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Ring-closing metathesis for the synthesis of heteroaromatics: evaluating routes to pyridines and pyridazines

Timothy J. Donohoe [a,*], John F. Bower [a], José A. Basutto [a], Lisa P. Fishlock [a], Panayiotis A. Procopiou [b], Cedric K.A. Callens [a,*,1]

[a] Department of Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford OX1 3TA, UK
[b] GlaxoSmithKline Research & Development Limited, Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, UK

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ABSTRACT

Ring-closing olefin metathesis (RCM) has been applied to the efficient synthesis of densely and diversely substituted pyridine and pyridazine frameworks. Routes to suitable metathesis precursors have been investigated and the scope of the metathesis step has been probed. The metathesis products function as precursors to the target heteroaromatic structures via elimination of a suitable leaving group, which also facilitates earlier steps by serving as a protecting group at nitrogen. Further functionalisation of the metathesis products is possible both prior to and after aromatisation. The net result is a powerful strategy for the *de novo* synthesis of highly substituted heteroaromatic scaffolds.

1. Introduction

Substituted pyridines and pyridazines represent privileged therapeutic agents and are the subunits of multiple classes of natural products.[1] As such, the development of synthetic methodologies, which combine high levels of regiocontrol and flexibility continue to be intensively researched within organic chemistry. In particular, approaches, which facilitate the *de novo* assembly of such heteroaromatic systems[2–4] have the potential to generate products, which would be difficult to assemble using more established transition metal-catalysed cross-coupling protocols.[5]

Recently, we have examined the scope of ring-closing olefin metathesis (RCM) for the synthesis of heteroaromatic frameworks.[6] This research is driven by the ease of handling, commercial availability and high substrate tolerance of *N*-heterocyclic carbene ligated catalysts such as the Grubbs–Hoveyda second generation system **1a**[7] and the Zhan 1B catalyst **1b**[8] (Fig. 1). Remarkably, and despite the routine use of olefin metathesis as a means of assembling carbo- and heterocyclic ring systems,[9] relatively little attention has been focussed upon the incorporation of this protocol into efficient strategies for the construction of aromatic and heteroaromatic compounds.[10–14] In this paper we present full details of recent studies from our laboratory on the application of RCM to the synthesis of pyridine and pyridazine scaffolds.[15–17]

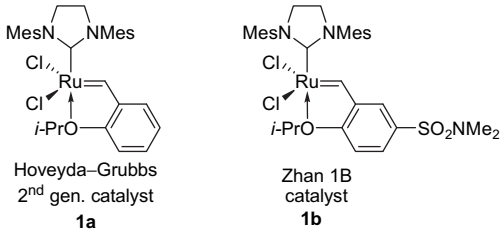

Figure 1. Commercially available olefin metathesis catalysts used in this study.

Two RCM-based scenarios for the synthesis of pyridines are delineated in Scheme 1. In the first (Route A), the corresponding α,β-unsaturated lactam **3**, which is potentially accessible via substrates such as **4**, represents the target for RCM. In this instance the amide nitrogen is equipped with a benzyloxy group, which acts as both a protecting group and as an inbuilt means of accessing the pyridine oxidation level via elimination. It was envisaged that the lactam carbonyl moiety could ultimately become a triflate group

* Corresponding authors. Tel.: +44 1865 275 649; fax: +44 1865 275 708.
E-mail address: timothy.donohoe@chem.ox.ac.uk (T.J. Donohoe).
[1] Author to whom correspondence regarding the X-ray crystal structures should be addressed.

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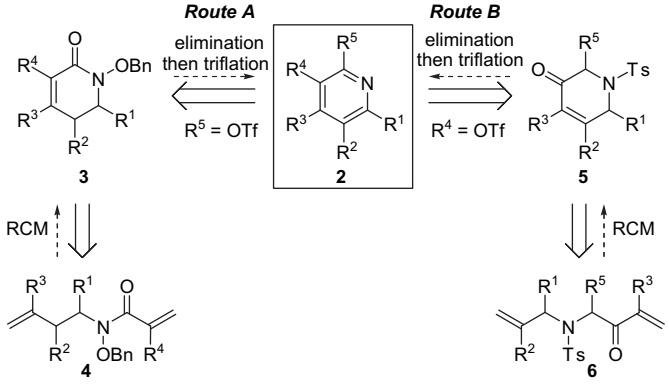
(R^5=OTf) and so provide opportunities for further functionalisation of the target pyridine **2**. In the second case (Route B), the carbonyl group is moved one further position around the ring to render **5** as the target for RCM. In this instance a tosyl group was considered optimal as the protecting/leaving group on nitrogen. Cyclic enone **5** is then potentially available via metathesis of substrates of general type **6**. In this case the carbonyl moiety potentially becomes a triflate group at R^4 with attendant opportunities for coupling.[18] For clarity, the substituent numbering used in Scheme 1 is retained throughout the subsequent Results and Discussion section.

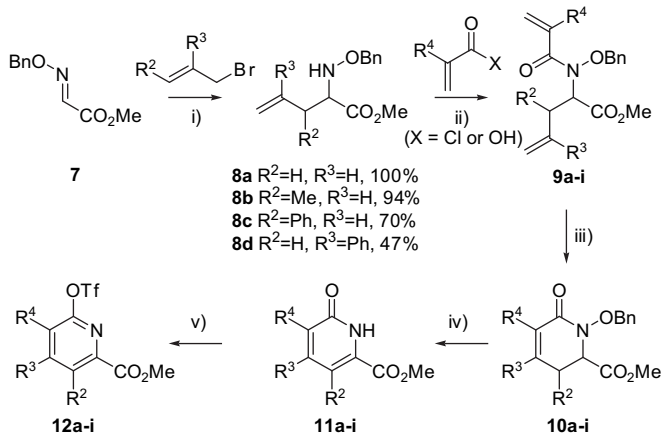


Scheme 1. Synthetic approaches to pyridines via RCM.

2. Results and discussion

2.1. Route A: acrylamide entry to pyridines

Our initial studies focussed on the generation of pyridines in accordance with the synthetic plan delineated in Route A (Scheme 2 and Table 1). To facilitate post-metathesis elimination of the alkoxy leaving group (and thus establish aromaticity) we initially chose to examine substrates where R^1 was a methyl carboxylate. As such, imino glyoxalate **7** became a suitable starting point.[19] This species is readily allylated in good yield (47–100%) by employing various allyl bromides under aqueous zinc-mediated conditions.[20] The resultant amino esters **8a–d** are then amenable to acylation with suitable acrylic acid or acryloyl chloride derivatives to provide the RCM precursors **9a–i** in high yield (58–97%).



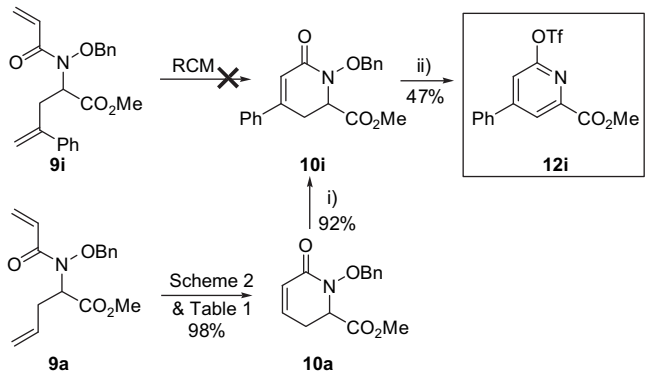
Scheme 2. Reagents and conditions: i) Zn, THF, aq NH_4Cl, rt, ii) Et_3N, CH_2Cl_2, rt, (for **9a–b**, **f–i**, X=Cl), or PPh_3, $(CCl_3)CN$, CH_2Cl_2, 0 °C to rt (for **9d** and **9e**, X=OH) or EDCI, CH_2Cl_2, −40 °C (for **9c**, X=OH), iii) **1a** (10 mol %), CH_2Cl_2, reflux or PhMe, 95 °C (for **10c**); iv) DBU, THF, rt, v) Comins' reagent, KHMDS, THF, −78 °C.

Table 1
Yields for the sequence depicted in Scheme 2

Entry	R^2	R^3	R^4	Yield (%)			
				ii)	iii)	iv)	v)
1 (a)	H	H	H	86	98	94	70
2 (b)	H	H	Me	83	88	89	94
3 (c)	H	H	CF_3	58	75	65	67
4 (d)	H	H	OEt	82	91	87	89
5 (e)	H	H	OBn	80	85	98	87
6 (f)	Me	H	H	90	97	93	n.d.
7 (g)	Ph	H	H	97	59	92	n.d.
8 (h)	Ph	H	Me	74	71	93	n.d.
9 (i)	H	Ph	H	91	<5	—	—

Using catalyst **1a**, examination of the key RCM step revealed a wide degree of flexibility with regard to substituents at R^2 (aryl and alkyl) and R^4 (alkyl, CF_3, alkoxy) and the corresponding α,β-unsaturated lactams **10a–h** were isolated in uniformly high yield.[21] Elimination of the benzyloxy group was then promoted using DBU to provide efficient access to the corresponding pyridones **11a–h**, which in turn, afforded the pyridine triflates **12a–e** when treated with Comins' reagent under basic conditions.[22] It is of note that the metathesis and aromatisation steps, if desired, can be conducted in one pot and with only minor decreases in synthetic efficiency. However, less colouration (presumably by traces of ruthenium) of the eventual pyridone products **11a–h** was observed when lactams **10a–h** were isolated prior to base-mediated elimination.

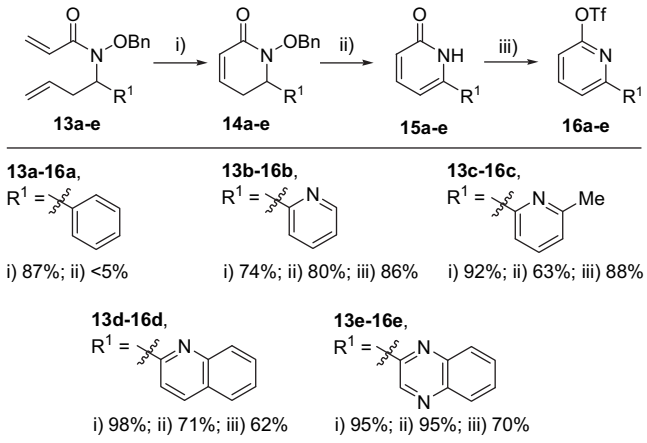
Limitations with respect to this approach to pyridines are evident when considering installation of substituents at R^3. For example, RCM of **9i** (Table 1, Entry 9), which requires catalyst initiation on either an electron deficient acrylamide moiety or a 1,1-disubstituted olefin, was not efficient and only traces of the target lactam **10i** were evident. A convenient and highly efficient solution to this problem involves modification of an appropriate substrate after the RCM step (Scheme 3). This is exemplified using the parent RCM product **10a**, which underwent smooth (oxidative) Heck reaction to furnish arylated derivative **10i**.[23] DBU promoted elimination and subsequent triflation then generated pyridine triflate **12i**. Evidently this sequence has the potential to introduce diverse R^3 substitution and, as such, the strategic value of effecting modifications to non-aromatic intermediates *en route* to the eventual aromatic target is clearly highlighted.



Scheme 3. Reagents and conditions: i) $Pd(OAc)_2$ (10 mol %), 1,10-phenanthroline (15 mol %), $PhB(OH)_2$, O_2, DMF, 50 °C, ii) a) DBU, THF, rt, b) Comins' reagent, KHMDS, THF, −78 °C to 0 °C.

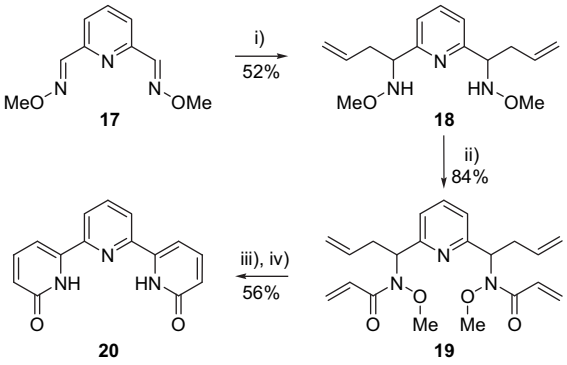
In the preceding examples, R^1 has been limited to a methyl ester substituent. Modification of this site has been investigated to assess the scope of the aromatising elimination step (Scheme 4). These studies revealed that an electron withdrawing group is required at

this site, presumably to acidify the adjacent proton. Thus, whereas phenyl derivative **14a** afforded none of the desired pyridone **15a** upon treatment with a variety of bases, pyridyl analogue **14b** was more amenable to elimination and pyridone **15b** was isolated in 80% yield after exposure to DBU. This chemistry can then be extended to other precursors bearing electron deficient heteroaromatic substituents (**14c**–**e**), which, as before, can be converted to the corresponding pyridine triflates **16a**–**e** after aromatisation. It is noteworthy that the RCM step, to convert **13a**–**e** to **14a**–**e**, requires significantly higher reaction temperatures (95 °C, PhMe) in these cases (cf. Scheme 2). This, in all likelihood, is a reflection of catalyst retardation by the Lewis basic groups present at R^1.



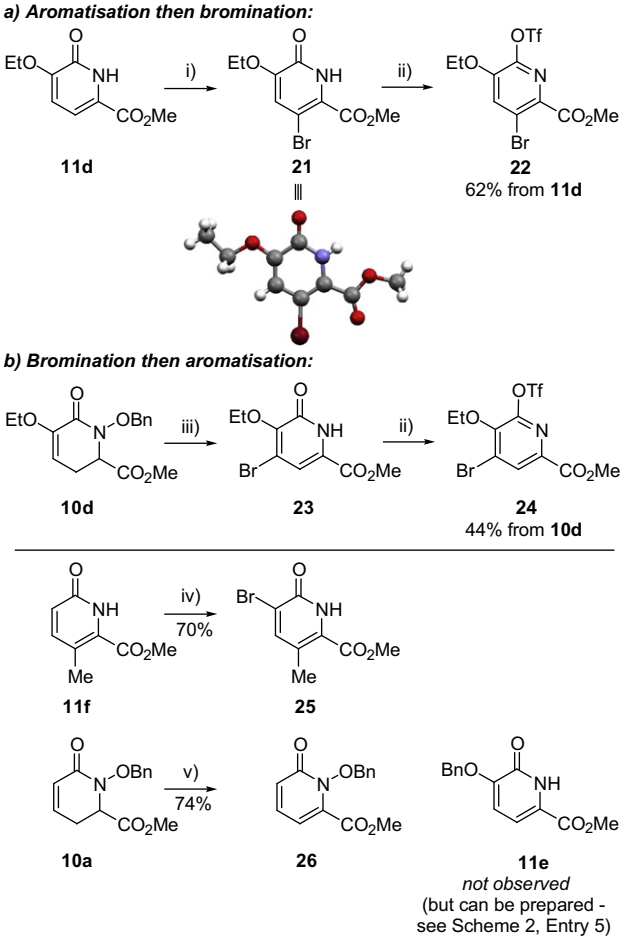
Scheme 4. Reagents and conditions: i) **1a** (10 mol %), PhMe, 95 °C, ii) DBU, THF, 50 °C, iii) Comins' reagent, KHMDS, THF, −78 °C.

The synthetic value of this chemistry is aptly showcased in the synthesis of tri-heteroaryl **20** (Scheme 5). Here, bis-allylation of symmetrical oxime **17** afforded **18**, which upon reaction with acryloyl chloride provided RCM precursor **19**. Cyclisation of **19** and elimination then provided an efficient entry to **20**. In this sequence, the use of an *N*-methoxy substituent *in lieu* of an *N*-benzyloxy group confers increased levels of reaction efficiency during the metathesis step, possibly due to the alleviation of steric factors.



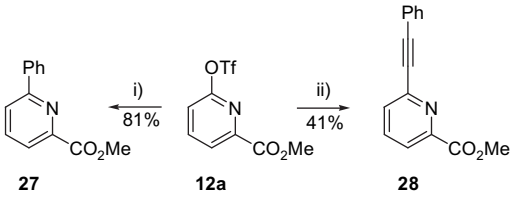
Scheme 5. Reagents and conditions: i) allyl bromide, Zn, THF, aq NH_4Cl, rt, ii) acryloyl chloride, Et_3N, CH_2Cl_2, rt, iii) **1a** (10 mol %), CH_2Cl_2, reflux, iv) DBU, THF, 50 °C.

It is also important to consider the combination of this RCM strategy with other more conventional approaches to heteroaromatic manipulation. In particular, the selective installation of halide substituents represents a very powerful avenue for further manipulation via transition metal-catalysed cross-coupling protocols.[5] In the context of the synthetic blueprint outlined above, one may consider halogenation both prior to and after aromatisation of the metathesis product (Scheme 6). This flexibility is notable as it allows sequence specific regiocontrol. For example, pyridone **11d** underwent bromination at R^2 to afford pyridine **22** after triflation (the structure of the bromination product **21** was confirmed by X-ray crystallographic analysis). On the other hand, upon bromination and subsequent treatment with DBU, lactam **10d** (the precursor to pyridone **11d**) afforded the alternative regioisomer **23**, which ultimately provided the alternative pyridine triflate **24**. Selective bromine installation at R^4 is also possible when the pyridone possesses an R^2 substituent (e.g., **11f** to **25**). Interestingly, lactam **10a** did not afford a brominated heteroaromatic upon base-mediated bromination but instead suffered oxidation to *N*-benzyloxy pyridone **26**. In our preliminary communication, the structure of **26** was mistakenly presented as that corresponding to the structural isomer **11e**[15]; our subsequent synthesis of **11e** (see Scheme 2 and Table 1) and comprehensive 2D NMR analysis of *N*-benzyloxy pyridone **26** corroborate the structural reassignment presented herein.



Scheme 6. Reagents and conditions: i) NBS, CH_2Cl_2, 40 °C, ii) Comins' reagent, KHMDS, THF, −78 °C, iii) Br_2, Et_3N, CH_2Cl_2, −10 °C, then DBU, THF, 50 °C, iv) NBS, MeCN, reflux, v) Br_2, CH_2Cl_2, 0 °C to rt, then DBU, THF, rt.

As alluded to in the Introduction section, the presence of an OTf group at R^5 was designed to provide further flexibility with regard to eventual pyridine derivatisation. To highlight this aspect of the strategy, pyridine **12a** was converted to biaryl **27** and alkynyl **28** derivatives under Suzuki and Sonogashira cross-coupling conditions, respectively, (both unoptimised, Scheme 7).[24] The efficient manipulation of the OTf group means that the viability of introducing substituents at every position (R^1–R^5) on the pyridine core has now been demonstrated.

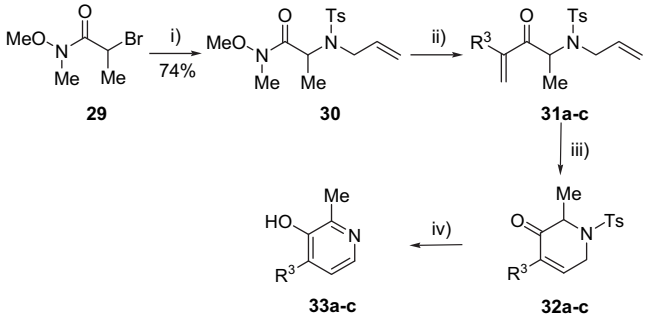


Scheme 7. Reagents and conditions: i) $Pd(PPh_3)_4$ (3 mol %), $PhB(OH)_2$, Na_2CO_3, 1,4-dioxane, 85 °C, ii) $Pd(PPh_3)_2Cl_2$ (8 mol %), phenyl acetylene, CuI (5 mol %), LiCl, Et_3N, DMF, 65 °C.

2.2. Route B: allylic amine entry to pyridines

Although our preliminary route to pyridines (Scheme 1, Route A) allowed access to differentially substituted motifs in a highly concise and efficient manner, specific limitations with this strategy prompted the evaluation of alternative sequences. In this context, the requirement of an acidifying substituent at R^5 (to enable alkoxy elimination) is potentially circumvented by moving the carbonyl unit one position around the ring system (as in **5**, Scheme 1, Route B). Additionally, for synthetic reasons, an alternative, sulfinate leaving group was deemed suitable and, as such, metathesis precursors of the general structure represented by **6** became the immediate targets.

Our initial route to compounds of this type is shown in Scheme 8 and Table 2. Here, displacement of α-bromo amide **29** with *N*-tosylallylamine, followed by vinylation of the Weinreb amide **30** provided a straightforward route to the target metathesis precursors **31a–c**.[25] Exposure of these substrates to catalyst **1a** in CH_2Cl_2 then effected highly efficient RCM to provide the corresponding cyclic enones **32a–c**. The target pyridines **33a–c** (R^4=OH) were then unmasked upon base-mediated elimination (DBU, THF, room temperature). As expected, these species are predominantly present as the indicated hydroxypyridines. A qualitative method for differentiating the phenolic and zwitterionic forms of a series of 3-hydroxypyridines by comparison of the observed chemical shift of C-3 in the ^{13}C NMR spectrum with a theoretical value has been reported previously.[26] Using this protocol, analysis of compound **33a** in $(CD_3)_2SO$ is not indicative of the predominance of the zwitterion in this instance. As before, bromination of these

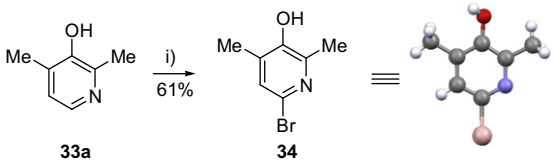


Scheme 8. Reagents and conditions: i) *N*-tosylallylamine, K_2CO_3, MeCN, reflux, ii) vinyl(R^3)Li, THF, −78 °C, iii) **1a** (1.5 mol %), CH_2Cl_2, reflux, (for **32a**), or **1a** (10 mol %) PhMe, 60–65 °C, (for **32b, c**), iv) DBU, THF, rt.

Table 2
Yields for the sequence depicted in Scheme 8

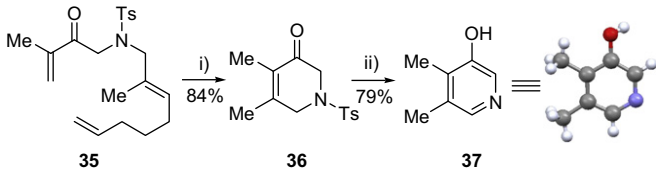
Entry	R^3	Yield (%)		
		ii)	iii)	iv)
1 (a)	Me	86	98	88
2 (b)	Ph	58	95	87
3 (c)	OEt	88	89	77

hydroxypyridine products (e.g., **33a** to **34**) is readily achieved and greatly expands the potential for further elaboration (Scheme 9). The structure of compound **34** was confirmed by X-ray crystallography.



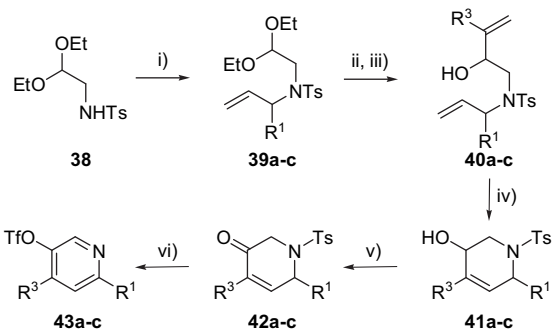
Scheme 9. Reagents and conditions: i) NBS, MeCN, reflux.

Difficulties associated with catalyst initiation on a 1,1-disubstituted or electron deficient olefin (cf. Section 2.1), mean that this approach does not facilitate the direct installation of substituents at R^2. In this instance, a ring-relay metathesis strategy was evaluated to circumvent this problem.[27] For example, upon treatment with catalyst **1a**, triene **35** efficiently afforded enone **36**, which contains a tetrasubstituted olefin; this sequence is presumably accompanied by expulsion of cyclopentene. Base-mediated elimination then delivered the target hydroxypyridine **37** in excellent overall yield. The outcome of this sequence was unambiguously determined by X-ray crystallographic analysis of **37** (Scheme 10).



Scheme 10. Reagents and conditions: i) **1a** (10 mol %), PhMe, 60 °C, ii) DBU, THF, rt.

In order to provide greater versatility with regard to substituent introduction at R^1 we have also explored a slightly different approach to the requisite metathesis precursors (Scheme 11 and Table 3). Here, the alternative pyridine C–N bond is formed by allylation of *N*-tosyl amine **38** under either Mitsunobu or Rh-catalysed[28] conditions (to afford **39a–c**). Acetal hydrolysis and vinylation of the resulting aldehydes then provided allylic alcohols **40a–c** in high yield. RCM of these allylic alcohol substrates **40a–c** was also highly efficient (80–91% yield of **41a–c**) and provided access to enones **42a–c** after oxidation with Jones' reagent or Dess–Martin periodinane. These substrates were then subjected to a smooth one-pot elimination–triflation sequence to ultimately generate the target pyridine triflates



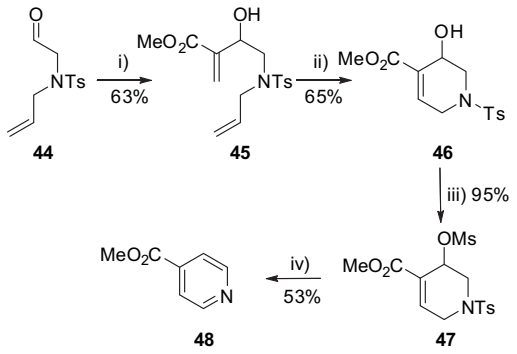
Scheme 11. Reagents and conditions: i) PPh_3, DIAD, THF, rt (for **39b**, **c**) or, $Rh(PPh_3)_3Cl$ (5 mol %), $P(OMe)_3$ (20 mol %), LiHMDS, THF, 30 °C (for **39a**), ii) aq HCl, acetone, 0 °C to rt, iii) vinyl(R^3)MgBr, THF, -78 °C to 0 °C, iv) **1a** (5 mol %), CH_2Cl_2, reflux, or 70 °C (for **41c**) v) Jones' reagent, acetone, 0 °C, or Dess–Martin, $NaHCO_3$, CH_2Cl_2, 0 °C (for **42c**), vi) DBU, THF, then $PhNTf_2$, rt.

Table 3
Yields for the sequence depicted in Scheme 11

Entry	R^1	R^3	Yield (%)					
			i)	ii)	iii)	iv)	v)	vi)
1 (a)	Ph	H	77	78	77	91	85	86
2 (b)	CH_2OBn	H	74	86	92	93	84	44
3 (c)	Me	Ph	88	95	68	80	67	77

43a–c in good yield. As such, the combination of two different C–N bond forming approaches facilitates introduction of substituents at all possible positions on the ring system.

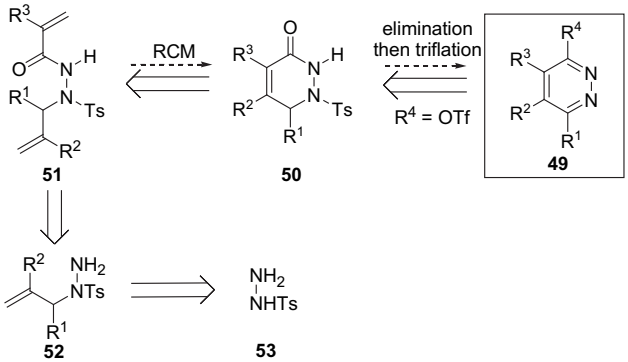
Clearly alternative routes to the metathesis precursors required for this heteroaromatisation approach can easily be envisaged. For example, allylic alcohols such as **45** are readily prepared via Morita–Baylis–Hillman reaction between aldehyde **44** and methyl acrylate and undergo efficient RCM to provide the corresponding cyclic system **46**.[29] In this case, activation of the alcohol as the mesylate **47** and double elimination, facilitated by the embedded acrylate moiety, provided pyridine **48** where R^3=CO_2Me (Scheme 12). Extension of this strategy, although not exhaustively assessed here, potentially provides an attractive entry to other more highly substituted pyridine derivatives.



Scheme 12. Reagents and conditions: i) Methyl acrylate, quinuclidine (25 mol %), MeOH, rt, ii) **1a** (5 mol %), CH_2Cl_2, reflux, iii) Ms_2O, Et_3N, CH_2Cl_2, rt, iv) KHMDS, THF, −78 °C to 0 °C.

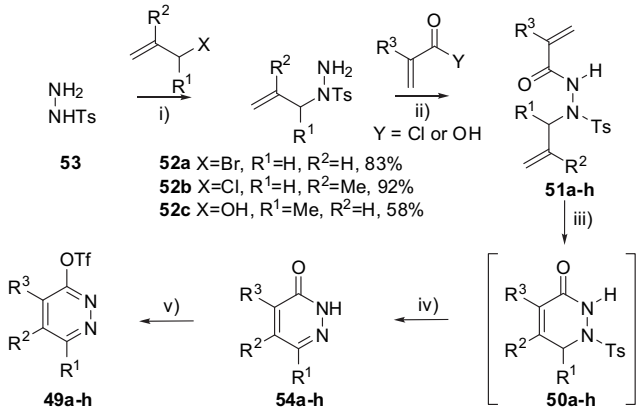
2.3. RCM approach to the synthesis of pyridazines

The success of our second generation approach to pyridines presented an opportunity to provide a related metathesis-based approach to pyridazines (Scheme 13). Specifically, RCM of substrates such as **51** should generate heterocycles **50**, which, upon elimination and triflation, provide the target structures **49**. The metathesis substrates **51** are potentially assembled by allylation of tosyl hydrazide **53** (to afford **52**) and subsequent acylation with appropriate acrylate derivatives.



Scheme 13.

Allylation of the sodium salt of commercially available tosyl hydrazide **53** was readily achieved at the more acidic NH using a variety of allyl chlorides or bromides in DMSO.[30] In the case of **52c** allylation was more efficient under Mitsunobu conditions.[31] Allylated tosyl hydrazides such as **52a–c** have been reported to decompose at room temperature to afford the corresponding deaminated olefins or rearrangement products.[30,31] Nevertheless, efficient coupling with a range of acryloyl chlorides or acrylic acid derivatives was realised to provide methathesis precursors **51a–h** in good yield. These intermediates were indefinitely stable under ambient conditions and readily purified by column chromatography. Examination of the proposed RCM/aromatisation protocol on the parent system **51a** indicated facile olefin metathesis (catalyst **1a**, CH_2Cl_2, 40 °C) to provide intermediate **50a**. Upon treatment with DBU, this species was eliminated in situ to ultimately generate pyridazinone **54a** in 87% yield over the one-pot, two-step sequence (Scheme 14 and Table 4).



Scheme 14. Reagents and conditions: i) NaH, DMSO, 0 °C to rt, (for X=Br or Cl), or PPh_3, DIAD, PhMe, 0 °C, (for X=OH), ii) *i*-Pr_2NEt, THF, 0 °C to rt (for **51a**, **b**, **f–h**, X=Cl), or Ghosez' reagent, *i*-Pr_2NEt, CH_2Cl_2, 0 °C to rt (for **51c**, **d**, X=OH), or EDCI, THF, −20 °C to rt, (for **51e**, X=OH), iii) **1a** (10 mol %), CH_2Cl_2, reflux, or (for **54f**), **1b** (10 mol %), CH_2Cl_2, 70 °C, iv) DBU, rt, v) Tf_2O, pyridine, 0 °C to rt.

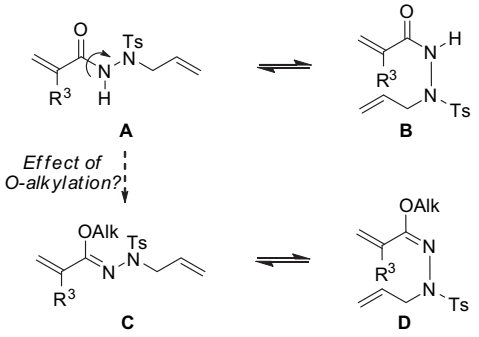
Table 4
Yields for the sequence depicted in Scheme 14

Entry	R^1	R^2	R^3	Yield (%)		
				ii)	iii, iv)	iv)
1 (a)	H	H	H	88	87	60
2 (b)	H	H	Me	75	91	86
3 (c)	H	H	OEt	59	<5%	—
4 (d)	H	H	Ph	30	<5%	—
5 (e)	H	H	CF_3	61	<5%	—
6 (f)	H	Me	H	80	70	72
7 (g)	H	Me	Me	52	<5%	—
8 (h)	Me	H	H	73	76	70

Extension of these conditions to more highly alkylated pyridazinones is achievable and, indeed, substituents can be introduced at all ring positions (Entries 2, 6 and 8, Table 4). In the case of **51f** (Entry 6), which requires non-trivial catalyst initiation, catalyst **1a** was inefficient but using **1b** (at 70 °C) allowed the formation of pyridazinone **54f** in 70% yield. Unfortunately, the formation of tetrasubstituted olefins, as required for **54g** (Entry 7), was not achievable, even under these modified conditions. The pyridazinone products are then readily converted to the corresponding pyridazine triflates **49** upon treatment with Tf_2O[32] and so are setup for further functionalisation via transition metal-catalysed cross-coupling.[5] It should be noted, that the pyridazine triflates described here were contaminated with ca. 4–8% of the corresponding

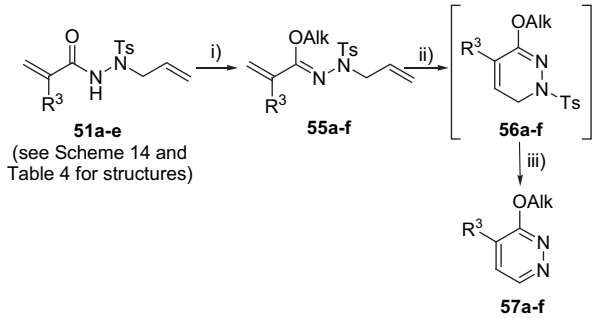
N-triflated pyridazinone. ^{1}H NMR monitoring of $CDCl_3$ solutions of, for example, **49b** shows gradual conversion to this byproduct at room temperature; related *O*→*N* rearrangements have been reported previously in the literature.[33]

A limitation of this approach to pyridazines resides in an inability to extensively manipulate the readily introducible R^3 substituent. For example, whereas alkyl groups (Entry 2) are tolerated at this site, other substituents (Entries 3–5) are not. This is particularly curious given the success of related systems described in the earlier pyridine oriented studies. We appreciated that successful ring-closing metathesis requires a suitable conformation (**A** vs **B**) about the amide moiety to bring the reactant olefin into the proximity of the tethered Ru-alkylidene. As such, we investigated the possibility of initial amide O-alkylation, with Meerwein's salt[34] and derivatives thereof, to enable RCM of the corresponding imidates. Here, we hoped that the presence of increased steric bulk at oxygen in conjunction with removal of any potentially unfavourable hydrogen bonding interactions between N–H and R^3 (especially when R^3=CF_3 or OEt) might influence the imidate geometry (**C** vs **D**) and facilitate successful RCM (Scheme 15).



Scheme 15.

Treatment of **51a** with either trimethyl- or triethyloxonium tetrafluoroborate cleanly produced the desired imidates **55a** and **55b**, which were isolated upon neutralisation with aq $NaHCO_3$.[35] These species underwent efficient metathesis (to **56a** and **56b**) and, upon treatment of the crude product with *t*-BuOK, the corresponding alkoxy-substituted pyridazines **57a**[36] and **57b**[37] were obtained in excellent yield (Scheme 16 and Table 5). Examination of the tolerance of the metathesis step to R^3 substitution revealed that, once again, alkyl groups performed well (Entry 3) but no further expansion of the scope of the metathesis was evident. For example, although **55e** (R^3=Ph) could be prepared, we were unable to induce RCM. Conversely, O-alkylation of **51c** or **51e**, to provide **55d** (R^3=OEt) or **55f** (R^3=CF_3), respectively, was not possible and only starting material was returned, even under forcing conditions (Scheme 16 and Table 5). Notably, these initial approaches to pyridazines provide methods for the regiodefined introduction of alkyl



Scheme 16. Reagents and conditions: i) Et_3OBF_4 or Me_3OBF_4, CH_2Cl_2, reflux, ii) **1a** (5 mol %), CH_2Cl_2, reflux, iii) *t*-BuOK, THF, 0 °C.

Table 5
Yields for the sequence depicted in Scheme 16

Entry	Alk	R^3	Yield (%)	
			i)	ii,iii)
1 (a)	Me	H	48	74
2 (b)	Et	H	95	83
3 (c)	Et	Me	84	88
4 (d)	Et	OEt	<5	—
5 (e)	Et	Ph	83	<5
6 (f)	Et	CF_3	<5	—

ring-substituents. Modification of a pre-established pyridazine core using conventional cross-coupling techniques would be expected to be less suitable for such a task. Nevertheless, the evaluation of alternative and more general strategies for preparing pyridazines represents a continuing aspect of our current research programme.

3. Conclusions

In summary, RCM of suitably functionalised precursors provides a powerful method for the regiodefined synthesis of diversely substituted heteroaromatics. In the present study we have assessed the scope and limitations of this concept in the context of strategies for the synthesis of pyridine and pyridazine scaffolds. Two distinct routes to pyridines have been presented, each ultimately providing efficient and flexible entries to the pyridine core. Modification of the metathesis products, both prior to and after aromatisation, has enabled the introduction of diverse substitution, including functionality amenable to further manipulation (e.g., halide and triflate substituents). Related strategies to pyridazines have also been presented. Clearly olefin metathesis offers significant potential for the *de novo* synthesis of diverse heteroaromatic classes. Studies towards this broad goal are continuing in our laboratory and will be reported in due course.

4. Experimental

4.1. General procedures and methods

All commercially available reagents were used without purification unless otherwise stated. CH_2Cl_2, PhMe, THF and Et_2O were dried by filtration through an activated alumina purification column. Petrol refers to petroleum ether in the boiling range 40–60 °C. Flash column chromatography (FCC) was performed using oven dried Merck Kieselgel 60 (40–63 μm). Proton nuclear magnetic resonance spectra (NMR) were recorded at 400 MHz or 500 MHz. ^{13}C NMR spectra were recorded at 100 MHz or 125 MHz as stated. Coupling constants are quoted to the nearest 0.5 Hz. Where mixtures of isomers (e.g., diastereoisomers and rotamers) have been characterized together integrals are normalized to the major isomer. Mass spectra under the conditions of electrospray ionisation (ESI) were recorded on a Fisons Platform II. Mass spectra under the conditions of field ionisation (FI) were recorded on a Micromass LCT. Mass spectra under the conditions of chemical ionisation (CI) were recorded on a Fisons Autospec-oaTof. Infrared spectra (IR) were recorded as evaporated films or KBr discs. Melting points were obtained using a Leica VMTG heated-stage microscope and are uncorrected.

*4.1.1. General procedure A: acylation of amine **8a** with α-alkoxyacrylic acids*[38]. Triphenylphosphine (300 mol %) was added portionwise to a solution of the corresponding acid (200 mol %) and trichloroacetonitrile (0.30 mL/mmol) in CH_2Cl_2 (0.90 mL/mmol) at 0 °C. After 30 min a solution of amine **8a** (100 mol %) and Et_3N (400 mol %) in CH_2Cl_2 (3 mL/mmol) was added dropwise. The

mixture was stirred at 0 °C for 1 h and then at room temperature overnight. The mixture was diluted with CH_2Cl_2 (10 mL/mmol) and washed with saturated aq $NaHCO_3$ (5 mL/mmol). The organic portion was dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by FCC, under the conditions noted, afforded the corresponding amide.

4.1.2. General procedure B: ring-closing metathesis of acrylamides and allylic alcohols. Catalyst **1a** (1–10 mol %) was added to a solution of the corresponding metathesis precursor (100 mol %) in the specified, argon sparged solvent (20 mL/mmol). The mixture was then heated at the specified temperature until TLC analysis indicated that starting material was fully consumed. The reaction mixture was concentrated in vacuo. Purification of the residue by FCC, under the conditions noted, afforded the corresponding product.

4.1.3. General procedure C: aromatisation of dihydropyridones. DBU (500 mol %) was added to a solution of the corresponding α,β-unsaturated lactam (100 mol %) in THF (2 mL/mmol) and the reaction was stirred at the indicated temperature until TLC analysis indicated that starting material was fully consumed. The reaction mixture was then concentrated in vacuo. Purification of the residue by FCC, under the conditions noted, afforded the corresponding pyridone.

4.1.4. General procedure D: triflation of pyridones. KHMDS (0.5 M in PhMe, 200 mol %) was added dropwise to a solution of the corresponding pyridone (100 mol %) and Comins' reagent[22] (200 mol %) in THF (10 mL/mmol) at −78 °C. The resulting brown mixture was stirred at −78 °C for 1 h and then warmed to room temperature over 3 h. The solution was then diluted with hexane (20 mL/mmol) and washed with saturated aq Na_2CO_3 (10 mL/mmol). The organic portion was dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by FCC, under the conditions noted, afforded the corresponding pyridine triflate.

4.1.5. General procedure E: O-alkylation of acrylamides. Trimethyloxonium or triethyloxonium tetrafluoroborate (300 mol %) was added to a solution of the appropriate acrylamide (100 mol %) in anhydrous CH_2Cl_2 (2 mL/mmol) and the resulting mixture was heated at reflux for 40 h. The mixture was then cooled to room temperature and poured into ice-cold, saturated aq $NaHCO_3$ solution (50 mL/mmol) and extracted with Et_2O (2×50 mL/mmol). The organic extracts were combined, washed with brine (50 mL/mmol), dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by FCC, under the conditions noted, afforded the corresponding *O*-alkylated adducts.

4.1.6. General procedure F: RCM and aromatisation of imidates. Argon sparged CH_2Cl_2 (20 mL/mmol) was added to an argon purged, resealable reaction tube containing the appropriate metathesis precursor (100 mol %) and catalyst **1a** (10 mol %). The reaction tube was sealed and then heated at 40 °C for the time stated. The mixture was then cooled to room temperature and concentrated in vacuo. The residue was dissolved in anhydrous THF (5 mL/mmol) and cooled to 0 °C. *t*-BuOK (200 mol %) was added and the mixture was warmed to room temperature. The mixture was stirred until elimination was complete (TLC monitoring, ca. 15–30 min) and was then diluted with CH_2Cl_2 (15 mL/mmol) prior to filtration through a plug of cotton wool. The eluent was concentrated in vacuo and the residue was purified by FCC, under the conditions noted, to afford the corresponding pyridazine.

4.2. Methods and data

Experimental procedures and spectroscopic data, which were included as Supplementary data within Refs 15 and 17 have been omitted from here. Information regarding crystallographic data for structures **34** and **37** is contained within Ref. 17. Crystallographic data for structure **21** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 735316.

4.2.1. 2-(Benzyloxy)acrylic acid. Sodium chlorite (19.3 g, 0.21 mol) was added to pH 7 phosphate buffer (0.75 M, 300 mL) and stirring was continued until full dissolution occurred. This solution was added to a solution of 2-(benzyloxy)acrylaldehyde[39] (5.95 g, 36.6 mmol), *t*-BuOH (150 mL) and 2-methyl-2-butene (30 mL, 0.28 mol) at 0 °C and stirring was continued at room temperature for 24 h. The organic layer was isolated, dried (Na_2SO_4) and then concentrated in vacuo. The residue was then recrystallised (petrol/EtOAc) to afford the title carboxylic acid (4.36 g, 67%) as a white solid; δ_H (400 MHz, CD_3Cl) 7.45–7.32 (5H, m), 5.59 (1H, d, J=3.0 Hz), 4.91 (2H, s), 4.82 (1H, d, J=3.0 Hz) (a signal attributable to CO_2H was not observed); δ_C (100 MHz, CD_3Cl) 167.5, 149.8, 135.4, 128.5, 128.0, 127.3, 97.1, 70.4. *The spectroscopic properties of this compound were consistent with the data reported in the literature.*[40]

*4.2.2. Methyl 2-(N-(benzyloxy)-2-ethoxyacrylamido)pent-4-enoate (**9d**).* Amine **8a** (834 mg, 3.54 mmol) and 2-(ethoxy)acrylic acid (785 mg, 6.76 mmol) were subjected to General Procedure A. Purification by FCC (5:1 to 1:1 petrol/EtOAc) afforded the title compound **9d** (974 mg, 82%) as a clear oil; ν_{max}/cm^{-1} 3450, 2883, 1711, 1639, 1608, 1219; δ_H (500 MHz, $CDCl_3$): 7.45–7.30 (5H, m), 5.83 (1H, ddt, J=17.0, 10.5, 7.0 Hz), 5.19 (1H, dd, J=17.0, 2.0 Hz), 5.13 (1H, dd, J=10.5, 1.0 Hz), 5.08 (1H, d, J=10.0 Hz), 5.02 (1H, d, J=10.0 Hz), 4.90–4.81 (2H, m), 4.44 (1H, d, J=3.0 Hz), 3.84 (2H, q, J=7.0 Hz), 3.76 (3H, s), 2.82–2.71 (2H, m), 1.33 (3H, t, J=7.0 Hz); δ_C (125 MHz, $CDCl_3$): 170.1, 167.0, 154.9, 135.1, 133.6, 128.8, 128.5, 128.4, 118.4, 90.1, 77.7, 63.8, 62.4, 52.5, 32.6, 14.1; HRMS (ESI^+) calcd for $C_{18}H_{23}NNaO_5$ $[M+Na]^+$: 356.1468, found: 356.1462.

*4.2.3. Methyl 2-(N-(benzyloxy)-2-ethoxyacrylamido)pent-4-enoate (**9e**).* Amine **8a** (270 mg, 1.14 mmol) and 2-(benzyloxy)acrylic acid (598 mg, 3.35 mmol) were subjected to General Procedure A. Purification by FCC (5:1 petrol/EtOAc) afforded the title compound **9e** (363 mg, 80%) as a colourless oil; ν_{max}/cm^{-1} 2883, 1746, 1673, 1621, 1262, 1212; δ_H (500 MHz, $CDCl_3$) 7.44–7.24 (10H, m), 5.76 (1H, m), 5.14 (1H, dd, J=16.5 Hz), 5.07 (1H, d, J=10.0 Hz), 5.04 (1H, m), 4.99 (1H, m), 4.94 (1H, m), 4.88 (1H, m), 4.86–4.82 (2H, m), 4.60 (1H, d, J=3.0 Hz), 3.69 (3H, s), 2.84–2.68 (2H, m); δ_C (125 MHz, $CDCl_3$) 169.9, 166.7, 154.7, 135.5, 134.9, 133.4, 128.8, 128.4 (2 signals), 128.3, 128.1, 127.7, 118.4, 91.2, 77.7, 70.2, 62.3, 52.4, 32.6; HRMS (ESI^+) calcd for $C_{23}H_{25}NNaO_5$ $[M+Na]^+$: 418.1625, found: 418.1624.

*4.2.4. Methyl 1-(benzyloxy)-5-ethoxy-6-oxo-1,2,3,6-tetrahydropyridine-2-carboxylate (**10d**).* Amide **9d** (267 mg, 0.80 mmol) and catalyst **1a** (23 mg, 5 mol %) were subjected to General Procedure B using CH_2Cl_2 (20 mL) at reflux for 16 h. Purification by FCC (5:1 to 1:1 petrol/EtOAc) afforded the title compound **10d** (222 mg, 91%) as a pale brown solid; mp 107–108 °C (CH_2Cl_2/petrol); ν_{max}/cm^{-1} 2983, 1742, 1692, 1637, 1257; δ_H (500 MHz, $CDCl_3$) 7.45–7.41 (2H, m), 7.39–7.34 (3H, m), 5.17 (1H, dd, J=6.0, 3.0 Hz), 5.04 (1H, d, J=11.0 Hz), 4.98 (1H, d, J=11.0 Hz), 3.91 (1H, dd, J=7.0, 3.0 Hz), 3.77 (2H, q, J=7.0 Hz), 3.73 (3H, s), 2.60 (1H, ddd, J=17.0, 7.0, 3.0 Hz), 2.54 (1H, ddd, J=17.0, 6.0, 3.0 Hz), 1.39 (3H, t, J=7.0 Hz); δ_C (125 MHz, $CDCl_3$): 170.8, 162.8, 146.5, 135.6, 129.8, 128.7, 128.4, 102.1, 77.5, 64.1, 62.4, 52.8, 25.4, 14.2; HRMS (ESI^+) calcd for $C_{16}H_{20}NO_5$ $[M+H]^+$: 306.1332, found: 306.1336.

*4.2.5. Methyl 1,5-bis(benzyloxy)-6-oxo-1,2,3,6-tetrahydropyridine-2-carboxylate (**10e**).* Amide **9e** (397 mg, 1.00 mmol) and catalyst **1a** (30 mg, 5 mol %) were subjected to General Procedure B using

CH_2Cl_2 (20 mL) at reflux for 16 h. Purification by FCC (7:3 petrol/EtOAc) afforded the title compound **10e** (312 mg, 85%) as a pale brown oil; ν_{max}/cm^{-1} 2956, 1750, 1700, 1645, 1259; δ_H (500 MHz, $CDCl_3$) 7.47–7.42 (2H, m), 7.42–7.28 (8H, m), 5.25 (1H, dd, J=6.5, 3.0 Hz), 5.07 (1H, d, J=11.0 Hz), 5.00 (1H, d, J=11.0 Hz), 4.92 (1H, d, J=12.5 Hz), 4.87 (1H, d, J=12.5 Hz), 3.92 (1H, dd, J=6.5, 3.0 Hz), 3.71 (3H, s), 2.58 (1H, ddd, J=17.0, 6.5, 3.0 Hz), 2.51 (1H, ddd, J=17.0, 6.5, 3.0 Hz); δ_C (125 MHz, $CDCl_3$) 170.7, 162.8, 146.1, 136.0, 135.5, 129.8, 128.8, 128.5 (2 signals), 127.9, 127.2, 104.6, 77.6, 70.5, 62.4, 52.8, 25.4; HRMS (ESI^+) calcd for $C_{21}H_{21}NNaO_5$ $[M+Na]^+$: 390.1312, found: 390.1309.

*4.2.6. Methyl 5-ethoxy-6-oxo-1,6-dihydropyridine-2-carboxylate (**11d**).* α,β-Unsaturated lactam **10d** (204 mg, 0.67 mmol) was subjected to General Procedure C. Purification by FCC (1:1:0 to 0:10:1 petrol/EtOAc/MeOH) afforded the title compound **11d** (115 mg, 87%) as a white solid; mp 146–147 (°C) (CH_2Cl_2/petrol); ν_{max}/cm^{-1} 2983, 1726, 1646, 1620, 1303, 1277; δ_H (400 MHz, $CDCl_3$) 10.46 (1H, br s), 6.90 (1H, d, J=7.5 Hz), 6.55 (1H, d, J=7.5 Hz), 3.97 (2H, q, J=7.0 Hz), 3.81 (3H, s), 1.38 (3H, t, J=7.0 Hz); δ_C (100 MHz, $CDCl_3$): 161.1, 157.1, 153.7, 124.1, 111.6, 110.7, 64.5, 52.6, 13.9; HRMS (ESI^+) calcd for $C_9H_{11}NNaO_4$ $[M+Na]^+$: 220.0580, found: 220.0583.

*4.2.7. Methyl 5-(benzyloxy)-6-oxo-1,6-dihydropyridine-2-carboxylate (**11e**).* α,β-Unsaturated lactam **10e** (116 mg, 0.31 mmol) was subjected to General Procedure C. Purification by FCC (1:1:0 to 0:10:1 to petrol/EtOAc/MeOH) afforded the title compound **11e** (80 mg, 98%) as a white solid; mp 170–171 °C (CH_2Cl_2/petrol); ν_{max}/cm^{-1} 3041, 1730, 1662, 1624, 1258; δ_H (500 MHz, $CDCl_3$): 9.54 (1H, br s), 7.45–7.41 (2H, m), 7.41–7.36 (2H, m), 7.34 (1H, m), 6.94 (1H, d, J=7.5 Hz), 6.67 (1H, d, J=7.5 Hz), 5.20 (2H, s), 3.92 (3H, s); δ_C (125 MHz, $CDCl_3$): 161.3, 157.0, 153.8, 135.1, 128.8, 128.4, 127.4, 124.6, 113.4, 110.6, 71.0, 53.0; HRMS (ESI^+) calcd for $C_{14}H_{13}NNaO_4$ $[M+Na]^+$: 282.0737, found: 282.0735.

*4.2.8. 5-Ethoxy-6-trifluoromethanesulfonyloxypyridine-2-carboxylic acid methyl ester (**12d**).* Pyridone **11d** (84 mg, 0.42 mmol) was subjected to General Procedure D. Purification by FCC (10:1 to 1:1 petrol/EtOAc) afforded the title compound **12d** (123 mg, 89%) as a white solid; mp 62–63 °C (CH_2Cl_2/petrol); ν_{max}/cm^{-1} 3086, 2962, 1736, 1602, 1563, 1215; δ_H (500 MHz, $CDCl_3$) 8.17 (1H, d, J=8.0 Hz), 7.43 (1H, d, J=8.0 Hz), 4.24 (2H, q, J=7.0 Hz), 3.96 (3H, s), 1.52 (3H, t, J=7.0 Hz); δ_C (125 MHz, $CDCl_3$) 163.9, 149.3, 144.1, 136.7, 127.7, 121.8, 118.5 (q, J=320 Hz), 65.8, 52.9, 14.1; HRMS (ESI^+) calcd for $C_{10}H_{11}NF_3O_6S$ $[M+H]^+$: 330.0254, found: 330.0249.

*4.2.9. 5-Benzyloxy-6-trifluoromethanesulfonyloxypyridine-2-carboxylic acid methyl ester (**12e**).* Pyridone **11e** (35 mg, 0.14 mmol) was subjected to General Procedure D. Purification by FCC (10:1 to 1:1 petrol/EtOAc) afforded the title compound **12e** (46 mg, 87%) as a colourless solid; mp 83–84 °C (CH_2Cl_2/petrol); ν_{max}/cm^{-1} 3073, 1738, 1600, 1424, 1213; δ_H (500 MHz, $CDCl_3$): 8.15 (1H, d, J=8.0 Hz), 7.47 (1H, d, J=8.0 Hz), 7.46–7.34 (5H, m), 5.29 (2H, s), 3.96 (3H, s); δ_C (125 MHz, $CDCl_3$): 163.8, 148.9, 144.3, 137.1, 134.0, 128.9, 128.8, 127.6, 127.2, 122.7, 118.5 (q, J=320 Hz), 71.6, 52.9; HRMS (ESI^+) calcd for $C_{15}H_{12}F_3NNaO_6S$ $[M+Na]^+$: 414.0230, found: 414.0222.

*4.2.10. Methyl 1-(benzyloxy)-6-oxo-4-phenyl-1,2,3,6-tetrahydropyridine-2-carboxylate (**10i**).* A solution of $Pd(OAc)_2$ (13 mg, 0.06 mmol) and 1,10-phenanthroline (17 mg, 0.09 mmol) in DMF (2.65 ml) was stirred at room temperature for 30 min. α,β-Unsaturated lactam **10a** (139 mg, 0.53 mmol) and phenyl boronic acid (138 mg, 1.13 mmol) were added and the reaction mixture was placed under an oxygen atmosphere (balloon pressure). After 48 h the reaction mixture was diluted with EtOAc (50 ml) and washed with saturated aq NH_4Cl (35 ml) and brine (35 ml). The organic portion was dried ($MgSO_4$) and concentrated in vacuo. Purification by FCC (7:3 petrol/EtOAc) afforded the title compound **10i** (164 mg, 92%) as a white solid; mp 149–150 °C (CH_2Cl_2/petrol); ν_{max}/cm^{-1} 3004, 2953, 1743, 1669, 1614, 1447, 1234, 1077; δ_H (400 MHz, $CDCl_3$) 7.54–7.33 (10H, m), 6.30 (1H, d, J=2.5 Hz), 5.09 (1H, d, J=11.5 Hz), 5.02 (1H, d, J=11.5 Hz), 4.07 (1H, dd, J=7.0, 3.0 Hz), 3.73 (3H, s), 3.10 (1H, dd, J=17.5, 3.0 Hz), 3.00 (1H, ddd, J=17.5, 7.0, 2.0 Hz); δ_C (100 MHz, $CDCl_3$) 170.6, 165.5, 147.1, 136.1, 135.6, 129.9, 129.7, 128.7, 128.7, 128.4, 125.7, 119.3, 77.5, 61.9, 52.8, 31.2; HRMS (ESI^+) calcd for $C_{20}H_{20}NO_4$ $[M+H]^+$: 338.1387, found: 338.1380.

*4.2.11. Methyl 6-oxo-4-phenyl-1,6-dihydropyridine-2-carboxylate (**11i**).* α,β-Unsaturated lactam **10i** (169 mg, 0.27 mmol) was subjected to General Procedure C. Purification by FCC (1:1:0 to 10:10:1 CH_2Cl_2/EtOAc/MeOH) afforded the title compound **11i** (101 mg, 88%) as a white solid; mp 181–183 °C (CH_2Cl_2/petrol); ν_{max}/cm^{-1} 3266, 2959, 1735, 1645, 1447, 1288, 1139; δ_H (400 MHz, $CDCl_3$) 9.60 (1H, br s), 7.65–7.58 (2H, m), 7.53–7.43 (3H, m), 7.29 (1H, d, J=2.0 Hz), 7.00 (1H, d, J=2.0 Hz), 4.01 (3H, s); δ_C (100 MHz, $CDCl_3$) 163.6, 161.4, 152.0, 136.6, 133.9, 129.8, 129.0, 126.7, 122.4, 109.5, 53.2; HRMS (ESI^+) calcd for $C_{13}H_{11}NKO_3$ $[M+K]^+$: 268.0371, found: 268.0361.

*4.2.12. 4-Phenyl-6-trifluoromethanesulfonyloxypyridine-2-carboxylic acid methyl ester (**12i**).* Pyridone **11i** (71 mg, 0.31 mmol) was subjected to General Procedure D. Purification by FCC (10:1 to 1:1 petrol/EtOAc) afforded the title compound **12i** (60 mg, 57%) as a white solid; mp 61–62 °C (CH_2Cl_2/petrol); ν_{max}/cm^{-1} 1727, 1609, 1437, 1219, 1073; δ_H (400 MHz, $CDCl_3$) 8.44 (1H, d, J=1.5 Hz), 7.74–7.65 (2H, m), 7.62–7.50 (4H, m), 4.04 (3H, s); δ_C (100 MHz, $CDCl_3$) 164.1, 156.0, 155.3, 147.5, 135.4, 130.7, 129.6, 127.2, 123.6, 118.6 (q, J=320 Hz), 116.1, 53.3; HRMS (ESI^+) calcd for $C_{14}H_{10}F_3KNO_5S$ $[M+K]^+$: 399.9863, found: 399.9861.

*4.2.13. Methyl 3-bromo-5-ethoxy-6-oxo-1,6-dihydropyridine-2-carboxylate (**21**).* *N*-Bromosuccinimide (109 mg, 0.61 mmol) and pyridone **11d** (0.12 g, 0.61 mmol) were dissolved in CH_2Cl_2 (15 mL) and the mixture was heated at reflux overnight with exclusion of light. The reaction mixture was then cooled to room temperature and concentrated in vacuo. The residue was purified by FCC (9:1 EtOAc/MeOH) to afford pyridone **21** (90 mg, 74%) as a white solid; mp 194–197 °C (CH_2Cl_2/petrol); ν_{max}/cm^{-1} 2983, 1727, 1664, 1319; δ_H (400 MHz, $CDCl_3$) 10.26 (1H, br s), 6.76 (1H, s), 4.06 (2H, q, J=7.0 Hz), 3.94 (3H, s), 1.49 (3H, t, J=7.0); δ_C (100 MHz, $CDCl_3$) 160.2, 156.0, 152.9, 122.4, 118.9, 104.4, 65.4, 53.1, 14.0; HRMS (ESI^+) calcd for $C_9H_{10}{}^{79}BrNNaO_4$ $[M+Na]^+$: 297.9685, found: 297.9685. The structure of this compound was confirmed by X-ray crystallographic analysis.

*4.2.14. 3-Bromo-5-ethoxy-6-trifluoromethanesulfonyloxypyridine-2-carboxylic acid methyl ester (**22**).* Pyridone **21** (86 mg, 0.31 mmol) was subjected to General Procedure D. Purification by FCC (1:0 to 3:2 petrol/CH_2Cl_2) afforded the title compound **22** (106 mg, 84%) as a colourless, clear oil; ν_{max}/cm^{-1} 2905, 1738, 1592, 1460, 1260, 1145; δ_H (400 MHz, $CDCl_3$) 7.60 (1H, s), 4.23 (2H, q, J=7.0 Hz), 3.97 (3H, s), 1.53 (3H, t, J=7.0 Hz); δ_C (100 MHz, $CDCl_3$) 163.3, 148.0, 142.4, 136.1, 127.5, 120.8, 118.5 (q, J=320 Hz), 66.3, 53.0, 14.0; HRMS (ESI^+) calcd for $C_{10}H_9{}^{79}BrF_3NNaO_6S$ $[M+Na]^+$: 429.9178, found: 429.9184.

*4.2.15. 4-Bromo-5-ethoxy-6-trifluoromethanesulfonyloxypyridine-2-carboxylic acid methyl ester (**24**).* Bromine (320 μl, 6.24 mmol) was added to a solution of α,β-unsaturated lactam **10d** (230 mg, 0.75 mmol) and Et_3N (0.51 ml, 3.73 mmol) in CH_2Cl_2 (20 ml) at 0 °C. After stirring for 2 h at this temperature, the reaction mixture was diluted with CH_2Cl_2 (20 ml) and washed with aq 10% $Na_2S_2O_3$ (2×30 ml) and then brine (30 ml). The organic portion was dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved in

THF (12 ml) and DBU (0.57 ml, 3.81 mmol) was added. After stirring at room temperature for 16 h the reaction mixture was concentrated in vacuo. The residue was filtered through a short plug of SiO_2 (9:1 EtOAc/MeOH) and the eluent was concentrated in vacuo. The resulting crude material was dissolved in THF (8 mL) and cooled to −78 °C. Comins' reagent[22] (295 mg, 0.75 mmol) and KHMDS (0.5 M in PhMe, 1.40 ml, 0.70 mmol) were then added sequentially and the mixture was stirred at −78 °C for 1 h and then at room temperature for 3 h. The mixture was then diluted with EtOAc (40 ml) and washed with saturated aq $NaHCO_3$ (2×30 ml) and then brine (30 ml). The organic portion was dried ($MgSO_4$) and concentrated in vacuo. Purification by FCC (1:0 to 1:1 petrol/EtOAc) afforded the title compound **24** (135 mg, 44%) as a white solid; mp 55–56 °C (CH_2Cl_2/petrol); ν_{max}/cm^{-1} 2990, 1747, 1378, 1245; δ_H (400 MHz, $CDCl_3$) 8.36 (1H, s), 4.30 (2H, q, J=7.0 Hz), 3.97 (3H, s), 1.50 (3H, t, J=7.0 Hz); δ_C (100 MHz, $CDCl_3$) 162.7, 148.4, 147.5, 140.5, 131.3, 130.2, 118.5 (q, J=320 Hz), 71.6, 53.3, 15.4; HRMS (ESI$^+$) calcd for $C_{10}H_9{}^{79}BrF_3NNaO_6S$ $[M+Na]^+$: 429.9178, found: 429.9184.

*4.2.16. Methyl 1-(benzyloxy)-6-oxo-1,6-dihydropyridine-2-carboxylate (**26**).* Bromine (188 μL, 3.67 mmol) was added dropwise to a solution of α,β-unsaturated lactam **10a** (70 mg, 0.27 mmol) in CH_2Cl_2 (5 mL) at 0 °C. Stirring was continued at room temperature for 2 h then the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 (5 mL) and DBU (404 μL, 2.77 mmol) was added dropwise. The solution was stirred at room temperature for 16 h and was then chromatographed directly (2:1 petrol/EtOAc) to afford the title compound **26** (51 mg, 74%) as a colourless oil; ν_{max}/cm^{-1} 3034, 1740, 1674, 1279, δ_H (500 MHz, $CDCl_3$) 7.58–7.25 (6H, m), 6.85–6.82 (1H, m), 6.50 (1H, m), 5.41 (2H, s), 3.86 (3H, s); δ_C (125 MHz, $CDCl_3$) 160.4, 158.8, 138.2, 137.2, 133.7, 130.1, 129.2, 128.5, 126.0, 107.9, 78.6, 53.2; HRMS (ESI$^+$) calcd for $C_{14}H_{14}NO_4$ $[M+H]^+$: 260.0923, found: 260.0916.

*4.2.17. 6-Phenylpyridine-2-carboxylic acid methyl ester (**27**).* A mixture of triflate **12a** (100 mg, 0.35 mmol), $Pd(PPh_3)_4$ (12 mg, 0.01 mmol), phenyl boronic acid (47 mg, 0.38 mmol) and Na_2CO_3 (54 mg, 0.51 mmol) in 1,4-dioxane (3 mL) was heated at 85 °C for 18 h. The mixture was then cooled to room temperature, diluted with saturated aq Na_2CO_3 (5 mL) and aq NH_3 (15 M, 1 mL) and extracted with CH_2Cl_2 (3×10 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by FCC (19:1 to 17:3 petrol/Et_2O) afforded the title compound **27** (66 mg, 81%) as a colourless oil; ν_{max}/cm^{-1} 2951, 1722, 1582, 1435, 1243, 1194; δ_H (400 MHz, $CDCl_3$) 8.08–8.03 (3H, m), 7.91–7.88 (2H, m), 7.52–7.41 (3H, m), 4.02 (3H, s); δ_C (100 MHz, $CDCl_3$) 166.0, 157.7, 148.0, 138.5, 137.7, 129.5, 128.8, 127.2, 123.8, 123.4, 52.9; HRMS (ESI$^+$) calcd for $C_{13}H_{12}NO_2$ $[M+H]^+$: 214.0863, found: 214.0860.

*4.2.18. 6-Phenylethynylpyridine-2-carboxylic acid methyl ester (**28**).* A solution of triflate **12a** (100 mg, 0.35 mmol), $Pd(PPh_3)_2Cl_2$ (20 mg, 0.03 mmol), LiCl (45 mg, 1.05 mmol), CuI (3 mg, 0.02 mmol) and Et_3N (4.5 mL) in DMF (5 mL) was stirred for 10 min at room temperature. Phenyl acetylene (46 μL, 0.42 mmol) was then added and the reaction mixture was heated at 65 °C. After 18 h the mixture was cooled to room temperature, diluted with water (10 mL) and extracted with Et_2O (3×10 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by FCC (9:1 petrol/EtOAc) afforded the title compound **28** (34 mg, 41%) as an orange oil; ν_{max}/cm^{-1} 3061, 2951, 1724, 1579, 1491, 1294s, 1195s; δ_H (400 MHz, $CDCl_3$) 8.08 (1H, dd, J=7.5, 1.0 Hz), 7.84 (1H, t, J=7.5 Hz), 7.70 (1H, dd, J=7.5, 1.0 Hz), 7.63–7.59 (2H, m), 7.40–7.34 (3H, m), 4.02 (3H, s); δ_C (100 MHz, $CDCl_3$) 165.3, 148.3, 143.7, 137.3, 132.2, 130.4, 129.3, 128.4, 124.0, 121.9, 90.4, 88.1, 53.1; HRMS (ESI$^+$) calcd for $C_{15}H_{11}NNaO_2$ $[M+Na]^+$: 260.0682, found: 260.0679.

*4.2.19. Methyl 4-(N-allyl-4-methylphenylsulfonamido)-3-hydroxy-2-methylenebutanoate (**45**).* Quinuclidine (81 mg, 0.68 mmol) was added to a solution of methyl acrylate (290 μl, 3.22 mmol), aldehyde **44** (689 mg, 2.72 mmol) and MeOH (90 μl, 2.20 mmol) at room temperature. The mixture was stirred at room temperature for 16 h and then concentrated in vacuo. Purification of the residue by FCC (1:0 to 1:1 petrol/EtOAc) afforded the title compound **45** (580 mg, 63%) as a brown oil; δ_H (400 MHz, $CDCl_3$) 7.71 (2H, d, J=8.5 Hz), 7.31 (2H, d, J=8.5 Hz), 6.38 (1H, t, J=1.5 Hz), 6.10 (1H, t, J=1.5 Hz), 5.62 (1H, ddt, J=17.0, 10.0, 7.0 Hz), 5.24–5.11 (2H, m), 4.67 (1H, m), 3.89 (2H, t, J=6.5 Hz), 3.75 (3H, s), 3.48 (1H, d, J=5.0 Hz), 3.32 (1H, dd, J=14.5, 4.0 Hz), 3.22 (1H, dd, J=14.5, 8.0 Hz), 2.43 (3H, s); δ_C (100 MHz, $CDCl_3$) 166.3, 143.7, 139.2, 136.2, 132.4, 129.8, 127.5, 127.3, 119.8, 69.4, 52.8, 52.3, 51.8, 21.5. *The spectroscopic properties of this compound were consistent with the data reported in the literature.*[29]

*4.2.20. Methyl 3-hydroxy-1-tosyl-1,2,3,6-tetrahydropyridine-4-carboxylate (**46**).* Allylic alcohol **45** (420 mg, 1.24 mmol) and catalyst **1a** (40 mg, 5 mol %) were subjected to General Procedure B using CH_2Cl_2 (25 mL) at reflux for 24 h. Purification by FCC (1:0 to 1:1 petrol/EtOAc) afforded the title compound **46** (253 mg, 65%) as a brown oil; δ_H (400 MHz, $CDCl_3$) 7.64 (2H, d, J=8.5 Hz), 7.30 (2H, d, J=8.5 Hz), 6.89 (1H, t, J=3.5 Hz), 4.57 (1H, dt, J=6.0, 4.0 Hz), 3.93 (1H, dd, J=19.0, 4.0 Hz), 3.72 (3H, s), 3.52–3.41 (2H, m), 3.18 (1H, d, J=6.5 Hz), 2.96 (1H, dd, J=12.0, 4.0 Hz), 2.38 (3H, s); δ_C (100 MHz, $CDCl_3$) 165.5, 144.0, 136.2, 132.4, 130.9, 129.7, 127.5, 62.1, 52.0, 49.1, 45.0, 21.3. *The spectroscopic properties of this compound were consistent with the data reported in the literature.*[29]

*4.2.21. Methyl 3-(methylsulfonyloxy)-1-tosyl-1,2,3,6-tetrahydropyridine-4-carboxylate (**47**).* Ms_2O (369 mg, 2.12 mmol) was added to a solution of cyclic alcohol **46** (321 mg, 1.03 mmol) and Et_3N (0.35 ml, 2.51 mmol) in CH_2Cl_2 (30 ml) at 0 °C. The reaction mixture was then stirred at room temperature for 5 h. The mixture was diluted with CH_2Cl_2 (50 ml) and washed sequentially with saturated aq NH_4Cl (30 ml), saturated aq $NaHCO_3$ (30 ml) and then brine (30 ml). The organic portion was dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by FCC (1:1 petrol/EtOAc) afforded the title compound **47** (381 mg, 95%) as an opaque oil; ν_{max}/cm^{-1} 2955, 1719, 1665, 1597, 1494, 1352, 1272, 1174; δ_H (400 MHz, $CDCl_3$) 7.70 (2H, d, J=8.5 Hz), 7.34 (2H, d, J=8.5 Hz), 7.19 (1H, dd, J=4.5, 2.5 Hz), 5.47 (1H, m), 4.34–4.19 (2H, m), 3.79 (3H, s), 3.46 (1H, d, J=19.5 Hz), 3.15 (3H, s), 2.82 (1H, dd, J=13.5, 1.5 Hz), 2.43 (3H, s); δ_C (100 MHz, $CDCl_3$) 164.1, 144.3, 141.3, 133.0, 129.9, 127.6, 125.8, 70.4, 52.4, 47.6, 44.5, 39.0, 21.5; HRMS (ESI$^+$) calcd for $C_{15}H_{19}NNaO_7S_2$ $[M+Na]^+$: 412.0495, found: 412.0501.

*4.2.22. Methyl isonicotinate (**48**).* KHMDS (0.5 M in PhMe, 3.60 ml, 1.80 mmol) was added to a solution of mesylate **47** (330 mg, 0.85 mmol) in THF (15 ml) at −78 °C. After 1 h the reaction mixture was warmed to 0 °C and stirring was continued for a further 3 h. The mixture was then diluted with EtOAc (60 ml) and washed with saturated aq $NaHCO_3$ (30 ml) and brine (30 ml). The organic portion was dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by FCC (9:1 CH_2Cl_2/EtOAc) afforded the title compound **48** (61 mg, 53%) as a clear oil; δ_H (500 MHz, $CDCl_3$) 8.80 (2H, d, J=4.5 Hz), 7.86 (2H, d, J=4.5 Hz), 3.97 (3H, s); δ_C (125 MHz, $CDCl_3$) 165.6, 150.6, 137.3, 122.9, 52.7. *The spectroscopic properties of this compound were consistent with the data reported in the literature.*[41]

*4.2.23. N-allyl-N′-(2-ethoxyacryloyl)-4-methylbenzenesulfonohydrazide (**51c**).* Ghosez' reagent[42] (135 μL, 1.02 mmol) was added to a solution of 2-ethoxyacrylic acid[43] (120 mg, 1.02 mmol) in

anhydrous CH_2Cl_2 (10 mL) at 0 °C. After 1 h, allyl hydrazide **52a** (226 mg, 1.00 mmol) and then *i*-Pr_2NEt (174 μL, 1.00 mmol) were added and the mixture was warmed to room temperature. After a further 30 h the mixture was diluted with CH_2Cl_2 (40 mL) and then washed successively with water (30 mL) and brine (30 mL). The organic portion was then dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by FCC (3:1 petrol/EtOAc) afforded acrylamide **51c** (195 mg, 59%) as a colourless solid; mp 101 °C (CH_2Cl_2/petrol); ν_{max}/cm^{-1} 3301, 2981, 1715, 1631, 1494, 1356, 1303, 1165, 1090; δ_H (400 MHz, $CDCl_3$) 8.04 (1H, br s), 7.78 (2H, d, *J*=8.5 Hz), 7.30 (2H, d, *J*=8.5 Hz), 5.85 (1H, ddt, *J*=17.0, 10.0, 7.0 Hz), 5.25 (1H, m), 5.22–5.20 (2H, m), 4.40 (1H, d, *J*=3.0 Hz), 4.13 (2H, d, *J*=7.0 Hz), 3.80 (2H, q, *J*=7.0 Hz), 2.42 (3H, s), 1.35 (3H, t, *J*=7.0 Hz); δ_C (100 MHz, $CDCl_3$) 160.4, 151.9, 144.5, 134.2, 131.3, 129.6, 128.4, 120.8, 91.7, 64.3, 52.7, 21.7, 14.3; *m*/*z* (EI) 324 ($[M]^+$, 100%); HRMS (EI) calcd for $C_{15}H_{20}N_2O_4S$ $[M]^+$: 324.1144, found: 324.1146.

*4.2.24. N-allyl-4-methyl-N′-(2-phenylacryloyl)benzenesulfonohydrazide (**51d**).* Ghosez' reagent[42] (275 μL, 2.08 mmol) was added to a solution of 2-phenylacrylic acid[44] (310 mg, 2.09 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0 °C. After 1.5 h, allyl hydrazide **52a** (452 mg, 2.00 mmol) and then *i*-Pr_2NEt (364 μL, 2.09 mmol) were added and the mixture was warmed to room temperature. After a further 28 h the mixture was diluted with CH_2Cl_2 (50 mL) and then washed successively with water (40 mL) and brine (40 mL). The organic portion was then dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by FCC (3:1 petrol/EtOAc) afforded acrylamide **51d** (212 mg, 30%) as a colourless, amorphous solid; mp 155–157 °C (CH_2Cl_2/petrol); ν_{max}/cm^{-1} 3229, 3024, 1682, 1527, 1357, 1166, 1089; δ_H (400 MHz, $CDCl_3$) 7.82 (2H, d, *J*=8.5 Hz), 7.36–7.30 (6H, m), 7.27–7.23 (2H, m), 5.94–5.82 (2H, m), 5.66 (1H, s), 5.29 (1H, d, *J*=5.0 Hz), 5.25 (1H, s), 4.19 (2H, d, *J*=7.0 Hz), 2.44 (3H, s); δ_C (100 MHz, $CDCl_3$) 165.9, 144.6, 142.6, 135.4, 134.3, 131.5, 129.7, 128.9, 128.7, 128.5, 127.6, 122.2, 121.0, 52.6, 21.7; HRMS (ESI^+) calcd for $C_{19}H_{20}N_2NaO_3S$ $[M+Na]^+$: 379.1087, found: 379.1087.

*4.2.25. N-allyl-4-methyl-N′-(2-(trifluoromethyl)acryloyl)benzenesulfonohydrazide (**51e**).* EDCI (250 mg, 1.30 mmol) was added to a solution of allyl hydrazide **52a** (200 mg, 0.88 mmol) and 2-(trifluoromethyl)acrylic acid (180 mg, 1.29 mmol) in anhydrous CH_2Cl_2 (8 mL) at −40 °C. After 2 h, the mixture was warmed to −15 °C and stirring was continued for a further 1 h. The mixture was diluted with Et_2O (30 mL) and then washed successively with water (20 mL), aq 1 M HCl (20 mL), saturated aq $NaHCO_3$ (20 mL) and brine (20 mL). The organic portion was then dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by FCC (2:1 petrol/EtOAc) afforded acrylamide **51e** (186 mg, 61%) as a colourless solid; mp 157–158 °C (CH_2Cl_2/petrol); ν_{max}/cm^{-1} 3223, 3042, 1695, 1539, 1361, 1168, 1139, 1086; δ_H (400 MHz, $CDCl_3$) 7.78 (2H, d, *J*=8.5 Hz), 7.44 (1H, br s), 7.33 (2H, d, *J*=8.5 Hz), 6.38 (1H, s), 6.25 (1H, s), 5.85 (1H, m), 5.31–5.22 (2H, m), 4.16 (2H, d, *J*=6.5 Hz), 2.45 (3H, s); δ_C (125 MHz, $CDCl_3$) 159.4, 144.9, 133.8, 132.2, 130.8, 130.2 (q, *J*=5.5 Hz), 129.8, 128.4, 121.6, 121.4 (q, *J*=273.0 Hz), 52.6, 21.7; HRMS (ESI^+) calcd for $C_{14}H_{15}F_3N_2NaO_3S$ $[M+Na]^+$: 371.0648, found: 371.0648.

*4.2.26. N′-Methacryloyl-4-methyl-N-(2-methylallyl)benzenesulfonohydrazide (**51g**).* Freshly distilled methacryloyl chloride (68 μL, 0.69 mmol) and then *i*-Pr_2NEt (120 μL, 0.69 mmol) were added to a solution of allyl hydrazide **52b** (159 mg, 0.66 mmol) in anhydrous THF (7 mL) at 0 °C. After 30 min, the mixture was warmed to room temperature and stirring was continued for a further 24 h. The mixture was diluted with Et_2O (40 mL) and then washed successively with water (20 mL) and brine (20 mL). The organic portion was then dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by FCC (4:1 to 3:4 petrol/EtOAc) afforded acrylamide **51g** (104 mg, 52%) as a colourless solid; mp 144–145 °C (CH_2Cl_2/petrol); ν_{max}/cm^{-1} 3254, 3031, 1680, 1635, 1530, 1357, 1164, 1093; δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J*=8.5 Hz), 7.57 (1H, br s), 7.30 (2H, d, *J*=8.5 Hz), 5.57 (1H, s), 5.34 (1H, s), 4.94 (1H, s), 4.88 (1H, s), 4.13 (2H, s), 2.42 (3H, s), 1.84–1.81 (6H, m); δ_C (100 MHz, $CDCl_3$) 166.6, 144.4, 139.3, 138.3, 134.8, 129.6, 128.3, 120.6, 116.3, 55.3, 21.7, 20.0, 18.5; *m*/*z* (EI) 308 ($[M]^+$, 100%); HRMS (EI) calcd for $C_{15}H_{20}N_2O_3S$ $[M]^+$: 308.1195, found: 308.1197.

*4.2.27. Methyl N′-allyl-N′-tosylacrylohydrazonate (**55a**).* Acrylamide **51a** (157 mg, 1.06 mmol) was subjected to General Procedure E. Purification by FCC (4:1 petrol/EtOAc) afforded the title compound **55a** (51 mg, 48%) as a colourless oil; ν_{max}/cm^{-1} 1647, 1574, 1448, 1353, 1325, 1167, 1080; δ_H (400 MHz, $CDCl_3$) 7.70 (2H, d, *J*=8.5 Hz), 7.34 (2H, d, *J*=8.5 Hz), 6.99 (1H, dd, *J*=17.5, 11.0 Hz), 6.07 (1H, dd, *J*=17.5, 1.5 Hz), 5.70–5.59 (2H, m), 5.10–5.04 (2H, m), 3.77 (3H, s), 3.64 (2H, d, *J*=7.0 Hz), 2.45 (3H, s); δ_C (100 MHz, $CDCl_3$) 171.4, 144.0, 132.1, 131.6, 129.3, 129.2, 125.3, 124.2, 119.7, 55.8, 54.4, 21.6; HRMS (ESI^+) calcd for $C_{14}H_{18}N_2NaO_3S$ $[M+Na]^+$: 317.0930, found: 317.0939.

*4.2.28. Ethyl N′-allyl-N′-tosylacrylohydrazonate (**55b**).* Acrylamide **51a** (205 mg, 1.08 mmol) was subjected to General Procedure E. Purification by FCC (4:1 petrol/EtOAc) afforded the title compound **55b** (105 mg, 95%) as a colourless oil; ν_{max}/cm^{-1} 2983, 1644, 1571, 1388, 1354, 1316, 1168, 1090; δ_H (400 MHz, $CDCl_3$) 7.70 (2H, d, *J*=8.5 Hz), 7.33 (2H, d, *J*=8.5 Hz), 7.00 (1H, dd, *J*=17.5, 10.5 Hz), 6.09 (1H, dd, *J*=17.5, 2.0 Hz), 5.70–5.59 (2H, m), 5.10–5.04 (2H, m), 4.15 (2H, q, *J*=7.0 Hz), 3.63 (2H, d, *J*=6.5 Hz), 2.45 (3H, s), 1.32 (3H, t, *J*=7.0 Hz); δ_C (100 MHz, $CDCl_3$) 171.0, 144.0, 132.2, 131.6, 129.2 (2 signals), 125.1, 124.4, 119.6, 62.9, 55.8, 21.6, 14.2; HRMS (ESI^+) calcd for $C_{15}H_{20}N_2NaO_3S$ $[M+Na]^+$: 331.1087, found: 331.1081.

*4.2.29. Ethyl N′-allyl-N′-tosylmethacrylohydrazonate (**55c**).* Acrylamide **51b** (150 mg, 0.51 mmol) was subjected to General Procedure E. Purification by FCC (4:1 petrol/EtOAc) afforded the title compound **55c** (138 mg, 84%, 1:0.2 rotamer ratio) as a colourless oil; ν_{max}/cm^{-1} 2981, 1597, 1304, 1168, 1090, 1027; δ_H (400 MHz, $CDCl_3$) 7.78 (2H, d, *J*=8.5 Hz), 7.73 (0.4H, d, *J*=8.0 Hz), 7.34–7.30 (2.4H, m), 5.71–5.51 (2.4H, m), 5.37–5.34 (1.2H, m), 5.12–5.00 (2.4H, m), 4.38 (2H, q, *J*=7.0 Hz), 4.12 (0.4H, q, *J*=7.0 Hz), 3.80 (2H, d, *J*=7.0 Hz), 3.54 (0.4H, d, *J*=7.0 Hz), 2.45 (0.6H, s), 2.44 (3H, s), 2.00 (0.6H, m), 1.90 (3H, m), 1.34 (3H, t, *J*=7.0 Hz), 1.30 (0.6H, t, *J*=7.0 Hz); δ_C (100 MHz, $CDCl_3$) 174.1, 164.6, 143.9, 137.4, 135.9, 132.6, 132.3, 131.8, 129.8, 129.4 (2 signals), 129.1, 128.4, 127.8, 121.6, 121.2, 119.6, 119.4, 68.1, 63.2, 56.4, 55.2, 21.6, 21.1, 19.6, 15.5, 14.2 (only 27 signals were observed); HRMS (ESI^+) calcd for $C_{16}H_{22}N_2NaO_3S$ $[M+Na]^+$: 345.1243, found: 345.1242.

*4.2.30. Ethyl N′-allyl-2-phenyl-N′-tosylacrylohydrazonate (**55e**).* Acrylamide **51d** (165 mg, 0.46 mmol) was subjected to General Procedure E. Purification by FCC (4:1 petrol/EtOAc) afforded the title compound **55e** (146 mg, 83%) as a colourless oil; ν_{max}/cm^{-1} 2984, 1611, 1496, 1349, 1214, 1166, 1090, 1047; δ_H (400 MHz, $CDCl_3$) 7.75 (2H, d, *J*=8.5 Hz), 7.48 (2H, m), 7.40–7.32 (3H, m), 7.28 (2H, d, *J*=8.5 Hz), 5.87 (1H, s), 5.82 (1H, m), 5.65 (1H, s), 5.21 (1H, m), 5.15 (1H, m), 3.94 (2H, q, *J*=7.0 Hz), 3.82 (2H, d, *J*=6.5 Hz), 2.40 (3H, s), 1.21 (3H, t, *J*=7.0 Hz); δ_C (100 MHz, $CDCl_3$) 168.9, 143.7, 140.6, 135.5, 133.1, 132.6, 129.3, 129.0, 128.8, 126.3, 120.1, 118.7, 66.8, 54.9, 21.6, 15.3 (only 16 signals were observed); HRMS (ESI^+) calcd for $C_{21}H_{24}N_2NaO_3S$ $[M+Na]^+$: 407.1400, Found: 407.1401.

*4.2.31. 3-Methoxypyridazine (**57a**).* Imidate **55a** (47 mg, 0.16 mmol) was subjected to General Procedure F. The metathesis step was conducted for 24 h. Purification by FCC (3:2 to 2:1 EtOAc/petrol)

afforded the title compound **57a** (12 mg, 74%) as a pale yellow oil; δ_H (400 MHz, $CDCl_3$) 8.83 (1H, dd, *J*=4.5, 1.0 Hz), 7.35 (1H, dd, *J*=9.5, 4.5 Hz), 6.97 (1H, dd, *J*=9.5, 1.0 Hz), 4.13 (3H, s); δ_C (100 MHz, $CDCl_3$) 165.1, 147.3, 128.8, 117.2, 54.7. *The spectroscopic properties of this compound were consistent with the data available in the literature*.[36]

*4.2.32. 3-Ethoxypyridazine (**57b**).* Imidate **55b** (102 mg, 0.33 mmol) was subjected to General Procedure F. The metathesis step was conducted for 32 h. Purification by FCC (1:1 to 2:1 EtOAc/petrol) afforded the title compound **57b** (34 mg, 83%) as colourless needles; mp 34–35 °C (CH_2Cl_2/petrol) [lit. 34 °C (no recrystallisation solvent quoted)][45]; δ_H (400 MHz, $CDCl_3$) 8.79 (1H, dd, *J*=4.5, 1.5 Hz), 7.33 (1H, dd, *J*=9.0, 4.5 Hz), 6.92 (1H, dd, *J*=9.0, 1.5 Hz), 4.56 (2H, q, *J*=7.0 Hz), 1.42 (3H, t, *J*=7.0 Hz); δ_C (100 MHz, $CDCl_3$) 165.0, 147.0, 128.8, 117.2, 63.1, 14.5. *The spectroscopic properties of this compound were consistent with the data available in the literature*.[37]

*4.2.33. 3-Ethoxy-4-methylpyridazine (**57c**).* Imidate **55c** (88 mg, 0.27 mmol) was subjected to General Procedure F. The metathesis step was conducted for 65 h. Purification by FCC (2:1 to 1:2 petrol/EtOAc) afforded the title compound **57c** (33 mg, 88%) as a pale yellow oil; ν_{max}/cm^{-1} 2981, 1596, 1561, 1448, 1376, 1346, 1296, 1214, 1033; δ_H (400 MHz, $CDCl_3$) 8.63 (1H, d, *J*=4.5 Hz), 7.14 (1H, dq, *J*=4.5, 1.0 Hz), 4.56 (2H, q, *J*=7.0 Hz), 2.20 (3H, d, *J*=1.0 Hz), 1.44 (3H, t, *J*=7.0 Hz); δ_C (100 MHz, $CDCl_3$) 164.5, 146.9, 128.6, 128.2, 63.0, 15.4, 14.6; HRMS (ESI^+) calcd for $C_7H_{10}N_2NaO$ $[M+Na]^+$: 161.0685, found: 161.0682.

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