Modular Synthesis of Polar Spirocyclic Scaffolds Enabled by Radical Chemistry

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Abstract: Exploration of three-dimensional structural space has become crucial for the development of novel bioactive molecules. In this context, polar spirocycles have emerged as key scaffolds due to their enhanced 3D character and well-defined spatial orientation. Herein, we report the development of a highly modular strategy to access β-spirocyclic pyrrolidine derivatives from readily available starting materials, *i.e.*, cyclic ketones and α-amino or oxamic acids. The sequence proceeds through a straightforward Knoevenagel condensation, followed by a domino Giese-type reaction/base-mediated cyclisation process, delivering a broad scope of polar spirocyclic scaffolds in good to excellent yields. The products can be readily diversified to access a wider range of spirocyclic cores (such as lactams or succinimides), thus increasing the versatility of our method to gain rapid access to libraries of potential drug-like molecules.

Polar azaheterocycles are prominent scaffolds in bioactive molecules, with most pharmaceuticals and agrochemicals containing at least one *N*-heterocycle.[1] The majority of these cores are rigid and planar unsaturated motifs, which enable control over the molecule's conformation and spatial orientation. However, with the emergence of concepts such as "*escape from the flatland*",[2] or "*conformational restriction*",[3] medicinal chemists have come to realise the value of exploring the chemical space beyond planar architectures. This has led to the development of novel candidates with a more pronounce 3D character and rich in Csp^3 bonds, often quantified by the *Fsp*^{3}, *i.e.* the fraction of sp^3-hybridised carbon atoms.[2, 4] However, the introduction of flexible saturated motifs can also result in unwanted consequences, for example by decreasing control over the molecule's conformation. Spirocyclic scaffolds have emerged as powerful tools to overcome this issue since they greatly increase the 3D character and *Fsp*^{3} of a given candidate, while enabling control over its conformation due to their well-defined spatial orientation.[5] This often results in enhanced binding affinities for molecules containing spirocyclic cores, since they can interact with three-dimensional binding pockets more efficiently than planar unsaturated motifs. Another key feature of spirocyclic scaffolds is the introduction of structural novelty, which enables access to unclaimed patent and chemical space. For these reasons, polar spirocycles are emerging as powerful structural motifs in the Life Science industry (Figure 1A).[5] Arguably, spirocyclic pyrrolidine derivatives are among the most popular spirocyclic cores (Figure 1B). However, their synthesis using two electron disconnection strategies often requires multistep and complex processes, limiting their synthetic availability.[6] The use of one electron disconnection logic,[7] in combination with the development of milder strategies to promote radical reactions,[8] has resulted in the invention of more direct and

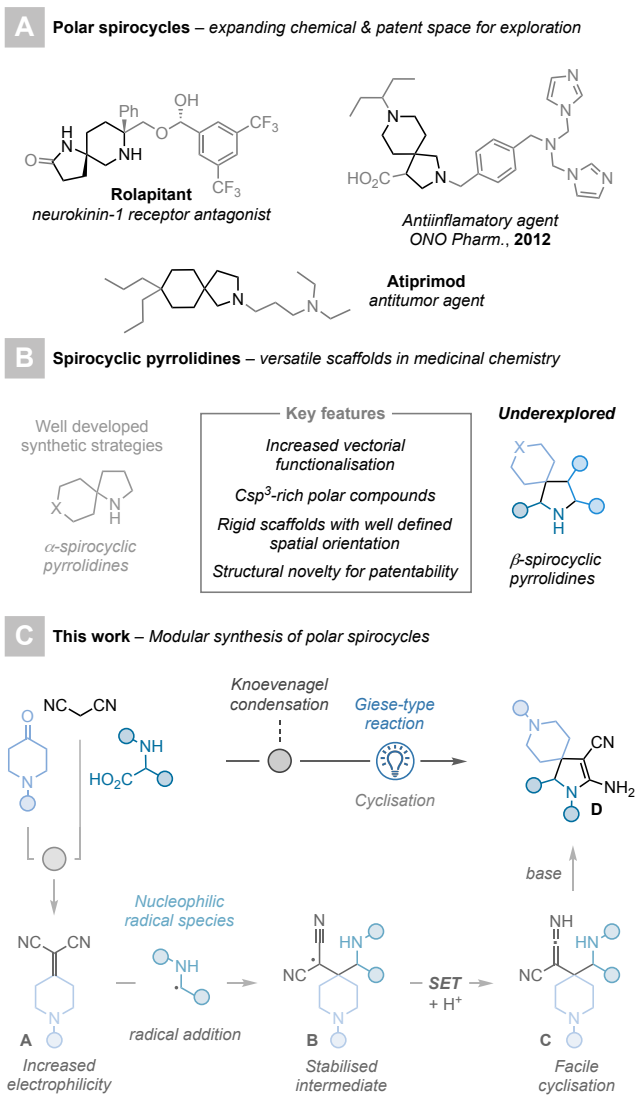


Figure 1. Concept & synthetic strategy.

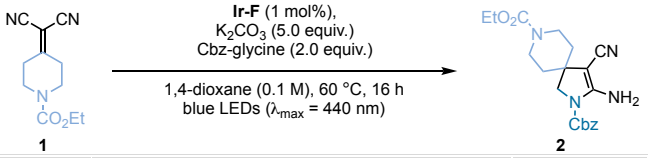
general procedures to access this key structural motif. Most of these novel methods focus on the synthesis of α-spirocyclic pyrrolidines,[9] while access to β-spirocyclic pyrrolidine derivatives remains largely underexplored despite their emergence in drug-like molecules.[10]

Herein, we report a straightforward and highly modular strategy to access β-spirocyclic pyrrolidine derivatives from readily available and abundant precursors, i.e., cyclic ketones and α-amino acids (Figure 1C). We envisioned a two-step strategy starting with a simple Knoevenagel condensation to access highly activated alkylidenemalononitriles (**A**), which are subsequently subjected to a domino[11] light-mediated Giese-type reaction and base-mediated cyclisation sequence. We hypothesised that the high electrophilicity of **A,** combined with the stability of the resulting intermediate from the radical addition (**B**), would assure that the Giese-type reaction proceeds smoothly. This is followed by a base-mediated cyclisation – proceeding through ketenimine intermediate **C** (*vide infra*) – to deliver the targeted spirocyclic scaffold **D**.

Optimisation of the reaction conditions revealed that irradiation with blue LEDs (32 W, λ_{max} = 440 nm) of a 1:2 mixture of piperidine-derived alkylidenemalononitrile **1** and CBz-glycine in the presence of Ir[(dF(CF$_3$)ppy)$_2$(dtbpy)]PF$_6$ (**Ir-F**, 1.0 mol%) and K$_2$CO$_3$ (5.0 equiv.), in 1,4-dioxane (0.1 M) at 60 °C afforded the targeted spirocyclic species **2** in 95% isolated yield (Table 1, entry 1). Control experiments showed that below 60 °C the yield of this

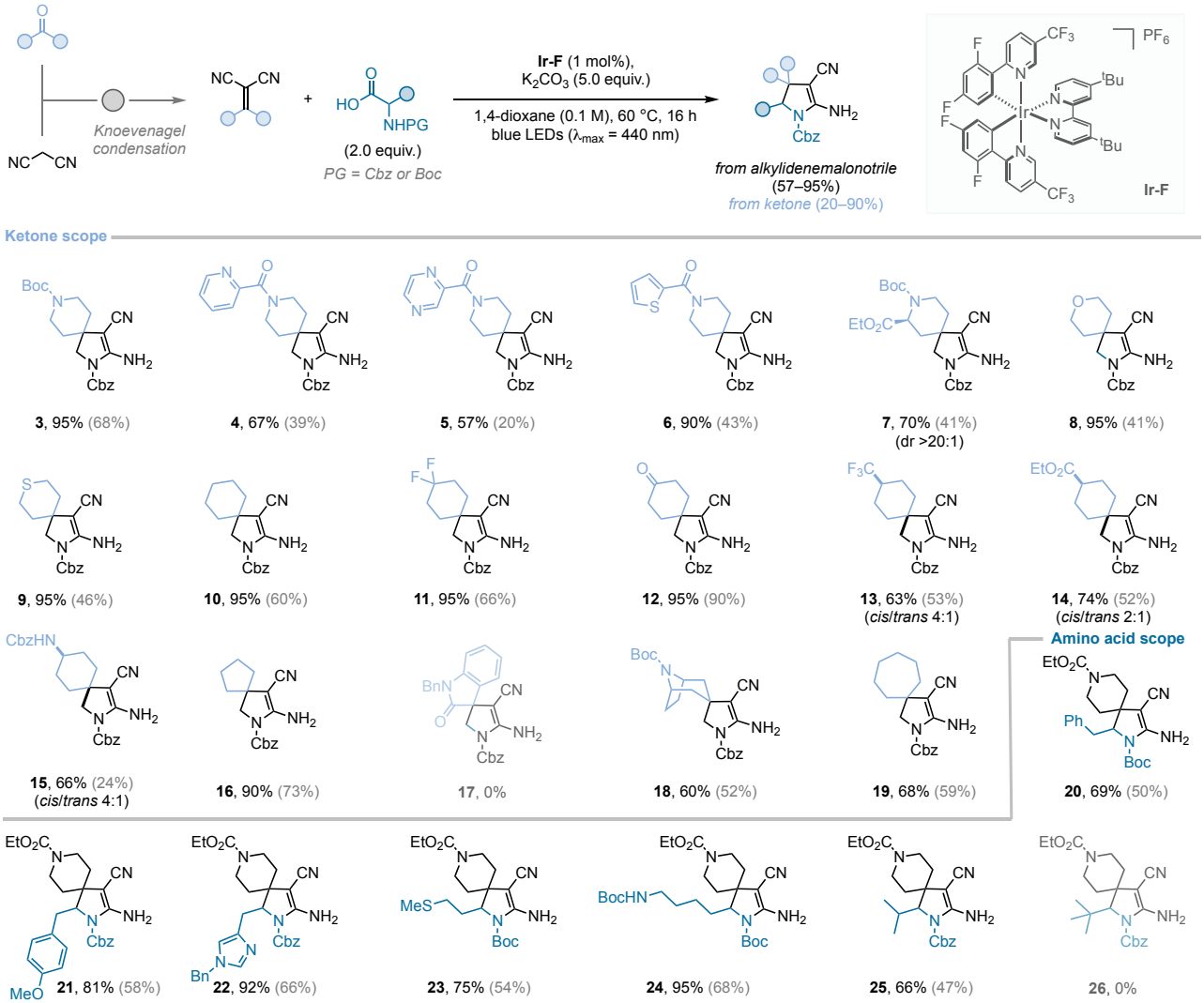
Table 1. Control reactions & optimized conditions.[a]

Giese-type reaction + cyclisation



Entry	Deviation from optimised conditions	Yield (%)
1	none	Quant. (95)
2	42 °C instead of 60 °C	8
3	No light	0
4	No photocatalyst	0

[a] Reactions conducted in 0.1 mmol scale. Yields determined by ^{1}H NMR using trichloroethylene as internal standard. Isolated yield in parenthesis.



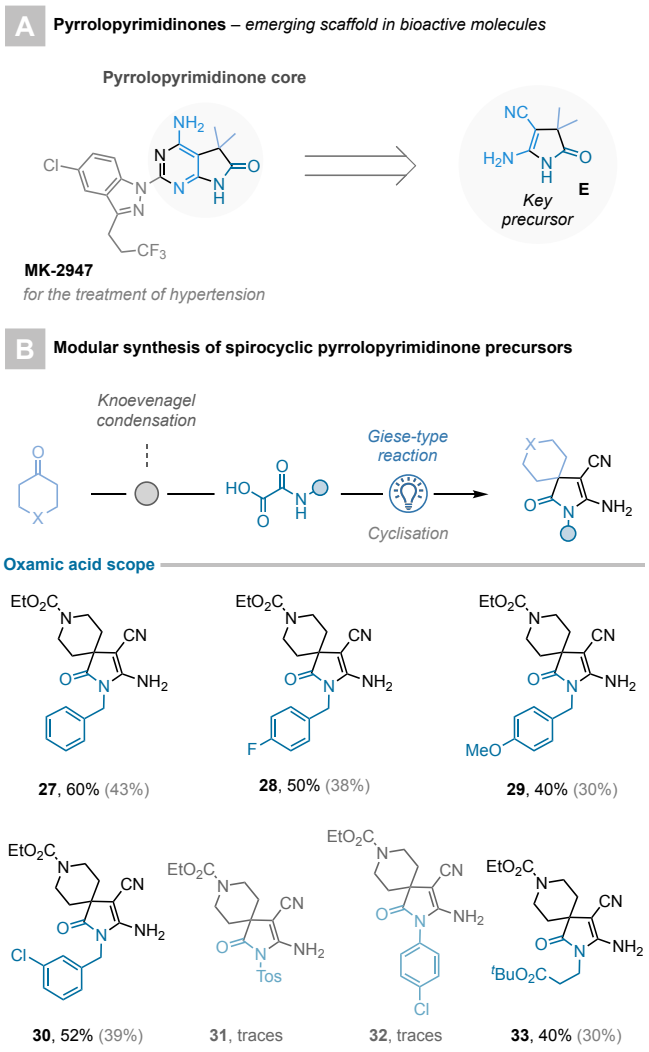
Scheme 1. Scope & limitations of the methodology. Reactions carried out in 0.3–0.5 mmol scale. Two-step yield from starting ketone in parenthesis and grey.

domino process dramatically decreases,[12] and that **Ir-F**, as well as light irradiation are needed for the reaction to proceed (Table 1, entries 2–4).[13]

With the optimised conditions in hand, we evaluated the generality of this modular strategy (Scheme 1). First, we investigated the ketone scope. Piperidine-derived spirocycles bearing acid sensitive Boc-protecting groups (**3**), basic heteroarenes such as pyridines (**4**) and pyrazines (**5**), or thiophenes (**6**) were obtained in good to excellent yields (57–95%). The use of an *L*-pipecolic ester derivative enabled the synthesis of **7** in excellent yield (70%) and diastereocontrol (d.r. > 20:1). Other saturated 6-membered heterocycles, such as oxanes or thianes, can also be converted to the corresponding spirocyclic species (**8–9**) in excellent yields (95%). Readily available cyclohexanone derivatives bearing diverse functional groups, such as *gem*-diflurides, ketones, esters or protected primary amines also afford the targeted polar species **10**–**15** in good to excellent yields (63–95%) and good *cis*/*trans* selectivity (up to 4:1). While the use of cyclopentatone enabled the synthesis of spirocycle **16**, the use of a more complex isatine-derived alkylidene malononitrile, failed to afford the targeted product (**17**). Interestingly, the use of Boc-protected nortropinone, as well as heptanone, afforded the corresponding spirocycles **18** and **19** in good yields (60–68%).

Next, we investigated the α-amino acid scope. While the use of protected α-amino acids bearing benzylic or aliphatic chains, such as phenylalanine, methylated tyrosine, benzyl protected histidine, methionine, and lysine enabled the synthesis of the targeted compounds **20**–**24** in excellent yields (69–95%); the use of more sterically hindered α-amino acids afforded slightly diminished yields. For example, valine derived spirocycle **25** was obtained in 66% yield, while *tert*-leucine did not provide the targeted compound (**26**).

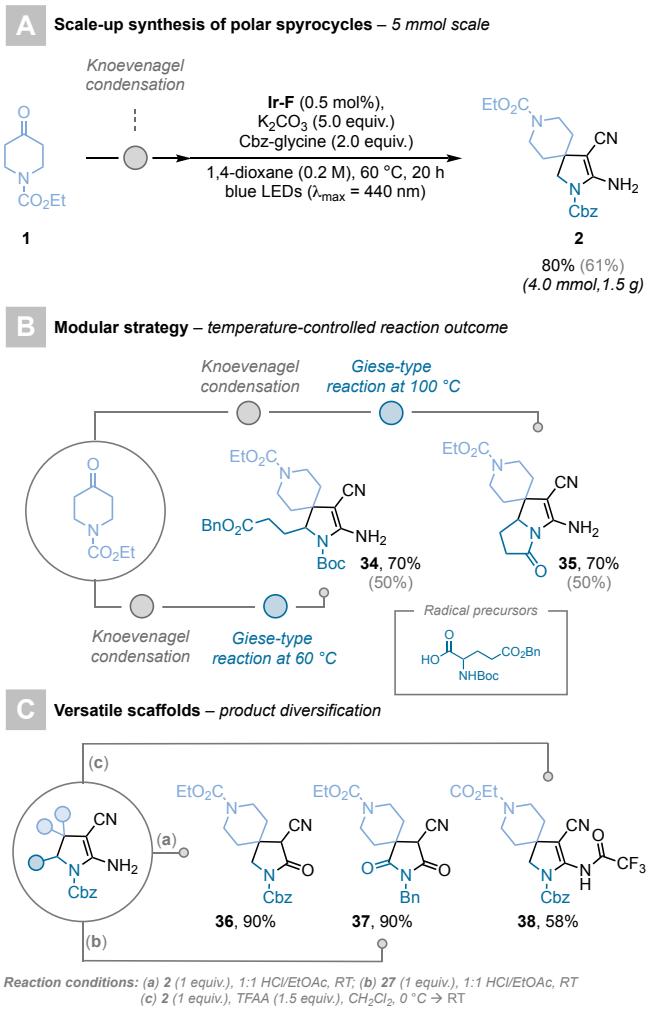
5,5-substituted pyrrolopyrimidinones have recently emerged as interesting bioactive scaffolds. For example, in 2020 Merck & Co. disclosed the discovery of MK-2947, a soluble guanylate cyclase stimulator for the treatment of hypertension.[14] A retrosynthetic analysis shows that the pyrrolopyrimidinone core could be accessed, for example, from compound **E** via condensation reactions (Scheme 2A).[15] With this in mind, we hypothesised that by changing the nature of the nucleophilic radical in our strategy – from an α-amino to a carbamoyl radical – we could access a wide range of potential 5,5-substituted pyrrolopyrimidinones precursors with increased 3D character and Fsp^3. Using our standard optimised conditions, and simply substituting α-amino acids for oxamic acids as radical sources, a new class of spirocyclic scaffolds were readily accessed (Scheme 2B). While the use of benzyl-derived oxamic acids as carbamoyl radical precursors afforded the targeted polar spirocycles (**27**–**30**) in good yields (40–60%), tosyl or phenyl derived oxamic acids afforded only traces of products (**31**–**32**). Gratifyingly, the use of a β-alanine derived oxamic acid afforded the desired spirocycle **33** in synthetically useful yields (40%).



Scheme 2. Scope & limitations of carbamoylation reaction. Reactions run in 0.5 mmol scale, using 2 equiv. of oxamic acid and standard reaction conditions. Two-step yield from starting ketone in parenthesis and grey.

To showcase the scalability of the process, a gram scale reaction starting from alkylidenemalonontrile **1** was carried out, lowering the catalyst loading (**Ir-F**, 0.5 mol%) and increasing the concentration (0.2 M). Gratifyingly, this afforded the targeted polar spirocyclic species **2** in excellent yield after the photochemical step (80%, 4.0 mmol, 1.5 g), and an overall 61% yield from the starting ketone (Scheme 3A).

The modularity of this strategy was further highlighted by the preparation of spirocycles **34** and **35** (Scheme 3B). If alkylidenemalononitrile **1** is subjected to the standard reaction conditions with Boc-glutamic acid, spirocycle **34** is formed in 70% yield. However, if the temperature is increased to 100 °C, polycyclic species **35** is generated in 50% from the starting ketone. In addition, the spirocyclic core can be converted to the corresponding lactam (**36**) or succinimide (**37**) scaffolds, and the free amino group can be used as a new vector for further functionalisation (**38**), thus highlighting the versatility offered by our strategy to access a wide range of diverse polar spirocyclic motifs (Scheme 3C).



Scheme 3. Scale-up & product diversification. Two-step yield from starting ketone in parenthesis and grey.

Finally, we propose a plausible reaction mechanism for the two key steps of this domino strategy: the light-mediated Giese-type reaction and the base-mediated spirocyclisation (Figure 2).

The light-mediated Giese-type reaction starts with the reductive quenching of the excited photocatalyst (***Ir-F^{III}**, $*E^{1/2}$ = +1.21 V vs SCE in CH_3CN)[16] by the corresponding α-amino carboxylate species ($E^{1/2}$ = +0.95 V versus SCE in CH_3CN);[17] this generates an acyloxy radical (**I**) that undergoes rapid decarboxylation, affording a nucleophilic α-amino radical (**II**). Subsequent addition of **II** to a highly electrophilic alkylidenemalononitrile (**III**) results in the formation of stabilised tertiary radical intermediate **IV**, which can undergo facile single electron transfer (SET) with the reduced photocatalyst (**Ir-F^{II}**, $E^{1/2}$ = −1.37 V vs SCE in CH_3CN),[16] to generate malononitrile derivative **V** after protonation. A similar catalytic cycle is expected for the carbamoylation reaction when using oxamic acids as radical precursors.

Intramolecular cyclisations involving malononitrile derivatives usually take place under acidic conditions.[18] Therefore, *in silico* studies were conducted to shed light on the second step of our domino reaction, the base-mediated spirocyclisation.[19] Experimentally, we found that the use of KOAc, instead of K_2CO_3, afforded **2** in similar yields.[20] Therefore, we modelled using KOAc as base instead of K_2CO_3 to simplify the DFT calculations. The most favoured pathway starts with the deprotonation of **V** to afford the stable anionic species **VI** (-14.9 kcal/mol), with the charge delocalized along the ketenimine moiety. A concerted 5-exo-dig cyclisation sequence, assisted by HOAc as the proton shuttle, yields intermediate **VIII**, through a free energy barrier of 22.2 kcal/mol. This intermediate can be easily protonated to exergonically afford the targeted spirocycle **IX** (-21.2 kcal/mol).[21]

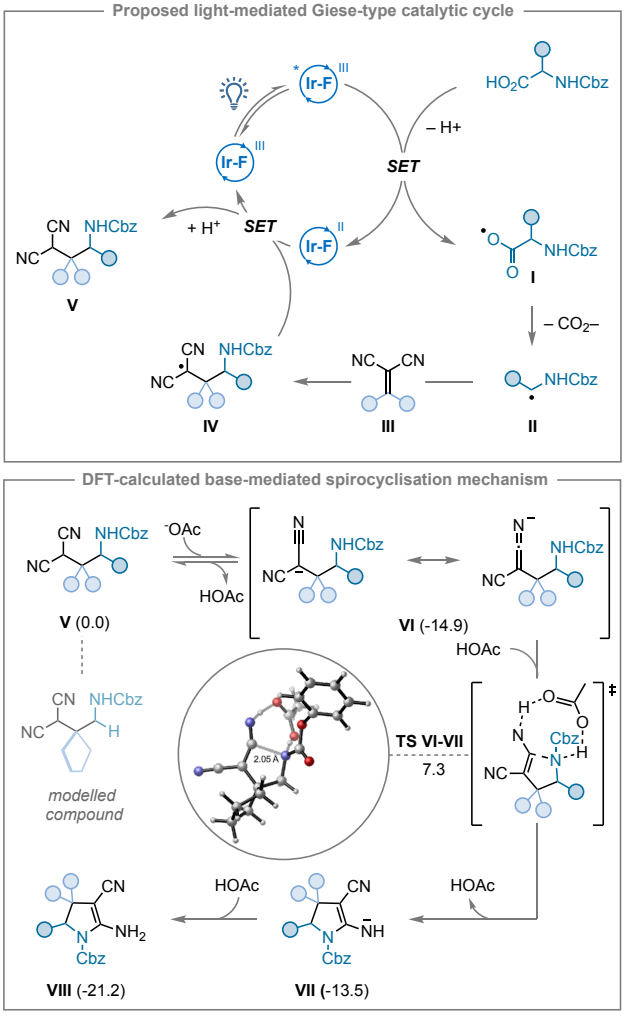


Figure 2. Proposed catalytic cycle for the light-mediated Giese-type reaction & DFT-calculated base-mediated spirocyclisation reaction mechanism (kcal/mol).

In conclusion, we have developed a highly modular strategy for the synthesis of a wide range of polar spirocyclic scaffolds from readily available starting materials, such as cyclic ketones, and α-amino or oxamic acids. This two-step process enables the preparation of β-spirocyclic pyrrolidine derivatives in synthetically useful yields (52% average yield from the starting ketone). In addition, by changing the nature of the nucleophilic radical species in the Giese-type reaction step, a new class of spirocyclic species can be obtained. This was demonstrated using oxamic acids as radical precursors to access potential 5,5-substituted pyrrolopyrimidinones precursors with increased 3D character and Fsp^3. Overall, the developed protocol presents a broad substrate scope, and can be readily scaled-up while reducing the catalyst

loading. Furthermore, the versatility of the accessed scaffolds was highlighted by a series of derivatisations to access diverse spirocyclic cores. Finally, *in silico* studies were carried out to support the proposed reaction pathway for the based-mediated cyclisation step.

Acknowledgements

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[12] At temperatures below 60 °C, the main product of the reaction is malononitrile intermediate **2a**. Independent experiments showed that **2a** can be converted to the targeted spirocyclic species **2** in the presence of 2.0 equiv. of K_2CO_3 at 60 °C. See Scheme S1 in the Supporting Information.

[13] See Table S1 in the Supporting Information for further optimisation studies.

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[19] See Supporting Information for further details.

[20] See Entry 12, Table S1 in the Supporting Information.

[21] An alternative mechanism involving deprotonation of the carbamate motif, followed by direct attack onto one of the nitrile groups was also investigated. However, this pathway is energetically disfavoured. See Figure S6 in the Supporting Information for further details.