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Article

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Catalyst-free conjugate addition of indolizines to *in situ* generated oxidized Morita–Baylis–Hillman adducts

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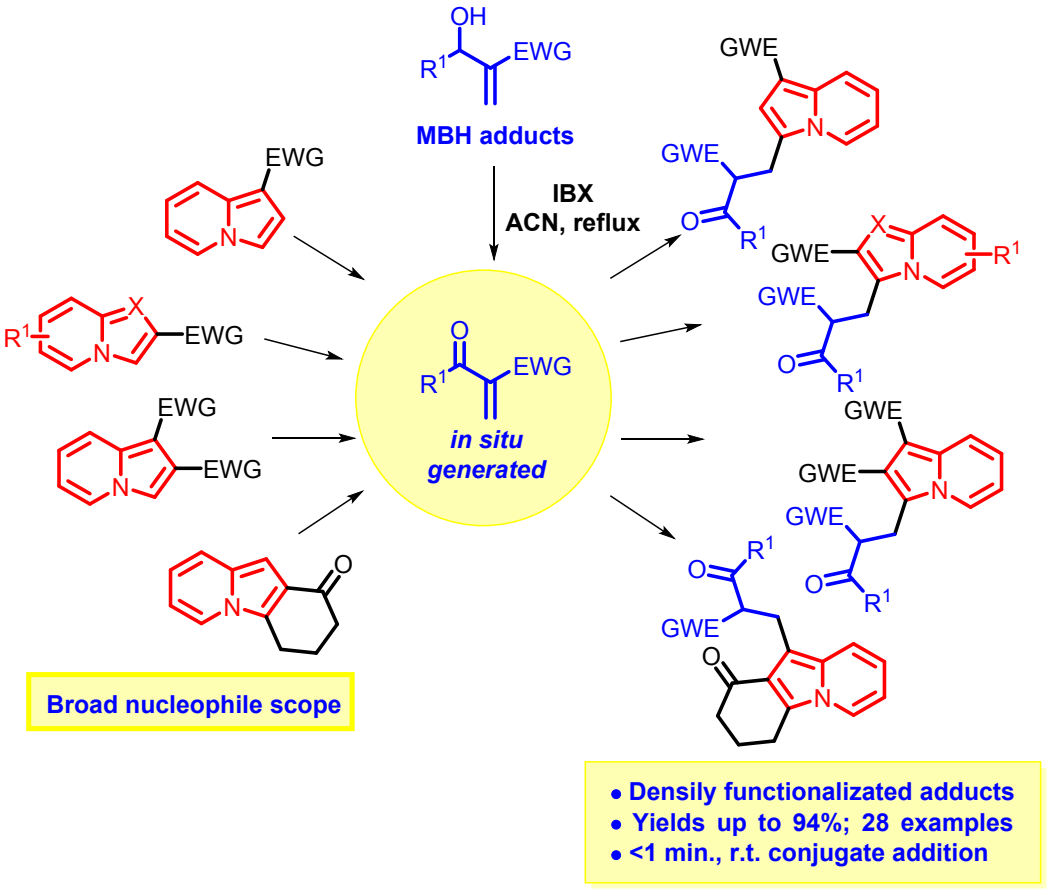
Abstract



A sequential one-pot 2-Iodoxybenzoic acid (IBX) oxidation of Morita–Baylis–Hillman (MBH) adducts followed by catalyst-free indolizine conjugate addition was developed. The wide scopes of MBH adducts and indolizines were investigated, and densely functionalized adducts were obtained in yields of up to 94%. The conjugate addition step occurred in less than a minute at room temperature with total regioselectivity toward indolizine C3 carbon. Less nucleophilic C1 carbon was also alkylated when C3-substituted indolizines were employed as the substrate.

Introduction

Nitrogen heterocycles compounds play a central role in the development of new drugs and materials.[1] Among the heterocycles, indolizines (and their derivatives) are present in a number of molecules and show a wide range of biological activities and fluorescent properties (**Figure 1**),[2–8] thus justifying current efforts toward the development of new methods to synthesize this core.[9]

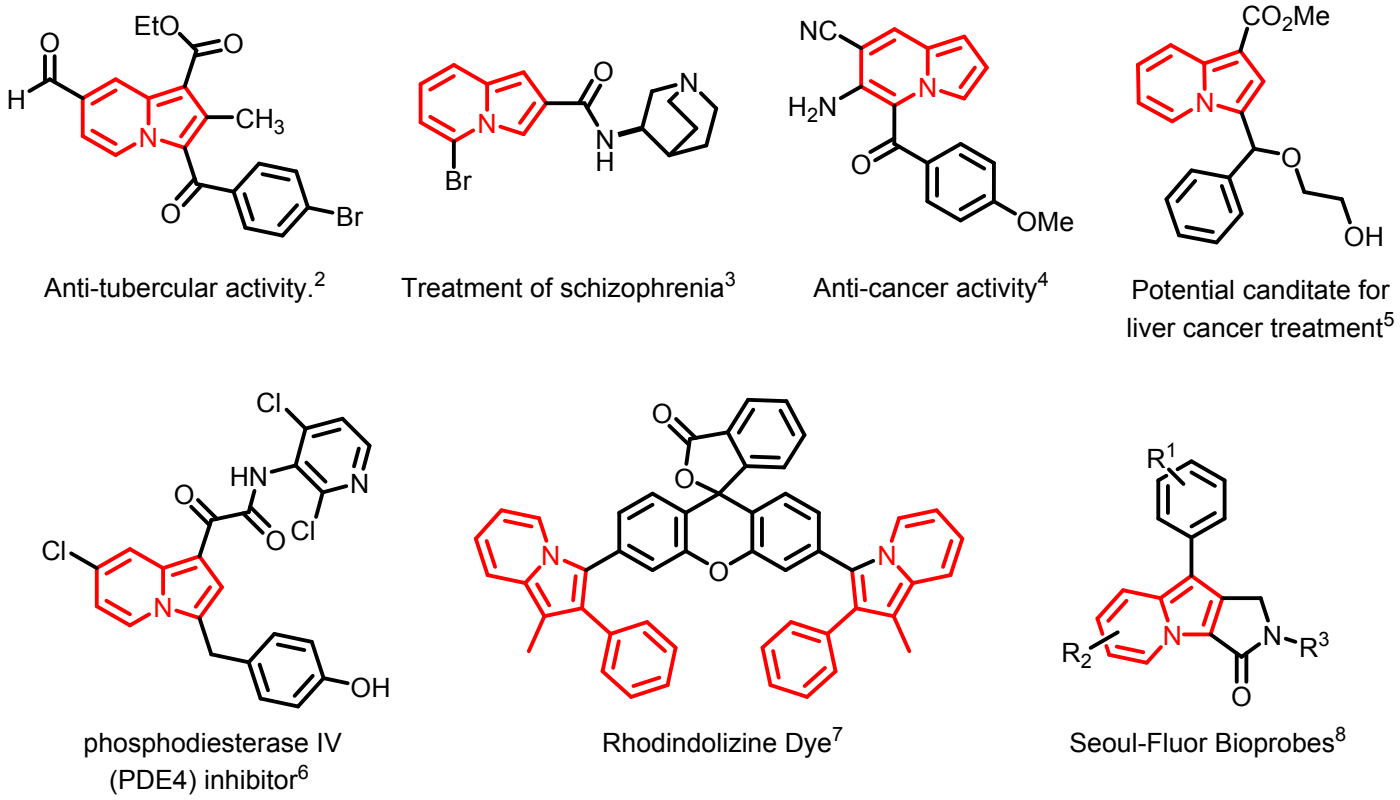


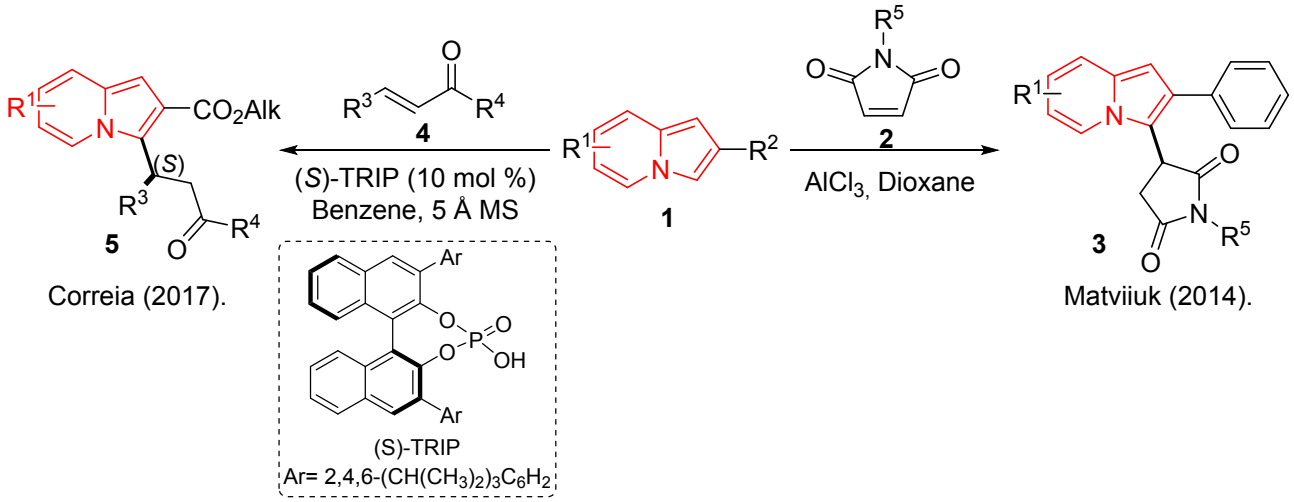
Figure 1. Some examples of bioactive and photo-sensible indolizines.

Equally important is the indolizine late-stage functionalization that enables structural diversity expansion through the formation of new C-C bonds. To do that, transition metals are widely employed in catalyzing arylation,[10] alkenylation,[11] borylation,[12] and propargylation[13] reactions. Metalation reactions provide an alternative route to functionalize indolizines with electrophiles,[14] and more recently, visible-light-induced processes have arisen as a new functionalization strategy.[15] Nevertheless, examples of conjugate addition reactions, a common method to functionalize nitrogenated π-electron-rich heteroaromatic compounds,[16] using indolizines as the nucleophile are still rare.

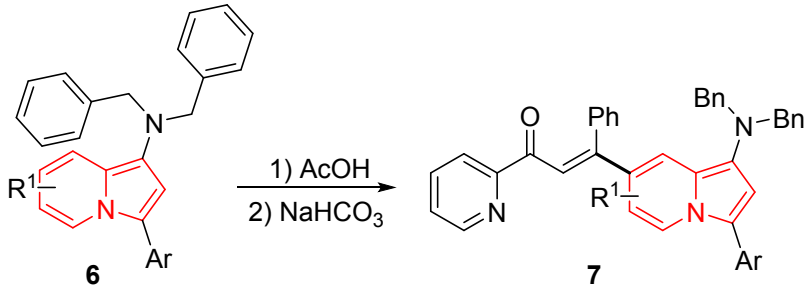
To the best of our knowledge, only three examples in the literature employed indolizines in conjugate additions (**Scheme 1**). The first example, described by Matviiuk *et al.*,[17] used Lewis acid catalysis to activate maleimides **2** toward indolizine conjugate addition. The second example was described by us[18] in collaboration with List's group, using chiral phosphoric acid (*S*)-TRIP as the organocatalyst in conjugate additions to enones. Most recently, an alkenylation protocol that begins with an unusual conjugate addition of indolizine **6** C7 carbon to an *in situ* formed iminium species was reported by Alonso.[19]

Following our research interest in indolizine functionalization,[18,20] we describe herein the use of this heterocycle as a nucleophile in catalyst-free conjugate additions to *in situ* formed Morita–Baylis–Hillman (MBH) ketones by 2-Iodoxybenozic acid (IBX) oxidation of MBH adducts **8** (**Scheme 1**). Previously, Yadav used this strategy to functionalize indoles (**Scheme 1**).[21] However, this approach has a significant drawback since less reactive indoles, such as 2-carboxyethylindole, react poorly in these conditions, as further demonstrated by Gu.[22] Thus, we report herein the successful use of indolizines as nucleophiles in catalyst-free conjugate additions to *in situ* oxidized MBH adducts.

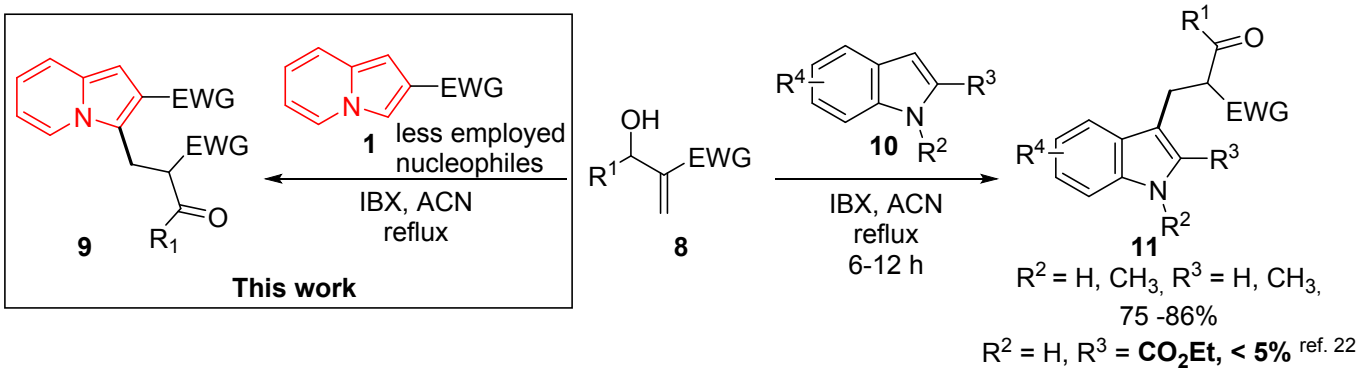
A) Conjugated additions at C3 position of indolizines nucleus.



B) C7 alkenylation of indolizines (Alonso, 2018).



C) Yadav previous work with indoles (2007) and present work with indolizines.

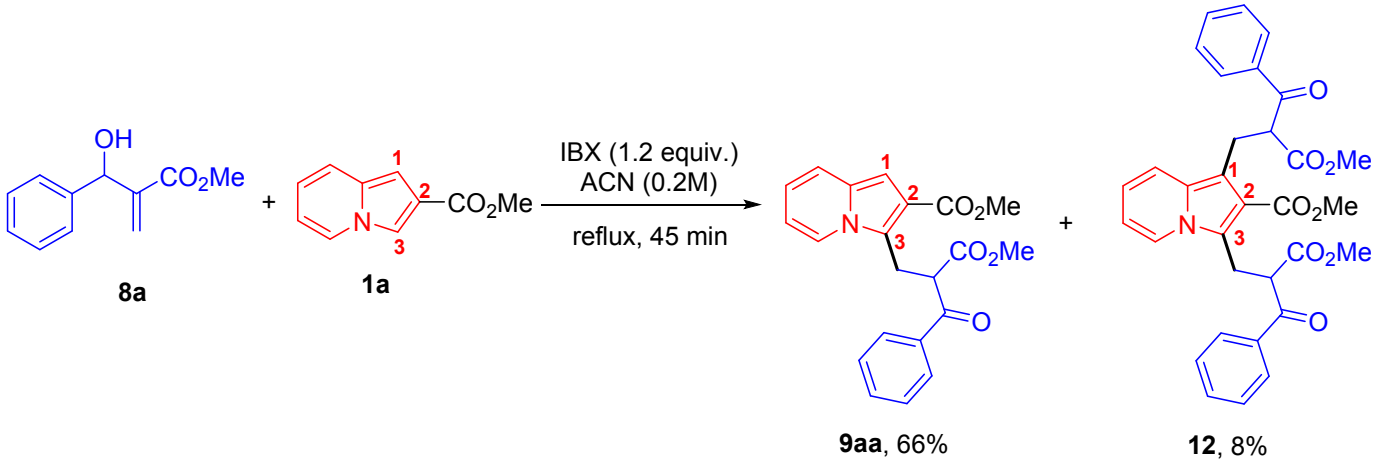


Scheme 1. Some examples of indolizines as nucleophilic partners in conjugate additions (A[17,18] and B[19]); Yadav's previous work with indoles and the present work (C).[21]

Results and Discussion

2-Carboxymethylindolizine (**1a)** was chosen as the nucleophile model. This substrate is quite challenging since it has two free nucleophile positions at C3 and C1, which could, in principle, generate selectivity issues. Moreover, an electron withdrawing group at C2 contributes to decreasing indolzine reactivity toward

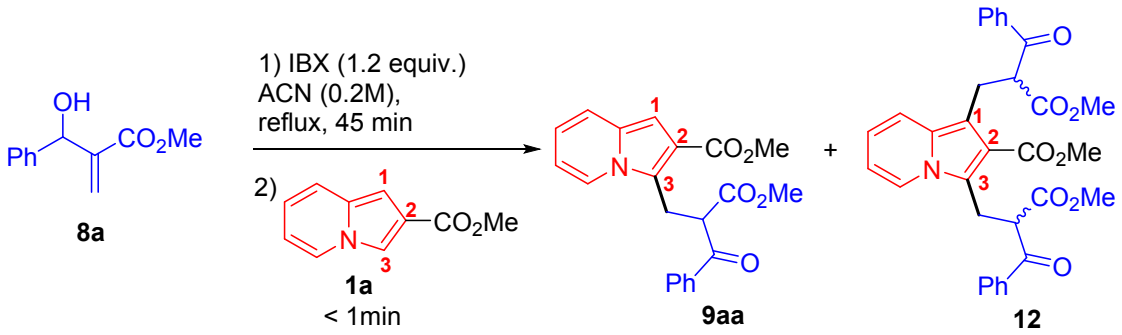
electrophilic aromatic substitutions.[10] We initiate our work using the same experimental protocol described by Yadav.[21] Thus, we added all the reactants and thereafter heated them under reflux (**Scheme 2**). After 45 min, we observed the complete consumption of the starting materials and the formation of the desired conjugate addition product **9aa (**with 66% yield) together with dialkylated by-product **12** (with 8% yield).. The reaction proceeded with high regioselectivity toward the indolizine C3 position. Most probably, the dialkylated product originated from the C3-alkylated product **9aa** since no C1 monoalkylated product was observed or detected. It is noteworthy that the *in situ* formed oxidized MBH adduct was not detected during the course of the reaction, suggesting its prompt consumption.



Scheme 2. Conjugate addition of indolizines to MBH ketones generated *in situ*.

To optimize the yield and minimize the formation of dialkylated product **12**, the reaction was carried out sequentially: MBH adduct **8a** was oxidized first and immediately followed by the addition of indolizine **1a** (**Table 1**, entry 1). Surprisingly, the conjugate addition step was completed in less than a minute and **9aa** was obtained with a better yield (84%). However, by-product **12** was also isolated with a yield of 8%. Attempts to improve the yield of the desired C3 product **9aa** by increasing the number of indolizine equivalents failed (**Table 1**, entries 2 and 3).

Table 1. Optimization study of indolizine conjugate addition.



Entry	Indolizine (equivalent)	T (second step)	Yield (%)[a] 9a	Yield (%)[a] 12[b]
1	1	Reflux	84	8
2	1.2	Reflux	82	n.d.
3	1.5	Reflux	82	n.d.
4	1	r.t.	90	3
5	1	0 °C	89	3
6	1.2	r.t.	94	Traces
7	1.5	r.t.	92	Traces
8	0.4	r.t.	n.d.	98%

The reactions were performed at the 0.2 mmol scale. [a] Isolated and purified products. [b] Yield based on the number of mmols of adduct that were incorporated in the dialkylated product. n.d.: not determined.

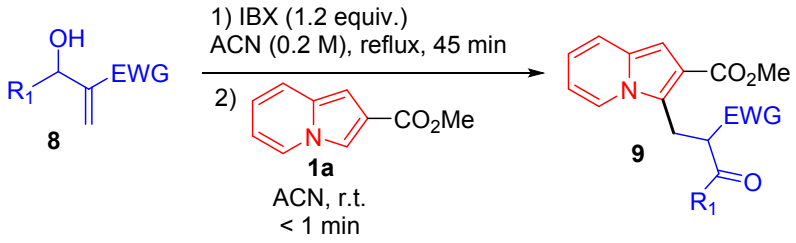
Since the C1 position of indolizine was less nucleophilic than that at C3 ,[10] mild conditions could reduce the formation of the undesired dialkylated **12.** To test this hypothesis, temperature of the second step was lowered to room temperature, and consequently, we observed an increase in the yield of **9aa** (to 90%) with a corresponding decrease in the yield of **12** (to 3%; **Table 1**, entry 4). Lowering the temperature beyond 0 °C did not improve either the yield or the regioselectivity (**Table 1**, entry 5). In both cases, when the temperature was lowered (**Table 1**, entries 4 and 5), we observed no difference in the reaction rate compared

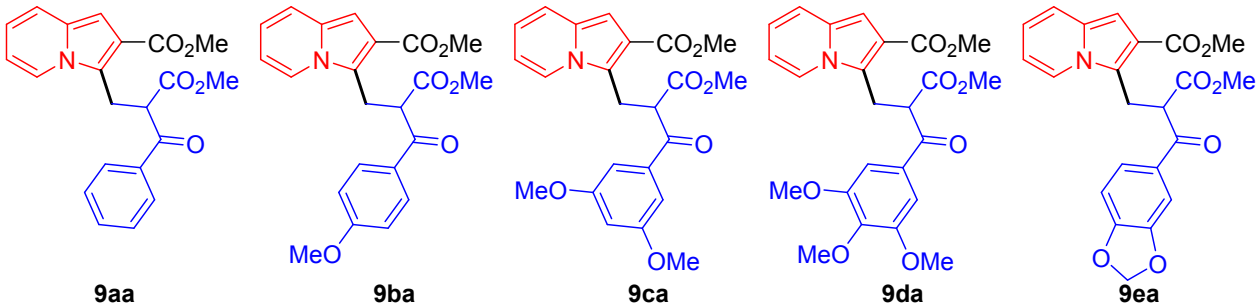
to the reflux reactions in acetonitrile (**Table 1**, entries 1–3). Typically, the catalyst-free Friedel–Crafts-like conjugate additions require refluxing temperatures to proceed.[23] In our case, we believe that the high electrophilicity of the MBH ketones is the likely cause of the observed short reaction time, even at 0 °C.

After obtaining good results by the lowering temperature, we decided to evaluate the influence of the indolizine concentration in the second step (**Table 1**, entries 6–7) of the reaction. Using 1.2 equivalents of indolizine caused the yield to increase from 90% to 94% (**Table 1**, entry 6). No improvement was observed when we further increased the number of equivalents to 1.5 (**Table 1**, entry 7). A decrease in the indolizine equivalents to 0.4 significantly altered the product distribution toward the densely functionalized dialkylated product **12** , (**Table 1**, entry 8), which was obtained with a yield of 98%. Therefore, controlling the concentration of indolizine facilitates the easy progress of the reaction toward monoalkylated or dialkylated compounds.

After identifying the optimized conditions, we evaluated the reaction scope. MBH adducts derived from the reactions between methyl acrylate and substituted benzaldehydes (bearing electron-donating or electron withdrawing substituents in the aromatic portion) were functionalized in good yields (**9aa–9ha**, **Table 2)**. The electronic nature of the substrates appears to have no influence on the reactivity; even the highly electron-rich trimethoxylated adduct **8da** could be successfully functionalized (yield: 88%, compound **9da**, **Table 2**). The MBH adducts with electron withdrawing groups were good substrates for this transformation as they provided excellent yields of the conjugate addition products (**9fa–9ia**, **Table 2**). These adducts would be expected to be more reactive and therefore more prone to suffer C1 alkylation. However, we did not observe this. The MBH adduct derived from furfural resulted in a good yield of the C3 product (**9ja**, **Table 2**). Substrate **8k**, containing a free phenolic hydroxyl group, provided the product with 48% yield (**9k**, **Table 2**). This yield is good if we consider the two transformations involved and the well-known tendency of this particular substrate to suffer phenolic oxidation in the presence of hypervalent iodine reagents.[24]

Table 2. Scope of MBH adducts in the studied transformation.





9aa 94% | **9ba** 95% | **9ca** 84% | **9da** 88% | **9ea** 88%

9fa 85% | **9ga** 91% | **9ha** 96% | **9ia** 85% | **9ja** 83%

9ka 48% | **9la** 92%[a] | **9ma** 73% | **9na** 72%[b]

The reactions were carried out at the 0.2 mmol scale, and the yields refer to isolated and purified products. [a] Just one equivalent of indolizine was used in this case due to the issues associated with purification. [b] The reaction was run at a 0.135 mmol scale.

MBH adducts containing compounds other than methyl esters as the electron withdrawing group were also evaluated (**8i** and **8l-8n**, **Table 2**). The MBH adduct **8i**, which contained ethyl acrylate moiety, furnished the product with 85% yield (**9ia**, **Table 2**). Less reactive *t*-butyl acrylate and acrylamide derivatives also

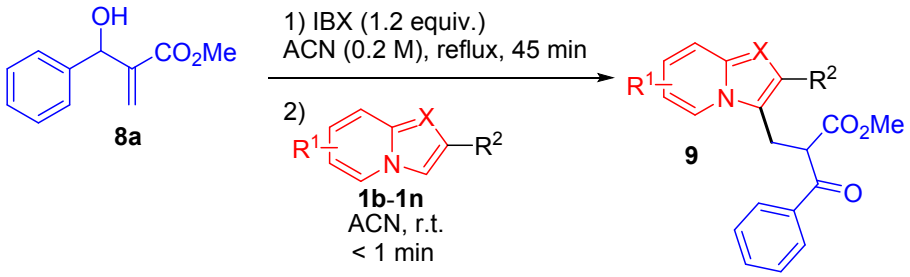
furnished the desired compounds in good yields (**9la** and **9ma**, **Table 2**). The vinyl-oxadiazole MBH adduct **8n**, which belongs to a class of MBH adducts recently discovered by our group,[25] was successfully employed as the electrophile partner in this conjugate addition, resulting in rapid formation of the molecular-hybridized compound **9na** with two biologically important heterocycles (**Table 2**).[26]

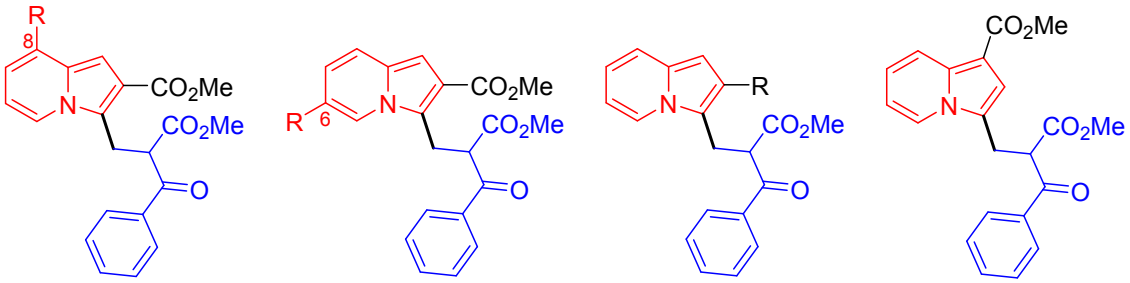
The substitution pattern in the indolizine structure was evaluated next. We began this part of our study by changing the substitution pattern at the pyridine subunit. In general, 2-carboxylindolizines containing donor or electron withdrawing groups in positions 6 or 8 gave products with moderate to excellent yields (compounds **9ab–9ag**, **Table 3**). These results are the opposite of those of our previous work, where substitutions at pyridine moiety resulted in a pronounced decrease in the indolizine conjugate addition reactivity toward enones.[18] Others substituents at C2 in indolizine were well tolerated, including a bulky *t*-butyl ester and less electron attracting groups, such as cyano and phenyl compounds (**9ah–9aj**, **Table 3**). C1 and C1-C2 substituted indolizines were good substrates to these transformations; in these cases, just one equivalent of nucleophile was employed since only the C3 site was free to react (compounds **9ak–9al**, **Table 3**).

The high reactivity of indolizine toward oxidized MBH adducts and the previous observation that even the less nucleophilic C1 carbon could be functionalized encouraged us to attempt using a polycyclic indolizine **1m** C3 and C2 substituted as the substrate for this reaction. In this case, only the C1 position was free, and the nucleophile contained a ketone group conjugated with the heteroaromatic system, which has a much higher electron attracting potential than the other known groups so far. Fortunately, the functionalization at C1 resulted in **9am** with 91% yield, once again in less than a minute (**Table 3**).

Due to the biological importance of imidazopyridines and their C3-derived compounds,[27] 2-phenylimidazopyridine (**1n**) was tested in our conjugate addition protocol. The reaction proceeded very well, furnishing the valuable C3-functionalized heteroaromatic compound **9an** with 84% yield (**Table 3**). Notably, in this case, the reaction no longer evolved after 1 min, and the unreacted MBH-oxidized adduct was recovered.

Table 3. Scope of indolizine derivatives.



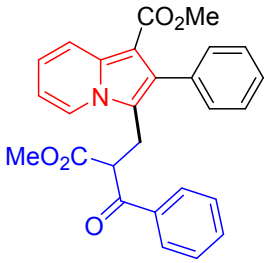


9ab, R = F, 79%
9ac, R = Me, 92%
9ad, R = OMe, 62%

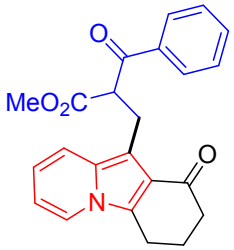
9ae, R = Me, 80%
9af, R = Cl, 95%
9ag, R = Br, 91%

9ah, R = CO_2*t*Bu, 92%
9ai, R = CN, 89%
9aj, R = Ph, 85%

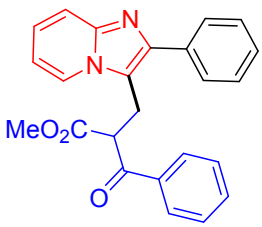
9ak, 86%[a]



9al
78%[a]



9am
91%[a]

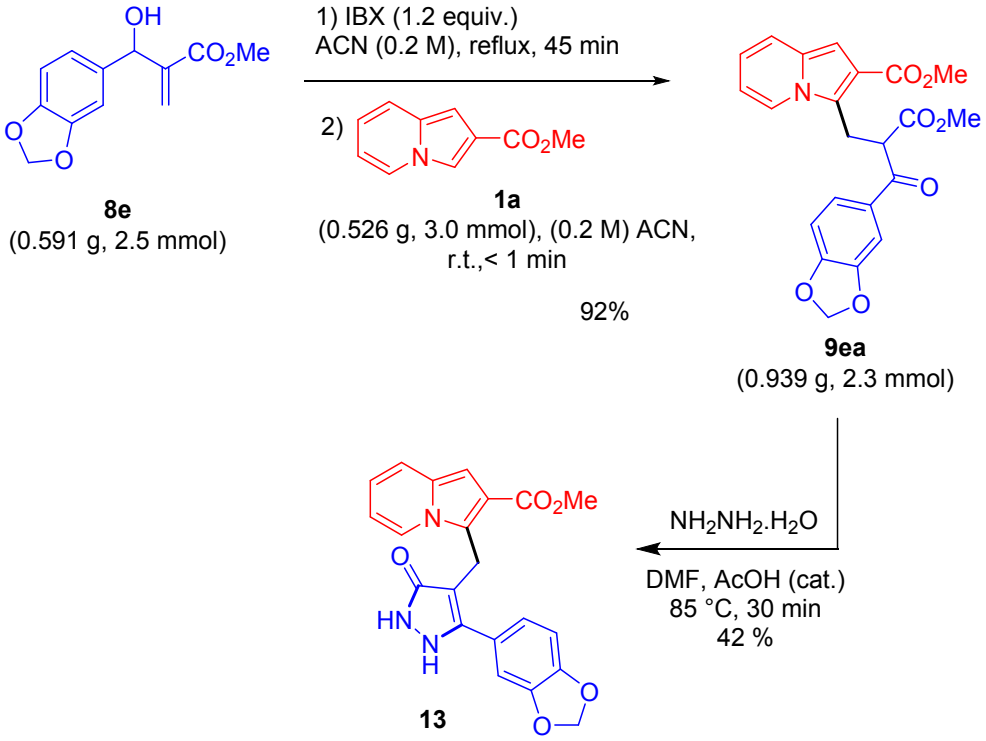


9an
84% (93% bsrm)[a]

The reactions were carried out at the 0.2 mmol scale, and the yields refer to isolated and purified products. [a] In these cases, one equivalent of indolizine was used.

To demonstrate the robustness of this transformation, we ran a gram-scale experiment at 2.5 mmol scale (a scale that was 12.5 times higher than that of the previous attempt) using MBH adduct **8e** and indolizine **1a** to produce **9ea** with 92% yield (**Scheme 3**). The yield of this reaction was higher than that of the reaction run at the 0.2 mmol scale (92% vs 88%, see compound **9ea** in **Table 2**). The synthetic usefulness of the new indolizine tethered β-keto esters was further demonstrated by the synthesis of pyrazolone **13** through

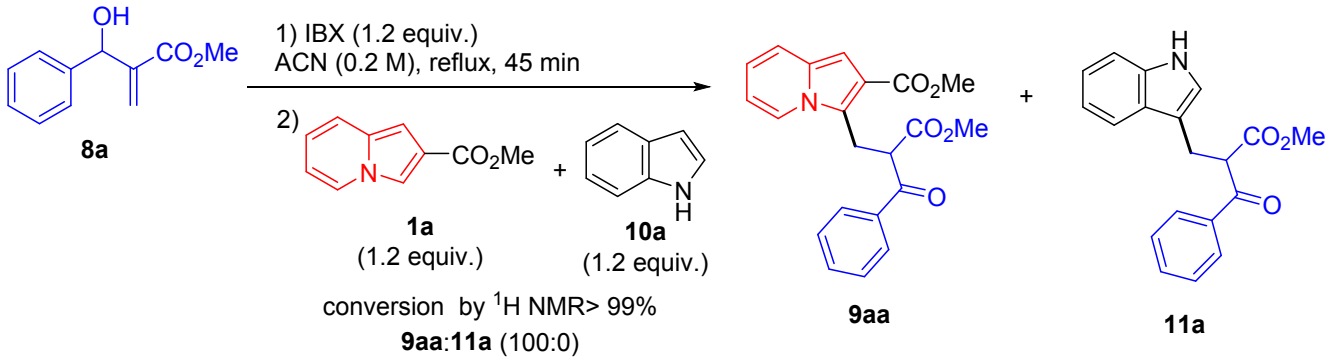
the reaction of poly-functionalized indolizine **9ea** with hydrazine hydrate in the presence of acetic acid (**Scheme 3**). It resulted in a pyrazolone–indolizine hybrid with an unprecedented substitution pattern.



Scheme 3. Gram-scale synthesis of indolizine conjugate addition adduct **9ea** and synthesis of a new disubstituted pyrazolone (0.15 mmol scale).

The exceptionally shorter reaction time observed in these conjugate addition reactions using indolizines as nucleophiles intrigued us since the two previous works with indoles reported longer reaction times (6–12 h) for the same electrophiles under reflux conditions.[21,28] Using the experimental conditions developed by us (see Experimental Section), the adduct generated from the indole conjugate addition **9aa** was obtained with 75% yield. This yield is comparable to those obtained by Santos[28] and Yadav (80%).[21] The fast reaction time observed in the indole conjugate addition does not allow a direct nucleophilicity comparison between indolizine **1a** and indole (**11a**). Thus, we ran a competitive experiment. We carried out an essay by adding simultaneously indole and indolizines to the oxidized MBH adduct obtained from **8a** (**Scheme 4**). Indolizine proved to be a superior nucleophile in these conditions since only the formation of the conjugated adduct **9aa** was observed (see SI, pages S62–S63).

It is worth noting that this conjugate addition reaction occurs without any catalyst.[36] Therefore, the bifunctional activation effect observed when N-H free indoles are nucleophiles is absent, allowing a direct nucleophilicity comparison with indolizine.[18,29,30] Recently, Zhang also demonstrated that indolizine **1a** is a better nucleophile than *N*-methyl indole in a copper-catalyzed asymmetric propargylation reaction.[13]



Scheme 4. Competitive conjugate addition between indole (**11a**) and indolizine **8a**.

Conclusion

In summary, we disclosed herein fast, mild, and atom-efficient post-functionalization of indolizines through a Friedel–Crafts-like conjugated addition reaction using oxidized MBH adducts. The use of a *sequential one-pot* strategy proved to be crucial in achieving better yields, allowing us to obtain highly functionalized indolizines even at room temperature in less than a minute. We expanded this oxidative-conjugate addition to MBH adducts derived from *t*-butyl acrylate, acrylamide, and especially vinyl-oxadiazole, thus facilitating the synthesis of new heterocycle assemblies with potential biological activity.

Indolizines with different substitution patterns were functionalized to provide good to excellent yields, and the resulting conjugated adduct was readily transformed into a pyrazolone–indolizine hybrid. The reactions were very regioselective toward C3 in indolizine, but when this position was unavailable, C1 carbon was also alkylated without any detectable loss in reactivity. The indolizine–indole relative nucleophilicity was investigated, and indolizine appeared to be a superior nucleophile in our conditions. Studies to evaluate the synthetic versatility of these highly functionalized indolizine conjugate adducts are ongoing in our

laboratory and the results will be disclosed in the due time. Apparently, these adducts can be used as building blocks for the synthesis of new bioactive molecules and fluorescent probes.

Experimental Section

Commercially available chemicals and solvents were used without further purification unless otherwise noted. All reactions were performed under ambient atmosphere in oven-dried open-flask glassware with magnetic stirring. Reaction progress was monitored by thin-layer chromatography (TLC) performed on silica gel (aluminum foils). The TLC plates were visualized with UV light (254 nm and/or 365 nm) and sulfuric vanillin followed by heating. Products purification were carried out by flash column chromatography using silica gel (230–400 mesh). ^{1}H NMR and proton-decoupled ^{13}C NMR spectra were measured at 250, 400,500 or 600 MHz for ^{1}H NMR and 63, 101, 126 or 151 MHz for ^{13}C NMR, in $CDCl_3$ and DMSO-d_6 at room temperature. Chemical shifts (δ) were reported in ppm and the coupling constants (*J*) in Hertz (Hz). Signal multiplicity was assigned as singlet (s), doublet (d), double doublet (dd), double triplet (dt), double of double doublet (ddd), triplet (t), triple doublet (td), multiplet (m), and broad singlet (bs). High-resolution mass spectrometry (HRMS) was performed using electrospray ionization (ESI) (Hybrid Quadrupole Orbitrap). Melting points measured and were corrected. All starting materials, MBH adducts and indolizines, were known compounds and synthesized according previous reports: MBH adducts **8a-8l**;[31] MBH adduct **8m**;[32] MBH adduct **8n**;[25] indolizines **1a-1i;**[3] indolizines **1j** and **1n**;[33] **1k** and **1l**;[34] **1m**.[35]

General Procedure A for the Synthesis of Indolizine Conjugated Adducts. *Typical procedure for a 0.2 mmol reaction scale*: To a 5 mL round-bottom flask, 2-iodoxybenzoic acid (IBX) (67.2 mg (0.240 mmol), 1.2 equiv.) was added to a 0.2 M solution of MBH adduct **8** (0.20 mmol, 1 equiv.) in acetonitrile. The solution was refluxed in an oil bath for 45 min and the complete consumption of the starting material was monitored by TLC (the oxidized adduct appears as a spot with higher Rf). After this time, the flask was removed from heating, cooled to room temperature and a 0.1 M solution of indolizine **1** (1.2 equiv.) in

acetonitrile was added. The resulting solution was stirred open to air and reaction monitored by TLC at intervals of 1 min, 2.5 min and 5 min (no progress was observed after one minute). The reaction mixture was filtered, solvent removed under reduced pressure and the residue purified by column chromatography.

Methyl 3-(2-benzoyl-3-methoxy-3-oxopropyl)indolizine-2-carboxylate (**9aa**). Following general procedure **A**, starting from 38.4 mg (0.20 mmol) of MBH adduct **8a**, compound **9aa** was obtained as a high viscous yellow oil (68.7 mg, 94% yield). Purification: 10%-15% AcOEt/Hexane. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.19 – 8.08 (m, 1H), 7.98 – 7.91 (m, 2H), 7.60 – 7.46 (m, 1H), 7.45 – 7.35 (m, 2H), 7.31 – 7.23 (m, 1H), 6.77 (s, 1H), 6.68 – 6.53 (m, 2H), 5.18 (t, J = 7.4 Hz, 1H), 4.24 – 3.73 (m, 5H), 3.58 (s, 3H). ^{13}C {^{1}H} NMR (63 MHz, $CDCl_3$) δ: 195.6, 170.0, 166.1, 136.0, 133.7, 132.0, 128.9, 128.7, 125.0, 123.1, 120.2, 117.8, 116.9, 112.1, 101.0, 52.7, 52.7, 51.5, 24.4. HRMS (ESI, *m*/*z*): Calcd. for $C_{21}H_{19}NO_5K^+$ 404.0895 $[M + K]^+$, found 404.0871.

Methyl 3-(3-methoxy-2-(4-methoxybenzoyl)-3-oxopropyl)indolizine-2-carboxylate (**9ba**). Following general procedure **A**, starting from 44.3 mg (0.200 mmol) of MBH adduct **8b,** compound **9ba** was obtained as a high viscous yellow oil. (75.0 mg, 95% yield). Purification: 20%-30% AcOEt/Hexane. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.15 (d, J = 7.1 Hz, 1H), 7.95 (d, J = 8.5 Hz, 2H), 7.26 (d, J = 9.0 Hz, 1H), 6.87 (d, J = 8.6 Hz, 2H), 6.78 (s, 1H), 6.70 – 6.50 (m, 2H), 5.13 (t, J = 7.4 Hz, 1H), 3.94 – 3.70 (m, 8H), 3.58 (s, 3H). ^{13}C {^{1}H} NMR (63 MHz, $CDCl_3$) δ: 194.0, 170.3, 166.1, 164.1, 132.0, 131.4, 129.1, 125.3, 123.3, 120.2, 117.8, 116.8, 113.9, 112.0, 101.0, 55.6, 52.6, 52.4, 51.5, 24.5. HRMS (ESI, *m*/*z*): Calcd for $C_{22}H_{21}NO_6Na^+$ 418.1261 $[M + Na]^+$, found 418.1259.

Methyl 3-(2-(3,5-dimethoxybenzoyl)-3-methoxy-3-oxopropyl)indolizine-2-carboxylate (**9ca**). Following general procedure A starting from 50.9 mg (0.202 mmol) of MBH adduct **8c**, compound **9ca** was obtained as a high viscous yellow (71.8 mg, 84 % yield). Purification: 20%-30% AcOEt/Hexane. ^{1}H NMR (400

MHz, $CDCl_3$) δ: 8.13 (d, J = 7.2 Hz, 1H), 7.30 – 7.26 (m, 1H), 7.12 (d, J = 2.3 Hz, 2H), 6.78 (s, 1H), 6.67 – 6.55 (m, 3H), 5.13 (t, J = 7.5 Hz, 1H), 3.87 (s, 3H), 3.85 – 3.73 (m, 8H), 3.59 (s, 3H). ^{13}C {^1H} NMR (63 MHz, $CDCl_3$) δ: 195.6, 170.1, 166.1, 160.9, 137.9, 132.0, 125.0, 123.2, 120.2, 117.8, 116.9, 112.1, 106.8, 106.4, 101.0, 55.7, 52.8, 52.7, 51.5, 24.6. HRMS (ESI, *m*/*z*): Calcd for $C_{23}H_{24}NO_7^+$ 426.1547 [M + H]$^+$, found 426.1570.

Methyl 3-(3-methoxy-3-oxo-2-(3,4,5-trimethoxybenzoyl)propyl)indolizine-2-carboxylate (**9da**). Following general procedure **A** starting from 57.0 mg (0.201 mmol) of MBH adduct **8d**, compound **9da** was obtained as a high viscous yellow oil (80.7 mg, 88 % yield). Purification: 20%-40% AcOEt/Hexane. ^1H NMR (250 MHz, $CDCl_3$) δ: 8.16 – 8.08 (m, 1H), 7.33 – 7.21 (m, 3H), 6.77 (s, 1H), 6.71 – 6.51 (m, 2H), 5.20 (t, J = 7.6 Hz, 1H), 3.89 – 3.85 (m, 9H), 3.78 (d, J = 7.8 Hz, 2H), 3.60 (s, 2H). ^{13}C {^1H} NMR (63 MHz, $CDCl_3$) δ: 195.1, 170.3, 166.2, 153.1, 143.2, 132.1, 131.1, 125.1, 123.3, 120.2, 117.9, 116.8, 112.1, 106.5, 101.0, 61.0, 56.4, 52.7, 52.4, 51.5, 24.9. HRMS (ESI, *m*/*z*): Calcd for $C_{24}H_{25}NO_8Na^+$ [M + Na]$^+$ 478.1472, found 478.1469.

Methyl 3-(3-(benzo[d][1,3]dioxol-5-yl)-2-(methoxycarbonyl)-3-oxopropyl)indolizine-2-carboxylate (**9ea**). Following general procedure **A** starting from 47.2 mg (0.200 mmol) of MBH adduct **8e**, compound **9ea** was obtained as a yellow solid (71.8 mg, 88 % yield). mp: 118-120 °C Purification: 20%-30% AcOEt/Hexane. ^1H NMR (250 MHz, $CDCl_3$) δ: 8.14 (d, J = 7.1 Hz, 1H), 7.59 (dd, J = 8.3, 1.8 Hz, 1H), 7.44 – 7.42 (m, 1H), 7.33 – 7.20 (m, 1H), 6.83 – 6.74 (m, 2H), 6.71 – 6.49 (m, 2H), 6.00 (s, 2H), 5.09 (t, J = 7.4 Hz, 1H), 3.88 (s, 3H), 3.85 – 3.71 (m, 2H), 3.58 (s, 3H). ^{13}C {^1H} NMR (63 MHz, $CDCl_3$) δ: 193.6, 170.1, 166.1, 152.5, 148.3, 132.0, 130.9, 125.8, 125.2, 123.2, 120.2, 117.8, 116.8, 112.0, 108.5, 108.0, 102.1, 101.0, 52.7, 52.5, 51.5, 24.6. HRMS (ESI, *m*/*z*): Calcd for $C_{22}H_{19}NO_7Na^+$ 432.1054 [M + Na]$^+$, found 432.1062.

Methyl 3-(2-(4-fluorobenzoyl)-3-methoxy-3-oxopropyl)indolizine-2-carboxylate (**9fa**). Following general procedure **A**, starting from 42.1 mg (0.200 mmol) of MBH adduct **8f**, compound **9fa** was obtained as a high viscous yellow oil (65.5 mg, 85 % yield). Purification: 5%-20% AcOEt/Hexane. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.14 (d, J = 7.1 Hz, 1H), 8.04 – 7.94 (m, 2H), 7.33 – 7.21 (m, 1H), 7.15 – 6.98 (m, 2H), 6.77 (s, 1H), 6.70 – 6.53 (m, 2H), 5.16 (t, J = 7.4 Hz, 1H), 3.88 (s, 3H), 3.86 – 3.73 (m, 2H), 3.59 (s, 3H). ^{13}C {^{1}H} NMR (63 MHz, $CDCl_3$) δ: 194.2, 169.9, 166.2 (d, $J_{F\text{-}C}$ = 256.1 Hz), 166.1, 132.4 (d, $J_{F\text{-}C}$ = 3.0 Hz), 132.0, 131.7 (d, $J_{F\text{-}C}$ = 9.5 Hz), 124.9, 123.1, 120.2, 117.8, 116.9, 115.9 (d, $J_{F\text{-}C}$ = 22.0 Hz), 112.1, 101.0, 52.7, 52.6, 51.5, 24.4. HRMS (ESI, *m*/*z*): Calcd for $C_{21}H_{19}FNO_5^+$ 384.1242 $[M + H]^+$, found 384.1228.

Methyl 3-(2-(4-chlorobenzoyl)-3-methoxy-3-oxopropyl)indolizine-2-carboxylate (**9ga**). Following general procedure **A**, starting from 45.4 mg (0.200 mmol) of MBH adduct **8g**, compound **9ga** was obtained as a high viscous yellow oil (69.8 mg, 91 % yield). Purification: 5%-10% AcOEt/Hexane. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14 – 8.11 (m, 1H), 7.92 – 7.86 (m, 2H), 7.41 – 7.35 (m, 2H), 7.29 – 7.24 (m, 1H), 6.77 (s, 1H), 6.64 (ddd, J = 9.0, 6.4, 0.8 Hz, 1H), 6.61 – 6.55 (m, 1H), 5.15 (t, J = 7.5 Hz, 1H), 3.88 – 3.81 (m, 4H), 3.78 (dd, J = 14.9, 7.3 Hz, 1H), 3.59 (s, 3H). ^{13}C {^{1}H} NMR (63 MHz, $CDCl_3$) δ: 194.6, 169.8, 166.1, 140.3, 134.3, 132.0, 130.3, 129.0, 124.8, 123.0, 120.2, 117.8, 116.8, 112.1, 101.0, 52.7, 52.7, 51.5, 24.4. HRMS (ESI, *m*/*z*): Calcd for $C_{21}H_{18}ClNO_5Na^+$ 422.0766 [M + Na], found 422.0796.

Methyl 3-(2-(4-bromobenzoyl)-3-methoxy-3-oxopropyl)indolizine-2-carboxylate (**9ha**). Following general procedure **A**, starting from 54.5 mg (0.201 mmol) of MBH adduct **8h**, compound **9ha** was obtained as a high viscous yellow oil (86.0 mg, 96 % yield). Purification: 5%-20% AcOEt/Hexane. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.13 (d, J = 7.1 Hz, 1H), 7.81 (d, J = 8.5 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.32 – 7.22 (m, 1H), 6.77 (s, 1H), 6.70 – 6.50 (m, 2H), 5.15 (t, J = 7.4 Hz, 1H), 3.88 (s, 3H), 3.85 – 3.71 (m, 2H), 3.59 (s, 3H). ^{13}C {^{1}H} NMR (63 MHz, $CDCl_3$) δ: 194.8, 169.8, 166.1, 134.7, 132.0, 130.4, 129.2, 124.8, 123.1, 120.2,

117.8, 116.9, 112.1, 101.0, 52.8, 52.7, 51.5, 24.4. HRMS (ESI, *m*/*z*): Calcd for $C_{21}H_{18}BrNO_5Na^+$ 466.0261 $[M + Na]^+$, found 466.0265.

Methyl 3-(3-ethoxy-2-(4-nitrobenzoyl)-3-oxopropyl)indolizine-2-carboxylate (**9ia**). Following general procedure **A**, starting from 48.0 mg (0.191 mmol) of MBH adduct **8i**, compound **9ia** was obtained as a high viscous yellow oil (69.0 mg, 85 % yield). Purification: 10%-20% AcOEt/Hexane. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.24 (d, J = 8.5 Hz, 2H), 8.16 – 8.06 (m, 3H), 7.31 – 7.24 (m, 1H), 6.77 (s, 1H), 6.73 – 6.54 (m, 2H), 5.21 (t, J = 7.5 Hz, 1H), 4.10 – 3.98 (m, 2H), 3.92 – 3.72 (m, 5H), 1.04 (t, J = 7.1 Hz, 3H). ^{13}C {^{1}H} NMR (63 MHz, $CDCl_3$) δ: 194.8, 168.9, 166.2, 150.6, 140.6, 132.1, 129.8, 124.6, 123.8, 123.0, 120.3, 118.0, 116.9, 112.3, 101.1, 62.0, 53.4, 51.6, 24.2, 13.9. HRMS (ESI, *m*/*z*): Calcd for $C_{22}H_{20}N_2O_7Na^+$ 447.1163 [M + Na], found 447.1190.

Methyl 3-(2-(furan-2-carbonyl)-3-methoxy-3-oxopropyl)indolizine-2-carboxylate (**9ja**). Following general procedure **A**, starting from 36.5 mg (0.201 mmol) of MBH adduct **8j**, compound **9ja** was obtained as a viscous yellow oil (59.4 mg, 83 % yield). Purification: 10%-20% AcOEt/Hexane. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.13 (d, J = 7.1 Hz, 1H), 7.55 (d, J = 1.3 Hz, 1H), 7.34 – 7.25 (m, 2H), 6.79 (s, 1H), 6.69 – 6.55 (m, 2H), 6.49 (dd, J = 3.6, 1.6 Hz, 2H), 4.88 (t, J = 7.4 Hz, 1H), 3.88 (s, 3H), 3.89 – 3.74 (m, 2H), 3.62 (s, 3H). ^{13}C {^{1}H} NMR (63 MHz, $CDCl_3$) δ: 183.5, 169.6, 166.0, 151.7, 147.7, 132.0, 124.8, 123.1, 120.1, 119.8, 117.8, 116.8, 112.7, 112.1, 101.0, 53.1, 52.7, 51.5, 24.0. HRMS (ESI, *m*/*z*): Calcd for $C_{19}H_{17}NO_6Na^+$ 378.0948 $[M + Na]^+$, found 378.0928.

Methyl 3-(2-(4-hydroxybenzoyl)-3-methoxy-3-oxopropyl)indolizine-2-carboxylate (9**ka**). Following general procedure **A** starting from 41.67 mg (0.200 mmol) of MBH adduct **8k**, compound **9ka** was obtained as a pale green oil (36.8 mg, 48% yield). *Note*: the reaction rapidly turns reddish during the first step. Purification: 30%-40% AcOEt/Hexane. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.12 (d, J = 7.2 Hz, 1H), 7.83 (d, J

=z 8.6 Hz, 2H), 7.29 – 7.23 (m, 1H), 7.10 (bs, 1H), 6.79 – 6.75 (m, 3H), 6.65 – 6.61 (m, 1H), 6.58 – 6.54 (m, 1H), 5.09 (t, J = 7.4 Hz, 1H), 3.92 – 3.84 (m, 4H), 3.79 (dd, J = 14.8, 7.2 Hz, 1H), 3.57 (s, 3H). ^{13}C {^{1}H} NMR (63 MHz, $CDCl_3$) δ: 194.0, 170.5, 166.7, 161.6, 132.1, 131.7, 128.6, 125.3, 123.1, 120.2, 117.9, 116.6, 115.6, 112.2, 101.1, 52.8, 52.4, 51.8, 24.5. HRMS (ESI, *m*/*z*): Calcd for $C_{21}H_{19}NO_6K^+$ 420.0844 [M + K]$^+$, found 420.0834.

Methyl 3-(2-benzoyl-3-(tert-butoxy)-3-oxopropyl)indolizine-2-carboxylate (**9la**). Following general procedure **A**, starting from 47.0 mg (0.201 mmol) of MBH adduct **8l** and adding 35.1 mg (0.201 mmol) of indolizine **1a** (35.2 mg (0.201 mmol) in a second step, compound **9la** was obtained as a viscous yellow oil (75.5 mg, 92% yield). Purification: 10% AcOEt/Hexane. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.14 (d, J = 7.1 Hz, 1H), 7.96 – 7.86 (m, 2H), 7.56 – 7.45 (m, 1H), 7.45 – 7.32 (m, 2H), 7.29 – 7.24 (m, 1H), 6.78 (s, 1H), 6.68 – 6.52 (m, 2H), 5.01 (t, J = 7.5 Hz, 1H), 3.89 – 3.83 (m, 4H), 3.78 (dd, J = 14.8, 7.5 Hz, 1H), 1.19 (s, 9H). ^{13}C {^{1}H} NMR (63 MHz, $CDCl_3$): δ 195.8, 168.6, 166.0, 136.4, 133.4, 131.9, 128.7, 128.5, 125.4, 123.3, 120.1, 117.6, 116.9, 112.0, 101.0, 82.1, 54.2, 51.4, 27.7, 23.9. HRMS (ESI, *m*/*z*): Calcd for $C_{24}H_{25}NO_5Na^+$ 430.1625 [M + Na]$^+$, found 430.1634.

Methyl 3-(3-amino-2-benzoyl-3-oxopropyl)indolizine-2-carboxylate (**9ma**). Following general procedure **A**, starting from 35.4 mg (0.200 mmol) of MBH adduct **8m**, compound **9ma** was obtained as a white solid (51.0 mg, 73% yield). M.p: 185-186 ºC Purification: 50%-80% AcOEt/Hexane. ^{1}H NMR (400 MHz, DMSO) δ: 8.19 – 8.14 (m, 1H), 8.03 – 7.96 (m, 2H), 7.67 – 7.58 (m, 1H), 7.56 (bs, 1H), 7.54 – 7.45 (m, 2H), 7.45 – 7.38 (m, 1H), 7.04 (bs, 1H), 6.77 (s, 1H), 6.72 (ddd, J = 9.0, 6.4, 1.0 Hz, 1H), 6.68 – 6.60 (m, 1H), 4.76 (t, J = 7.0 Hz, 1H), 3.78 (s, 3H), 3.78 – 3.71 (m, 2H). ^{13}C {^{1}H} NMR (126 MHz, DMSO) δ: 195.26, 169.99, 165.09, 135.79, 133.40, 131.13, 128.64, 128.26, 125.98, 123.49, 119.81, 117.77, 116.06, 111.80, 100.41, 53.91, 51.13, 23.85. HRMS (ESI, *m*/*z*): Calcd for $C_{20}H_{19}N_2O_4^+$ 351.1339 [M + H]$^+$, found 351.1325.

Methyl 3-(3-(4-chlorophenyl)-3-oxo-2-(3-phenyl-1,2,4-oxadiazol-5-yl)propyl)indolizine-2-carboxylate (**9na**). Following general procedure **A**, starting from 42.1 mg (0.135 mmol) of MBH adduct **8n**, compound **9na** was obtained as a yellow solid (47.0 mg, 72% yield). mp.: 119-121 °C. Purification: 5%-10% AcOEt/Hexane. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.18 (dd, J = 7.4, 1.0 Hz, 1H), 8.01 – 7.93 (m, 4H), 7.50 – 7.37 (m, 5H), 7.30 – 7.23 (m, 1 H), 6.79 (s, 1H), 6.63 (ddd, J = 9.0, 6.5, 1.1 Hz, 1H), 6.61 – 6.53 (m, 1H), 5.88 (t, J = 7.5 Hz, 1H), 4.12 (dd, J = 14.8, 7.2 Hz, 1H), 4.05 (dd, J = 14.8, 8.0 Hz, 1H), 3.91 (s, 3H). ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ: 193.28, 176.15, 168.59, 166.18, 140.79, 133.64, 132.20, 131.36, 130.43, 129.23, 128.84, 127.60, 126.49, 123.84, 122.96, 120.28, 117.98, 117.21, 112.25, 101.26, 51.67, 45.55, 25.69. HRMS (ESI, *m*/*z*): Calcd for $C_{27}H_{21}ClN_3O_4^+$ 486.1215 $[M + H]^+$, found 486.1219.

Methyl 3-(2-benzoyl-3-methoxy-3-oxopropyl)-8-fluoroindolizine-2-carboxylate (**9ab**). Following general procedure **A**, starting from 38.7 mg (0.201 mmol) of MBH adduct **8a**, compound **9ab** was obtained as a pale white solid (60.8 mg, 79% yield). m.p: 113-115 °C. Purification: 10%-15% AcOEt/Hexane. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.00 – 7.92 (m, 3H), 7.54 (t, J = 7.3 Hz, 1H), 7.41 (t, J = 7.6 Hz, 2H), 6.95 (s, 1H), 6.58 – 6.47 (m, 1H), 6.33 (dd, J = 10.3, 7.3 Hz, 1H), 5.20 (t, J = 7.4 Hz, 1H), 3.89 (s, 3H), 3.89 – 3.71 (m, 2H), 3.59 (s, 3H). ^{13}C {^{1}H} NMR (63 MHz, $CDCl_3$) δ: 195.5, 169.9, 165.6, 154.8 (d, J_{F-C} = 249.7 Hz), 135.9, 133.9, 128.9, 128.8, 127.1, 124.6 (d, J_{F-C} = 37.5 Hz), 119.7 (d, J_{F-C} = 4.5 Hz), 117.2, 111.1 (d, J_{F-C} = 7.7 Hz), 99.9 (d, J_{F-C} = 17.2 Hz), 98.9 (d, J_{F-C} = 3.0 Hz), 52.8, 52.6, 51.6, 24.8. HRMS (ESI, *m*/*z*): Calcd for $C_{21}H_{18}FNO_5Na^+$ 406.1061 $[M + Na]^+$, found 406.1065.

Methyl 3-(2-benzoyl-3-methoxy-3-oxopropyl)-8-methylindolizine-2-carboxylate (**9ac**). Following general procedure **A**, starting from 38.4 mg (0.200 mmol) of MBH adduct **8a**, compound **9ac** was obtained as a viscous yellow oil (69.9 mg, 92% yield). Purification: 10% AcOEt/Hexane. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.02 (d, J = 7.2 Hz, 1H), 7.98 – 7.91 (m, 2H), 7.57 – 7.48 (m, 1H), 7.44 – 7.36 (m, 2H), 6.78 (s, 1H),

6.53 (t, J = 6.9 Hz, 1H), 6.49 – 6.42 (m, 1H), 5.17 (t, J = 7.4 Hz, 1H), 3.88 (s, 3H), 3.87 – 3.77 (m, 2H), 3.58 (s, 3H), 2.33 (s, 3H). ^{13}C {^{1}H} NMR (63 MHz, $CDCl_3$) δ: 195.5, 170.0, 166.1, 136.0, 133.7, 133.1, 129.2, 128.9, 128.7, 125.6, 121.0, 116.9, 116.4, 112.3, 99.6, 52.8, 52.7, 51.5, 24.6, 18.0. HRMS (ESI, *m*/*z*): Calcd for $C_{22}H_{22}NO_5^+$ 380.1492 $[M + H]^+$,found 380.1468.

Methyl 3-(2-benzoyl-3-methoxy-3-oxopropyl)-8-methoxyindolizine-2-carboxylate (**9ad**). Following general procedure **A**, starting from 23.5 mg (0.122 mmol) of MBH adduct **8a**, compound **9ad** was obtained as a pale yellow foam (37.2 mg, 77% yield). Purification: 15% AcOEt/Hexane. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 – 7.93 (m, 2H), 7.78 (d, J = 7.2 Hz, 1H), 7.55 – 7.48 (m, 1H), 7.41 – 7.37 (m, 2H), 6.93 (s, 1H) 6.50 (t, J = 7.2 Hz, 1H), 5.93 (d, J = 7.3 Hz, 1H), 5.17 (t, J = 7.4 Hz, 1H), 3.87 (s, 3H), 3.86 – 3.83 (m, 4H), 3.80 (dd, J = 14.9, 7.2 Hz, 1H) 3.57 (s, 3H). ^{13}C {^{1}H} NMR (63 MHz, $CDCl_3$) δ: 195.6, 170.0, 166.1, 151.9, 136.1, 133.7, 128.9, 128.7, 126.9, 126.2, 116.5, 116.2, 112.1, 99.5, 93.7, 55.4, 52.7, 52.7, 51.5, 24.7. HRMS (ESI, *m*/*z*): Calcd for $C_{22}H_{22}NO_6Na^+$ 418.1261 $[M + Na]^+$, found 418.1277.

Methyl 3-(2-benzoyl-3-methoxy-3-oxopropyl)-6-methylindolizine-2-carboxylate (**9ae**). Following general procedure **A**, starting from 38.9 mg (0.202 mmol) of MBH adduct **8a**, compound **9ae** was obtained as a pale yellow solid (61.7 mg, 80% yield). mp: 125-127 °C. Purification: 15%-20% AcOEt/Hexane. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.99 – 7.88 (m, 2H), 7.87 (s, 1H), 7.57 – 7.48 (m, 1H), 7.46 – 7.32 (m, 2H), 7.18 (d, J = 9.2 Hz, 1H), 6.73 (s, 1H), 6.50 (dd, J = 9.2, 1.4 Hz, 1H), 5.16 (t, J = 7.5 Hz, 1H), 3.88 – 3.73 (m, 5H), 3.59 (s, 3H), 2.25 (d, J = 0.8 Hz, 3H) ^{13}C {^{1}H} NMR (63 MHz, $CDCl_3$) δ: 195.7, 170.0, 166.1, 136.0, 133.7, 130.9, 128.8, 128.7, 124.5, 121.5, 121.3, 120.3, 119.5, 116.5, 100.9, 52.7, 52.6, 51.4, 24.5, 18.8. HRMS (ESI, *m*/*z*): Calcd for $C_{22}H_{22}NO_5^+$ 380.1492 $[M + H]^+$, found 380.1468.

Methyl 3-(2-benzoyl-3-methoxy-3-oxopropyl)-6-chloroindolizine-2-carboxylate (**9af**). Following general procedure **A**, starting from 38.5 mg (0.200 mmol) of MBH adduct **8a**, compound **9af** was obtained as a

high viscous yellow oil (76.2 mg, 95% yield). Purification: 10%-20% AcOEt/Hexane. **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.23 – 8.22 (m, 1H), 8.00 – 7.94 (m, 2H), 7.59 – 7.50 (m, 1H), 7.47 – 7.36 (m, 2H), 7.23 (d, J = 9.5 Hz, 1H), 6.82 (s, 1H), 6.62 (dd, J = 9.5, 1.4 Hz, 1H), 5.17 (t, J = 7.4 Hz, 1H), 3.87 (s, 3H), 3.84 – 3.70 (m, 2H), 3.61 (s, 3H). ^{13}C {^{1}H} NMR (63 MHz, $CDCl_3$) δ 195.3, 169.8, 165.6, 135.9, 133.8, 130.2, 128.9, 128.7, 125.7, 121.0, 120.8, 120.6, 119.5, 117.6, 102.5, 52.7, 52.7, 51.6, 24.5. HRMS (ESI, *m*/*z*): Calcd for $C_{21}H_{18}ClNO_5K^+$ 438.0505 $[M + K]^+$, found 438.0505

Methyl 3-(2-benzoyl-3-methoxy-3-oxopropyl)-6-bromoindolizine-2-carboxylate (**9ag**). Following general procedure **A**, starting from 38.9 mg (0.202 mmol) of MBH adduct **8a**, compound **9ag** was obtained as a high viscous yellow oil (82.0 mg, 91% yield). Purification: 5%-10% AcOEt/Hexane. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.00 – 7.94 (m, 2H), 7.61 – 7.47 (m, 1H), 7.48 – 7.36 (m, 2H), 7.18 (d, J = 9.5 Hz, 1H), 6.82 (s, 1H), 6.74 – 6.67 (m, 1H), 5.16 (t, J = 7.4 Hz, 1H), 3.87 (s, 3H), 3.85 – 3.70 (m, 2H), 3.61 (s, 3H). ^{13}C {^{1}H} NMR (63 MHz, $CDCl_3$) δ 195.3, 169.8, 165.6, 135.9, 133.8, 130.1, 128.9, 128.7, 125.6, 123.2, 121.4, 120.8, 117.4, 107.6, 102.5, 52.8, 52.7, 51.6, 24.4. HRMS (ESI, *m*/*z*): Cald for $C_{21}H_{18}BrNO_5Na^+$ 466.0261 $[M + Na]^+$, found 466.0236.

tert-Butyl 3-(2-benzoyl-3-methoxy-3-oxopropyl)indolizine-2-carboxylate (**9ah**). Following general procedure **A**, starting from 39.2 mg (0.204 mmol) of MBH adduct **8a**, compound **9ah** was obtained as a high viscous yellow oil (76.1 mg, 92% yield). Purification: 20% AcOEt/Hexane. ^{1}H NMR (250 MHz, CDCl3) δ 8.06 (d, J = 7.1 Hz, 1H), 7.92 – 7.87 (m, 2H), 7.57 – 7.44 (m, 1H), 7.41 – 7.33 (m, 2H), 7.27 – 7.18 (m, 1H), 6.72 (s, 1H), 6.67 – 6.49 (m, 2H), 5.18 (t, J = 7.6 Hz, 1H), 3.95 – 3.72 (m, 2H), 3.58 (s, 3H), 1.59 (s, 9H). ^{13}C {^{1}H} NMR (63 MHz, $CDCl_3$) δ 195.8, 170.1, 165.0, 136.1, 133.7, 131.7, 128.8, 128.6, 124.1, 122.9, 120.1, 119.0, 117.5, 111.9, 101.4, 80.5, 52.6, 52.5, 28.5, 24.4. HRMS (ESI, *m*/*z*) calculated for $C_{24}H_{25}NO_5Na^+$ 430.1625 $[M + Na]^+$, found 430.1633.

Methyl 2-((2-cyanoindolizin-3-yl)methyl)-3-oxo-3-phenylpropanoate (**9ai**). Following general procedure **A**, starting from 38.8 mg (0.202 mmol) of MBH adduct **8a**, compound **9ai** was obtained as a white solid (59.5 mg, 89% yield). mp: 123-124 °C Purification: 10%-20% AcOEt/Hexane. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.03, (d, J = 7.2 Hz, 1H), 8.01 – 7.94 (m, 2H), 7.62 – 7.52 (m, 1H), 7.52 – 7.38 (m, 2H), 7.30 (d, J = 9.2 Hz, 1H), 6.81 – 6.64 (m, 2H), 6.62 (s, 1H), 4.97 (t, J = 7.5 Hz, 1H), 3.98 – 3.67 (m, 2H), 3.65 (s, 3H). ^{13}C {^{1}H} NMR (63 MHz, $CDCl_3$) δ 194.0, 169.1, 135.4, 134.1, 132.6, 128.9, 128.8, 126.5, 122.7, 119.9, 118.9, 116.5, 113.0, 102.2, 97.0, 53.0, 52.5, 24.0. HRMS (ESI, *m*/*z*): Calcd for $C_{20}H_{16}N_2O_3K^+$ 371.0793 $[M + K]^+$, found 371.0795.

Methyl 2-((2-cyanoindolizin-3-yl)methyl)-3-oxo-3-phenylpropanoate (**9aj**). Following general procedure **A** starting from 38.4 mg (0.200 mmol) of MBH adduct **8a**, compound **9aj** was obtained as a high viscous yellow oil (65.3 mg, 85% yield). Purification: 5%-10% AcOEt/Hexane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.96 (m, 1H), 7.60 – 7.57 (m, 2H), 7.51 – 7.46 (m, 1H), 7.45 – 7.38 (m, 4H), 7.35 – 7.28 (m, 4H), 6.64 (ddd, J = 8.9, 6.5, 0.8 Hz, 1H), 6.59 – 6.51 (m, 1H), 6.44 (s, 1H), 4.54 (t, J = 7.3 Hz, 1H), 3.88 (dd, J = 15.7, 7.7 Hz, 1H), 3.75 (dd, J = 15.7, 6.8 Hz, 1H), 3.44 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 195.0, 169.7, 136.6, 135.7, 133.6, 132.5, 129.0, 128.9, 128.7, 128.6, 128.5, 126.7, 122.4, 119.0, 116.6, 116.5, 110.6, 99.8, 52.5, 52.2, 23.6. HRMS (ESI, *m*/*z*): Calcd for $C_{25}H_{21}NO_3Na^+$ 406.1414 $[M + Na]^+$, found 406.1396.

Methyl 3-(2-benzoyl-3-methoxy-3-oxopropyl)indolizine-1-carboxylate (**9ak**). Following general procedure **A**, starting from 37.7 mg (0.196 mmol) of MBH adduct **8a** and adding 34.4 mg (0.196 mmol, 1 equiv.) of indolizine **1k** in the second step, compound **9ak** was obtained as a high viscous yellow oil (61.9 mg, 86% yield). Purification: 20% AcOEt/Hexane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (dt, J = 9.1, 1.2 Hz, 1H), 8.03 – 7.95 (m, 3H), 7.62 – 7.56 (m, 1H), 7.51 – 7.42 (m, 2H), 7.08 – 7.02 (m, 2H), 6.79 (td, J = 6.9, 1.3 Hz, 1H), 4.86 (t, J = 7.2 Hz, 1H), 3.85 (s, 3H), 3.67 (s, 3H), 3.64 – 3.46 (m, 2H). ^{13}C {^{1}H} NMR (63 MHz, $CDCl_3$) δ 193.8, 169.4, 165.3, 136.1, 135.7, 134.0, 128.9, 128.8, 122.9, 121.8, 121.8, 120.0, 114.7, 112.7,

103.1, 53.0, 52.5, 50.9, 24.9. HRMS (ESI, *m/z*): Calcd for $C_{21}H_{19}NO_5Na^+$ 388.1155 $[M + Na]^+$, found 388.1172.

Methyl 3-(2-benzoyl-3-methoxy-3-oxopropyl)-2-phenylindolizine-1-carboxylate (**9al**). Following general procedure **A**, starting from 23.1 mg (0.120 mmol) of MBH adduct **8a** and adding 30.2 mg (0.120 mmol, 1 equiv.) of indolizine **1l** in the second step, compound **9al** was obtained as a high viscous yellow oil (41.6 mg, 78% yield). Purification: 20% AcOEt/Hexane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 7.3 Hz, 1H), 8.26 – 8.18 (m, 1H), 7.56 – 7.39 (m, 6H), 7.37 – 7.29 (m, 4H), 7.08 (ddd, J = 9.1, 6.6, 1.0 Hz, 1H), 6.83 (td, J = 6.9, 1.4 Hz, 1H), 4.41 (dd, J = 8.7, 6.0 Hz, 1H), 3.66 (s, 3H), 3.59 (dd, J = 15.5, 8.7 Hz, 1H), 3.49 – 3.41 (m, 4H). ^{13}C {^{1}H} NMR (63 MHz, $CDCl_3$) δ 194.8, 169.6, 165.3, 136.0, 135.5, 135.3, 133.9, 131.1, 130.1, 128.8, 128.7, 128.2, 127.4, 123.8, 122.2, 120.1, 120.0, 112.6, 102.3, 52.7, 52.6, 50.6, 23.2. HRMS (ESI, *m/z*) calculated for $C_{27}H_{23}NO_5Na^+$ 464.1468 [M + Na], found 464.1492.

Methyl 3-oxo-2-((1-oxo-1,2,3,4-tetrahydropyrido[1,2-a]indol-10-yl)methyl)-3-phenylpropanoate (**9am**). Following general procedure **A**, starting from 38.5 mg (0.200 mmol) of MBH adduct **8a** and adding 37.1 mg (0.200 mmol, 1 equiv.) of indolizine **1m** in the second step, compound **9am** was obtained as a high viscous yellow oil (68.7 mg, 91% yield). Purification: 10%-20% AcOEt/Hexane. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 – 8.03 (m, 2H), 7.58 – 7.45 (m, 3H), 7.45 – 7.37 (m, 2H), 6.64 (ddd, J = 9.3, 6.4, 0.9 Hz, 1H), 6.52 – 6.49 (m, 1H), 5.25 (t, J = 7.7 Hz, 1H), 3.57 (d, J = 7.8 Hz, 2H), 3.56 (s, 3H), 2.95 – 2.80 (m, 2H), 2.69 – 2.55 (m, 2H), 2.33 – 2.16 (m, 2H). ^{13}C {^{1}H} NMR (63 MHz, CDCl3) δ 197.1, 196.5, 170.3, 136.5, 133.3, 132.0, 131.1, 129.0, 128.5, 121.8, 120.7, 119.6, 117.5, 112.5, 107.5, 53.9, 52.2, 39.3, 24.9, 23.5, 21.1. HRMS (ESI, *m/z*) calculated for $C_{23}H_{21}NO_4K^+$ 414.1102 $[M + K]^+$, found 414.1090.

Methyl 3-oxo-3-phenyl-2-((2-phenylimidazo[1,2-a]pyridin-3-yl)methyl)propanoate (**9an**). Following general procedure **A**, starting from 38.4 mg (0.200 mmol) of MBH adduct **8a** and adding 38.8 mg (0.200 mmol, 1 equiv.) of imidazopyridine **1n** in the second step, compound **9an** was obtained as a yellow foam

(65.0 mg, 84% yield). Purification: 30%-40% AcOEt/Hexane. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, J = 6.9 Hz, 1H), 7.80 – 7.75 (m, 2H), 7.69 – 7.64 (m, 3H), 7.54 – 7.45 (m, 3H), 7.42 – 7.39 (m, 1H), 7.35 – 7.32 (m, 2H), 7.25 – 7.21 (m, 1H), 6.92 (t, J = 6.8 Hz, 1H), 4.69 (t, J = 7.3 Hz, 1H), 3.93 (dd, J = 15.9, 7.4 Hz, 1H), 3.82 (dd, J = 15.9, 7.2 Hz, 1H), 3.50 (s, 3H).^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 194.6, 169.3, 144.7, 143.3, 135.5, 134.5, 133.9, 128.8, 128.7, 128.5, 128.2, 127.9, 124.2, 123.7, 117.4, 116.6, 112.2, 52.7, 51.8, 22.9. HRMS (ESI, *m*/*z*) calculated for $C_{24}H_{20}N_2O_3Na^+$ 407.1366 $[M + Na]^+$, found 407.1404.

General Procedure for the Synthesis of Dialkylated Product 12. To a 5 mL round-bottom flask IBX (66.75 mg, 0.238 mmol, 1.2 equiv) was added to a 0.2 M solution of MBH adduct **8a** (38.2 mg 0.199 mmol, 1 equiv.) in acetonitrile. The solution was refluxed in an oil bath for 45 min and the complete consume of starting material was monitored by TLC. After this time, the flask was removed from heating, cooled to room temperature and a 0.1 M solution of indolizine **1a** (13.9 mg, 0.079 mmol 0.4 equiv.) in acetonitrile was added. The resulting solution was stirred open to air until no detectable progress (< 1 min), filtered, solvent removed under reduced pressure and the residue purified by column chromatography (AcOEt/Hex: 10-20%), affording the dialkylated product in an inseparable diasteroismeric mixture (1:1 *d.r.*) as a high viscous yellow oil (43.1 mg, *d.r.*: 1:1, 98% yield).

Dimethyl 2,2'-((2-(methoxycarbonyl)indolizine-1,3-diyl)bis(methylene))bis(3-oxo-3-phenylpropanoate) (**12**)**.** ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 – 7.95 (m, 2H), 7.92 – 7.82 (m, 8H), 7.55 – 7.41 (m, 6H), 7.41 – 7.31 (m, 8H), 6.63 – 6.59 (m, 2H), 6.54 – 6.49 (m, 2H), 5.00 – 4.95 (m, 2H), 4.91 – 4.87 (m, 2H), 3.84 – 3.75 (m, 10H), 3.65 – 3.58 (m, 4H), 3.58 (s, 3H), 3.55 (s, 3H), 3.54 (s, 3H), 3.52 (s, 3H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 195.9, 195.8, 195.5, 195.4, 170.4, 170.4, 170.1, 170.1, 166.2, 136.6, 136.6, 136.1, 136.0, 133.8, 133.4, 131.0, 128.8, 128.8, 128.8, 128.7, 128.7, 128.6, 128.6, 125.3, 122.6, 118.9, 118.9, 117.4, 115.3, 112.5, 110.9, 54.9, 54.9, 52.9, 52.8, 52.7, 52.5, 52.5, 51.4, 25.0, 25.0, 24.7, 24.7. HRMS (ESI, *m*/*z*) calculated for $C_{32}H_{30}NO_8^+$ 556.1966 $[M + H]^+$, found 556.1979.

Gram-Scale Synthesis of conjugated adduct 9ea. To a 50 mL round-bottom flask IBX (0.840 mg, 3 mmol) was added to a 0.2 M solution of MBH adduct **8a** (0.591 g, 2.5 mmol) in acetonitrile (12.5 mL), and resulting solution refluxed in an oil bath until complete consume of starting material (45 minutes). After that, flask was removed from heating, cooled to room temperature and a 0.2 M solution of indolizine **1a** (0.526 g, 3 mmol) in acetonitrile (15 mL) was added and the solution stirred open to air until complete consume of the starting material (< 1 minute). The solution was then vacuum filtered in a Buchner funnel, solvent removed under reduced pressure and residue purified by column chromatograpy (20%-30% AcOEt/Hexane) affording **9ea** as a yellow solid (0.939 g, 92%).

Procedure for Synthesis of pyrazolone 13. In a 4 mL vial flask, conjugated adduct **n** (61.4 mg, 0.150 mmol) was dissolved in DMF (0.3 mL) and a drop of acetic acid was added. The solution was sonicated to complete the dissolution of the substrate and 0.5 mL of hydrazine hydrate (80% solution in water, 37.8 mg, 0.756 mmol) was added. The reaction mixture was heated in an oil bath at 85 °C for 30 minutes, cooled to room temperature and diluted in EtOAc (25 mL). The organic phase was washed with water (2 x 10 mL), brine (1 x 10 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue purified by column chromatography (MeOH/DCM: 2.5-5%), affording pyrazolone **13** as a white solid (24.9 mg, 42% yield).

Methyl 3-((5-(benzo[d][1,3]dioxol-5-yl)-3-oxo-2,3-dihydro-1H-pyrazol-4-yl)methyl)indolizine-2-carboxylate (**13**). mp: 185-187 °C. ^{1}H NMR (500 MHz, DMSO) δ 7.83 (d, J = 7.2 Hz, 1H), 7.37 (d, J = 9.1 Hz, 1H), 6.82 – 6.79 (m, 2H), 6.76 (dd, J = 8.1, 1.5 Hz, 1H), 6.69 – 6.62 (m, 2H), 6.57 – 6.49 (m, 1H), 6.00 (s, 2H), 4.47 (s, 2H), 3.76 (s, 3H). ^{13}C {^{1}H} NMR (126 MHz, DMSO) δ 165.5, 160.0, 147.1, 146.9, 140.3, 130.6, 126.4, 124.1, 123.1, 121.0, 120.0, 117.5, 115.7, 111.7, 108.0, 107.6, 101.1, 100.0, 95.8, 51.1, 17.3. HRMS (ESI, *m*/*z*) calculated for $C_{21}H_{18}N_3O_5^+$ 392.1241 $[M + H]^+$, found 392.1217.

Procedure for synthesis of indole conjugated adduct 11a. Following general procedure **A**, starting from 39.7 mg (0.206 mmol) of MBH adduct **8a**, and adding indole **11a** (24.2 mg, 0.206 mmol) in the second step, compound **11a** was obtained as a yellow oil (47.5 mg, 75% yield). Purification: 10%-15% AcOEt/Hexane.

Methyl 2-((1H-indol-3-yl)methyl)-3-oxo-3-phenylpropanoate (**11a**).[25] ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.12 (bs, 1H), 7.99 – 7.94 (m, 2H), 7.67 – 7.50 (m, 2H), 7.48 – 7.38 (m, 2H), 7.35 – 7.29 (m, 1H), 7.24 – 7.11 (m, 2H), 7.01 (d, J = 2.3 Hz, 1H), 4.81 (t, J = 7.2 Hz, 1H), 3.66 (s, 3H), 3.58 – 3.45 (m, 2H).

Procedure for competitive experiment between indolizine 1a and indole 11a. To a 0.2 M solution of MBH adduct **8a** (40 mg, 0.208 mmol) in acetonitrile, IBX (77.7 mg, 0.250 mmol) was added and reaction mixture refluxed for 45 mintures. After cooling the system to room temperature, a 0.2 M acetonitrile solution containing indolizine **1a** (43.8, 0.250 mmol) and indole **(11a)** (29.25 mg, 0.250 mmol) were added. Stirring was maintained for a minute, then the solution was filtered and the solvent removed under reduced pressure. The crude reaction was analyzed by ^{1}H NMR indicating the complete consumption of MBH adduct and the exclusive formation of indolizine conjugated adduct (**9aa**).

Supporting information

Mono- and bidimensional ^{1}H and ^{13}C NMR spectra (PDF)

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