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Studies towards the synthesis of indolizin-5(3*H*)-one derivatives and related 6,5-azabicyclic scaffolds by ring-closing metathesis

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ABSTRACT

Herein, we report on work towards the development of a new strategy for the synthesis of rare and biologically interesting indolizin-5(3*H*)-ones, which is based around the use of ring-closing metathesis to construct the carbocyclic ring system. This study has provided insights into the general stability of indolizin-5(3*H*)-ones and their tendency to exist as the tautomeric indolizin-5-ols. Furthermore, this approach has allowed access to other novel structurally related compounds based around unusual 6,5-azabicyclic scaffolds, which are also difficult to generate using typical methods. The azabicyclic compounds synthesized in this study reside in attractive regions of heterocyclic chemical space that are underexploited in current drug and agrochemical discovery efforts.

1. Introduction

Heterocyclic ring systems play an immensely important role in the discovery of biologically active agents. Indeed, a large proportion of all pharmaceuticals and agrochemicals are based around heterocyclic scaffolds.[1] However, chemists' exploration of heterocyclic chemical space to date (indeed, chemical space in general) has been strikingly uneven and unsystematic; traditionally, investigations have focused on a relatively small number of scaffolds, with a huge emphasis placed on those with both proven biological relevance and facile synthetic accessibility.[2,3] Unsurprisingly therefore, there is considerable interest in the development of new synthetic approaches to access 'atypical' heterocyclic scaffolds that have been largely ignored and underexploited in drug and agrochemical discovery. Such scaffolds may be associated with unusual and useful biological and/or physico-chemical properties, as well as offering a chemical opportunity to secure novel intellectual property.[3,4]

One such underexplored class of heterocyclic scaffolds are indolizin-5(3*H*)-ones, compounds comprised of a 6,5-fused ring system with a ring-junction nitrogen atom (Fig. 1). In contrast, the structurally related indolizines have been widely investigated, and found to be associated with a broad range of useful biological and physical properties.[5] There are some examples of biologically active compounds containing an indolizin-5-one-type core, most notably the antitumour agent camptothecin[6] (Fig. 1).

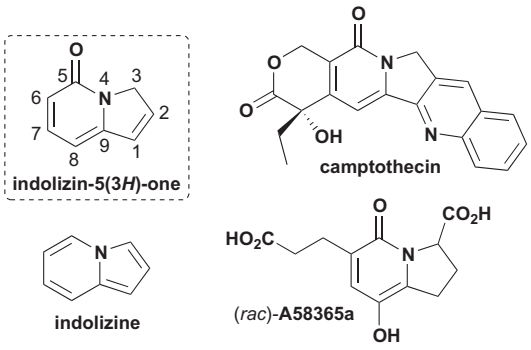

Figure 1. The indolizin-5(3*H*)-one core ring system together with some examples of biologically active compounds based around close variants of this scaffold. Camptothecin is an antitumour agent[6] and (*rac*)-A58365A[7] is an angiotensin-converting enzyme inhibitor.

Overall however, indolizin-5(3*H*)-ones are largely under-represented in current small molecule screening collections.

The relative paucity of compounds based around the indolizin-5(3*H*)-one scaffold can be attributed primarily to synthetic intractability; indeed, there are few widely applicable methods for

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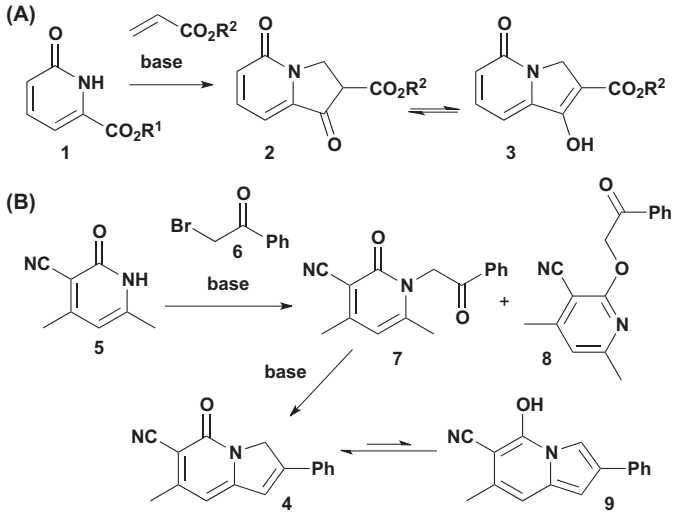
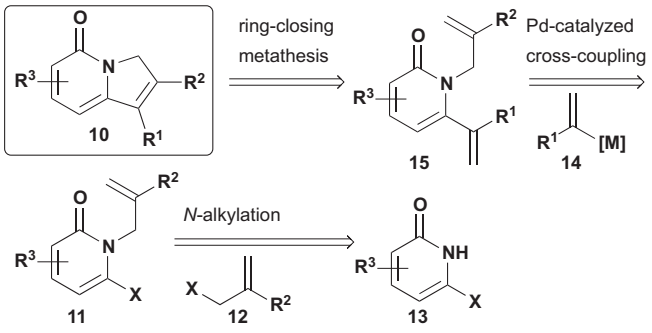


Scheme 1. Some commonly employed routes towards indolizin-5(3*H*)-one systems: (A) 1,4-addition followed by Claisen condensation,[8] (B) N-alkylation followed by cyclization.[9,10] Babaev et al. assumed the existence of **9**, a tautomeric form of **4**.[10]

the construction of this molecular framework. A commonly employed route involves the 1,4-addition of 1,6-dihydropicolinates **1** to unsaturated esters, followed by an intramolecular Claisen condensation to generate the corresponding ketone **2**, which is tautomeric with the indolizin-5-one **3** (Scheme 1).[8] Gewald et al.[9] and Babaev et al.[10] have reported an alternative strategy for the synthesis of 2-aryl-6-cyano-7-methylindolizin-5-ones **4**. This route involved the alkylation of pyridone **5** with α-bromoketone **6** to yield a mixture of N-alkylated and O-alkylated products **7** and **8**. Addition of base (either to the mixture in the work of Gewald et al.,[9] or after separation and isolation of the N-alkylated derivatives in the case of Babaev et al.[10]) then resulted in intramolecular cyclization and formation of the indolizin-5-one core **4**. Overall, only a small number of routes currently exist towards indolizin-5(3*H*)-ones and only a limited range of substitution patterns have been explored to date. Thus, there is a need for the development of new methods of broad utility for the synthesis of indolizin-5(3*H*)-ones so that the physicochemical properties (including stability) and biological usefulness of this heterocyclic scaffold can be investigated further.

Recently, we reported the development of a novel approach towards quinolizin-4-ones that was based around the use of ring-closing metathesis (RCM) to construct the carbocyclic ring.[11,12] We envisaged that this concept could be leveraged in the design of a new RCM-based strategy for the synthesis of indolizin-5-ones **10** (Scheme 2). Selective N-alkylation of readily accessible pyridones **13** with alkyl halides **12** would furnish compounds



Scheme 2. Retrosynthetic strategy towards the indolizin-5(3*H*)-one scaffold {[M] = unspecified metal, X = unspecified halide}.

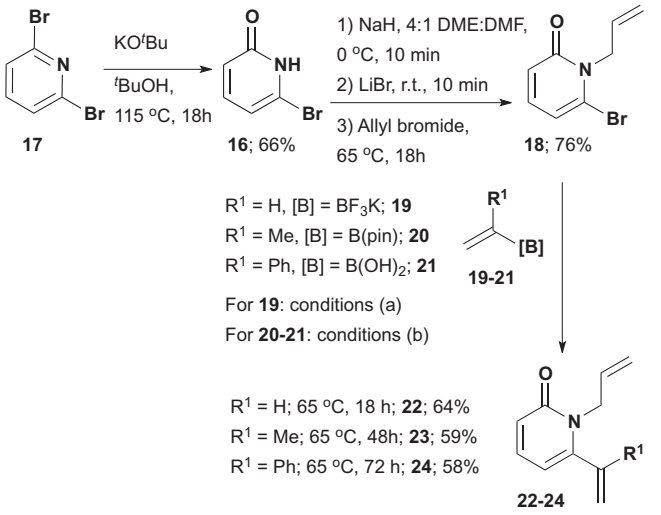
11 and subsequent palladium catalyzed cross-coupling with suitable coupling partners **14** would lead to dienes **15**. Finally, RCM would generate the desired indolizin-5-ones **10**. This would represent an unprecedented approach towards this scaffold type. The strategy is step-efficient and also inherently modular in nature; in principle a range of novel analogues could be readily accessed through variation in the building blocks used. This may also include indolizin-5-ones with unprecedented carbon derivatization at the 1-position, as well as other positions around the heterocyclic core. Herein, we describe work thus far on the development of this strategy. This has provided new valuable insights into the general stability of indolizin-5(3*H*)-ones, and also their tendency to exist as the tautomeric indolizin-5-ols. Furthermore, this general synthetic approach has provided access to other novel compounds based around unusual structurally related azabicyclic scaffolds; these are traditionally synthetically challenging molecules which would be expected to be of pharmaceutical and agrochemical interest.

2. Results and discussion

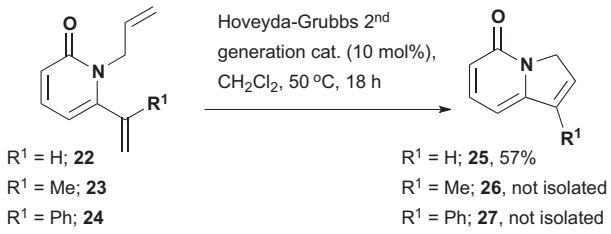
2.1. Initial studies

Initial studies focused on target scaffolds where both R^2 and R^3 (in general structure **10**) were hydrogen atoms (Scheme 3). Thus, 6-bromopyridin-2-one (**16**) was required, which was readily accessed by the hydrolysis of commercially available 2,6-dibromopyridine (**17**). Alkylation with allyl bromide according to the procedure of Liu et al.[13] furnished **18** in a good yield, with a high level of regioselectivity for the pyridone nitrogen atom over the oxygen atom observed.[11] Suzuki cross-coupling of **18** with boronic coupling partners **19**–**21** generated products **22**–**24**.

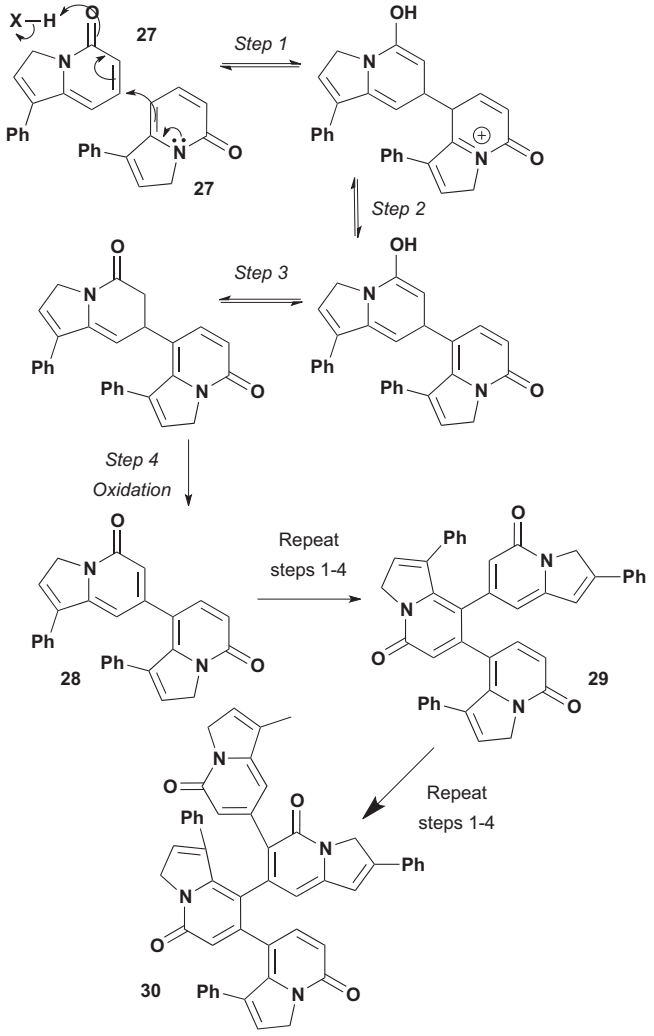
With pyridones **22**–**24** in hand, we were ready to examine the key RCM reaction step in an attempt to access the corresponding indolizin-5(3*H*)-ones **25**–**27**. The substrates were treated with Hoveyda–Grubbs second-generation catalyst (Scheme 4) and the reactions monitored by liquid chromatography mass spectrometry (LC–MS). In all cases, a mass peak consistent with the formation of the desired indolizin-5(3*H*)-one was observed. Pleasingly, a pure sample of unsubstituted derivative **25** could be obtained by col-



Scheme 3. Synthesis of RCM substrates **22**–**24**. Reagents and conditions: (a) Pd(dppf)Cl_2 (10 mol %), K_2CO_3, 10:1 THF/H_2O, time and temperature as shown; (b) Pd(dppf)Cl_2·CH_2Cl_2 (10 mol %), K_2CO_3, 10:1 THF/H_2O, time and temperature as shown. B(pin) = 4,4,5,5-tetramethyl-1,3,2-dioxaborolane. dppf = 1,1′-bis(diphenylphosphino) ferrocene.



Scheme 4. Synthesis of indolizin-5(3*H*)-one **25** and attempted synthesis of compounds **26** and **27**. Compound **25** was found to be unstable to storage and decomposed within a 24 h period.



Scheme 5. A possible oligomerization-oxidation pathway leading to the formation of compounds **28**–**30** from **27**. *Step 1*: Nucleophilic attack from the 8-position of the indolizin-5(3*H*)-one core. *Step 2*: Tautomerization (re-aromatization). *Step 3*: Keto-enol tautomerization. *Step 4*: Oxidation (re-aromatization). In *Step 1* the 6- position represents a plausible alternative nucleophilic site; this would generate derivatives with the same mass values as **28**–**30**.[14] The 2-position of the scaffold also represents a plausible alternative electrophilic site (treating the entire system as an extended Michael acceptor).

umn chromatography on silica. However, the isolated yield was only moderate, which could be attributed to rapid degradation of the product on silica. Furthermore, purified **25** was found to be unstable in solution, with extensive precipitation of an unidentifiable black solid observed within a 24 h time period. In addition it did not prove possible to isolate pure samples of **26** and **27** due to their rapid degradation in solution and on silica.

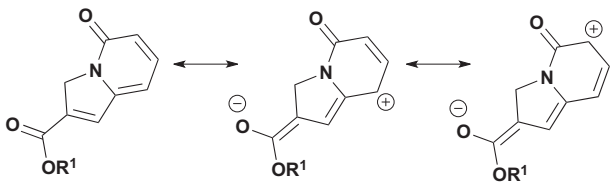


Figure 2. An illustration of the deactivation of the 6- and 8-positions of the indolizin-5(3*H*)-one core towards reaction with an electrophile by the introduction of an electron withdrawing group (for example, an ester as shown here) at the 2-position of the bicyclic scaffold.

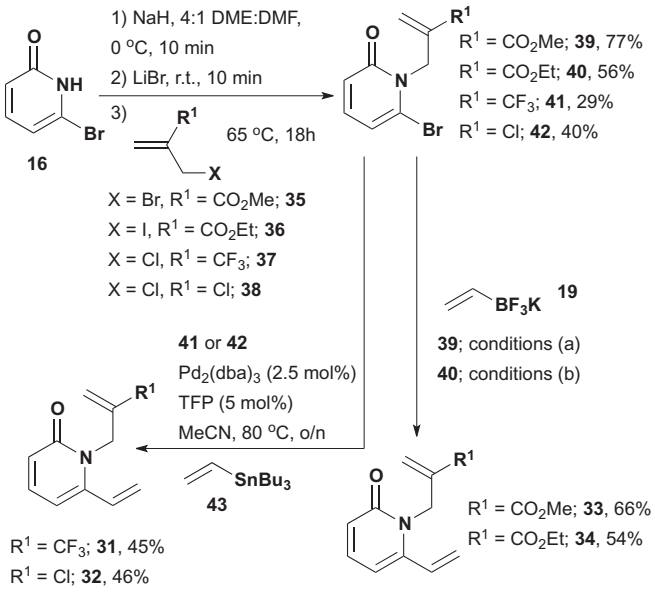
In an attempt to gain more insight into this stability problem, the material obtained after attempted purification of **27** by column chromatography on silica was analyzed by high resolution mass spectrometry (HRMS). The resulting spectrum contained peaks that could tentatively be attributed to compounds **28**, **29** and **30** (or isomers thereof, Scheme 5). It was hypothesized that these compounds could be formed from the indolizin-5(3*H*)-one **27** by a facile oligomerization-oxidation pathway (illustrated in Scheme 5) that proceeds via initial nucleophilic attack from either the 6- or 8-position of one indolizin-5(3*H*)-one molecule onto the 7-position of another.[14] This pathway could potentially continue on beyond **30**, leading to polymerization and precipitation. This polymerization pathway may provide an explanation for the observed instability of **27**. Presumably, a similar pathway would also account for the instability of the other indolizin-5(3*H*)-ones **25**–**26**. It was hypothesized that the polymerization process could be inhibited (and thus derivatives of the target scaffold stabilized) by the presence of an electron-withdrawing group at the 2-position of the indolizin-5(3*H*)-one core; this would be expected to decrease the electron density, and thus nucleophilicity, of the ring system as a whole (and particularly the 6- and 8-positions if electron withdrawal was possible through the π system, Fig. 2). Indolizin-5(3*H*)-ones which contained an electron-withdrawing group at the 2-position were therefore targeted.

2.2. Synthesis of indolizin-5(3*H*)-one scaffold bearing one electron-withdrawing group at the 2-position

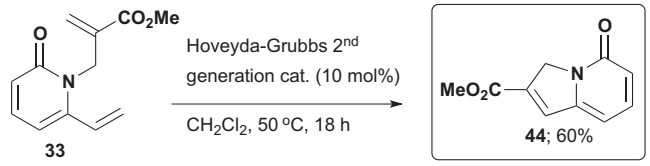
It was anticipated that indolizin-5(3*H*)-ones bearing an electron-withdrawing group at the 2-position could be accessed by RCM of allylic pyridone substrates of the form **15** (Scheme 2 where R^2 was the electron withdrawing group in question and both R^1 and R^3 were hydrogen atoms. Thus, compounds **31**–**34** were prepared in two steps from **16** (Scheme 6). Regioselective N-alkylation with various allylic halides **35**–**38** led to compounds **39**–**42**. Subsequent Pd-catalyzed cross coupling with either potassium vinyltrifluoroborate (**19**) or tributyl(vinyl)tin (**43**)[11,15,16] led to the desired RCM substrates. Compounds **31**–**34** were then treated with Hoveyda–Grubbs second-generation catalyst (conditions as given in Scheme 4). Unfortunately, in the majority of cases (compounds **31**, **32**, **34**), it did not prove possible to isolate the desired 2-substituted indolizin-5(3*H*)-ones. For most substrates, there was evidence that the target scaffolds were generated, however, rapid decomposition was then observed, either under the reaction conditions or during purification (on silica and/or alumina) possibly via a similar pathway to that described previously (see Scheme 5).

For substrate **33** it did prove possible to isolate the corresponding substituted indolizin-5(3*H*)-one derivative **44** and this was found to be much more stable than compounds **25**–**27** both before and after purification (Scheme 7).

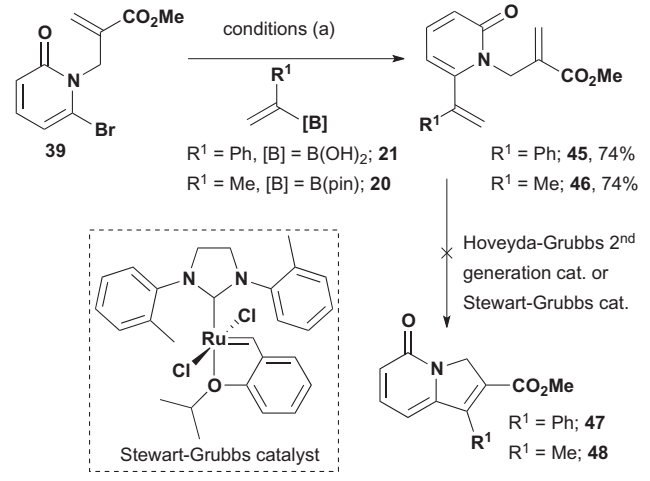
Overall however, this study suggested that the introduction of a single electron-withdrawing group at the 2-position of indolizin-5(3*H*)-one scaffold was not a reliable strategy for the improvement



Scheme 6. Synthesis of allylic pyridone derivatives **31**–**34**. Reagents and conditions: (a) $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (10 mol %), K_2CO_3, 10:1 THF/H_2O, 65 °C, 50 h; (b) $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), K_2CO_3, THF, 65 °C, overnight. dppf = 1,1′-bis(diphenylphosphino)ferrocene. TFP = tri(2-furyl)phosphine. dba = dibenzylideneacetone.



Scheme 7. Successful synthesis and isolation of 2-substituted indolizin-5(3*H*)-one **44**.



Scheme 8. Studies towards the synthesis of 1,2-disubstituted indolizin-5(3*H*)-ones **47** and **48**. Reagents and conditions (a): $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (10 mol %), K_2CO_3, 10:1 THF/H_2O, 65 °C, 18 h. B(pin) = 4,4,5,5-tetramethyl-1,3,2-dioxaborolane. dppf = 1,1′-bis(diphenylphosphino)ferrocene.

of compound stability. Attention was then directed towards the synthesis of derivatives that also contained an additional substituent at the 1-position, to see if this had any additional impact upon product stability.

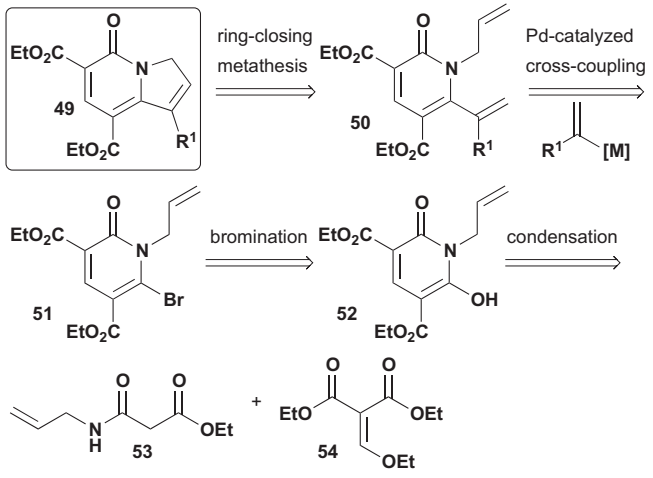
2.3. Towards 1,2-disubstituted indolizin-5(3*H*)-one scaffolds

It was anticipated that the desired 1,2-disubstituted indolizin-5(3*H*)-ones could be accessed by RCM of allylic pyridone substrates of the form **15** (Scheme 2) where R^1 was a methyl ester and R^2 an electron withdrawing group. Towards this end, compounds **45**–**46** were generated by the Pd-catalyzed cross-coupling of **39** with organoboron species **21** and **20**, respectively (Scheme 8). Disappointingly, treatment of these compounds under the previously employed RCM conditions (Scheme 7) did not lead to the formation of the corresponding indolizin-5(3*H*)-ones **47**–**48**, with only trace consumption of the starting material observed in both cases. The reactions were repeated at a higher temperature but again essentially only residual starting material was observed in the crude reaction mixtures.

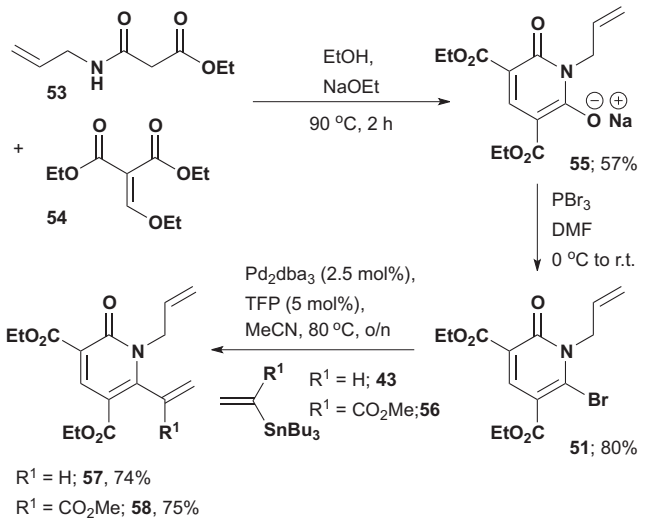
RCM to form tetrasubstituted alkenes, such as those present in the target scaffolds **47** and **48**, is known to be challenging since the catalytic cycle is thought to involve passage through a sterically hindered metallocyclobutane species.[17] The RCM reactions of **45** and **46** were attempted again using Stewart-Grubbs catalyst, a less sterically bulky version of the Hoveyda–Grubbs second generation catalyst that has been reported to be effective for the formation of tetrasubstituted alkenes via RCM.[17] Unfortunately, no reaction was observed in either case, presumably due to prohibitively unfavorable steric factors.

2.4. Synthesis of indolizin-5(3*H*)-one scaffolds substituted on the six-membered ring

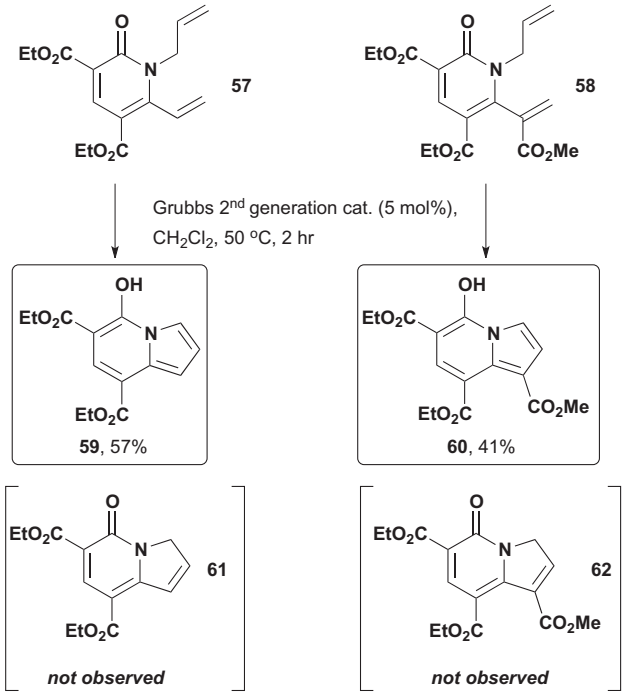
Given the difficulties associated with the formation and isolation of indolizin-5(3*H*)-ones substituted on the five membered ring, attention was turned towards the synthesis of indolizin-5(3*H*)-ones that were substituted with electron withdrawing ester group(s) on the six-membered ring, and which were also either unfunctionalized at the 1- and 2-positions of the core, or contained a group at one of these positions but not both. It was hoped that such derivatives may be more stable than the indolizin-5(3*H*)-ones examined thus far. Furthermore, it was expected that these new target molecules would benefit from improved synthetic tractability relative to the 1,2-disubstituted indolizin-5(3*H*)-one derivatives previously examined, since the RCM step to forge the five-membered ring system would be expected to be less sterically challenging). The synthesis of derivatives **49** containing an ethyl ester group at the 6- and 8-positions of the scaffold was first examined



Scheme 9. Retrosynthetic strategy towards 6,8-ester substituted indolizin-5(3*H*)-ones **49**. {[M] = unspecified metal}.



Scheme 10. Synthesis of RCM-substrates **57** and **58**. TFP = tri(2-furyl)phosphine. dba = dibenzylideneacetone.



Scheme 11. Synthesis of stable indolizin-5-ol derivatives **61** and **62**.

(Scheme 9). A slightly modified version of the original synthetic strategy was envisaged. Compound **49** was to be accessed from **50**, which in turn would be generated from bromide **51**. It was anticipated that the bromide **51** would result from the bromination of hydroxyl-pyridone **52** which in turn could be synthesized by a condensation reaction between β-ester amide **53** and malonate derivative **54**.[18]

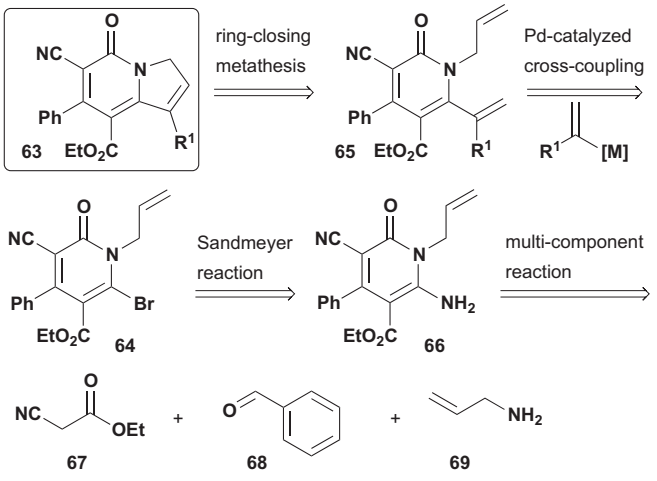
Reaction of **53** and **54** furnished heterocycle **55** (the sodium salt of **52**). Bromination with PBr_3 furnished **51** (Scheme 11.[11] Subsequent Stille cross-coupling with organostannanes **43** and **56** furnished RCM-substrates **57** and **58**, respectively.

Compounds **57** and **58** were then treated with Grubbs second generation catalyst to effect ring-closure (Scheme 11). Unexpectedly however, ^{1}H NMR analyses indicated that both ring-closed products existed entirely in their enol forms **59** and **60** (i.e., indolizin-5-ols), with no evidence for the presence of the anticipated keto tautomeric forms (**61** and **62**, respectively). As shown in Scheme 1, Babaev et al. have previously reported the synthesis of indolizin-one **4**.[10] Treatment of **4** with phosphorus oxychloride led to substitution of the carbonyl group with chlorine, and the authors assumed that this process proceeded through **9**, the tautomeric form of **4**, although ^{1}H NMR suggested that the amount of tautomer **9** was negligibly small. It can be argued that that the enol forms of compounds **61** and **62** are more stable than the enol form of **4**, due to the presence of the two electron withdrawing ester groups on the six-membered ring, which allows for increased delocalization of the π electron density. This would explain why **61** and **62** are observed to exist entirely in their enol forms **59** and **60**, respectively, whilst **4** is not enolised to any detectable extent. Compound **60** was found to be much more stable that **59** to chromatography on silica and storage.[19] This may be attributed to the presence of an additional ester group on the five membered ring, which provides scope for further stabilization through additional π electron delocalization over the extended conjugation system.

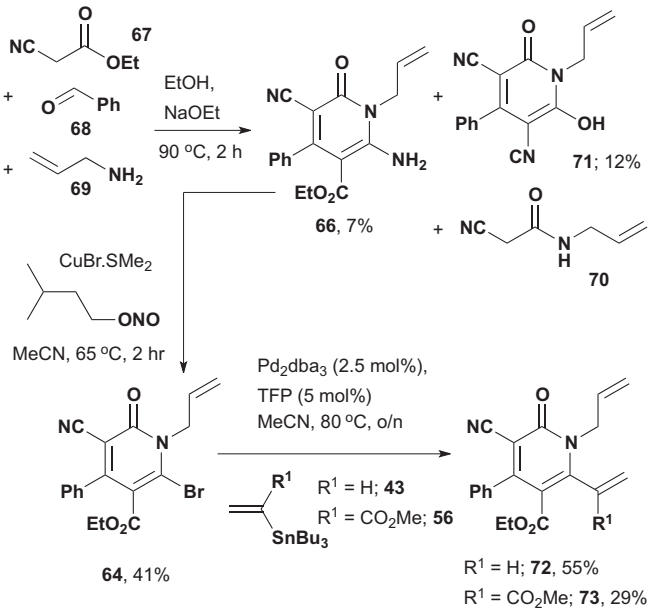
These results demonstrated that substitution of the 6- and 8-positions of the indolizine core with electron withdrawing groups did indeed help to improve compound stability (albeit of the tautomeric forms), presumably due to electronic effects. It was hoped that stability could be further improved through the introduction of a third substituent at the 7-position of the core scaffold since this may disfavor intermolecular attack (and thus resulting polymerization) due to steric hindrance. As a proof-of-principle we targeted the synthesis of derivatives of the general form **63** (Scheme 12). We envisaged a similar synthetic strategy to that employed previously, whereby **63** would be accessed from **64** via Pd-catalyzed cross-coupling to generate **65** followed by RCM. It was anticipated that bromide **64** could be generated by a Sandmeyer reaction on **66**, which in turn could be formed from a multi-component reaction (MCR) of **67**–**69**.[20]

The yield of the MCR reaction was very low (Scheme 13). In addition to the desired product **66**, a small quantity of **71** was isolated. *N*-allyl cyanoacetamide **70** was found to be the major side product (which leads to an unproductive reaction pathway). Nonetheless, sufficient material was obtained to continue with the synthesis. The Sandmeyer reaction proceeded smoothly to furnish bromide **64**. Subsequent Stille cross-coupling with vinyl stannanes **43** and **56** generated compounds **72** and **73**, respectively.

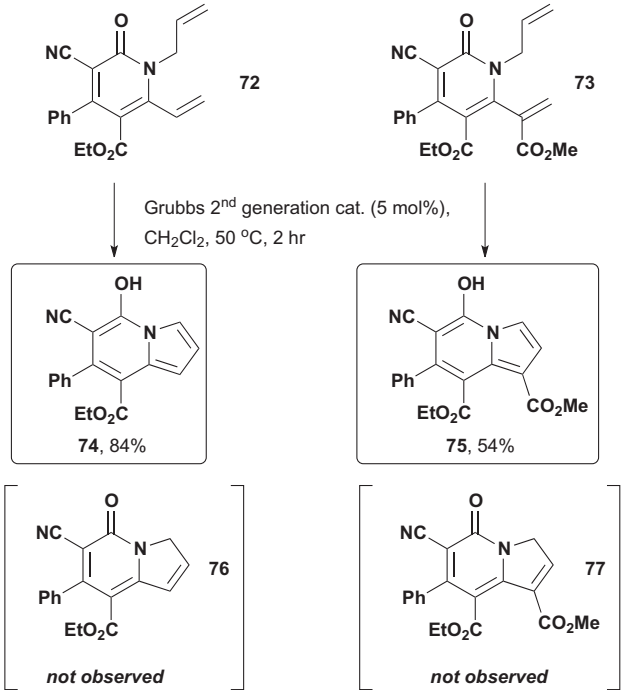
Treatment of **72** and **73** with Grubbs second generation catalyst led to the desired ring-closure in both cases, with the cyclic products again found to exist entirely in their enol forms **74** and **75** (the



Scheme 12. Retrosynthetic strategy towards 6,7,8-substituted derivatives **63**.



Scheme 13. Synthesis of RCM-substrates **72** and **73**. TFP = tri(2-furyl)phosphine.

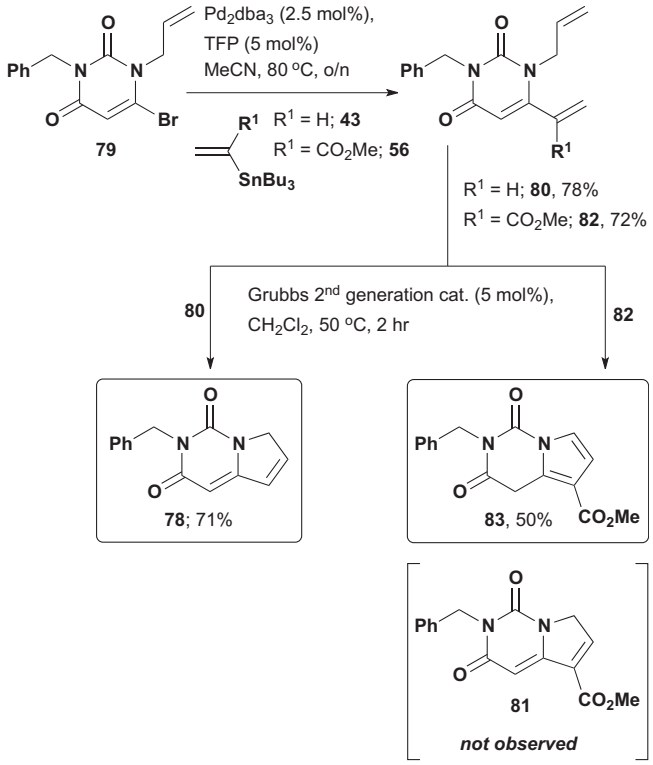


Scheme 14. Synthesis of stable indolizin-5-ol derivatives **76** and **77**.

corresponding keto tautomeric forms **76** and **77** were not observed, Scheme 14). Pleasingly, both **74** and **75** were found to be stable to purification and storage.[21,22]

2.5. Synthesis of related 6,5-azabicyclic scaffolds with a higher nitrogen content

On the basis of our investigations into the synthesis of indolizin-5(3*H*)-ones, it was postulated that structurally related 6,5-azabicyclic scaffolds with a higher nitrogen content would exhibit increased stability, due to additional electron withdrawal from the ring system. We first targeted the synthesis of uracil-type



Scheme 15. Synthesis of azabicyclic derivatives **78** and **83**. Note that compound **82** was isolated as a mixture of acrylic isomers (85:15 ratio of desired/undesired acrylic isomers by ^{1}H NMR analysis) due to the use of geometrically impure **56**.

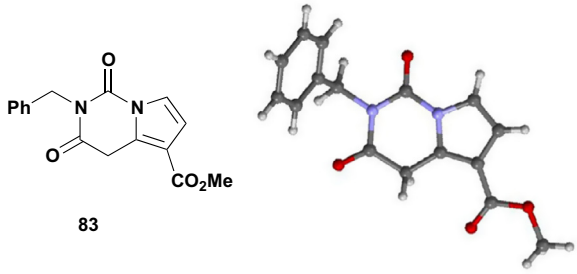


Figure 3. X-ray crystal structure of compound **83**.

derivative **78** (Scheme 15). Compound **79** was prepared using previously reported methods.[11] Stille cross-coupling with tributyl(vinyl)tin (**43**) furnished compound **80**. Reaction with Grubbs second generation catalyst proceeded smoothly to furnish the target azabicyclic compound **78** in a good yield, which was found to be stable to chromatography on silica and storage. It was envisaged that ester substituted derivative **81** could be generated using the same sequence. Thus, compound **82** was generated by the cross-coupling of **79** with **56**. Subjection to standard RCM conditions led to complete consumption of the starting material. However, the major product isolated from the reaction was **83**, rather than **81**. Presumably, **81** is generated initially, which then undergoes a rearrangement process to form **83**, perhaps driven by the formation of an aromatic five-membered ring system. Compound **83** was found to be stable to chromatography on silica and storage. An X-ray crystal structure of **83** was obtained (Fig. 3) in which the hydrogen atoms on the unsubstituted alkene were located and their positions were refined satisfactorily, confirming the aromatic nature of the five-membered ring.

3. Conclusions

In conclusion, we have proposed a novel RCM-based strategy for the synthesis of rare and biologically interesting indolizin-5(3*H*)-ones. Initial studies on the synthesis of unsubstituted and 1-substituted derivatives demonstrated that this was indeed a feasible method for the construction of the core ring scaffold. However, it was found that these compounds were generally quite unstable, both in solution and to purification on silica. Evidence suggested that the instability of these compounds originated from their ready formation of dimers, and, to some extent, higher order oligomers. It was thought that the introduction of electron withdrawing groups(s) around the scaffold would decrease the propensity of the systems to polymerize and thus increase compound stability. Substitution of the five-membered ring was first investigated, and pleasingly it did prove possible to isolate one indolizin-5(3*H*)-one which contained an electron-withdrawing group at the 2-position. However, in general the introduction of a single electron-withdrawing group at the 2-position of the scaffold was not found to be a reliable strategy for improving compound stability, and preliminary studies demonstrated that 1,2-disubstituted derivatives would be challenging synthetic targets. Thus, attention was turned towards the introduction of electron-withdrawing groups on the six-membered ring of the indolizin-5(3*H*)-one core. Pleasingly, it was found that the introduction of two ester substituents at the 6- and 8-positions did lead to the formation and isolation of stable products. However, all products were found to exist entirely in their enol forms, which was unexpected but may be crucial for improved compound stability. Additional substitution at the 7-position was also possible, which may further assist compound stabilization through steric factors. Preliminary studies demonstrated that the RCM-based strategy could also be successfully applied to the synthesis of inherently less electron-rich systems containing a second nitrogen atom in the six-membered ring.

Overall, this work suggests that indolizin-5(3*H*)-ones are, in general, a relatively unstable class of compounds that are prone to rapid degradation (polymerization) and therefore very difficult to isolate. Indeed, only two indolizin-5(3*H*)-one derivatives, **25** and **44**, were successfully isolated in this study. Of these, compound **44** was found to be considerably more stable, which was attributed to the presence of an electron withdrawing methyl ester group on the scaffold. However, the analogous ethyl ester derivative could not be isolated. This would suggest that it is difficult to predict (and indeed rationalise) the stability of substituted indolizin-5(3*H*)-ones. The lack of indolizin-5(3*H*)-ones in current small molecule screening collections may be a result of their inherent instability; given this, and the difficulties associated with predicting the relative stability of indolizin-5(3*H*)-ones, it may not be possible (or indeed desirable) to investigate this class of compounds further. Interestingly, this work has highlighted the propensity of some 6, 8-disubstituted indolizin-5(3*H*)-ones to tautomerize to, and to behave to all intents and purposes as, the corresponding aromatic indolizin-5-ols. Though not the exact intended target of this study, compounds of this form are relatively rare, underexplored in drug and agrochemical discovery and therefore of interest. It may be possible to adapt the RCM-based strategy so as to be able to access stable indolizin-5-ol-type derivatives with other substitution patterns. Substrates of the general form **15** could be prepared and subjected to RCM conditions. After consumption of the starting material, an appropriate electrophile (such as an alkyl halide) could be added in an attempt to trap the enol form (for example, as an enol ether) in situ (similar to the chlorination pathway suggested by Babaev et al.[10]). Potentially, such derivatives may be more stable than their 'parent' indolizin-5(3*H*)-ones, thus making isolation and purification easier. In addition to indolizin-5(3*H*)-ones and the corresponding enol derivatives, the RCM-based synthetic approach allowed access to other novel compounds based around unusual azabicyclic scaffolds. These biologically interesting scaffolds are typically difficult to access using typical methods, highlighting the value of this novel protocol. Overall, the work described herein illustrates the usefulness of the RCM-based strategy for accessing synthetically challenging and biologically interesting azabicyclic scaffolds,[23] and represents an exciting platform for further studies, the results of which will be reported in due course.

4. Experimental

4.1. General experimental details

All non-aqueous reactions were performed under a constant stream of dry nitrogen using oven-dried glassware. Standard practices were employed when handling moisture and air-sensitive materials. Room temperature (rt) refers to ambient temperature. All temperatures below 0 °C are those of the external baths. Temperatures of 0 °C were maintained using an ice-water bath. Temperatures below 0 °C were maintained using an acetone-cardice bath. All reagents and solvents were used as received unless otherwise stated. Toluene, acetonitrile, dichloromethane and methanol were distilled from calcium hydride. Tetrahydrofuran was dried over Na wire and distilled from a mixture of lithium aluminium hydride and calcium hydride with triphenylmethane as indicator. Diethylether was distilled from a mixture of calcium hydride and lithium aluminium hydride. Petroleum ether was distilled before use and refers to the fraction between 40 and 60 °C. Dichloromethane and methanol were distilled from calcium hydride. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. Where possible, reactions were monitored by thin layer chromatography (TLC) performed on commercially prepared glass plates pre-coated with Merck silica gel 60 F254 or aluminium oxide 60 F254. Visualisation was by the quenching of UV fluorescence (ν_{max} = 254 nm) or by staining with potassium permanganate or by low resolution mass spectrometry (LC–MS) analysis using an Agilent 1200 series LC system with an ESCi Multi-Mode Ionization Waters ZQ spectrometer using MassLynx 4.0 software. Flash column chromatography was carried out using slurry-packed Merck 9385 Kieselgel 60 SiO_2 (230–400 mesh) under a positive pressure of compressed air. Melting points were obtained on a Büchi B-545 melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer Spectrum One spectrometer with internal referencing. Selected absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}) with the following abbreviations: w, weak; med, medium; str, strong; br, broad. Proton magnetic resonance spectra were recorded using an internal deuterium lock at ambient probe temperatures (unless otherwise stated) on the following instruments: Bruker DPX-400 (400 MHz), Bruker Avance 400 QNP (400 MHz) and Bruker Avance 500 Cryo Ultrashield (500 MHz). Chemical shifts (δ_H) are quoted in ppm, to the nearest 0.01 ppm, and are referenced to the residual non-deuterated solvent peak. Coupling constants (*J*) are reported in Hertz (Hz) to the nearest 0.1 Hz. Data are reported as follows: chemical shift, integration, multiplicity (br = broad; s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; or as a combination of these), coupling constant(s) and assignment. The numbering/lettering on selected structures does not follow the IUPAC naming system and is used for the assignment of the ^1H NMR and ^{13}C NMR spectra. Proton assignments were determined either on the basis of unambiguous chemical shift, coupling pattern, by patterns observed in 2D experiments (^1H–^1H COSY, HMBC and HMQC) or by analogy to fully interpreted spectra for related compounds. Carbon magnetic resonance spectra

were recorded by broadband proton spin decoupling at ambient probe temperatures using an internal deuterium lock on the following instruments: Bruker DPX-400 (100 MHz), Bruker Avance 400 QNP (100 MHz) and Bruker Avance 500 Cryo Ultrashield (125 MHz). Chemical shifts (δ_C) are quoted in ppm, to the nearest 0.1 ppm, and are referenced to the residual non-deuterated solvent peak. Assignment was based on chemical shift, DEPT editing and where appropriate, HMQC and HMBC experiments or by analogy to fully interpreted spectra of related compounds. X-ray crystal structure data were obtained using a Nonius Kappa CCD instrument. High resolution mass spectrometry (HRMS) measurements were recorded on a Bruker Bioapex 4.7e FTICR or a Waters LCT Premier Time of Flight (TOF) mass spectrometer or a Micromass Quadrapole Time of Flight (TOF) mass spectrometer. Mass values are quoted within the error limits of ±5 ppm mass units. ESI refers to the electrospray ionization technique. Grubbs second generation catalyst = (1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene) dichloro(phenylmethylene)(tricyclohexylphosphine)ruthenium. Hoveyda–Grubbs second generation catalyst = (1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(*o*-isopropoxyphenylmethylene)ruthenium.

4.2. General procedures

4.2.1. General procedure 1—N-alkylation of 2-Pyridones

Adapted from the method of Liu et al.[13] and used in the report of Alanine et al.[11] NaH (60% in mineral oil, 1.1 equiv) was added portion wise to a stirred solution of the 2-pyridone (1 equiv) in 4:1 DME/DMF (2.5 mL/mmol) at 0 °C. The reaction was left to stir at 0 °C for 15 minutes and then left to warm to room temperature. LiBr (2 equiv) was then added. The reaction was left to stir at room temperature for a further 15 min. The allylic halide (2 equiv unless otherwise stated) was then added, and the reaction was heated to 65 °C for 18 h (or until TLC indicated complete consumption of starting material). The reaction was then poured onto brine (30 mL) and the organic layer separated. The aqueous layer was then extracted with EtOAc (4 × 25 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by column chromatography to yield the title compounds.

4.2.2. General procedure 2—Suzuki coupling with Pd(II)chloride catalyst

To a stirred, degassed mixture of heteroaryl bromide (1 equiv), anhydrous K_2CO_3 (3 equiv) and $Pd(dppf)Cl_2$ or $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (as shown in Schemes, 0.1 equiv) in 10:1 THF/H_2O (6.4 ml) was added the appropriate boronic coupling partner (1.5 equiv). The reaction was degassed again, then stirred at 65 °C until TLC analysis indicated complete consumption of starting material. After cooling to room temperature, the mixture was filtered through Celite®, then poured onto brine (60 mL), and the organic layer separated. The aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was purified by column chromatography to yield the title compounds.

4.2.3. General procedure 3—Stille coupling

Prepared according to the method of Alanine et al.[11] Pd_2dba_3 (0.025 equiv) was added to a stirred solution of the heteroaryl bromide (1 equiv) and tri-(2-furyl)phosphine (0.05 equiv) in anhydrous MeCN (0.1 M) at room temperature. The mixture was then degassed with N_2 and the vinylic tin reagent (1.1 equiv) was then added. The mixture was heated to 80 °C until TLC analysis indicated consumption of starting material. The solvent was removed under reduced pressure. The residue obtained was diluted with Et_2O (10 mL) and 10% aqueous KF (2 mL). The mixture was stirred at room temperature for 10 min. The organic layer was then separated, and the aqueous layer was extracted with Et_2O (20 mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was purified by column chromatography (9:1 SiO_2/KF) according to the method of Harrowven et al.[16] and employed in the study of Alanine *et al.*[11] to yield the title compound.

4.2.4. General procedure 4—ring closing metathesis

To a stirred solution of substrate (1 equiv) in anhydrous CH_2Cl_2 (10.0 ml/mmol) was added Grubbs second generation catalyst or Hoveyda–Grubbs second generation catalyst (5–10 mol %) under nitrogen. The solution was heated at 50 °C until TLC analysis indicated complete consumption of starting material. The solvent was removed under reduced pressure and the residue was purified by column chromatography to yield the title compounds.

4.3. Experimental details

4.3.1. 6-Bromopyridine-2(1*H*)-one (16)

To a stirred solution of 2,6-dibromopyridine (**17**, 8.00 g, 33.91 mmol) in anhydrous *tert*-butanol (200 mL) was added potassium *tert*-butoxide (40.00 g, 356.47 mmol). The reaction mixture was stirred at 115 °C overnight, then allowed to cool to room temperature. The solvent was removed under reduced pressure, then ice-water (100 mL) was added slowly with stirring. Chloroform (50 mL) was then added, and the organic layer separated. The aqueous layer was extracted with chloroform (2 × 50 mL), then neutralised to pH 7 with HCl (10% aqueous solution). It was then extracted with chloroform (2 × 50 mL) and acidified to pH 1 with HCl (10% aqueous solution). After a final extraction with chloroform (2 × 50 mL), the combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure to afford **16** as a pale yellow solid (3.89 g, 22.36 mmol, 66%), with no further purification required. R_f 0.22 (SiO_2, 4:1 petroleum ether/EtOAc). Mp 121.2–122.5 °C (petroleum ether), literature value 119–120 °C.[21] IR ν_{max} (cm^{-1}) (neat): 2546 (br med, O–H/N–H), 1647 (str, C=O), 1589 (str, C=C), 1466 (str, C=C). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.49 (1H, br s), 7.44 (1H, dd, *J* = 8.7, 7.5 Hz), 6.84 (1H, dd, *J* = 7.5, 0.8 Hz), 6.71 (1H, dd, *J* = 8.5, 0.8 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 165.0, 142.0, 131.9, 116.3, 113.0 ppm. HRMS (ESI+): *m*/*z* found $[M+H]^+$ 173.9554, $C_5H_5NO^{79}Br^+$ required 173.9549. These data are in accordance with those previously reported.[24]

4.3.2. 1-Allyl-6-bromopyridin-2(1*H*)-one (18)

Prepared according to general procedure 1 using 6-bromopyridin-2(1*H*)-one (**16**, 870 mg, 5.00 mmol) and allyl bromide (1.21 g, 0.87 ml, 10.00 mmol). The crude reaction material was purified by column chromatography (SiO_2, 4:1 petroleum ether/EtOAc) to afford the title compound **18** as a pale yellow solid (820 mg, 3.83 mmol, 76%). R_f 0.29 (SiO_2, 1:1 petroleum ether/EtOAc). Mp 53.6–54.5 °C (EtOAc). IR ν_{max} (cm^{-1}) (neat): 3104 (w, C–H), 3087 (w, C–H), 2983 (w, C–H), 2952 (w, C–H), 1648 (str, C=O), 1581 (str, C=C), 1505 (str, C=C). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.13 (1H, dd, *J* = 9.2, 7.2 Hz), 6.51 (1H, dd, *J* = 9.2, 1.2 Hz), 6.46 (1H, dd, *J* = 7.2, 1.2 Hz), 5.92 (1H, ddt, *J* = 17.2, 10.4, 5.2 Hz), 5.24 (1H, ddd, *J* = 10.4, 2.5, 1.5 Hz), 5.16 (1H, ddd, *J* = 17.2, 2.7, 1.7 Hz), 4.90 (2H, dt, *J* = 5.2, 1.5) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 162.7, 139.2, 131.2, 127.2, 119.1, 118.0, 111.2, 51.1 ppm. HRMS (ESI+) *m*/*z* found $[M+H]^+$ 213.9867, $C_8H_9NO^{79}Br^+$ required 213.9862. These data are in accordance with those previously reported.[11]

4.3.3. 1-Allyl-6-vinylpyridin-2(1*H*)-one (22)

Prepared according to general procedure 2 using 1-allyl-6-bromopyridin-2(1*H*)-one (**18**, 100 mg, 0.47 mmol), $Pd(dppf)Cl_2$ (38 mg, 0.047 mmol) and potassium vinyltrifluoroborate (**19**,

94 mg, 0.71 mmol). Note that the reaction was degassed again prior to heating at 65 °C overnight. The crude reaction material was purified by column chromatography (SiO_2, 1:1 petroleum ether/EtOAc) to afford **22** as an orange oil (120 mg, 0.74 mmol, 64%). R_f 0.29 (SiO_2, EtOAc). IR ν_{max} (cm^{-1}) ($CDCl_3$): 3088 (w, C–H), 2940 (w, C–H), 1653 (str, C=O), 1621 (med, C=C), 1577 (med, C=C), 1543 (str, C=C). ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.28 (1H, ddd, J = 9.1, 7.0, 0.2 Hz), 6.64 (1H, ddd, J = 17.1, 11.0, 0.2 Hz), 6.54 (1H, dd, J = 9.1, 1.2 Hz), 6.28 (1H, dd, J = 7.0, 1.2 Hz), 5.93 (1H, ddt, J = 17.2, 10.5, 4.7 Hz), 5.73 (1H, dd, J = 17.1, 1.2 Hz), 5.45 (1H, dd, J = 11.0, 1.1 Hz), 5.19 (1H, dtd, J = 10.4, 1.8, 1.0 Hz), 5.01 (1H, dtd, J = 17.2, 1.8, 1.0 Hz), 4.67 (2H, dt, J = 4.7, 1.8 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 162.7, 147.6, 138.9, 132.1, 130.3, 121.5, 119.5, 116.6, 104.9, 46.6 ppm. HRMS (ESI+) m/z found $[M+H]^+$ 162.0916, $C_{10}H_{12}NO^+$ required 162.0913 and $[M+Na]^+$ 184.0734, $C_{10}H_{11}NONa^+$ required 184.0733.

4.3.4. 1-Allyl-6-(prop-1-en-2-yl)pyridin-2(1*H*)-one (23)

Prepared according to General Procedure 2 using 1-allyl-6-bromopyridin-2(1*H*)-one (**18**, 145 mg, 0.68 mmol), Pd(dppf)Cl_2·CH_2Cl_2 (63 mg, 0.068 mmol) and isopropenylboronic acid pinacol ester (**20**, 181 mg, 0.20 ml, 1.08 mmol). Note that the reaction was degassed again prior to heating at 65 °C for 48 h. The crude reaction material was purified by column chromatography (SiO_2, 1:1 petroleum ether/EtOAc) to afford **23** as a yellow oil (70 mg, 0.40 mmol, 59%). R_f 0.18 (SiO_2, 1:1 petroleum ether/EtOAc). IR ν_{max} (cm^{-1}) (neat): 2986 (w, C–H), 1659 (str, C=O), 1578 (med, C=C), 1547 (str, C=C). ^1H NMR (500 MHz, $CDCl_3$) δ_H = 7.27 (1H, dd, J = 9.2, 6.7 Hz), 6.50 (1H, dd, J = 9.2, 1.5 Hz), 5.98 (1H, dd, J = 6.7, 1.5 Hz), 5.95 (1H, ddt, J = 17.4, 10.4, 5.1 Hz), 5.29 (1H, app quintet, J = 1.5 Hz), 5.16 (1H, ddd, J = 10.4, 2.8, 1.5 Hz), 5.10 (1H, app dt, J = 2.4, 1.0 Hz), 5.01 (1H, ddd, J = 17.4, 2.8, 1.5 Hz), 4.59 (2H, dt, J = 5.1, 1.5 Hz), 2.02 (3H, dd, J = 1.5, 1.0 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 163.0, 151.6, 139.6, 139.1, 133.1, 119.2, 119.0, 116.5, 105.5, 47.8, 23.8 ppm. HRMS (ESI+) m/z found $[M+H]^+$ 176.1068, $C_{11}H_{14}NO^+$ required 176.1075.

4.3.5. 1-Allyl-6-(1-phenylvinyl)pyridin-2(1*H*)-one (24)

Prepared according to general procedure 2 using 1-allyl-6-bromopyridin-2(1*H*)-on (**18** 250 mg, 1.17 mmol), Pd(dppf)Cl_2·CH_2Cl_2 (109 mg, 0.12 mmol) and 1-phenylvinylboronic acid (**21**, 259 mg, 1.75 mmol). Note that the reaction was degassed again prior to heating at 65 °C for 72 h. The crude reaction material was purified by column chromatography (SiO_2, 3:2 petroleum ether/EtOAc) to afford **24** as an orange oil (160 mg, 0.67 mmol, 58%). R_f 0.21 (SiO_2, 1:1 petroleum ether/EtOAc). IR ν_{max} (cm^{-1}) (neat): 3080 (w, C–H), 1653 (str, C=O), 1579 (med, C=C), 1544 (str, C=C), 1494 (med, C=C), 1446 (med, C=C). ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.35 (1H, dd, J = 9.2, 6.7), 7.35–7.31 (3H, m), 7.29–7.26 (2H, m), 6.60 (1H, dd, J = 9.2, 1.4 Hz), 6.18 (1H, dd, J = 6.7, 1.4 Hz), 5.83 (1H, d, J = 0.7 Hz), 5.69 (1H, ddt, J = 17.2, 10.4, 5.2 Hz), 5.41 (1H, d, J = 0.7 Hz), 4.98 (1H, ddd, J = 10.4, 2.8, 1.4 Hz), 4.84 (1H, ddd, J = 17.2, 2.8, 1.6 Hz), 4.35 (2H, d, J = 5.2 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 163.2, 149.2, 143.2, 138.9, 137.5, 132.3, 129.0, 128.9, 126.1, 120.1, 118.5, 116.8, 108.3, 47.9 ppm. HRMS (ESI+) m/z found $[M+H]^+$ 238.1239, $C_{16}H_{16}NO^+$ required 238.1232.

4.3.6. Indolizin-5(3*H*)-one (25)

Prepared according to general procedure 4 using 1-allyl-6-vinylpyridin-2(1*H*)-one (**22**, 27 mg, 0.17 mmol) and Hoveyda–Grubbs second generation catalyst (11 mg, 0.017 mmol). Note that the solution was degassed prior to being stirred at 50 °C overnight. The crude reaction material was purified by column chromatography (SiO_2, gradient 20:1 to 19:1 to 18:2 CH_2Cl_2/MeOH) to gie **25** as an orange-brown oil (13 mg, 0.098 mmol, 57%). R_f 0.18 (SiO_2, 19:1 CH_2Cl_2/MeOH). IR ν_{max} ($CDCl_3$)/cm^{-1} 2927 (str, C–H), 2852 (med, C–H), 1661 (str, C=O), 1595 (med, C=C). ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.48 (1H, dd, J = 9.1, 7.0 Hz), 6.84 (1H, dt, J = 6.1, 2.0 Hz), 6.69 (1H, dt, J = 6.1, 2.0 Hz), 6.49 (1H, d, J = 9.1 Hz), 6.38 (1H, d, J = 7.0 Hz), 4.72 (2H, t, J = 2.0 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 161.6, 150.7, 140.1, 134.7, 126.4, 116.1, 100.5, 55.1 ppm. HRMS (ESI+) m/z found $[M+H]^+$ 134.0603, $C_8H_8NO^+$ required 134.0606.

4.3.7. Methyl 2-((6-bromo-2-oxopyridin-1(2*H*)-yl)methyl)acrylate (39)

Prepared according to general procedure 1 using 6-bromopyridin-2(1*H*)-one (**16**, 400 mg, 2.53 mmol) and methyl-2-(bromomethyl)acrylate (**35**, 819 mg, 0.55 mL, 4.60 mmol). The crude reaction material was purified by column chromatography (SiO_2, gradient 7:3 to 1:1 petroleum ether/EtOAc) to afford **39** as an off-yellow solid (484 mg, 1.78 mmol, 77%). R_f 0.37 (SiO_2, 3:7 petroleum ether/EtOAc). Mp 68.8–70.2 °C ($CDCl_3$). IR ν_{max} (cm^{-1}) ($CDCl_3$): 3113 (w, C–H), 2953 (w, C–H), 1718 (str, C=O of ester), 1665 (str, C=O of pyridone), 1589 (med, C=C), 1510 (str, C=C). ^1H NMR (500 MHz, $CDCl_3$) δ_H = 7.21 (1H, dd, J = 9.3, 7.2 Hz), 6.57 (1H, dd, J = 9.3, 1.2 Hz), 6.53 (1H, dd, J = 7.2, 1.2 Hz), 6.30 (1H, t, J = 1.9 Hz), 5.20 (1H, t, J = 1.9 Hz), 5.16 (2H, t, J = 1.9 Hz), 3.83 (3H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 165.6, 162.6, 139.5, 134.1, 127.2, 124.3, 119.2, 111.4, 52.1, 49.0 ppm. HRMS (ESI+) m/z found $[M+H]^+$ 271.9927, $C_{10}H_{11}NO_3^{79}Br^+$ required 271.9922 and $[M+Na]^+$ 293.9750, $C_{10}H_{10}NO_3^{79}BrNa^+$ required 293.9742. These data are in accordance with those previously reported.[11]

4.3.8. Ethyl 2-((6-bromo-2-oxopyridin-1(2*H*)-yl)methyl)acrylate (40)

Prepared according to general procedure 1 using 6-bromopyridin-2(1*H*)-one (**16**, 0.63 g, 3.66 mmol) and ethyl(2-bromomethyl)acrylate (**36**, 0.61 ml, 4.39 mmol, 1.2 equiv). The crude reaction material was purified by column chromatography (SiO_2, 1:1 petroleum ether/EtOAc) to afford **40** as a black solid (0.59 g, 2.06 mmol, 56%). R_f 0.45 (SiO_2, 1:1, petroleum ether/EtOAc). Mp: 77–78 °C (1:1 petroleum ether/EtOAc). IR ν_{max} (cm^{-1}) (neat): 2987 (w, C–H), 1721 (med, C=O), 1713 (med, C=O), 1656 (str, C=O), 1583 (med, C=C), 1506 (str, C=C), 1423 (med, C=C). ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.18 (1H, dd, J = 9.2, 7.2 Hz), 6.54 (1H, dd, J = 9.2, 1.2 Hz), 6.50 (1H, dd, J = 7.2, 1.2 Hz), 6.27 (1H, t, J = 1.8 Hz), 5.16 (1H, t, J = 2.0 Hz), 5.13 (2H, t, J = 1.9 Hz, 4.26 (2H, q, J = 7.1 Hz), 1.31 (3H, t, J = 7.1 Hz) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ_H 165.1, 162.6, 139.4, 134.3, 127.2, 123.9, 119.1, 111.4, 61.2, 49.0, 14.1 ppm. HRMS (ESI+): m/z found $[M+H]^+$ 286.0081, $C_{11}H_{13}NO_3^{79}Br^+$ required 286.0079.

4.3.9. 6-Bromo-1-(2-(trifluoromethyl)allyl)pyridin-2(1*H*)-one (41)

Prepared according to general procedure 1 using 6-bromopyridin-2(1*H*)-one (**16**, 0.61 g, 3.53 mmol) and 2-(bromomethyl)-3,3,3-trifluoropropene (**37**, 0.82 g, 4.36 mmol, 1.2 equiv). The crude reaction material was purified by column chromatography (SiO_2, 4:1 petroleum ether/EtOAc) to afford **41** as a red solid (0.28 g, 1.00 mmol, 29%). R_f 0.18 (SiO_2, 4:1 petroleum ether/EtOAc). Mp: 56–57 °C (4:1 petroleum ether/EtOAc). IR ν_{max} (cm^{-1}) (neat): 3111 (w, C–H), 3012 (w, C–H), 1655 (str, C=O), 1582 (str, C=C), 1509 (str, C=C), 1427 (med, C=C), 1141 (str, C–F), 1110 (str, C–F). ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.20 (1H, dd, J = 9.2, 7.1 Hz), 6.56 (1H, dd, J = 9.3, 1.2 Hz), 6.53 (1H, dd, J = 7.2, 1.2 Hz), 5.79 (1H, heptet, J = 1.4 Hz), 5.07–5.04 (2H, m), 5.04–5.02 (1H, m) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 162.4, 139.6, 132.6 (q, J = 30.3 Hz), 126.8, 124.0, 119.2, 117.9, 111.6, 46.9 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ_F = -67.95 ppm. HRMS (ESI+): m/z found $[M+H]^+$ 281.9731, $C_9H_8NOF_3^{79}Br^+$ required 281.9741.

4.3.10. 6-Bromo-1-(2-chloroallyl)pyridine-2(1*H*)-one (42)

Prepared according to general procedure 1 using 6-bromopyridin-2(1*H*)-one (**16**, 0.50 g, 2.85 mmol) and 2,3-dichloropropene (**38**, 0.32 ml, 3.43 mmol, 1.2 equiv). The crude reaction material was purified by column chromatography (SiO_2, 3:1 petroleum ether/EtOAc) to afford **42** as a brown liquid (0.28 g, 1.14 mmol, 40%). R_f 0.29 (SiO_2, 3:1 petroleum ether/EtOAc). IR ν_{max} (cm^{-1}) (CH_2Cl_2): 3048 (w, C–H), 1669 (med, C=O), 1641 (w), 1590 (w, C=C), 1513 (med, C=C. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.19 (1H, dd, *J* = 9.2, 7.2 Hz), 6.55 (1H, dd, *J* = 9.2, 1.2 Hz), 6.51 (1H, dd, *J* = 7.2, 1.2 Hz), 5.37 (1H, dt, *J* = 2.7, 1.5 Hz), 5.05 (1H, dd, *J* = 2.4, 1.6 Hz), 5.03 (2H, d, *J* = 1.6 Hz) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ_c = 162.5, 139.8, 135.0, 127.1, 119.5, 113.0, 111.6, 53.3 ppm. HRMS (ESI+): *m*/*z* found $[M+H]^+$ 247.9475, $C_8H_8NO^{35}Cl^{79}Br^+$ required 247.9478.

4.3.11. 1-(2-(Trifluoromethyl)allyl)-6-vinylpyridin-2(1*H*)-one (31)

Prepared by general procedure 3 using 6-bromo-1-(2-(trifluoromethyl)allyl)pyridin-2(1*H*)-one (**41**, 105.8 mg, 0.38 mmol) and tributyl(vinyl)tin (**43**, 114 μL, 0.39 mmol). The crude reaction material was purified by column chromatography (9:1 SiO_2/KF, 2:1 petroleum ether/EtOAc) to afford **31** as a yellow solid (38.4 mg, 0.18 mmol, 45%). R_f 0.17 (SiO_2, 1:1 petroleum ether/EtOAc). Mp: 125–126 °C (2:1 petroleum ether/EtOAc). IR ν_{max} (cm^{-1}) (neat): 1659 (med, C=O), 1586 (med, C=C), 1546 (med, C=C). ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.33 (1H, dd, *J* = 9.2, 6.9 Hz), 6.56 (1H, ddd, *J* = 9.1, 3.5, 1.3 Hz), 6.46 (1H, ddd, *J* = 17.0, 11.0, 0.7 Hz), 6.36–6.30 (1H, m), 5.80–5.73 (2H, m, 2H), 5.50 (1H, dd, *J* = 11.0, 1.0 Hz, 1H), 5.02 (1H, tq, *J* = 2.3, 1.2 Hz), 4.81 (2H, d, *J* = 2.6 Hz) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 162.4, 147.2, 139.4, 133.4, 129.3, 124.1, 122.6, 119.6, 118.0, 105.3, 42.5 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ_F = -68.35 ppm. HRMS (ESI+): *m*/*z* found $[M+H]^+$ 230.0782, $C_{11}H_{11}NOF_3^+$ required 230.0793.

4.3.12. 1-(2-Chlorallyl)-6-vinylpyridin-2(1*H*)-one (32)

Prepared by general procedure 3 using 6-bromo-1-(2-chloroallyl)pyridine-2(1*H*)-one (**42**, 100.7 mg, 0.41 mmol) and tributyl(vinyl)tin (**43**, 114 μL, 0.39 mmol). The crude reaction material was purified by column chromatography (9:1 SiO_2/KF, 2:1 petroleum ether/EtOAc) to afford **32** as a yellow solid (36.7 mg, 0.19 mmol, 46%). R_f 0.18 (SiO_2, 2:1 petroleum ether/EtOAc). Mp: 212–213 °C (2:1, petroleum ether/EtOAc). IR ν_{max} (cm^{-1}) (neat): 2947 (w, C–H), 2170 (w, C–H), 2018 (w), 1656 (str, C=O), 1582 (str, C=C), 1545 (str, C=O), 1428 (med, C=C). ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.32–7.27 (1H, m), 6.58 (1H, dd, *J* = 17.1, 11.0 Hz), 6.54–6.49 (1H, m), 6.34–6.27 (1H, m), 5.78–5.72 (1H, m), 5.49 (1H, dd, *J* = 11.0, 1.1 Hz), 5.32 (1H, q, *J* = 1.8 Hz), 4.99 (1H, q, *J* = 2.0 Hz), 4.76 (2H, s) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 162.3, 147.2, 139.4, 135.5, 129.7, 122.4, 119.6, 112.6, 105.1, 49.2 ppm. HRMS (ESI+): *m*/*z* found $[M+H]^+$ 196.0524, $C_{10}H_{11}NO^{35}Cl^+$ required 196.0529.

4.3.13. Methyl 2-((2-oxo-6-vinylpyridin-1(2*H*)-yl)methyl)acrylate (33)

Prepared according to general procedure 2 using methyl 2-((6-bromo-2-oxopyridin-1(2*H*)-yl)methyl)acrylate (**39**, 200 mg, 0.74 mmol), $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (69 mg, 0.074 mmol) and potassium vinyltrifluoroborate (**19**, 149 mg, 1.11 mmol). The crude reaction material was purified by column chromatography (SiO_2, 1:1 petroleum ether/EtOAc) to afford **22** as a yellow gum (109 mg, 0.49 mmol, 66%). R_f 0.16 (SiO_2, 3:7 petroleum ether/EtOAc). IR ν_{max} (cm^{-1}) ($CDCl_3$): 2952 (w, C–H), 1718 (str, C=O of ester), 1659 (str, C=O of pyridone), 1583 (med, C=C), 1542 (str, C=C). ^1H NMR (500 MHz, $CDCl_3$) δ_H = 7.36 (1H, dd, *J* = 9.2, 7.0 Hz), 6.64 (1H, dd, *J* = 9.2, 1.2 Hz), 6.50 (1H, dd, *J* = 17.0, 10.9 Hz), 6.38 (1H, dd, *J* = 7.0, 1.2 Hz), 6.30 (1H, t, *J* = 1.8 Hz), 5.78 (1H, dd, *J* = 17.0, 0.9 Hz), 5.48 (1H, dd, *J* = 10.9, 0.9 Hz), 5.23 (1H, t, *J* = 1.8 Hz), 4.94 (2H, t, *J* = 1.8 Hz), 3.83 (3H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 165.7, 162.6, 147.4, 139.3, 134.5, 129.8, 124.9, 122.2, 119.4, 105.4, 52.2, 44.7 ppm. HRMS (ESI+) *m*/*z* found $[M+H]^+$ 220.0979, $C_{12}H_{14}NO_3^+$ required 220.0974 and $[M+Na]^+$ 242.0798, $C_{12}H_{13}NO_3Na^+$ required 242.0793.

4.3.14. Ethyl 2-((2-oxo-6-vinylpyridin-1-(2*H*)-yl)methyl-acrylate (34)

To a stirred solution of ethyl 2-((6-bromo-2-oxopyridin-1(2*H*)-yl)methyl)acrylate (**40**, 0.10 g, 0.41 mmol, 1 equiv) and triphenylphosphine (10 mol %) in anhydrous THF (10 ml/mmol) was added potassium carbonate (3 equiv) and palladium acetate (5 mol %) under nitrogen. Potassium vinyltrifluoroborate (**19**, 1.2 equiv) was added and the solution was heated overnight at 65 °C. After TLC showed full conversion the cooled solution was poured into water (200 mL) and extracted with CH_2Cl_2 (4 × 100 mL). The combined organic phases were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified via column chromatography (SiO_2, 3:2 petroleum ether/EtOAc) to afford **34** as a brownish solid (0.04 g, 0.20 mmol, 54%). R_f 0.24 (SiO_2, 3:2 petroleum ether/EtOAc). Mp 116–117 °C (3:2 petroleum ether/EtOAc). IR ν_{max} (cm^{-1}) (CH_2Cl_2) 2917(w, C–H), 2850 (w, C–H), 1717 (med, C=O), 1658 (med, C=O), 1583 (med, C=C), 1545 (med, C=C), 1445 (w, C=C). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.32 (1H, dd, *J* = 9.2, 6.9 Hz), 6.60–6.51 (1H, m), 6.51–6.42 (1H, m), 6.33 (1H, dt, *J* = 7.0, 1.9 Hz), 6.27 (1H, t, *J* = 1.9 Hz), 5.74 (1H, dd, *J* = 16.9, 1.1 Hz), 5.45 (1H, dd, *J* = 11.0, 1.1 Hz), 5.19 (1H, t, *J* = 2.0 Hz), 4.91 (2H, t, *J* = 1.9 Hz), 4.26 (2H, q, *J* = 7.0 Hz), 1.33–1.31 (3H, m) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 165.3, 162.6, 147.3, 139.1, 134.9, 129.9, 124.5, 122.0, 119.6, 105.0, 61.2, 44.7, 14.2 ppm. HRMS (ESI+): *m*/*z* found $[M+H]^+$ 234.1123, $C_{13}H_{16}NO_3^+$ required 234.1130.

4.3.15. Methyl 5-oxo-3,5-dihydroindolizine-2-carboxylate (44)

Prepared by general procedure 4 using methyl 2-((2-oxo-6-vinylpyridin-1(2*H*)-yl)methyl)acrylate (**33**, 100 mg, 0.45 mmol) and Hoveyda–Grubbs 2nd generation catalyst (29 mg, 0.045 mmol). Note that the mixture was degassed prior to being stirred at 50 °C for approximately 18 h. The crude reaction material was purified by column chromatography (SiO_2 97:3 CH_2Cl_2/MeOH) to afford **44** as a brown solid (52 mg, 0.27 mmol, 60%). R_f 0.16 (SiO_2, 97:3 CH_2Cl_2/MeOH). Mp 118.5–121.0 °C ($CDCl_3$). IR ν_{max} (cm^{-1}) ($CDCl_3$): 3094 (w, C–H), 2951 (w, C–H), 2852 (w, C–H), 1713 (str, C=O of ester), 1650 (str, C=O of pyridone), 1608 (med, C=C), 1573 (str, C=C), 1542 (med, C=C), 1513 (str, C=C). ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.47 (1H, dd, *J* = 9.1, 6.9 Hz), 7.33 (1H, t, *J* = 1.8 Hz), 6.57 (1H, d, *J* = 9.1 Hz), 6.50 (1H, d, *J* = 6.9 Hz), 4.85 (2H, t, *J* = 0.8 Hz), 3.85 (3H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 162.5, 160.9, 148.9, 139.8, 137.7, 132.8, 119.3, 103.9, 54.0, 52.5 ppm. HRMS (ESI+) *m*/*z* found $[M+H]^+$ 192.0661, $C_{10}H_{10}NO_3^+$ required 192.0655.

4.3.16. Methyl 2-((2-oxo-6-(1-phenylvinyl)pyridin-1(2*H*)-yl)methyl)acrylate (45)

Prepared according to general procedure 2 using methyl 2-((6-bromo-2-oxopyridin-1(2*H*)-yl)methyl)acrylate (**39**, 300 mg, 1.10 mmol), $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (103 mg, 0.11 mmol) and 1-phenylvinylboronic acid (**21**, 245 mg, 1.65 mmol). The crude reaction material was purified by column chromatography (SiO_2, 1:1 petroleum ether/EtOAc) to afford **45** as a yellow gum (240 mg, 0.81 mmol, 74%). R_f 0.28 (SiO_2, 3:7 petroleum ether/EtOAc). Mp 83.6–84.5 °C (EtOAc). IR ν_{max} (cm^{-1}) ($CDCl_3$): 2954 (w, C–H), 1716 (str, C=O of ester), 1658 (str, C=O of pyridone), 1583 (str, C=C), 1546 (str, C=C), 1494 (w, C=C). ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.31 (1H, dd, *J* = 8.8, 6.4 Hz), 7.32–7.30 (3H, m), 7.24–7.21 (2H, m), 6.65 (1H, d), 6.24 (1H, d, *J* = 6.4 Hz), 6.06 (1H, s), 5.75 (1H, s), 5.35 (1H, s), 5.05 (1H, s), 4.63 (2H, s), 3.68 (3H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$)

δ_C = 165.7, 163.0, 149.4, 143.2, 139.3, 137.2, 134.7, 129.0, 128.9, 126.3, 124.2, 120.1, 118.8, 108.5, 51.9, 45.7 ppm. HRMS (ESI+) *m*/*z* found $[M+H]^+$ 296.1280, $C_{18}H_{18}NO_3^+$ required 296.1287 and $[M+Na]^+$ 318.1101, $C_{18}H_{17}NO_3Na^+$ required 318.1106.

4.3.17. Methyl 2-((2-oxo-6-(prop-1-en-2-yl)pyridin-1(2*H*)-yl)-methyl)acrylate (46)

Prepared according to general procedure 2 using methyl 2-((6-bromo-2-oxopyridin-1(2*H*)-yl)methyl)acrylate (**39**, 280 mg, 1.03 mmol), $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (97 mg, 0.10 mmol) and isopropenylboronic acid pinacol ester (**20**, 277 mg, 0.31 mL, 1.65 mmol). The crude reaction material was purified by column chromatography (SiO_2, gradient 8:2 to 7:3 petroleum ether/EtOAc) to afford **46** as a pale orange-brown solid (109 mg, 0.493 mmol, 74%). R_f 0.37 (SiO_2, 19:1 CH_2Cl_2/MeOH). Mp 40.9–42.3 °C (1,2-dichloroethane). IR ν_{max} (cm^{-1}) ($CDCl_3$): 2954 (w, C–H), 1717 (str, C=O of ester), 1657 (str, C=O of pyridone), 1580 (med, C=C), 1546 (str, C=C), 1512 (med, C=C). ^1H NMR (500 MHz, $CDCl_3$) δ_H = 7.34 (1H, dd, *J* = 8.9, 6.7 Hz), 6.58 (1H, d, *J* = 8.9 Hz), 6.26 (1H, s), 6.06 (1H, d, *J* = 6.7 Hz), 5.26 (1H, t, *J* = 1.4 Hz), 5.15 (1H, s), 5.06 (1H, s), 4.83 (2H, s), 3.80 (3H, s), 1.99 (3H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 165.8, 162.7, 151.8, 139.6, 139.2, 135.4, 124.1, 119.5, 119.1, 106.0, 52.1, 45.9, 23.6 ppm. HRMS (ESI+) *m*/*z* found $[M+H]^+$ 234.1136, $C_{13}H_{16}NO_3^+$ required 234.1130 and $[M+Na]^+$ 256.0954, $C_{13}H_{15}NO_3Na^+$ required 256.0950.

4.3.18. Sodium 1-allyl-3,5-bis(ethoxycarbonyl)-6-oxo-1,6-dihydropyridin-2-olate (55)

To a stirred solution of **53** (1.00 g, 5.86 mmol, 1 equiv) in EtOH (6 mL) were added diethyl ethoxymethylenemalonate (**54**, 1.26 mL, 6.29 mmol, 1.1 equiv) and EtONa (0.39 g, 5.79 mmol, 1 equiv). The reaction mixture was heated at 90 °C for 2 h. The solution was then cooled down and a precipitate formed. The solid was filtered off and dried giving the title compound as yellow solid (1.05 g, 3.32 mmol, 57 %). A small sample was dissolved in conc. HCl and extracted with chloroform to give the neutral compound. The characterization data for the neutral compound is given below: R_f = 0.15 (SiO_2, 9:1 CH_2Cl_2/MeOH). Mp >210 °C (decomp., CH_2Cl_2/MeOH). IR ν_{max} (cm^{-1}) (neat): 3304 (sharp, w, O–H), 2977 (w, C–H), 1743 (C=O), 1701 (med, C=O), 1675 (str, C=O), 1650 (str, C=O), 1608 (med, C=C), 1525 (str, C=C or C=N), 1415 (str, C=C). ^1H NMR (500 MHz, DMSO-d_6) δ_H = 8.50 (1H, s), 5.80–5.73 (1H, m), 4.96–4.92 (2H, m), 4.41 (2H, d, *J* = 4.9 Hz), 4.09 (4H, q, *J* = 7.0), 1.20 (6H, t, *J* = 7.0 Hz) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ_C = 165.2, 162.2, 146.7, 134.6, 115.4, 97.1, 58.9, 40.7, 14.6 ppm. HRMS (ESI+) *m*/*z* found $[M+H]^+$ 296.1145, $C_{14}H_{18}NO_6^+$ required 296.1134.

4.3.19. Diethyl 1-allyl-6-bromo-2-oxo-1,2-dihydropyridine-3,5-dicarboxylate (51)

To a stirred solution of sodium 1-allyl-3,5-bis(ethoxycarbonyl)-6-oxo-1,6-dihydropyridin-2-olate (**55**, 1.00 g, 3.15 mmol, 1.0 equiv) in DMF (47.3 mL) at 0 °C was added PBr_3 (0.5 mL, 4.73 mmol, 1.5 equiv). The mixture was allowed to warm to room temperature and stirred for 8 h. More PBr_3 (0.1 mL) was added and the mixture stirred for an additional hour. The solvent was removed under reduced pressure. Water and Et_2O were added to the residue. The organic and aqueous layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure to give a pale yellow solid. This was purified by column chromatography (SiO_2, 8:2 petroleum ether/EtOAc) to give **51** was a beige solid (905.5 mg, 2.53 mmol, 80%).[11]

4.3.20. Diethyl 1-allyl-2-oxo-6-vinyl-1,2-dihydropyridine-3,5-dicarboxylate (57)

Prepared by general procedure 3 using diethyl 1-allyl-6-bromo-2-oxo-1,2-dihydropyridine-3,5-dicarboxylate (**51** 0.40 g, 1.13 mmol, 1.0 equiv) and tributyl(vinyl)tin (**43**, 359 μL, 1.13 mmol). The crude reaction material was purified by column chromatography (9:1 SiO_2/KF, 3:2 petroleum ether/EtOAc) to afford **57** as a white solid (0.26 g, 0.84 mmol, 75%). R_f 0.33 (SiO_2, 3:2 petroleum ether/EtOAc). Mp 37–38 °C (3:2 petroleum ether/EtOAc). IR ν_{max} (cm^{-1}) (neat): 3086 (w, C–H), 2992 (w, C–H), 1715 (med), 1692 (str, C=O), 1673 (str, C=O), 1593 (med, C=C), 1520 (med, C=C). ^1H NMR (400 MHz, $CDCl_3$) δ_H = 8.58 (1H, s), 6.79 (1H, dd, *J* = 17.8, 11.9 Hz), 5.88 (1H, ddt, *J* = 17.2, 10.3, 5.1 Hz), 5.67 (1H, dd, *J* = 11.9, 0.8 Hz), 5.45 (1H, dd, *J* = 17.9, 0.8 Hz), 5.21 (1H, dq, *J* = 10.4, 1.3 Hz), 5.06 (1H, dtd, *J* = 17.2, 1.8, 0.9 Hz), 4.75 (2H, dt, *J* = 5.2, 1.7 Hz), 4.37 (2H, q, *J* = 7.1 Hz), 4.25 (2H, q, *J* = 7.1 Hz, 2H), 1.37 (3H, t, *J* = 7.1 Hz), 1.31 (3H, t, *J* = 7.1 Hz) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 164.8, 164.6, 158.8, 155.9, 144.4, 131.4, 129.4, 123.2, 118.3, 117.9, 109.3, 61.5, 61.3, 48.4, 14.3, 14.1 ppm. HRMS (ESI+): *m*/*z* found $[M+H]^+$ 306.1326, $C_{16}H_{20}NO_5^+$ required 306.1341.

4.3.21. Diethyl 1-allyl-6-(3-methoxy-3-oxoprop-1-en-2-yl)-2-oxo-1,2-dihydropyridine-3,5-dicarboxylate (58)

Prepared by general procedure 3 using diethyl 1-allyl-6-bromo-2-oxo-1,2-dihydropyridine-3,5-dicarboxylate (**51** 99.5 mg, 0.28 mmol, 1.0 equiv) and methyl 2-(tributylstannyl)acrylate (**56**, 0.11 mL, 0.31 mmol). The crude reaction material was purified by column chromatography (9:1 SiO_2/KF, gradient 7:3 to 4:1 to 1:1 petroleum ether/EtOAc) to afford **58** as a yellow liquid (74.8 mg, 0.21 mmol, 75%). R_f 0.16 (SiO_2, 2:1 petroleum ether/EtOAc). IR ν_{max} (cm^{-1}) (CH_2Cl_2): 2988 (w, C–H), 1738 (med, C=O), 1715 (med, C=O), 1667 (med, C=O), 1596 (w, C=C), 1534 (med, C=C). ^1H NMR (500 MHz, $CDCl_3$) δ_H =8.66 (1H, s), 6.66 (1H, s), 5.83 (1H, ddt, *J* = 17.2, 10.6, 5.4 Hz), 5.74 (1H, s), 5.19 (1H, dq, *J* = 10.3, 1.3 Hz), 5.09–5.01 (1H, m), 4.92 (1H, ddt, *J* = 15.3, 5.2, 1.7 Hz), 4.39 (2H, q, *J* = 7.1 Hz), 4.30 (1H, ddt, *J* = 15.4, 5.8, 1.5 Hz), 4.24 (2H, qd, *J* = 7.1, 2.2 Hz), 3.78 (3H, s), 1.39 (3H, t, *J* = 7.1 Hz), 1.29 (3H, t, *J* = 7.1 Hz) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 164.5, 163.9, 163.7, 158.8, 153.9, 144.1, 134.7, 131.5, 129.6, 119.3, 118.3, 109.3, 61.6, 61.5, 52.8, 49.3, 14.3, 14.1 ppm. HRMS (ESI+): *m*/*z* found $[M+H]^+$ 364.1384, $C_{18}H_{22}NO_7^+$ required 364.1396.

4.3.22. Diethyl 5-hydroxyindolizine-6,8-dicarboxylate (59)

Prepared by general procedure 4 using diethyl 1-allyl-2-oxo-6-vinyl-1,2-dihydropyridine-3,5-dicarboxylate (**57**, 101.9 mg, 0.32 mmol) and Hoveyda–Grubbs 2nd generation catalyst (5 mol %). The crude reaction material was purified by column chromatography (SiO_2, gradient 98:2 to 4:6 to 0:100 petroleum ether/EtOAc) to afford **61** as a green liquid (50.4 mg, 0.18 mmol, 57%). R_f 0.47 (SiO_2, EtOAc). IR ν_{max} (cm^{-1}) (CH_2Cl_2): 2980 (w, C–H), 1646 (str, C=O), 1575 (med, C=C), 1556 (med, C=C). ^1H NMR (500 MHz, DMSO-d_6) δ_H = 8.24–7.97 (1H, m), 7.51 (1H, s), 6.81–6.32 (2H, m), 4.36–4.13 (4H, m), 1.35–1.22 (6H, m) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ_C = 167.9, 164.9, 159.1, 129.1, 113.0, 111.2, 103.5, 101.7, 89.0, 59.3, 14.6. HRMS (ESI+): *m*/*z* found $[M+Na]^+$ 300.0827, $C_{14}H_{15}O_5N^{23}Na^+$ required 300.0842.

4.3.23. 6,8-Diethyl 1-methyl 5-hydroxyindolizine-1,6,8-tricarboxylate (60)

Prepared by general procedure 4 using diethyl 1-allyl-6-(3-methoxy-3-oxoprop-1-en-2-yl)-2-oxo-1,2-dihydropyridine-3,5-dicarboxylate (**58**, 137.5 mg, 0.36 mmol) and Hoveyda–Grubbs 2nd generation catalyst (5 mol %). The crude reaction material was purified by column chromatography (SiO_2, EtOAc) to afford **60** as a green liquid (52.2 mg, 0.16 mmol, 41%) R_f 0.26 (SiO_2, EtOAc). IR ν_{max} (cm^{-1}) (CH_2Cl_2): 2988 (w, C–H), 1658 (med, C=O), 1566 (med, C=C), 1534 (med, C=C). ^1H NMR (500 MHz, DMSO-d_6) δ_H = 7.86 (1H, s), 7.47 (1H, d, *J* = 3.2 Hz), 6.73 (1H, s), 4.14 (4H, dq, *J* = 27.5, 7.0 Hz), 3.65 (3H, s), 1.26 (3H, t, *J* = 7.1 Hz), 1.19 (3H, t, *J* = 7.1 Hz) ppm. ^{13}C NMR (126 MHz,

DMSO-d_6) δ_C = 167.4, 165.4, 157.5, 133.4, 113.6, 111.5, 109.0, 106.3, 104.0, 91.7, 59.8, 59.2, 50.8, 14.5 ppm. HRMS (ESI+): *m*/*z* found $[M+Na]^+$ 358.0888, $C_{16}H_{17}O_7N^{23}Na^+$ required 358.0897.

4.3.24. Ethyl 1-allyl-2-amino-5-cyano-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxylate (66)

To a stirred solution of ally amine (**69**, 3 mL, 40.0 mmol, 1 equiv) and ethyl 2-cyanoacetate (**67**, 8.5 mL, 80.1 mmol, 2 equiv) in EtOH (24 mL) was added benzaldehyde (**68**, 4 mL, 40.0 mmol, 1 equiv) and heated at 90 °C overnight. To the cooled solution water (200 mL) was added and the mixture was basified with NaOH pellets. The aqueous phase was extracted with EtOAc (3 × 200 mL) the combined organic phases dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, gradient 1:1 to 2:3 petroleum ether/EtOAc then 99:1 MeOH/CH_2Cl_2) to afford **66** as a white solid (0.92 g, 2.84 mmol, 7%). R_f 0.16 (SiO_2, 1:1 petroleum ether/EtOAc). Mp 190.3–191.0 °C (99:1 MeOH/CH_2Cl_2). IR ν_{max} (cm^{-1}) (neat): 3378 (med, N–H), 3176 (med, N–H), 3085 (w, C–H), 2990 (w, C–H), 2211 (med, C≡N), 1659 (str, C=O), 1600 (str, C=C), 1546 (str, C=C), 1499 (med, C=C), 1485 (med), 1467 (str, C=C). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.55 (2H, s), 7.45–7.37 (3H, m), 7.25–7.21 (2H, m), 5.91 (1H, ddt, *J* = 17.4, 10.6, 5.3 Hz), 5.47–5.32 (2H, m), 4.85 (2H, dt, *J* = 5.5, 1.8 Hz), 3.78 (2H, q, *J* = 7.1 Hz), 0.60 (3H, t, *J* = 7.1 Hz) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 167.4, 161.7, 158.9, 156.5, 138.5, 130.2, 128.7, 128.1, 126.8, 119.3, 115.8, 92.4, 92.1, 60.7, 44.8, 12.9 ppm. HRMS (ESI+): *m*/*z* found $[M+H]^+$ 324.1354, $C_{18}H_{18}N_3O_3^+$ required 324.1348.

4.3.25. Ethyl 1-allyl-2-bromo-5-cyano-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxylate (64)

To a stirred solution of ethyl 1-allyl-2-amino-5-cyano-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxylate (**66**, 0.21 g, 0.64 mmol, 1 equiv) in anhydrous MeCN (6 mL) was added CuBr·SMe_2 (0.25 g, 1.19 mmol, 1.9 equiv). The reaction mixture was heated at 65 °C and isoamylnitrite (0.17 ml, 1.24 mmol, 1.9 equiv) in MeCN (2.5 mL) was added drop wise. The solution was heated for 2 h and monitored by TLC. After complete consumption of starting material, 1 M HCl (20 mL) was added to the cooled solution and extracted with EtOAc (4 × 20 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was purified by column chromatography (SiO_2, 1:1, petroleum ether/EtOAc) to afford **64** as a red film (0.10 g, 0.26 mmol, 41 %). R_f 0.8 (SiO_2, 1:1 petroleum ether/EtOAc). IR ν_{max} (cm^{-1}) (CH_2Cl_2): 2367 (w), 2231 (w, C≡N), 2162 (w), 1731 (med, C=O), 1667 (str, C=O), 1572 (med, C=C), 1534 (med), 1518 (med), 1483 (str, C=C). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.50–7.43 (3H, m), 7.40–7.34 (2H, m), 5.93 (1H, ddt, *J* = 16.7, 10.8, 5.8 Hz), 5.42–5.33 (2H, m), 5.02 (2H, dt, *J* = 5.8, 0.3 Hz), 3.96 (2H, q, *J* = 7.2 Hz), 0.90 (3H, t, *J* = 7.2 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C = 164.4, 158.6, 157.4, 133.7, 132.6, 130.5, 129.3, 128.8, 127.5, 120.5, 118.9, 114.1, 103.4, 62.4, 52.7, 13.3 ppm. HRMS (ESI+): *m*/*z* found $[M+H]^+$ 387.0353, $C_{18}H_{16}N_2O_3^{79}Br^+$ required 387.0344.

4.3.26. Ethyl 1-allyl-5-cyano-6-oxo-4-phenyl-2-vinyl-1,6-dihydropyridine-3-carboxylate (72)

Prepared by general procedure 3 using ethyl 1-allyl-2-bromo-5-cyano-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxylate (**64**, 96.2 mg, 0.25 mmol) and tributyl(vinyl)tin (**43**, 90.0 μL, 0.31 mmol). The crude reaction material was purified by column chromatography (9:1 SiO_2/KF, 3:2 petroleum ether/EtOAc) to afford **72** as a yellow solid (45.8 mg, 0.14 mmol, 55%). R_f 0.32 (SiO_2, 3:2, petroleum ether/EtOAc). Mp 98–99 °C (3:2 petroleum ether/EtOAc). IR ν_{max} (cm^{-1}) (neat): 2929 (w, C–H), 2335 (w, C–H), 2224 (med, C≡N), 2162 (w), 1732 (str, C=O), 1654 (str, C=O), 1638 (str, C=O), 1582 (med, C=C), 1568 (med; C=C), 1509 (str, C=C). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.48–7.41 (3H, m), 7.38–7.31 (2H, m), 6.71–6.57 (1H, m), 5.90 (1H, ddt, *J* = 17.2, 10.5, 5.3 Hz), 5.78–5.66 (2H, m), 5.34–5.28 (1H, m), 5.19 (1H, dtd, *J* = 17.2, 1.7, 0.8 Hz), 4.71 (2H, dt, *J* = 5.4, 1.6 Hz), 3.84 (2H, q, *J* = 7.2 Hz, 2H), 0.86 (3H, t, *J* = 7.1 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 165.5, 159.0, 157.9, 150.0, 134.5, 130.3, 130.1, 128.7, 128.0, 127.5, 126.2, 118.8, 115.3, 114.6, 103.4, 61.9, 48.4, 13.4 ppm. HRMS (ESI+): *m*/*z* found $[M+H]^+$ 335.1381, $C_{20}H_{19}N_2O_3^+$ required 335.1396.

4.3.27. Ethyl 1-allyl-5-cyano-2-(3-methoxy-3-oxoprop-1-en-2-yl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxylate (73)

Prepared by general procedure 3 using ethyl 1-allyl-2-bromo-5-cyano-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxylate (**64**, 104.1 mg, 0.27 mmol) and methyl 2-(tributylstannyl)acrylate (**56**, 120 μL, 0.32 mmol). The crude reaction material was purified by column chromatography (9:1 SiO_2/KF, 1:1 petroleum ether/EtOAc) to afford **73** as a yellow film (31.0 mg, 0.08 mmol, 29%). R_f 0.56 (SiO_2, 1:1, petroleum ether/EtOAc). IR ν_{max} (cm^{-1}) (CH_2Cl_2): 2985 (w, C–H), 2229 (med, C≡N), 1725 (str, C=O), 1661 (str, C=O), 1572 (med, C=C), 1513 (str, C=C). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.46 (3H, qd, *J* = 5.2, 2.7 Hz), 7.42–7.34 (2H, m), 6.71 (1H, s), 5.92 (1H, s), 5.85 (1H, ddt, *J* = 17.1, 10.4, 5.6 Hz), 5.25 (1H, dq, *J* = 10.3, 1.3 Hz), 5.13 (1H, dq, *J* = 17.2, 1.4 Hz), 4.92 (1H, ddt, *J* = 15.3, 5.4, 1.6 Hz), 4.25 (1H, ddt, *J* = 15.3, 5.8, 1.5 Hz), 3.91–3.75 (5H, m), 0.83 (3H, t, *J* = 7.1 Hz) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 164.8, 163.6, 159.1, 158.1, 148.9, 134.8, 133.5, 132.7, 130.6, 130.2, 128.7, 127.5, 119.0, 115.4, 114.5, 104.5, 61.9, 53.1, 49.5, 13.2 ppm. HRMS (ESI+): *m*/*z* found $[M+H]^+$ 393.1465, $C_{22}H_{21}N_2O_5^+$ required 393.1450.

4.3.28. Ethyl 6-cyano-5-hydroxy-7-phenylindolizine-8-carboxylate (74)

Prepared by general procedure 4 using ethyl 1-allyl-5-cyano-6-oxo-4-phenyl-2-vinyl-1,6-dihydropyridine-3-carboxylate (**72**, 46.6 mg, 0.13 mmol) and Hoveyda–Grubbs 2nd generation catalyst (5 mol %). The crude reaction material was purified by column chromatography (SiO_2, EtOAc) to afford **74** as a yellow/green film (36.0 mg, 0.12 mmol, 41%). R_f 0.13 (SiO_2, EtOAc). IR ν_{max} (cm^{-1}) ($CH_2Cl_{2=}$): 3053 (w, C–H), 2983 (w, C–H), 2192 (med, C≡N), 1661 (med, C=O), 1590 (med, C=C), 1548 (med, C=C), 1512 (med), 1489 (med, C=C). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H = 7.37 (1H, dd, *J* = 2.9, 1.8 Hz), 7.34–7.25 (3H, m), 7.16–7.13 (2H, m), 6.51 (1H, dd, *J* = 3.5, 1.8 Hz), 6.49 (1H, dd, *J* = 3.5, 2.9 Hz), 3.73 (2H, q, *J* = 7.1 Hz), 0.70 (3H, t, *J* = 7.1 Hz) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ_C = 166.0, 158.3, 143.5, 141.3, 131.5, 128.3, 127.3, 126.5, 121.5, 112.4, 109.4, 101.6, 100.7, 75.2, 58.5, 13.5 ppm. HRMS (ESI+): *m*/*z* found $[M+Na]^+$ 329.0886, $C_{16}H_{17}O_7N^{23}Na^+$ required 329.0897.

4.3.29. 8-Ethyl 1-methyl 6-cyano-5-hydroxy-7-phenylindolizine -1, 8-dicarboxylate (75)

Prepared by general procedure 4 using ethyl 1-allyl-5-cyano-2-(3-methoxy-3-oxoprop-1-en-2-yl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxylate (**73**, 43.7 mg, 0.11 mmol) and Hoveyda–Grubbs 2nd generation catalyst (5 mol %). The crude reaction material was purified by column chromatography (SiO_2, EtOAc) to afford **74** as a yellow/green film (21.9 mg, 0.06 mmol, 54%) R_f 0.14 (SiO_2, EtOAc). IR ν_{max} (cm^{-1}) (CH_2Cl_2): 2984 (w, C–H), 2200 (w, C≡N), 1706 (med, C=O), 1662 (med, C0O), 1618 (med, C=C), 1525 (med, C=C), 1493 (med, C=C). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H = 7.50–7.47 (3H, m), 7.40–7.29 (3H, m), 7.19–7.17 (1H, m), 6.83–6.77 (1H, m), 3.80–3.71 (2H, m), 3.58 (3H, s), 0.83–0.75 (3H, m) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ_C = 166.4, 164.1, 160.0, 142.8, 138.5, 135.5, 128.6, 128.4, 127.5, 120.6, 115.2, 113.9, 110.5, 104.5, 103.1, 59.3, 50.4, 13.5 ppm. HRMS (ESI+): *m*/*z* found $[M+Na]^+$ 387.0936, $C_{20}H_{16}O_5N_2^{23}Na^+$ required 387.0951.

4.3.30. 1-Allyl-3-benzyl-6-vinylpyrimidine-2,4(1*H*,3*H*)-dione (80)

Prepared by general procedure 3 using 1-allyl-3-benzyl-6-bromopyrimidine-2,4(1*H*,3*H*)-dione (**79**, 0.15 g, 0.47 mmol) and tributyl(vinyl)tin (**43**, 0.15 mL, 0.51 mmol). The crude reaction material was purified by column chromatography (9:1 SiO_2/KF, 3:2 petroleum ether/EtOAc) to afford **80** as a white solid (0.10 g 0.37 mmol, 78%). R_f = 0.17 (SiO_2, 7:3 petroleum ether/EtOAc). Mp (CH_2Cl_2): 124–128 °C (3:2 petroleum ether/EtOAc). IR ν_{max} (cm^{-1}) (neat): 3370 (med, N–H), 3209 (med, N–H), 2985 (w, C–H), 2220 (med, C≡N), 1694 (med), 1667 (str, C=O), 1645 (w), 1616 (str, C=O), 1546 (str, C=C), 1509 (med, C=C), 1470 (str, C=C). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.44 (2H, d, J = 7.2 Hz), 7.30–7.10 (3H, m), 6.46 (1H, dd, J = 16.8, 10.8 Hz), 5.90–5.70 (3H, m), 5.55 (1H, d, J = 16.8 Hz), 5.14–5.06 (3H, m), 4.20 (2H, dt, J = 4.8. 1.6 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 162.5, 152.2, 151.7, 136.9, 131.9, 129.0, 128.5, 128.4, 127.6, 124.5, 117.2, 99.5, 47.4, 44.5 ppm. HRMS (ESI+) m/z found $[M+H]^+$ 269.1297, $C_{16}H_{17}N_2O_2^+$ required 269.1290.

4.3.31. Methyl 2-(3-allyl-1-benzyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)acrylate (82)

Prepared by general procedure 3 using 1-allyl-3-benzyl-6-bromopyrimidine-2,4(1*H*,3*H*)-dione (**79**, 0.15 g, 0.47 mmol) and methyl 2-(tributylstannyl)acrylate (**56**, 0.19 mL, 0.51 mmol). The crude reaction material was purified by column chromatography (9:1 SiO_2/KF, gradient 4:1 to 7:3 petroleum ether/EtOAc) to afford **82** as a pale yellow gum (0.11 g 0.34 mmol, 72%, 85:15 ratio of desired to undesired acrylic isomers). R_f = 0.27 (SiO_2, 7:3 petroleum ether/EtOAc). IR ν_{max} (cm^{-1}) (neat): 2955 (w, C–H), 1704 (med, C=O), 1656 (str, C=O). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.50 (2H, d, J = 7.0 Hz), 7.33–7.22 (3H, m), 6.60 (1H, d, J = 0.6 Hz), 5.96 (1H, d, J = 0.6 Hz), 5.75 (1H, ddt, J = 17.1, 10.7, 5.2 Hz), 5.65 (1H, s), 5.15–5.09 (3H, m), 5.03 (1H, dq, J = 17.2, 1.4 Hz), 4.25 (2H, br d), 3.78 (3H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C = 165.8, 162.0, 151.4, 150.2, 136.6, 134.7, 133.1, 131.8, 129.1, 128.3, 127.6, 117.4, 103.4, 52.8, 48.5, 44.5 ppm. HRMS (ESI+) m/z found $[M+H]^+$ 327.1340, $C_{18}H_{19}N_2O_4^+$ required 327.1345.

4.3.32. 2-Benzylpyrrolo[1,2-*c*]pyrimidine-1,3(2*H*,7*H*)-dione (78)

Prepared according to general procedure 4 using 1-allyl-3-benzyl-6-vinylpyrimidine-2,4(1*H*,3*H*)-dione (**80**, 0.03 g, 0.10 mmol) and Grubbs second generation catalyst (0.004 mg, 0.005 mmol). The crude reaction material was purified by column chromatography (SiO_2, 1:1 petroleum ether/EtOAc) to give **78** as an brown gum (0.02 g, 0.07 mmol, 71%). R_f = 0.07 (SiO_2, 1:1 petroleum ether/EtOAc). IR ν_{max} (cm^{-1}) (CH_2Cl_2): 3099 (w, C–H), 2922 (w, C–H), 2853 (w, C–H), 1782 (w, C=O), 1685 (med, C=O), 1646 (str, br, C=O). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.52–7.48 (2H, m), 7.32–7.27 (3H, m), 6.82 (1H, dt, J = 5.8, 2.1 Hz, H3), 6.49 (1H, dt, J = 6.1, 2.0 Hz), 5.80 (1H, s), 5.14 (2H, s), 4.66–4.64 (2H, m) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 164.2, 154.5, 149.7, 138.7, 137.1, 129.1, 128.4, 127.5, 125.6, 94.1, 55.0, 43.9 ppm. HRMS (ESI+) m/z found $[M+H]^+$ 241.0972, $C_{14}H_{13}N_2O_2^+$ required 241.0977.

4.3.33. Methyl 2-benzyl-1,3-dioxo-1,2,3,4-tetrahydropyrrolo[1,2-*c*]pyrimidine-5-carboxylate (83)

Prepared according to general procedure 4 using methyl 2-(3-allyl-1-benzyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)acrylate (**82**, 0.06 g, 0.20 mmol) and Grubbs second generation catalyst (0.01 g, 0.01 mmol). The crude reaction material was purified by column chromatography (SiO_2, 4:1 petroleum ether/EtOAc) to give **83** as a white solid (0.03 g, 0.10 mmol, 50%). R_f = 0.20 (SiO_2, 1:1 petroleum ether/EtOAc). Mp: 169–170 °C (hexane/EtOAc). IR ν_{max} (cm^{-1}) (neat): 3122 (w, C–H), 2955 (w, C–H), 2907 (w, C–H), 1738 (w, C=O), 1690 (str, br, C=O), 1589 (str, C=C). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.44 (2H, dd, J = 8.4, 2.0 Hz), 7.38 (1H, d, J = 3.2 Hz), 7.32–7.24 (3H, m), 6.68 (1H, d, J = 3.2 Hz), 5.10 (2H, s), 4.28 (2H, s), 3.81 (3H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 166.7, 163.9, 147.1, 135.9, 129.2, 128.6, 128.5, 128.1, 118.2, 115.6, 113.2, 51.6, 44.6, 32.2. HRMS (ESI+) m/z found $[M+Na]^+$ 321.0836, $C_{16}H_{14}N_2O_4Na^+$ required 321.0846. Crystal data for **83**: M = 298.29, monoclinic, a = 14.6992(3) Å, b = 11.7785(3) Å, c = 8.1996(2) Å, α = 90°, β = 102.716(2)°, γ = 90°, V = 1384.81(6) Å^3, T = 180(2) K, space group P2(1)/c, Z = 4, 16607 reflections collected, 4778 independent reflections (R_{int} = 0.0271). The final R_1 values were 0.04452 ($I > 2\sigma(I)$). The final $wR(F^2)$ values were 0.1070 ($I > 2\sigma(I)$). The final R_1 values were 0.0660 (all data). The final $wR(F^2)$ values were 0.1191 (all data).

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