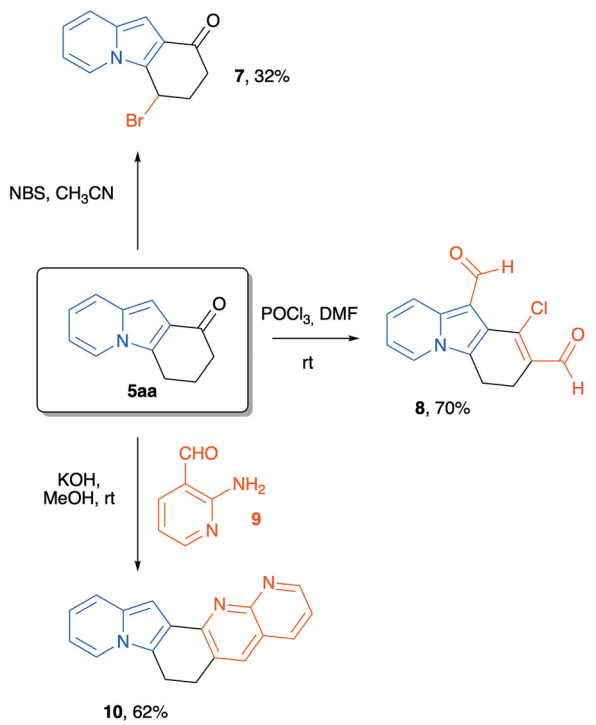
Fig. 4 Calculated energy barriers for the ring closing step obtained at the ωB97xD/aug-cc-pVTZ theoretical level. (A) In water solution. (B) In the gas phase.

To further explore the chemical potentiality of these tricyclic indolizines, we treated **5aa** with $NaBH_4$ in methanol at rt to afford the corresponding benzylic alcohol in almost quantitative yield, after 15 min. The racemic alcohol **11** was pure enough to avoid any additional purification step. This result, associated with the structural difference between the substituents of the carbonyl group stimulated us to evaluate the behavior of this compound when treated with the Corey–Bakshi–Shibata (CBS) catalyst and borane.[31] So, **5aa** was reduced with the (*S*)-CBS reagent (at the 1 g scale) to provide the corresponding alcohol (*R*)-**11** in 95% yield (Scheme 8). This compound was determined to have a 93% e.e., as analyzed by HPLC with a chiral stationary phase (Chiralpak® IA column).



Scheme 8 Racemic and asymmetric carbonyl reduction of the tricyclic indolizine **5aa**.

This set of simple chemical transformations demonstrate unambiguously the potentiality of these tricyclic indolizines as platforms for the synthesis of compounds with new carbon arrangements.



Scheme 7 Synthetic exploration of the tricyclic indolizine **5aa**.

Conclusions

In summary, we have developed a straightforward approach for the synthesis of tricyclic indolizines, based on aqueous Morita–Baylis–Hillman (MBH) reactions between 2-pyridinecarbaldehydes and cyclic enones, organocatalyzed by a readily available, bi-functional Lewis base (BIA). This is the first systematic study of an organocatalyzed method for the synthesis of this class of heterocycles, starting from simple building blocks. In a single step, it was possible to prepare a set of tricyclic indolizines in isolated yields ranging from 16% to up 70%, in aqueous solution at 60 °C. The catalytic role of the bicyclic imidazolyl alcohol is restricted to the initial formation of the MBH adducts, that when generated in water can cyclize to give a zwitterionic intermediate that upon dehydration gives rise to the indolizine compounds. The facility of the cyclization strongly depends on the size of the cycloalkenone ring: while adducts derived from six-, seven- or even eight-membered cycloenones are readily transformed into the corresponding indolizines, cyclopentenone-derived MBH adducts do not cyclize. Strongly electron-withdrawing substituents, particularly when located in position 5 of the 2-pyridincarboxaldehyde, also difficult the aza-Michael cyclization step, probably

due to the diminished nucleophilicity of the pyridine nitrogen. Some chemical transformations were performed on these novel heterocycles to demonstrate their synthetic usefulness.

Theoretical calculations were performed to rationalize the reason why the cyclization step fails when cyclopentenones were employed. The calculations demonstrated that the transition state energies for the intramolecular aza-Michael step, that is disfavored according to Baldwin's ring-closure rules and that leads to a *zwitterionic* intermediate, (a) are substantially lower in water solution than in the gas-phase, and (b) are much higher for MBH adducts derived from five-membered cycloenones than for those derived from 6- and 7-membered cycloenones.

Experimental

General methods

All chemicals were used as purchased, unless otherwise noticed. Reaction progress was monitored by thin layer chromatography on silica gel (aluminum foils) and spotted under UV light (254 nm), followed by staining with ethanolic 25% phosphomolybdic acid solution, aqueous $KMnO_4$ or vanillin in acetic acid. Purification by column chromatography was carried out with silica gel (70–230 or 230–400 Mesh). The non-commercial enones **3d**, **3e**, and **3f** were prepared according to Yamamoto *et al.*[26] Enone **3g** was prepared according to List *et al.*[27]

^{1}H NMR spectra were acquired at 600, 500, 400 or 250 MHz; ^{19}F NMR spectra at 471 or 235 MHz; and ^{13}C NMR spectra at 152, 126, 100 or 62.5 MHz, in $CDCl_3$, CD_2Cl_2 or C_6D_6, at room temperature. Chemical shifts (δ) were reported in ppm and were calibrated against tetramethylsylane or the solvent residual signal according to the literature. The coupling constants (J) are reported in Hertz (Hz) and the signal multiplicity was assigned as s (singlet), d (doublet), t (triplet), dd (double doublet), dt (double triplet), td (triple doublet), tt (triple triplet), ddd (double double doublet), dddd (double double double doublet), quartet (q), multiplet (m) and broad singlet (br).

The high-resolution mass spectrometric analyses (HRMS) were performed in a Q-Tof instrument, equipped with an ESI ionization source operating in the positive mode (ESI(+)-MS). The samples were injected by direct infusion in a 40 μL min^{-1} flow. The following parameters were used: 3 kV capillary voltage, 20 V cone voltage, source temperature of 120 °C and nebulization gas flow of 0.5 L h^{-1}. Before every analysis, the instrument was calibrated with an H_3PO_4 solution (0.005% in H_2O/CH_3CN 1 : 1) from m/z 100 to 1000. Melting points were obtained using an Electrothermal equipment model 9100 and are corrected. Compounds were named according to IUPAC rules using the program MarvinSketch 17.8.

Computational calculations

Conformational search calculations for all species were carried out in water by applying the analytical linearized Poisson–Boltzmann (ALPB)[32] solvent model to find the lowest energy conformers within calculated energies below than 10 kcal mol^{-1} at the GFN2-xTB[33] level using CREST 2.11 software. The resulting conformers were reoptimized using Gaussian 16 Rev C.01[34] at the M06-2X/aug-cc-pVTZ level and using the IEFPCM[35] implicit solvent model with parameters of water. Frequency calculations at the same level of the optimizations were carried out to confirm the converged geometries as either minima (without negative frequencies) or transition states (one negative frequency). A benchmarking study was carried out by calculating single point energies using several DFT functionals and the DLPNO-CCSD(T)/def2-TZVP level as the reference. DLPNO-CCSD(T)/def2-TZVP single point calculations were run using ORCA 5.0.1 package of programs.[36] The ωB97xD/aug-cc-pVTZ showed the best performance when compared to the DLPNO-CCSD(T)/def2-TZVP level, being all optimization and frequency calculations repeated at this DFT level. Intrinsic reaction coordinate (IRC) calculations[37] at the ωB97xD/aug-cc-pVTZ level were carried out to assess whether the obtained transition states were connected with two minima.

Synthetic procedures and characterization

Synthesis of 7-hydroxy-6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazole (BIA, 1).[25] In a 250 mL round-bottomed flask containing 6.52 g (1.0 equiv., 96 mmol) of imidazole dissolved in 1,4-dioxane (100 mL), 0.40 mL of acetic acid (6.8 mmol, 7 mol%) and 9.8 mL (1.5 equiv., 146.8 mmol) of acrolein were added. The reaction mixture was kept under magnetic stirring for 36 h and was monitored by TLC until the reaction showed no further evolution. After the completion of the reaction, the solvent was removed under reduced pressure and the crude mixture was purified by flash column chromatography using 5% MeOH in ethyl acetate as the eluent to furnish 6.53 g of the catalyst **1**, as a white solid in 55% yield. Mp = 152–154 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (br, 1H), 7.05 (d, J = 1.0 Hz, 1H), 6.82 (d, J = 1.2 Hz, 1H), 5.18 (dd, J = 7.3, 3.1 Hz, 1H), 4.17 (ddd, J = 10.6, 7.9, 6.4 Hz, 1H), 3.89 (ddd, J = 10.6, 8.6, 4.1 Hz, 1H), 2.97–2.85 (m, 1H), 2.60–2.50 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.6, 132.6, 114.3, 63.7, 43.2, 36.4.

General procedure for the synthesis of indolizines

To a 5 mL round-bottomed flask were added 1.0 mmol of the pyridinecarbaldehyde **2**, 2.0 mmol of the α,β-unsaturated cyclic ketone **3** (2.0 equiv.), 0.65 mmol of the BIA catalyst **1** (170 mg, 0.65 equiv.), 0.1 mmol of sodium dodecylsulfate (0.1 equiv., 28.8 mg) and 0.5 mL of distilled water (2 M concentration with respect to aldehyde). The flask was then sealed with a rubber septum and was magnetically stirred at 60 °C. After 12 h, the solvent was evaporated, the remaining wet solid was extracted with dichloromethane and purified using flash column chromatography (SiO_2) eluting with a gradient of Hex : AcOEt (95 : 05–60 : 40) to give the desired indolizine (**5**), or the corresponding MBH adduct (**4**), or the aldol adduct (**6**).

1*H*,2*H*,3*H*,4*H*-Pyrido[1,2-*a*]indol-1-one (5aa).[18i] 70% yield (129.7 mg), yellow solid, mp >182 °C (*decomp.*). ^{1}H NMR

(500 MHz, C_6D_6) δ 6.99 (dt, J = 9.2, 1.1 Hz, 1H), 6.98 (s, 1H), 6.86 (dq, J = 7.1, 1.0 Hz, 1H), 6.26 (ddd, J = 9.2, 6.4, 1.0 Hz, 1H), 6.05 (ddd, J = 7.2, 6.4, 1.2 Hz, 1H), 2.40–2.28 (m, 2H), 2.04 (t, J = 6.2 Hz, 2H), 1.64 (dq, J = 7.6, 6.3 Hz, 2H). ^{13}C NMR (126 MHz, C_6D_6) δ 194.0, 132.9, 131.5, 124.1, 122.4, 121.0, 117.6, 111.6, 96.2, 38.9, 23.4, 20.7. HRMS (ESI): m/z calcd for $C_{12}H_{12}NO$ $[M + H]^+$: 186.0913, found: 186.0924.

8-Methyl-1*H*,2*H*,3*H*,4*H*-pyrido[1,2-*a*]indol-1-one (5ba). 62% yield (123.5 mg), brown viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 7.3 Hz, 1H), 7.11 (d, J = 1.2 Hz, 1H), 6.60 (s, 1H), 6.40 (dd, J = 7.3, 1.7 Hz, 1H), 2.94 (t, J = 6.2 Hz, 2H), 2.61 (dd, J = 7.3, 5.6 Hz, 2H), 2.34–2.23 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.1, 133.2, 131.6, 128.1, 123.2, 121.7, 118.6, 115.1, 93.5, 38.5, 23.6, 21.0, 21.0. HRMS (ESI): m/z calcd for $C_{13}H_{14}NO$ $[M + H]^+$: 200.1070, found: 200.1075.

9-Methoxy-1*H*,2*H*,3*H*,4*H*-pyrido[1,2-*a*]indol-1-one (5ca). 61% yield (131.3 mg), light green solid, mp = 125–126 °C. ^{1}H NMR (250 MHz, C_6D_6) δ 7.51 (s, 1H), 6.83 (d, J = 7.0 Hz, 1H), 6.22 (t, J = 7.2 Hz, 1H), 5.62 (d, J = 7.3 Hz, 1H), 3.40 (s, 3H), 2.48–2.34 (m, 2H), 2.19 (t, J = 6.2 Hz, 2H), 1.71 (dd, J = 12.7, 6.3 Hz, 2H). ^{13}C NMR (63 MHz, C_6D_6) δ 193.9, 153.0, 132.6, 128.2, 123.5, 115.8, 111.9, 94.8, 93.7, 54.8, 38.9, 23.5, 21.0. HRMS (ESI): m/z calcd for $C_{13}H_{14}NO_2$ $[M + H]^+$: 216.1019, found: 216.1027.

7-Methyl-1*H*,2*H*,3*H*,4*H*-pyrido[1,2-*a*]indol-1-one (5da). 33% yield (65.8 mg), yellow solid, mp >116 °C (*decomp.*). ^{1}H NMR (250 MHz, C_6D_6) δ 7.32 (s, 1H), 7.08 (d, J = 9.3 Hz, 1H), 6.91 (s, 1H), 6.29 (dd, J = 9.3, 1.1 Hz, 1H), 2.59–2.45 (m, 2H), 2.24 (t, J = 6.2 Hz, 2H), 1.98 (d, J = 0.9 Hz, 3H), 1.88–1.75 (m, 2H). ^{13}C NMR (63 MHz, C_6D_6) δ 193.7, 131.7, 130.8, 123.7, 120.8, 120.6, 120.3, 119.4, 95.8, 38.7, 23.3, 20.5, 18.0. HRMS (ESI): m/z calcd for $C_{13}H_{14}NO$ $[M + H]^+$: 200.1070, found: 200.1078.

8-Ethyl-1*H*,2*H*,3*H*,4*H*-pyrido[1,2-*a*]indol-1-one (5ea). 45% yield (96.0 mg), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 7.3 Hz, 1H), 7.15–7.08 (m, 1H), 6.62 (s, 1H), 6.43 (dd, J = 7.3, 1.7 Hz, 1H), 2.93 (t, J = 6.2 Hz, 2H), 2.64–2.49 (m, 4H), 2.33–2.22 (m, 2H), 1.22 (t, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.1, 134.3, 133.3, 131.6, 123.2, 121.9, 117.1, 114.2, 93.8, 38.5, 28.2, 23.6, 21.0, 14.2. HRMS (ESI): m/z calcd for $C_{14}H_{16}NO$ $[M + H]^+$: 214.1226, found: 214.1238.

9-Fluoro-1*H*,2*H*,3*H*,4*H*-pyrido[1,2-*a*]indol-1-one (5fa). 19% yield (38.6 mg), white solid, mp >169 °C (*decomp.*). ^{1}H NMR (500 MHz, C_6D_6) δ 7.24 (d, J = 0.5 Hz, 1H), 6.52 (d, J = 7.0 Hz, 1H), 5.93 (dd, J = 10.7, 7.3 Hz, 1H), 5.78 (td, J = 7.2, 5.0 Hz, 1H), 2.31–2.24 (m, 2H), 1.92 (t, J = 6.2 Hz, 2H), 1.55 (dt, J = 7.5, 6.3 Hz, 2H). ^{13}C NMR (126 MHz, C_6D_6) δ 193.1 (s), 155.4 (d, J = 250.0 Hz), 132.8 (s), 125.1 (d, J = 37.4 Hz), 123.8 (s), 118.3 (d, J = 4.4 Hz), 110.2 (d, J = 7.7 Hz), 99.4 (d, J = 17.5 Hz), 93.7 (d, J = 3.2 Hz), 38.4 (s), 22.8 (s), 20.5 (s). ^{19}F NMR (470 MHz, C_6D_6) δ −124.25. HRMS (ESI): m/z calcd for $C_{12}H_{11}FNO$ $[M + H]^+$: 204.0819, found: 204.0829.

7-Chloro-1*H*,2*H*,3*H*,4*H*-pyrido[1,2-*a*]indol-1-one (5ga). 16% yield (35.1 mg), yellow solid, mp >125 °C (*decomp.*). ^{1}H NMR (500 MHz, C_6D_6) δ 6.93–6.87 (m, 2H), 6.65 (d, J = 9.6 Hz, 1H), 6.20 (dd, J = 9.6, 1.7 Hz, 1H), 2.31–2.25 (m, 2H), 1.77 (t, J = 6.2 Hz, 2H), 1.58–1.45 (m, 2H). ^{13}C NMR (126 MHz, C_6D_6) δ 193.4, 142.6, 131.6, 130.6, 124.2, 121.2, 119.8, 118.6, 97.3, 38.4, 22.8, 20.0. HRMS (ESI): m/z calcd for $C_{12}H_{11}ClNO$ $[M + H]^+$: 220.0524, found: 220.0531.

7-Bromo-1*H*,2*H*,3*H*,4*H*-pyrido[1,2-*a*]indol-1-one (5ia). 26% yield (68.7 mg), gray solid, mp >136 °C (*decomp.*). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.41–7.11 (m, 1H), 6.81 (s, 1H), 6.75 (dd, J = 9.6, 1.7 Hz, 1H), 2.96 (t, J = 6.2 Hz, 2H), 2.65 (dd, J = 7.3, 5.6 Hz, 2H), 2.32 (p, J = 6.4 Hz, 2H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 195.7, 132.3, 131.0, 123.6, 122.2, 121.5, 107.5, 96.8, 38.5, 23.4, 20.9. HRMS (ESI): m/z calcd for $C_{12}H_{11}BrNO$ $[M + H]^+$: 264.0019; found: 264.0017.

3-Phenyl-1*H*,2*H*,3*H*,4*H*-pyrido[1,2-*a*]indol-1-one (5ae). 28% yield (73.2 mg), dark green solid, mp >180 °C (*decomp.*). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (dq, J = 7.2, 1.1 Hz, 1H), 7.36–7.25 (m, 5H), 7.26–7.20 (m, 1H), 6.73 (d, J = 0.7 Hz, 1H), 6.73 (d, J = 0.7 Hz, 1H), 6.61 (ddd, J = 9.2, 6.4, 1.1 Hz, 1H), 6.53–6.46 (m, 1H), 3.63–3.53 (m, 1H), 3.21 (ddd, J = 16.0, 5.0, 0.7 Hz, 1H), 3.03 (dd, J = 16.0, 11.2 Hz, 1H), 2.87 (dd, J = 16.3, 12.4 Hz, 1H), 2.79 (ddd, J = 16.3, 4.3, 1.0 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 194.8, 143.2, 133.3, 128.8, 127.2, 126.8, 122.2, 121.1, 118.2, 112.4, 95.5, 45.6, 42.3, 29.3. HRMS (ESI): m/z calcd for $C_{18}H_{16}NO$ $[M + H]^+$: 262.1226, found: 262.1236.

3-(2*H*-1,3-Benzodioxol-5-yl)-1*H*,2*H*,3*H*,4*H*-pyrido[1,2-*a*]indol-1-one (5af). 33% yield (100.8 mg), white solid, mp >200 °C (*decomp.*). ^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.71 (dd, J = 7.2, 0.9 Hz, 1H), 7.43 (d, J = 9.2 Hz, 1H), 6.90 (d, J = 1.3 Hz, 1H), 6.88–6.82 (m, 2H), 6.77–6.71 (m, 2H), 6.66–6.60 (m, 1H), 6.00 (s, 2H), 3.65–3.56 (m, 1H), 3.29 (dd, J = 15.9, 4.9 Hz, 1H), 3.07 (dd, J = 16.0, 11.1 Hz, 1H), 2.88 (dd, J = 16.2, 12.6 Hz, 1H), 2.82–2.75 (m, 1H). ^{13}C NMR (151 MHz, CD_2Cl_2) δ 194.2, 147.9, 146.5, 137.5, 133.3, 131.3, 122.8, 122.4, 120.8, 119.9, 118.2, 112.2, 108.3, 107.2, 101.2, 95.0, 46.0, 42.0, 29.4. HRMS (ESI): m/z calcd for $C_{19}H_{16}NO_3$ $[M + H]^+$: 306.1125, found: 306.1114.

6*H*,7*H*,8*H*,9*H*,10*H*-Cyclohepta[*b*]indolizin-10-one (5ac). 66% yield (131.5 mg), yellow solid, mp >72 °C (*decomp.*). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 7.3 Hz, 1H), 7.36 (d, J = 9.1 Hz, 1H), 6.89 (s, 1H), 6.66 (dd, J = 8.6, 6.7 Hz, 1H), 6.61–6.53 (m, 1H), 3.10–3.02 (m, 2H), 2.89–2.81 (m, 2H), 2.21–2.08 (m, 2H), 2.05–1.92 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.2, 131.7, 127.1, 126.7, 122.1, 120.7, 117.4, 112.2, 100.0, 44.4, 26.6, 25.7, 22.8. HRMS (ESI): m/z calcd for $C_{13}H_{14}NO$ $[M + H]^+$: 200.1070, found: 200.1083.

2-Methyl-6*H*,7*H*,8*H*,9*H*,10*H*-cyclohepta[*b*]indolizin-10-one (5bc). 45% yield (96.0 mg), green solid, mp >95 °C (*decomp.*). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.59 (d, J = 7.4 Hz, 1H), 7.12 (q, J = 1.4 Hz, 1H), 6.42 (dd, J = 7.4, 1.8 Hz, 1H), 3.18–2.93 (m, 2H), 2.95–2.71 (m, 2H), 2.27 (d, J = 1.2 Hz, 3H), 2.22–2.08 (m, 2H), 2.06–1.92 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 199.3, 132.1, 127.6, 126.7, 126.6, 121.7, 118.3, 115.2, 98.1, 44.5, 26.7, 25.8, 22.9, 21.0. HRMS (ESI): m/z calcd for $C_{14}H_{16}NO$ $[M + H]^+$: 214.1226; found: 214.1225.

3-Methyl-6*H*,7*H*,8*H*,9*H*,10*H*-cyclohepta[*b*]indolizin-10-one (5dc). 31% yield (66.1 mg), yellow solid, mp >132 °C (*decomp.*). ^{1}H NMR (250 MHz, C_6D_6) δ 7.28 (s, 1H), 6.97 (d, J = 9.2 Hz, 1H), 6.82 (s, 1H), 6.15 (dd, J = 9.2, 1.2 Hz, 1H), 2.75–2.57 (m, 2H), 2.25 (t, J = 5.9 Hz, 2H), 1.86 (d, J = 1.1 Hz, 3H), 1.73–1.32 (m, 4H). ^{13}C NMR (63 MHz, C_6D_6) δ 196.7, 130.6, 127.2, 125.9,

120.6, 120.2, 120.1, 119.3, 100.7, 44.5, 26.2, 25.6, 22.6, 18.2. HRMS (ESI): *m*/*z* calcd for $C_{14}H_{16}NO$ $[M + H]^+$: 214.1226, found: 214.1237.

1-Methoxy-6*H*,7*H*,8*H*,9*H*,10*H*-cyclohepta[*b*]indolizin-10-one (5cc). 50% yield (114.6 mg), green solid, mp >109 °C (*decomp.*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 7.2 Hz, 1H), 7.06 (d, J = 0.6 Hz, 1H), 6.52 (t, J = 7.2 Hz, 1H), 5.97 (d, J = 7.3 Hz, 1H), 3.93 (s, 3H), 3.10–3.02 (m, 2H), 2.89–2.81 (m, 2H), 2.19–2.08 (m, 2H), 2.04–1.93 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.0, 152.6, 128.3, 126.9, 126.2, 115.6, 112.4, 98.6, 93.5, 55.5, 44.5, 27.0, 25.8, 22.9. HRMS (ESI): *m*/*z* calcd for $C_{14}H_{16}NO_2$ $[M + H]^+$: 230.1176, found: 230.1184.

1-Fluoro-6*H*,7*H*,8*H*,9*H*,10*H*-cyclohepta[*b*]indolizin-10-one (5fc). 53% yield (115.1 mg), white solid, mp = 99–102 °C. ^{1}H NMR (500 MHz, C_6D_6) δ 7.46 (d, J = 0.6 Hz, 1H), 6.66 (d, J = 7.1 Hz, 1H), 5.96 (dd, J = 10.4, 7.2 Hz, 1H), 5.86 (td, J = 7.2, 5.2 Hz, 1H), 2.63–2.57 (m, 2H), 2.20–2.14 (m, 2H), 1.51–1.38 (m, 4H). ^{13}C NMR (126 MHz, C_6D_6) δ 196.6 (s), 155.5 (d, J = 249.4 Hz), 128.5 (s), 127.6 (s), 124.4 (d, J = 37.5 Hz), 118.7 (d, J = 4.2 Hz), 110.6 (d, J = 7.7 Hz), 99.4 (d, J = 17.6 Hz), 98.6 (d, J = 3.1 Hz), 44.6 (s), 26.6 (s), 25.6 (s), 22.7 (s). ^{19}F NMR (470 MHz, C_6D_6) δ −124.82. HRMS (ESI): *m*/*z* calcd for $C_{13}H_{13}FNO$ $[M + H]^+$: 218.0976, found: 218.0987.

3-Chloro-6*H*,7*H*,8*H*,9*H*,10*H*-cyclohepta[*b*]indolizin-10-one (5gc). 62% yield (144.9 mg), yellow solid, mp >127 °C (*decomp.*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.30 (d, J = 9.5 Hz, 1H), 6.91 (s, 1H), 6.61 (dd, J = 9.5, 1.5 Hz, 1H), 3.05–2.95 (m, 2H), 2.87–2.77 (m, 2H), 2.19–2.04 (m, 2H), 2.02–1.86 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.9, 130.0, 127.6, 127.5, 121.3, 120.8, 120.0, 119.2, 101.6, 44.5, 26.7, 25.7, 22.8. HRMS (ESI): *m*/*z* calcd for $C_{13}H_{13}ClNO$ $[M + H]^+$: 234.0680, found: 234.0687.

1,3-Dibromo-6*H*,7*H*,8*H*,9*H*,10*H*-cyclohepta[*b*]indolizin-10-one (5hc). 49% yield (175.0 mg), yellow solid, mp: >182 °C (*decomp.*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (t, J = 0.9 Hz, 1H), 7.10 (d, J = 0.7 Hz, 1H), 7.03 (d, J = 1.3 Hz, 1H), 3.09–3.01 (m, 2H), 2.90–2.82 (m, 2H), 2.21–2.10 (m, 2H), 2.05–1.92 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.4, 129.5, 129.0, 127.4, 123.2, 121.5, 115.2, 106.0, 103.8, 44.3, 26.9, 25.5, 22.5. HRMS (ESI): *m*/*z* calcd for $C_{13}H_{12}Br_2NO$ $[M + H]^+$: 355.9280, found: 355.9285.

3-Bromo-6*H*,7*H*,8*H*,9*H*,10*H*-cyclohepta[*b*]indolizin-10-one (5ic). 43% yield (119.6 mg), brown solid, mp: >130 °C (*decomp.*). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (s, 1H), 7.13 (s, 1H), 6.65 (d, J = 9.5 Hz, 1H), 6.34 (dd, J = 9.5, 1.5 Hz, 1H), 2.71–2.54 (m, 2H), 2.01–1.83 (m, 2H), 1.40–1.34 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.3, 129.6, 128.3, 126.7, 122.2, 121.2, 120.2, 106.9, 102.2, 44.4, 25.7, 25.4, 22.4. HRMS (ESI): *m*/*z* calcd for $C_{13}H_{13}BrNO$ $[M + H]^+$: 278.0175, found: 278.0174.

3-(Trifluoromethyl)-6*H*,7*H*,8*H*,9*H*,10*H*-cyclohepta[*b*]indolizin-10-one (5jc). 18% yield (48.1 mg), yellow solid, mp >110 °C (*decomp.*). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.14 (p, J = 1.4 Hz, 1H), 7.51 (d, J = 9.3 Hz, 1H), 6.95 (s, 1H), 6.81 (dd, J = 9.5, 1.5 Hz, 1H), 3.52–3.02 (m, 2H), 2.99–2.66 (m, 2H), 2.31–2.10 (m, 2H), 2.08–1.80 (m, 2H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 198.3, 131.1, 129.3, 128.4, 124.1 (q, J = 270.4 Hz), 122.0 (q, J = 6.2 Hz), 121.3, 115.8 (q, J = 33.2 Hz), 112.8 (q, J = 2.6 Hz), 101.4, 44.3, 26.4, 25.5, 22.6. HRMS (ESI): *m*/*z* calcd for $C_{14}H_{13}F_3NO$ $[M + H]^+$: 268.0944; found: 268.0941.

6*H*,7*H*,8*H*,9*H*,10*H*,11*H*-Cycloocta[*b*]indolizin-11-one (5ag). 22% yield (46.9 mg), yellow oil. ^{1}H NMR (400 MHz, C_6D_6) δ 7.28 (s, 1H), 7.10–6.95 (m, 2H), 6.41–6.18 (m, 1H), 6.09–5.96 (m, 1H), 2.75 (t, J = 7.2 Hz, 2H), 2.57 (t, J = 6.5 Hz, 2H), 1.71–1.48 (m, 2H), 1.32–1.11 (m, 4H). ^{13}C NMR (101 MHz, C_6D_6) δ 197.3, 132.0, 129.6, 125.4, 122.0, 121.1, 116.8, 111.7, 100.4, 42.1, 24.5, 24.3, 23.9, 23.3. HRMS (ESI): *m*/*z* calcd for $C_{14}H_{16}NO$ $[M + H]^+$: 214.1226, found: 214.1223.

(2*Z*)-8-[Hydroxy(pyridin-2-yl)methyl]cyclooct-2-en-1-one (6ag, *syn* + *anti*). Diastereomers could be separated by column chromatography, but relative stereochemistry was not assigned. ***Major diastereomer***: 46% yield (106.4 mg), colorless oil. ^{1}H NMR (400 MHz, C_6D_6) δ 8.38 (ddd, J = 4.9, 1.8, 0.9 Hz, 1H), 7.62 (d, J = 7.9 Hz, 1H), 7.16–7.01 (m, 1H), 6.60 (dd, J = 7.5, 4.8 Hz, 1H), 6.11 (dd, J = 12.4, 2.1 Hz, 1H), 5.79 (ddd, J = 12.4, 8.9, 7.4 Hz, 1H), 5.47 (d, J = 3.0 Hz, 1H), 4.70 (s, 1H), 3.91 (ddd, J = 11.0, 6.2, 3.1 Hz, 1H), 2.59–2.44 (m, 1H), 2.12–1.95 (m, 1H), 1.77–1.65 (m, 1H), 1.30–0.96 (m, 5H). ^{13}C NMR (101 MHz, C_6D_6) δ 207.6, 162.0, 148.7, 142.35, 136.35, 135.1, 121.9, 121.6, 74.1, 54.6, 27.3, 23.8, 23.1, 22.9. HRMS (ESI): *m*/*z* calcd for $C_{14}H_{18}NO_2$ $[M + H]^+$: 232.1332, found: 232.1330. ***Minor diastereomer***: 32% yield (74.0 mg), colorless oil. ^{1}H NMR (400 MHz, C_6D_6) δ 8.34 (ddd, J = 4.8, 1.8, 1.0 Hz, 1H), 7.51 (dt, J = 7.9, 1.0 Hz, 1H), 7.09 (td, J = 7.7, 1.8 Hz, 1H), 6.56 (ddd, J = 7.7, 4.8, 1.2 Hz, 1H), 6.02 (dd, J = 12.4, 2.2 Hz, 1H), 5.75 (ddd, J = 12.4, 8.9, 7.3 Hz, 1H), 4.97 (dd, J = 6.3, 3.7 Hz, 1H), 4.78 (d, J = 9.2 Hz, 1H), 4.02 (ddd, J = 12.0, 6.3, 4.2 Hz, 1H), 2.64–2.44 (m, 1H), 2.27–2.07 (m, 1H), 1.71 (dddd, J = 14.7, 8.9, 5.6, 3.4 Hz, 1H), 1.39–1.22 (m, 4H), 1.13–0.99 (m, 1H). ^{13}C NMR (101 MHz, C_6D_6) δ 207.25, 163.2, 148.6, 141.6, 136.3, 135.8, 122.0, 121.7, 76.8, 54.2, 54.2, 27.6, 27.4, 23.9, 22.9. HRMS (ESI): *m*/*z* calcd for $C_{14}H_{18}NO_2$ $[M + H]^+$: 232.1332, found: 232.1327.

5-[Hydroxy(5-(trifluoromethyl)pyridin-2-yl)methyl]cyclohex-2-en-1-one (4ja). 75% yield (203.4 mg), pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 (dt, J = 2.1, 1.0 Hz, 1H), 7.65 (td, J = 7.7, 1.8 Hz, 1H), 7.92 (ddd, J = 8.3, 2.3, 0.7 Hz, 1H), 7.68 (dq, J = 8.2, 0.8 Hz, 1H), 7.08 (td, J = 4.2, 1.0 Hz, 1H), 5.69 (s, 1H), 4.64 (br s, 1H O**H**), 2.88–2.31 (m, 4H), 2.19–1.83 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.6, 164.5, 148.4, 145.2 (q, J = 4.1 Hz), 139.9, 134.0 (q, J = 3.3 Hz), 125.5 (q, J = 32.9 Hz), 123.5 (q, J = 272.3 Hz), 121.2, 71.3, 38.4, 25.9, 22.4. HRMS (ESI): *m*/*z* calcd for $C_{13}H_{13}F_3NO_2$ $[M + H]^+$: 272.0893, found: 272.0890.

5-[Hydroxy(pyridin-2-yl)methyl]cyclopent-2-en-1-one (4ab).[18b] 65% yield (123.0 mg), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (dt, J = 5.0, 1.3 Hz, 1H), 7.65 (td, J = 7.7, 1.8 Hz, 1H), 7.55 (td, J = 2.8, 1.1 Hz, 1H), 7.48 (d, J = 7.9 Hz, 1H), 7.18 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 5.57 (d, J = 1.9 Hz, 1H), 2.58 (ddt, J = 11.1, 6.5, 2.1 Hz, 2H), 2.42 (ddd, J = 10.1, 5.8, 3.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.79, 159.98, 159.17, 148.09, 147.60, 136.96, 136.79, 122.84, 122.74, 121.37, 121.26, 68.29, 35.31, 26.68.

2-[(4-Ethylpyridin-2-yl)(hydroxy)methyl]cyclopent-2-en-1-one (4eb). 27% yield (58.7 mg), yellow oil. ^{1}H NMR (400 MHz,

$CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (dd, J = 5.2, 0.8 Hz, 1H), 7.56 (d, J = 1.2 Hz, 0H), 7.35–7.29 (m, 1H), 7.04 (dd, J = 5.1, 1.6 Hz, 1H), 5.56 (d, J = 1.7 Hz, 1H), 2.68–2.54 (m, 4H), 2.52–2.36 (m, 2H), 1.23 (t, J = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.9, 159.9, 159.0, 154.3, 147.9, 147.8, 122.6, 120.7, 68.2, 35.3, 28.3, 26.7, 14.3. HRMS (ESI): m/z calcd for $C_{13}H_{16}NO_2$ $[M + H]^+$: 218.1176, found: 218.1176.

5-[(5-Chloropyridin-2-yl)(hydroxy)methyl]cyclopent-2-en-1-one (4gb). 69% yield (154.3 mg), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, J = 2.4 Hz, 1H), 7.65 (dd, J = 8.4, 2.4 Hz, 1H), 7.55 (td, J = 2.7, 1.2 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 5.57 (d, J = 1.7 Hz, 1H), 2.68–2.53 (m, 2H), 2.51–2.39 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.95, 160.15, 160.07, 157.48, 147.05, 136.68, 122.01, 68.40, 35.24, 26.69. HRMS (ESI): m/z calcd for $C_{11}H_{11}ClNO_2$ $[M + H]^+$: 224.0473, found: 224.0480.

5-[(4-Ethylpyridin-2-yl)(hydroxy)methyl]cyclopent-2-en-1-one (6eb). Major isomer, relative stereochemistry not assigned, 14% yield (30.4 mg), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 5.1 Hz, 1H), 7.71 (dt, J = 5.5, 2.7 Hz, 1H), 7.16 (s, 1H), 7.07 (dd, J = 5.3, 1.6 Hz, 1H), 6.38–6.18 (m, 1H), 5.35 (d, J = 2.6 Hz, 1H), 2.73–2.55 (m, 4H), 2.33 (ddt, J = 19.2, 6.8, 2.5 Hz, 1H), 1.25 (dt, J = 9.6, 7.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.0, 165.2, 160.0, 154.4, 147.7, 134.2, 122.4, 119.6, 70.7, 51.3, 29.3, 28.3, 14.2. HRMS (ESI): m/z calcd for $C_{13}H_{15}NNaO_2$ $[M + Na]^+$: 240.0995, found: 240.0999.

Synthesis of 4-bromo-1*H*,2*H*,3*H*,4*H*-pyrido[1,2-*a*]indol-1-one (7)

In a flame-dried 5 mL round-bottomed flask, a solution of indolizine **5aa** (185.2 mg, 1.0 mmol, 1 equiv.) in anhydrous CH_3CN (1 mL) was prepared under nitrogen atmosphere. Then, freshly recrystallized *N*-bromosuccinimide (178.0 mg, 1.0 mmol, 1 equiv.) was added to the flask under magnetic stirring. The reaction mixture was stirred for 2 hours until complete conversion of starting material, as assessed by TLC analysis. The solvent was removed under reduced pressure, and the residue was directly purified by flash column chromatography (SiO_2) eluting with hexane : ethyl acetate (95 : 5) to give **7** in 32% yield (84.5 mg) as a viscous brown oil. ^{1}H NMR (500 MHz, C_6D_6) δ 6.92 (s, 1H), 6.84 (d, J = 9.2 Hz, 1H), 6.65 (dd, J = 7.2, 1.0 Hz, 1H), 6.20–6.13 (m, 1H), 5.96–5.89 (m, 1H), 4.43–4.38 (m, 1H), 2.42 (ddd, J = 16.0, 9.7, 5.0 Hz, 1H), 1.90–1.84 (m, 1H), 1.79 (ddd, J = 16.0, 5.0, 3.0 Hz, 1H), 1.76–1.69 (m, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 187.2, 133.5, 129.7, 122.2, 121.1, 120.8, 117.9, 112.0, 97.5, 51.0, 32.1, 18.0. HRMS (ESI): m/z calcd for $C_{12}H_{11}BrNO$ $[M + H]^+$: 264.0019, found: 264.0014.

Synthesis of 1-chloro-3,4-dihydropyrido[1,2-*a*]indole-2,10-dicarbaldehyde (8)

In a flame-dried 25 mL round-bottomed flask, phosphorous oxychloride (76.0 μL, 0.81 mmol) was added to anhydrous DMF (2.70 mL, 0.1 M) at 0 °C under a nitrogen atmosphere. After being stirred for 1 h indolizine **5aa** (50.0 mg, 0.27 mmol, 1.0 equiv.) was added and the mixture was stirred for 15 min at 0 °C. The reaction was then heat at 60 °C for 24 h. After cooling, the mixture was quenched with saturated $NaHCO_3$ and the product was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic fraction were washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (SiO_2) eluting with hexane : ethyl acetate (60 : 40) to give **8** in 70% yield (181.8 mg) as a viscous yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.76 (s, 1H), 10.36 (s, 1H), 8.55 (d, J = 9.0 Hz, 1H), 7.84 (d, J = 6.8 Hz, 1H), 7.23 (dd, J = 9.1, 6.6 Hz, 1H), 6.97 (t, J = 6.8 Hz, 1H), 3.15–2.83 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.5, 185.7, 142.7, 137.1, 129.5, 127.2, 125.4, 122.6, 122.3, 121.8, 115.7, 22.3, 18.8. HRMS (ESI): m/z calcd for $C_{14}H_{11}ClNO_2$ $[M + H]^+$: 260.0473, found: 260.0469.

Synthesis of 6,7-dihydropyrido[1′,2′:1,2]indolo[4,5-*b*][1,8]naphthyridine (10)

In a 5 mL round-bottomed flask, **5aa** (185.2 mg, 1.0 mmol, 1 equiv.), 2-amino-3-pyridinecarboxaldehyde **9** (122.1 mg, 1 mmol, 1 equiv.) and MeOH (1 ml) were added sequentially. The solution was magnetically stirred, and solid KOH (112 mg, 2.0 mmol, 2 equiv.) was added in a single portion. The mixture was then heated to 40 °C until complete consumption of the starting material by TLC. After the reaction was complete, the solvent was evaporated, and the mixture was redissolved in dichloromethane. Water was then added (50 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated. The crude was then purified using flash column chromatography (SiO_2) eluting with hexane : ethyl acetate (50 : 50) to give **10** in 62% yield (168.2 mg) as a yellow solid, mp >200 °C (*decomp.*). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.97 (dd, J = 4.2, 2.0 Hz, 1H), 8.01 (dd, J = 8.0, 1.9 Hz, 1H), 7.84 (t, J = 1.2 Hz, 1H), 7.65 (ddd, J = 7.1, 2.1, 1.0 Hz, 1H), 7.43 (dt, J = 9.1, 1.1 Hz, 1H), 7.33 (dd, J = 8.0, 4.3 Hz, 1H), 7.29 (s, 1H), 6.64 (ddd, J = 9.1, 6.4, 1.0 Hz, 1H), 6.55–6.48 (m, 1H), 3.35 (t, J = 7.1 Hz, 1H), 3.14 (t, J = 7.3 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.3, 156.1, 152.4, 136.1, 134.0, 134.0, 130.5, 125.6, 124.1, 121.8, 121.8, 120.9, 120.6, 117.0, 111.3, 96.0, 28.8, 19.7. HRMS (ESI): m/z calcd for $C_{18}H_{14}N_3$ $[M + H]^+$: 272.1182, found: 272.1188.

Reduction of 5aa using $NaBH_4$ (*rac*-11)

A solution of indolizine **5aa** (185.2 mg, 1.0 mmol, 1 mmol) in methanol (10 mL) was prepared in a 25 mL round-bottomed flask. While kept under magnetic stirring, $NaBH_4$ (75.7 mg, 2.0 mmol, 2 equiv.) was added in a single portion. After checking the total consumption of the starting material (TLC), the solvent was removed under reduced pressure, redissolved in diethyl ether (50 mL) and extracted with aq. saturated NH_4Cl (1 × 10 mL), distilled water (2 × 10 mL) and brine (1 × 10 mL). The organic layer was then dried over Na_2SO_4, filtered, and evaporated under reduced pressure to provide the racemic alcohol **11** as a colorless solid in 99% yield (185.4 mg), mp: >100 °C (*decomp.*). ^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.67 (ddd, J = 7.0, 2.0, 1.1 Hz, 1H), 7.37 (dt, J = 9.0, 1.1 Hz, 1H), 6.69–6.63 (m, 1H), 6.54 (ddd, J = 7.0, 6.5, 1.3 Hz, 1H), 6.45 (s, 1H), 4.98 (t, J = 5.0 Hz, 1H), 2.78 (dt, J = 15.6, 6.0 Hz, 1H), 2.73–2.65 (m, 1H),

2.22–2.12 (m, 1H), 2.11–2.03 (m, 1H), 1.99–1.93 (m, 1H), 1.87 (dddd, J = 13.1, 8.3, 5.7, 2.7 Hz, 1H). ^{13}C NMR (151 MHz, CD_2Cl_2) δ 132.0, 126.6, 121.6, 120.5, 118.9, 115.8, 109.7, 95.8, 64.9, 33.2, 21.0, 19.0. HRMS (ESI): m/z calcd for $C_{12}H_{14}NO$ $[M + H]^+$: 188.1070, found: 188.1079.

Synthesis of enantiomerically enriched ((*R*)-11)

A solution of (*S*)-(−)-2-methyl-CBS-oxazaborolidine (277.1 mg, 1.0 mmol, 0.2 equiv.) in anhydrous THF (20 mL) was cooled to −10 °C under N_2 atmosphere. To this solution, using a syringe pump (2 mL per h flow), indolizine **5aa** (926 mg, 5.0 mmol, 1 equiv.) in anhydrous THF (1 mL) was added for 30 minutes. After the addition was complete, the reaction was warmed to rt, was diluted with diethyl ether (100 mL) and was extracted with aq. saturated NH_4Cl (3 × 50 mL), distilled water (2 × 50 ml) and saturated NaCl (1 × 50 mL). The organic layer was then dried over Na_2SO_4, filtered through a pad of silica gel using ethyl acetate and evaporated to provide enantiomerically enriched alcohol (*R*)-**11** as a colorless solid in 90% yield (168.5 mg) and 93% ee determined by HPLC (Chiralpak® IA column, eluting with hexane : 2-propanol (95 : 05), 25 °C, 1 mL min^{-1}). $[\alpha]_D$ = −17 (c = 0.8, $CHCl_3$). Spectral data were identical to those determined for the racemic compound.

Author contributions

Conceptualization, funding acquisition, supervision: AM and FC; investigation: LAZ, LVA, MTR and HS (experimental), RAC and JCP (computational calculations); writing – original draft: all authors; writing – review and editing: AM.

Conflicts of interest

There are no conflicts to declare.

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