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Investigations into the radical cascade route to a spiro-azaindane

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The paper is dedicated to Professor Samir Zard in appreciation of his chemistry and personal qualities during his career

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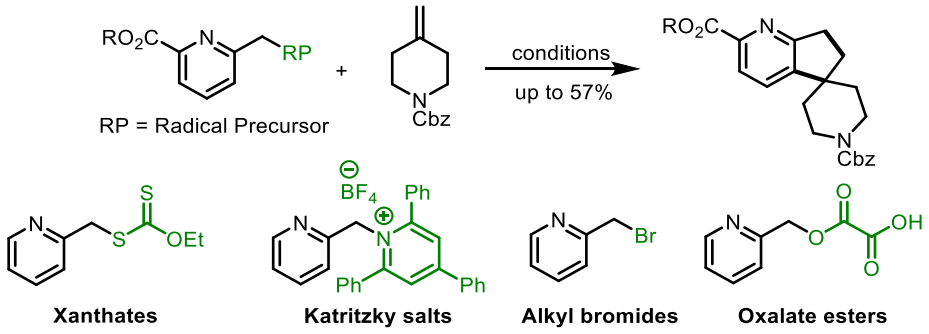
Abstract

The combination of modern radical generation strategies and the radical C-H functionalisation of heteroaromatics (the Minisci reaction) offers attractive routes to the preparation of complex fused heteroaromatic compounds. In this work, the one-step preparation of a trifunctionalised spiro-azaindane was investigated through a radical cascade route. In an effort to determine the most efficient approach, this cascade was initiated by 4 different radical precursors, in varying yields, adapting recently developed protocols. The best results were achieved using a triphenylpyridinium salt (Katritzky salt) under visible light irradiation.



Keywords: Katritzky salts, xanthates, photoredox, energy transfer, Minisci, light activation.

Introduction

Heteroaromatic groups are common scaffolds for drug leads in medicinal chemistry as they usually exhibit desirable physicochemical properties (lower metabolic clearance, higher aqueous solubility etc.).[1] Despite these advantages, the synthesis of complex molecular architectures containing heteroaromatics, whilst often required during drug development efforts, can represent a significant undertaking. Radical chemistry furnishes distinct synthetic transformations and can help in overcoming synthetic challenges encountered in "classic" two-electron processes. Specifically, the Minisci reaction is a particularly powerful approach to functionalise heteroaromatics using free radicals, formally achieving sp^2-sp^3 couplings on heteroaromatic compounds without the need for pre-functionalisation. The original conditions developed by Minisci and co-workers make use of carboxylic acids as radical precursors and the reaction proceeds through the generation of nucleophilic carbon-centred radicals after oxidative decarboxylation by the use of a silver catalyst and persulfate.[2, 3]

Over the past several years there have been a large number of advances in the Minisci reaction[4,5] involving replacing the carboxylic acid with other radical precursors such as oxalate esters,[6-8] boronic acids,[9-11] trifluoroborates,[12-14] Katritzky salts,[15] halides[16-18] and xanthates.[19-23] In some of these new protocols, the use of stoichiometric amounts of strong oxidant (i.e. persulfate) is replaced by milder protocols, in particular the combination of iridium catalysts and visible light irradiation (photoredox catalysis).

In the course of a medicinal chemistry project, we became interested in the synthesis of azaindane target **A** (Figure 1). It was envisaged that the preparation of target **A** could be achieved through a series of radical processes starting with benzylic radical **C** adding onto alkene **D** to give an intermediate tertiary radical **B** which, in turn, would be well set to add onto the tethered pyridine activated under acidic conditions and by the presence of an ester group in the *para*-position to give **A** after a final oxidation.

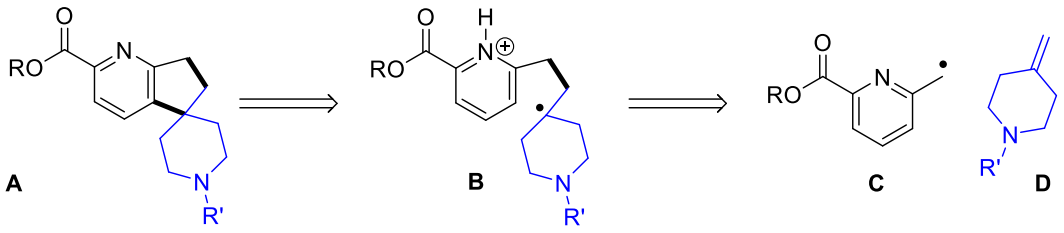
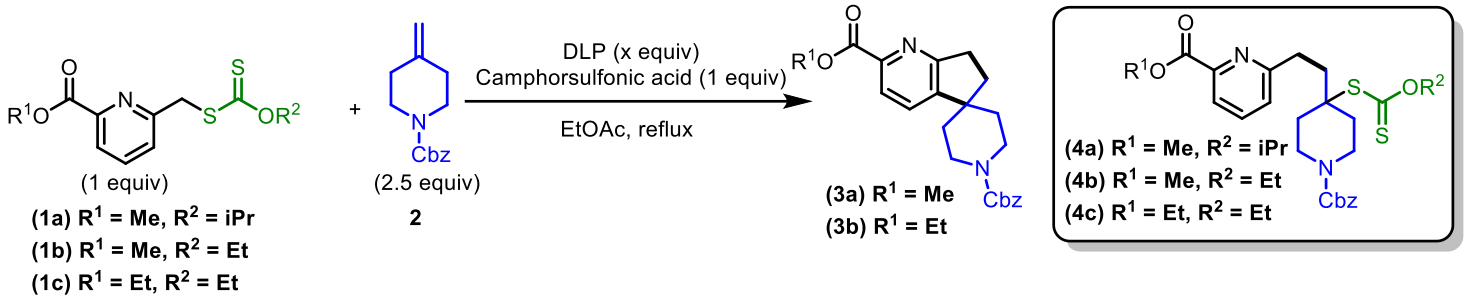


Figure 1: Radical retrosynthesis to target **A**.

Results and Discussion

Zard and co-workers reported a related convergent route to functionalised azaindanes via a two-step protocol using S-linked xanthate esters as radical precursors.[24] This methodology relies first on the insertion of an alkene into the C-S bond of the starting xanthate in the presence of stoichiometric amounts of dilauroyl peroxide (DLP), followed by an intramolecular "Minisci-like" reaction. The adaptation of this protocol to the preparation of **3a** in our hands led to an isolated yield of 41% in a single step (Scheme 1). No corresponding intermediate xanthate **4a**, was identified in the reaction mixture. The outcome of this reaction was found to be dependent on the work-up protocol used (Table 1, entry 1 and 2), as separation of the desired product **3a** from excess DLP and associated by-product was found to be particularly arduous. Alternative peroxides, such as potassium persulfate, only delivered low amounts of desired product **3a** (4% isolated yield, see experimental section). Replacement of

xanthate precursor **1a** by **1c** (Table 1, entry 3 and 4), along with a lower loading of DLP (1.5 equiv) led to further improvement and the isolation of **3a** and **3b** in yields of 47% and 57% respectively. Despite the usefulness of this protocol to achieve a first synthesis of azaindanes **3a-b**, the use of stoichiometric peroxide DLP, and the separation of the desired product from DLP-derived by-products, limits the scalability of this protocol. This motivated our exploration of alternative protocols for the preparation of **3a-b** which circumvents the use of stoichiometric amounts of high molecular weight oxidants such as DLP.



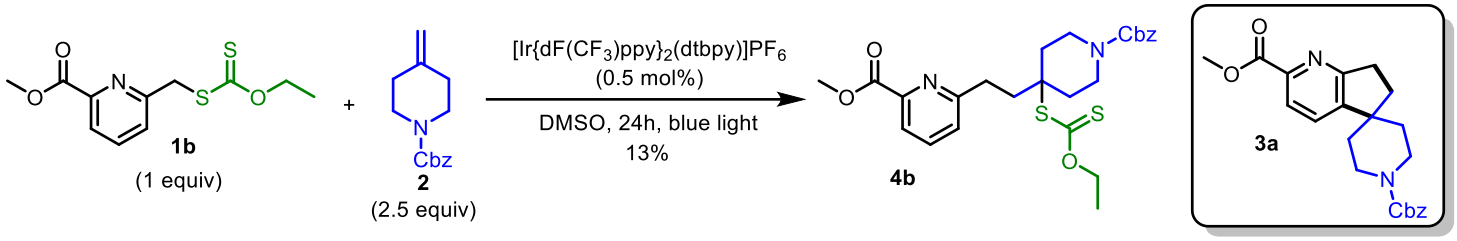
Scheme 1: Preparation of azaindane **3a-b** using an adaption of Zard's protocol.

Table 1: Yields and conditions of adapted Zard protocol on azaindane **1**. [a]Method A: Addition of barium hydroxide followed by filtration;[25] Method B: Addition of potassium carbonate followed by filtration.

Entry	Xanthate	DLP equivalents	Work up method[a]	Product Yield (%)
1	**1a**	3	Method A	21 (**3a**)
2	**1a**	3	Method B	41 (**3a**)
3	**1b**	1.5	Method B	47 (**3a**)
4	**1c**	1.5	Method B	57 (**3b**)

Chiba and co-workers reported a protocol for the triplet sensitisation of S-xanthates using an iridium catalyst under blue light irradiation.[26] These conditions led to the insertion of alkenes into the C-S bond, thus realising the first step of the sequence used by Zard and co-workers, but in the absence of stochiometric oxidant. Applying Chiba's conditions to **1b** (Table 2), xanthate **4b** was indeed isolated, albeit in a low yield of 13%, and no cyclised product **3a** was observed (Table 2**,** entry 1). We found that this process could progress to the desired cyclised product through the addition of acid, camphorsulfonic acid (CSA), in combination with substoichiometric amounts of DLP (Table 2, entry 3), or alone (Table 2, entry 4), but not by DLP alone (Table 2, entry 2). Using only CSA as stoichiometric additive, variations in the catalyst loading (Table 2, entry 5) as well as the electronic nature of the iridium catalyst (Table 2, entry 6), the stoichiometry of acid additive (Table 2, entry 8), the solvent (Table 2, entry 9), or the light source emission setting (Table 2, entry 10) led to little improvement. In all cases, varying amounts of intermediate xanthate **4b** were observed.

Table 2: Optimisation of iridium catalysed photosensitisation of xanthate **1b**.

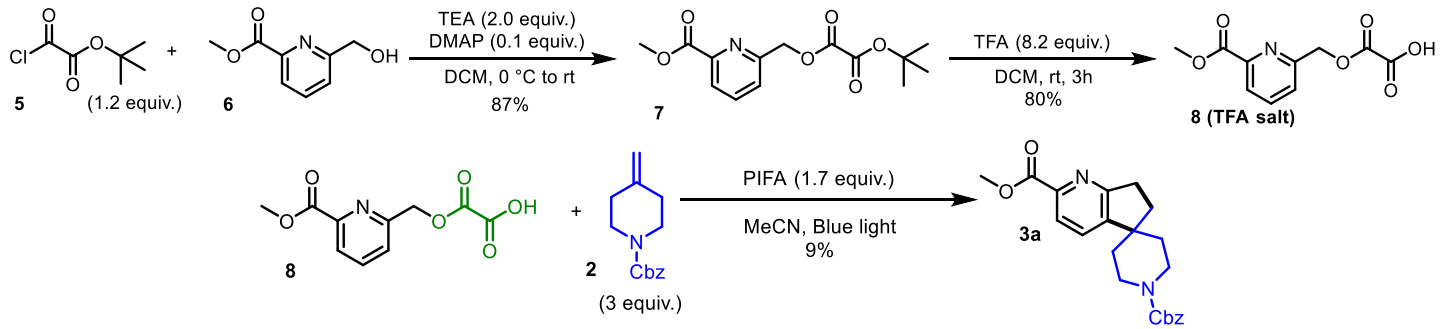


Entry	Conditions	Solvent	Yield, %[a]
1	$[Ir\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$ (0.5 mol%)	DMSO	13 (**4b**), 0 (**3a**)
2	$[Ir\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$ (0.5 mol%), DLP (20 mol%)[b]	DMSO	19 (**4b**), 0 (**3a**)
3	$[Ir\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$ (0.5 mol%), DLP (20 mol%), CSA (1 equiv)[c]	DMSO	30 (**3a**)
4	$[Ir\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$ (0.5 mol%), CSA (1 equiv)	DMSO	9 (**4b**), 20 (**3a**)
5	$[Ir\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$ (2 mol%), CSA (1 equiv)[d]	DMSO	26 (**3a**)
6	$[Ir\{dF(CF_3)ppy\}_2(bpy)]PF_6$ (0.5 mol%), CSA (1 equiv)[d]	DMSO	25 (**3a**)
7	$[Ir\{dF(CF_3)ppy\}_2(bpy)]PF_6$ (2 mol%), CSA (1 equiv)[e]	DMSO	12 (**3a**)
8	$[Ir\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$ (2 mol%), CSA (2 equiv)[c]	DMSO	26 (**3a**)
9	$[Ir\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$ (2 mol%), CSA (1 equiv)	MeCN	32 (**3a**)
10	$[Ir\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$ (2 mol%), CSA (1 equiv)[f]	DMSO	28 (**3a**)

[a]Reactions were conducted with 1 equivalent of xanthate **1b** and 2.5 equivalents of alkene **2** and irradiated with blue light for 24 h; [b] Reaction duration was 43 h; [c] Reaction duration was 23h; [d] Reaction duration was 18 h; [e] Reaction duration was 46 h; [f] Kessil® A160WE Tuna Blue lamp colour setting set to 0% rather than 100%.

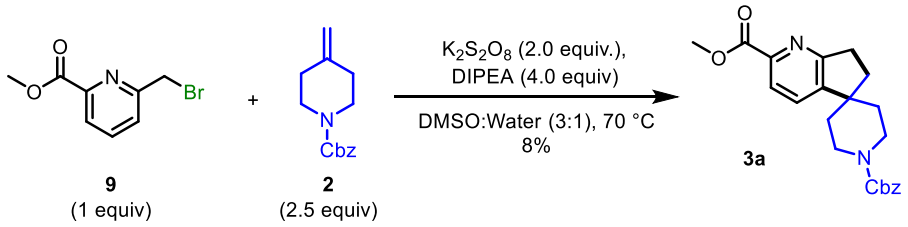
Despite promising results using a photosensitisation strategy to enable the desired cyclisation to proceed, attention now turned to alternative radical precursors.

Oxalate esters have been reported as radical precursors in the functionalisation of heteroarenes mediated by PIFA (phenyliodine bis(trifluoroacetate)) under blue light irradiation.[6] After optimisation, the synthesis of the desired oxalate ester **8** as a trifluoroacetate (TFA) salt was achieved by a sequence of esterification and *tert*-butyl group deprotection (Scheme 2). Submitting this ester to PIFA and blue light irradiation in the presence of alkene **2** (3 equiv) led to the isolation of desired product **3a** in a low yield (9%). It was noted that 2-electron processes were impacting the outcome of this reaction. This was attributed to the electrophilic character of benzylic oxalate ester **8** which was found to liberate compound **6**.



Scheme 2: Preparation of oxalate TFA salt **8** and subsequent radical reaction.

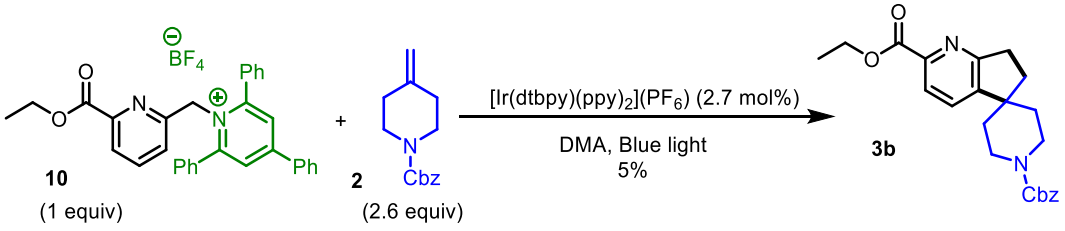
Leonori and co-workers reported a XAT (halogen atom transfer) process enabled by intermediary aminoalkyl radicals, whereby alkyl and aryl bromides can be used as radical precursors applied in Minisci-style reactions.[18] Bromide **9** was originally used as a starting material for the synthesis of xanthates **1a-b**, therefore a protocol enabling its direct use as a radical precursor would be of clear value in shortening the route to target **3a**. Under the reported conditions and in presence of alkene **2** (2.5 equiv) (Scheme 3), the desired product was only obtained in 8% yield, once again due to competing 2-electron processes driven by the electrophilic character of bromide **9,** readily producing the corresponding benzyl alcohol under these conditions**.**



Scheme 3: Reaction of bromide **9** using adapted Leonori and co-worker's protocol towards target **3a**.[18]

Our attention then turned to triphenylpyridinium salts, also widely referred to as Katritzky salts (KS). These species are known to be efficient radical precursors which have been shown to participate in a variety of radical processes, and are easily prepared from the corresponding amine through condensation with a pyrylium salt.[27,28,29] Interestingly, they have been used for the C-H functionalisation of heterocycles by Glorius and co-workers through a process reminiscent of the Minisci reaction.[15]

Pyridinium salt **10** was prepared and submitted to the conditions described by Glorius and co-workers in the presence of alkene **2**.[15] Encouragingly, the desired product **3b** was observed, but isolation afforded a 5% yield (Scheme 4). Addition of CSA as an acid source led to decomposition of the iridium catalyst.



Scheme 4: Reaction of KS **10**, under conditions adapted from Glorius and co-workers.[15]

KS pyridinium species have also been shown to participate in the formation of Electron Donor-Acceptor (EDA) complexes which can be activated by visible light to initiate radical processes (see Figure 2, showing EDA complex formation with a Hantzsch ester). Although EDA complexes involving KS have not been applied to the C-H functionalisation of heteroaromatics, to the best of our knowledge, they have been applied in other radical processes such as the addition to electron-deficient olefins (Giese reaction).[30,28] It was therefore hypothesised that this activation method could be applied to the synthesis of **3b**.

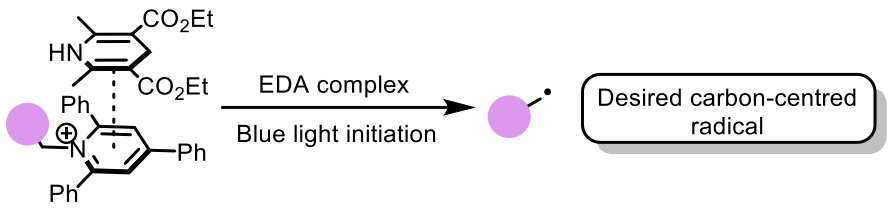
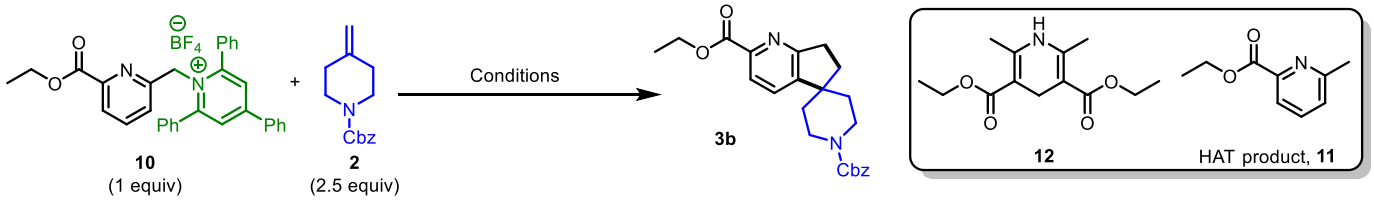


Figure 2: Depiction of an EDA complex driven radical generation method.

Hantzsch esters (HE) have been described to act as suitable donors for the formation and productive use of EDA complexes in conjunction with KS.[28,30] Adapting a literature procedure using a HE **12** in dimethylacetamide (DMA) as the solvent (Scheme 5),[31] gave no desired product **3b**. The predominant product observed under these conditions was methyl pyridine **11**. We proposed that this product arose from a hydrogen atom transfer (HAT) process from HE **12** to a benzyl radical derived from pyridinium **10**, suggesting productive radical generation. Strikingly, a change of solvent from DMA to water:acetonitrile (1:1) (Table 3**,** entry 2) led to a marked improvement, and desired product **3b** was obtained in 40% isolated yield. This strong solvent effect was highlighted in a report by Blakey and co-workers.[32] In their work, this behaviour was attributed to a decrease in the fraction of HE **12** in solution in the water:acetonitrile solvent system, which is proposed to limit the rate of HAT side-reactions. However, water alone was not an appropriate solvent for this process (Table 3**,** entry 4), but acetonitrile was perfectly suitable and led to an isolated yield of 47% of **3b** (Table 3**,** entry 3) (average of 3 reactions). Whilst omitting both the HE **12** and CSA led to no conversion (Table 3, entry 5), we were pleasingly surprised to find that the process did not require addition of HE **12** (Table 3, entry 6).



Scheme 5: Synthesis of azaindane **3b** from KS **10**.

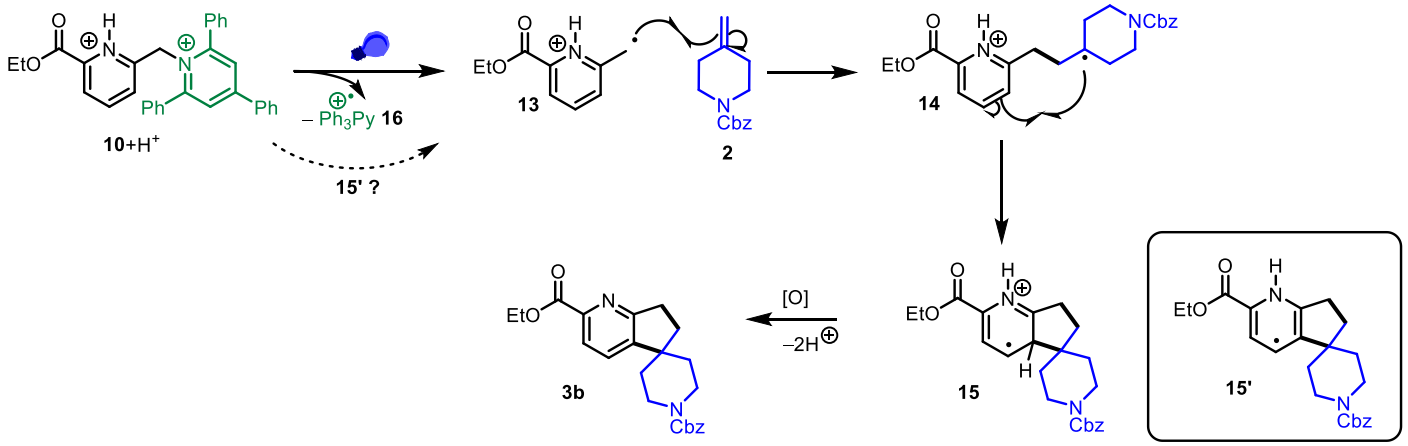
Table 3: Condition screen for the synthesis of **3b** form KS **10.** [a] Average of 3 reactions; [b] Average of 2 reactions

Entry	Conditions	Yield of 3b (%)
1	DMA, blue light, HE **12** (2 equiv), CSA (2 equiv)	0
2	H_2O:MeCN (1:1), blue light, HE **12** (2 equiv), CSA (2 equiv)	40
3	MeCN, blue light, HE **12** (2 equiv), CSA (2 equiv)	47[a]
4	H_2O, blue light, HE **12** (2 equiv), CSA (2 equiv)	4
5	MeCN, blue light	0
6	MeCN, blue light, CSA (2 equiv)	50[b]

Whilst the exact mechanism responsible for the productive generation of radical **13** from pyridinium **10** remains to be elucidated, it appears distinct from previous reports based on iridium photocatalysts or EDA complex formation. A possible mechanism is presented in Scheme 6. Based on a number of prior reports on the reactivity of Katritzky salts,[33] and on the observed formation of HAT by-product **11** we postulated a radical

mechanism. In an initial photoinduced decomposition event promoted by the presence of acid,[34,35] carbon-centred radical **13** is produced and trapped by alkene **2** to generate tertiary radical **14**. This species is well set-up to undergo an intramolecular cyclisation on the tethered activated pyridinium to give radical cation **15** which requires a further oxidation to yield rearomatised **3b**. The nature of the final oxidant remains to be elucidated, and a chain mechanism, whereby **15'** (arising by reversible proton loss from the very acidic **15**) is involved in a propagation step to generate **13** from **10**, is not excluded.

It is worth noting that this current process for the synthesis of **3b** represents an improvement upon the initial xanthate-based protocol as the isolation of the desired product is greatly facilitated in the absence of stoichiometric amounts of DLP by-product and the reaction is observed to proceed with no added oxidant.



Scheme 6: Proposed mechanism for generation of **3b** from experimental observation.

Conclusions

In conclusion, 4 different radical precursors have been explored for the radical cascade process leading to the synthesis of azaindanes **3a-b**. Initial success was encountered by adapting Zard's protocol using xanthates. An attempt to avoid the use of stoichiometric peroxide oxidant led alternative radical generation methodologies to be considered. The exploration uncovered the potential of Katritzky salts for the synthesis of azaindanes **3a-b** in a single step. Strikingly, this result was achieved without activations as EDA complex or (photo)catalysis, contrasting with previous reports and providing a synthesis with limited additives. The final protocol compares positively with the initially described process utilising S-xanthates as radical precursors, as the use of excess amount of organic peroxide is avoided, thus simplifying product isolation. Studies to explore the mechanism at play in this process, as well as an investigation into the substrate scope (heteroaromatic, alkene) of the reaction are underway and will be reported in due course.

Experimental Section

General. All chemicals and solvents were obtained from commercial suppliers and used without further purification unless otherwise stated. Reactions sensitive to humidity or air were carried out under a nitrogen atmosphere. Temperatures of 0 °C were achieved with ice baths and those between 0 °C and -78 °C were achieved with dry ice/acetone bath.

Photochemistry based reactions were performed using a Kessil® 160WE Tuna Blue lamp (100% colour, 100% intensity) unless otherwise state and housed within a HepatoChem EvoluChem™ PhotoRedOx mirror box. Internal and external reaction temperatures were not measured, fan system was used to provide cooling.

Flash column chromatography (FCC) was performed on disposable normal-phase silica cartridges, used on Teledyne ISCO Combi*Flash*® Rf+ apparatus.

Preparative HPLC/Reverse phase chromatography was performed using a Teledyne ISCO ACCQPrep® HP125 apparatus equipped with a Waters XSelect® CSH™ OBD Prep C18 column (30 × 100 mm, 5 µm particle size, 130 Å pore size). The column was eluted using the specified gradient of acetonitrile in 10 mM aqueous ammonium bicarbonate or 0.1% aqueous formic acid (40 mL/min flow rate).

Mass-directed HPLC auto-purification (MDAP) was performed in reverse phase using a Waters AutoPurification system, comprising of Waters XSelect® CSH™ OBD Prep C18 column and a Waters ZQ™ or Waters Acquity qDa™ mass detector using alternate-scan positive and negative electrospray ionisation.

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded in the solvent stated on Bruker NMR spectrometers (AVIII 400 MHz, 101 MHz and 376 MHz respectively). Spectra were referenced to the residual non-deuterated solvent peak and processed using ACD/Spectrus 2020.2.0. Chemical shifts (δ) are quoted in parts per million (ppm) to the nearest 0.01 ppm for ^{1}H/^{19}F NMR spectroscopy and 0.1 ppm for ^{13}C NMR spectroscopy. The spin multiplicities are expressed as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and coupling constants (*J*) are quoted in Hz to the nearest 0.1 Hz. The abbreviation “br” denotes “broad”.

HRMS data were recorded using solutions in acetonitrile by the internal analytical service at GSK Stevenage, using a Waters Xevo® G2-XS QToF instrument.

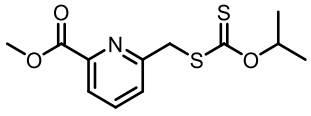
Infrared spectra were obtained on a Perkin Elmer Spectrum Two FTIR fitted with a Perkin Elmer UATR diamond sampling accessory.

Liquid chromatography mass spectra (LCMS) were recorded by UPLC analysis conducted on an Acquity UPLC CSH C18 column (50 mm × 2.1 mm i.d. 1.7 µm packing diameter), 1 mL/min flow rate at 40 °C using the following methods:

High pH: 40 °C, 1 mL min^{-1} flow rate, 2-minute run. A = 10 mM ammonium bicarbonate in water adjusted to pH 10 with ammonia solution, B = Acetonitrile. Gradient: 0.0–1.5 min: 0–97% B; 1.5–1.9 min: 97% B; 1.9–2.0 min: 97–0% B.

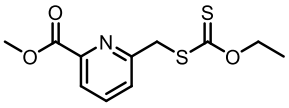
Formic: 40 °C, 1 mL min^{-1} flow rate, 2-minute run. A = 0.1% v/v solution of formic acid in water, B = 0.1% v/v solution of formic acid in acetonitrile. Gradient: 0.0–1.5 min: 3–97% B; 1.5–1.9 min: 97% B; 1.9–2.0 min: 97–2% B.

Xanthate based reactions.

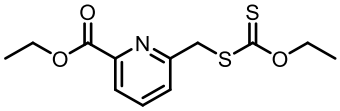


Synthesis of methyl 6-(((isopropoxycarbonothioyl)thio)methyl)picolinate (1a). A round-bottomed flask was charged with methyl 6-(bromomethyl)picolinate 9 (1 g, 4.35 mmol, 1.00 eq) in acetone (14 mL) and cooled to 0 °C. Potassium O-isopropyl carbonodithioate (0.796 g, 4.56 mmol, 1.05 eq) was added slowly to the solution leading to a cloudy white solution. The solution was warmed to room temperature and stirred for 90 min. Water (20 mL) was added to the mixture. The solution was extracted with dichloromethane (DCM) (2 x 20 mL). The organic layers were combined and concentrated under reduced pressure yielding methyl 6-(((isopropoxycarbonothioyl)thio)methyl)picolinate 1a (1.18 g, 4.13 mmol, 95% yield) as a pale-yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.03 (dd, 1H, *J* 7.8, 1.0 Hz), 7.81 (t, 1H, *J* 7.8 Hz), 7.66 (dd, 1H, *J* 7.8, 1.0 Hz), 5.75 (sept, 1H, *J* 6.2 Hz), 4.62 (s, 2H), 4.01 (s, 3H), 1.37 (d, 6H, *J* 6.1 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 213.0, 165.9, 157.6, 148.1, 137.9, 126.8, 124.2, 78.8, 53.3, 41.8, 21.6; FTIR (neat) $\tilde{\nu}_{max}$ (cm^{-1}) 2980, 2950, 1722, 1586, 1456, 1436, 1373, 1316, 1231, 1132, 1085, 1032, 992, 900, 831, 797, 706, 667, 597; HRMS (ESI-TOF) *m/z* Calcd. for $C_{12}H_{16}NO_3S_2$ [M+H$^+$] requires 286.0566. Found [M+H$^+$] 286.0582.

Synthesis of methyl 6-(((ethoxycarbonothioyl)thio)methyl)picolinate (1b) and ethyl 6-(((ethoxycarbonothioyl)thio)methyl)picolinate (1c)

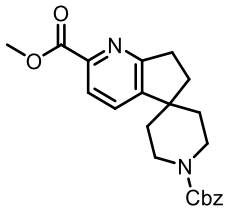


Methyl 6-(((ethoxycarbonothioyl)thio)methyl)picolinate (1b). Methyl 6-(bromomethyl)picolinate **9** (1.51 g, 6.56 mmol, 1.00 eq) and acetone (25 mL) were cooled to 0°C. Potassium xanthogenate (1.56 g, 9.73 mmol, 1.50 eq) was added slowly and the solution was heated to room temperature. This was stirred for 2 h. The solution was washed with water (35 mL) and DCM (2 x 35 mL). The resulting solution was concentrated under reduced pressure to give a colourless oil, methyl 6-(((ethoxycarbonothioyl)thio)methyl)picolinate **1b** (1.85 g, 6.4 mmol, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.03 (dd, 1H, *J* 7.8, 1.0 Hz), 7.81 (t, 1H, *J* 7.7 Hz), 7.65 (dd, 1H, *J* 7.8, 1.0 Hz), 4.69-4.63 (q + s, 4H) (overlap of quartet and singlet peaks), 4.01 (s, 3H), 1.41 (t, 3H, *J* 7.1 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 213.6, 165.5, 157.1, 147.8, 137.6, 126.6, 123.9, 70.5, 53.0, 41.7, 13.7; FTIR (neat) $\tilde{\nu}_{max}$ (cm^{-1}) 2992, 2981, 2954, 1718, 1652, 1589, 1474, 1456, 1440, 1390, 1359, 1314, 1233, 1209, 1195, 1117, 1053, 993, 862, 771, 746, 709, 662, 603, 510; HRMS (ESI-TOF) *m/z* Calcd. for ($C_{11}H_{14}NO_3S_2$) [M+H$^+$] requires 272.0410 Found [M+H$^+$] 272.0452.



Ethyl 6-(((ethoxycarbonothioyl)thio)methyl)picolinate (1c). During the 0.5 g scale synthesis of **1b**, by-product **ethyl 6-(((ethoxycarbonothioyl)thio)methyl)picolinate 1c** was isolated. This was proposed to form due to the possible decomposition of potassium xanthogenate, releasing CS_2 and ethanol which resulted in transesterification of the methyl ester to an ethyl ester when concentrated under reduced pressure to give ethyl 6-(((ethoxycarbonothioyl)thio)methyl)picolinate **1c**. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.02 (dd, 1H, *J* 7.8, 1.0 Hz), 7.79 (t, 1H, *J* 7.8 Hz), 7.64 (dd, 1H, *J* 7.8, 1.0 Hz), 4.69-4.64 (q + s, 4H) (overlap of quartet and singlet peaks), 4.49 (q, 2H, *J* 7.1 Hz), 1.46-1.40 (2 x t, 6H) (overlap of two triplets); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 213.4, 165.0, 157.1, 148.1, 137.6, 126.4, 123.8, 70.4, 62.0, 41.7, 14.3, 13.8; LCMS (Formic, ESI) t_R = 1.25 min, [M+H$^+$] 285.89

Synthesis of 1'-benzyl 2-methyl 6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidine]-1',2-dicarboxylate (3a)



Method 1 – Use of DLP:

3 Equivalents:

Iteration 1 (Method B): Potassium carbonate work-up. Methyl 6-(((isopropoxycarbonothioyl)thio)methyl)picolinate **1a** (200 mg, 0.701 mmol, 1.00 eq), CSA (163 mg, 0.701 mmol, 1.00 eq) and DLP (838 mg, 2.102 mmol, 3.00 eq) were added to a vial. The vial was placed under nitrogen and benzyl 4-methylenepiperidine-1-carboxylate **2** (0.361 mL, 1.738 mmol, 2.50 eq) was added followed by ethyl acetate (3.5 mL). The solution was heated to reflux for 2 h then the reaction was cooled to room temperature and concentrated under reduced pressure. MeCN (4 mL) was added to the orange oil followed by potassium carbonate (407 mg) and the solution was vigorously stirred for 1 h. MeCN (10 mL) was added, and the solution was filtered washing with MeCN (10 mL). Filtrate was concentrated under reduced pressure. The crude orange oil was purified by FCC on silica (40 g cartridge) with elution gradient cyclohexane:ethyl acetate (0-100% ethyl acetate) yielding 1'-benzyl 2-methyl 6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidine]-1',2-dicarboxylate **3a** (158 mg, 0.290 mmol, 41 % yield) (80% purity), as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.99 (d, 1H, *J* 7.8 Hz), 7.53 (d, 1H, *J* 7.8 Hz), 7.41-7.28 (m, 5H), 5.17 (s, 2H), 4.20 (br s, 2H), 4.00 (s, 3H), 3.15 (t, 2H, *J* 7.6 Hz), 3.05 (br t, 2H, *J* 12.0 Hz), 2.16 (t, 2H, *J* 7.6 Hz), 1.79 (br t, 2H, *J* 12.0 Hz), 1.59 (br d, 2H, *J* 13.2 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 165.9, 165.1, 155.3, 147.8, 147.1, 136.7, 131.0, 128.5, 128.0, 127.9, 123.7, 67.2, 52.8, 45.0, 41.0, 36.1, 32.3, 31.6; FTIR (neat) $\tilde{\nu}_{max}$ (cm^{-1}) 2949, 1693, 1567, 1427, 1332, 1276, 1230, 1165, 1122, 1106, 1035, 994, 921, 857, 791, 762, 731, 697, 626, 591, 551; HRMS (ESI-TOF) *m/z* Calcd. for $C_{22}H_{25}N_2O_4$ [M+H$^+$] requires 381.1809. Found [M+H$^+$] 381.1817.

Iteration 2 (Method A): Barium hydroxide work-up. Methyl 6-(((isopropoxycarbonothioyl)thio)methyl)picolinate **1a** (200 mg, 0.701 mmol, 1.00 eq), CSA (163 mg, 0.701 mmol, 1.00 eq) and DLP (838 mg, 2.102 mmol, 3.00 eq) were added to a vial. The vial was placed under nitrogen and benzyl 4-methylenepiperidine-1-carboxylate **2** (0.364 mL, 1.752 mmol, 2.50 eq) was added followed by ethyl acetate (3.5 mL). The solution was heated to reflux for 2 h. The yellow solution was concentrated under reduced pressure. DCM (3.5 mL) and water (3.5 mL) were added to the orange oil, followed by barium hydroxide (504 mg) forming a dark blue solid this was vigorously stirred for 1 h. DCM (2 mL) was added, the solid was filtered out of solution and the organic layer was separated. The aqueous layer was extracted with DCM (5 mL) and the organic layers were combined and concentrated under reduced pressure. The crude black oil was purified by FCC on silica (40 g cartridge) with elution gradient cyclohexane:ethyl acetate (0-100% ethyl acetate) yielding 1'-benzyl 2-methyl-6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidine]-1',2-dicarboxylate **3a** (54.7 mg, 0.144 mmol, 21 % yield) (89% purity) as a light yellow oil.

1.5 equivalents from ethyl xanthate starting material (1b). Methyl 6-(((ethoxycarbonothioyl)thio)methyl)picolinate **1b** (74.9 mg, 276 µmol, 1.00 eq) was dissolved in ethyl acetate (1 mL). DLP (160 mg, 402 µmol, 1.50 eq) and CSA (64.1 mg, 276 µmol, 1.00 eq) were added to a vial and placed under nitrogen. The solution of methyl 6-(((ethoxycarbonothioyl)thio)methyl)picolinate **1b** in ethyl acetate was added followed by benzyl 4-methylenepiperidine-1-carboxylate **2** (0.14 mL, 690 µmol, 2.50 eq). This was heated

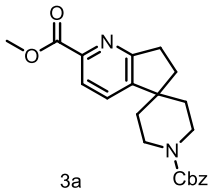
to reflux for 2 h. The yellow solution was concentrated under reduced pressure to give a yellow oil. MeCN (5 mL) was added to the yellow oil followed by potassium carbonate (114 mg), and this was stirred for 1 h. The solid was filtered and the filtrate was concentrated under reduced pressure to give a brown oil. The product was purified using FCC on silica (24g cartridge) using eluent cyclohexane:ethyl acetate (60-100% ethyl acetate), the relevant fractions were combined and concentrated under reduced pressure to give a colourless oil, 1'-benzyl 2-methyl 6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidine]-1',2-dicarboxylate **3a** (59.1 mg, 0.13 mmol, 47% yield) (84% purity).

Method 2 – Use of potassium persulfate as oxidant. Methyl 6-(((isopropoxycarbonothioyl)thio)methyl)picolinate **1a** (150 mg, 0.53 mmol, 1.00 eq), potassium persulfate (284 mg, 1.05 mmol, 2.00 eq) and CSA (122 mg, 0.53 mmol, 1.00 eq) were added to a vial and placed under nitrogen. Benzyl 4-methylenepiperidine-1-carboxylate **2** (0.27 mL, 1.31 mmol, 2.50 eq), DMSO (2.5 mL) and water (0.05 mL) were added, and the solution was heated to 70 °C for 5 h. The reaction mixture was diluted with water (15 mL) and washed with ethyl acetate (15 mL). The aqueous layer was further washed with ethyl acetate (2 x 15 mL). The organic layers were combined and washed with brine (15 mL). The pale-yellow organic layer was then concentrated under reduced pressure to give a brown oil. The product was purified using FFC on silica (24 g cartridge) using eluent cyclohexane:ethyl acetate (60-100% ethyl acetate), the relevant fractions were combined and concentrated under reduced pressure to give a yellow oil. This was dissolved in DMSO:MeOH (1:1) (1 mL) and submitted to an acidic reverse phase purification MDAP. The relevant fractions were combined, and these were concentrated under reduced pressure to give a colourless oil, 1'-benzyl 2-methyl 6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidine]-1',2-dicarboxylate **3a** (9 mg, 0.47 µmol, 4% yield) (91% purity).

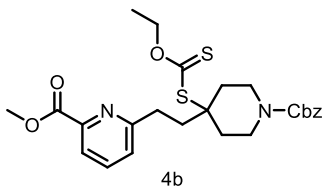
Photosensitisation

General procedure. Methyl 6-(((ethoxycarbonothioyl)thio)methyl)picolinate **1b** (1.00 eq), CSA (1.00 eq), and Ir photocatalyst (0.02 eq,) were added to a microwave vial and placed under nitrogen. After this, Benzyl 4-methylenepiperidine-1-carboxylate **2** (2.50 eq) and reaction solvent (1 mL) were added, and the solution was degassed for 5 min. The yellow solution was then irradiated with blue light for 24 h. The solution was diluted with ethyl acetate (10 mL) and water (10 mL). The organic layer was separated, and the aqueous layer was washed ethyl acetate (3 x 15 mL). The organic layers were combined and washed with brine (20 mL). The yellow organic layer was collected and concentrated under reduced pressure to give an orange oil. The product was purified using FCC on silica (24 g cartridge) using eluent cyclohexane:ethyl acetate (50-100% ethyl acetate). The relevant fractions were combined and concentrated under reduced pressure to give a pale oil, 1'-benzyl 2-methyl 6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidine]-1',2-dicarboxylate **3a.**

Synthesis of 1'-benzyl 2-methyl 6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidine]-1',2-dicarboxylate (3a) and methyl 6-(2-(1-((benzyloxy)carbonyl)-4-((ethoxycarbonothioyl)thio)piperidin-4-yl)ethyl)picolinate (4b):



3a



4b

Table 2, Entry 1. [Ir{dF(CF$_3$)ppy}$_2$(dtbpy)]PF$_6$ Methyl 6-(((ethoxycarbonothioyl)thio)methyl)picolinate **1b** (100.00 mg, 369 µmol, 1.00 eq) and [Ir{dF(CF$_3$)ppy}$_2$(dtbpy)]PF$_6$ (2.0 mg, 1.78 µmol, 0.005 eq,) were added to a microwave vial and placed under nitrogen. After this, benzyl 4-methylenepiperidine-1-carboxylate **2** (0.19 mL,

915 µmol, 2.50 eq) and DMSO (1 mL) were added, and the solution was degassed for 5 min. The yellow solution was then irradiated with blue light for 43 h. The solution was diluted with ethyl acetate (15 mL) and water (15 mL). The organic layer was separated, and the aqueous layer was washed ethyl acetate (2 x 15 mL). The organic layers were combined, washed with brine (20 mL) and concentrated under reduced pressure to give an orange oil. The product was purified using FCC on silica (24 g cartridge) using eluent cyclohexane:ethyl acetate (0-100% ethyl acetate). The relevant fractions were combined and concentrated under reduced pressure to give a brown oil. This was dissolved in DMSO:MeOH (1:1) (1 mL) and submitted to an acidic reverse phase purification MDAP. The relevant fractions were combined and concentrated under reduced pressure to give a colourless oil, methyl 6-(2-(1-((benzyloxy)carbonyl)-4-((ethoxycarbonothioyl)thio)piperidin-4-yl)ethyl)picolinate **4b** (23.8 mg, 0.047 mmol, 13%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm); 7.95 (dd, 1H, *J* 7.8, 1.0 Hz), 7.74 (t, 1H, *J* 7.7 Hz), 7.40-7.29 (m, 6H), 5.13 (s, 2H), 4.65 (q, 2H, *J* 7.1 Hz), 3.99 (s, 3H), 3.92 (br s, 2H), 3.34 (br t, 2H, *J* 11.7 Hz), 3.09-3.02 (m, 2H), 2.45-2.39 (m, 2H), 2.18 (br d, 2H, *J* 13.9 Hz), 1.74-1.63 (m, 2H), 1.43 (t, 3H, *J* 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 211.7, 165.8, 162.0, 155.1, 147.7, 137.3, 136.7, 128.5, 128.0, 127.9, 126.2, 122.8, 69.6, 67.2, 58.0, 52.8, 40.2, 39.5, 34.9, 33.1, 13.7; LCMS (Formic, ESI) t_R = 1.49 min, [M+H$^+$] 503.04
LCMS showed no production of **3a**.

Table 2, Entry 2. [Ir{dF(CF$_3$)ppy}$_2$(dtbpy)]PF$_6$ and DLP Methyl 6-(((ethoxycarbonothioyl)thio)methyl)picolinate **1b** (100 mg, 0.369 mmol, 1.00 eq), [Ir{dF(CF_3)ppy}$_2$(dtbpy)]PF_6 (2 mg, 1.78 µmol, 0.005 eq) and DLP (32 mg, 0.080 mmol, 0.22 eq) were added to a vial and placed under nitrogen. Benzyl 4-methylenepiperidine-1-carboxylate **2** (0.19 mL, 0.915 mmol, 2.5 eq) and DMSO (1 mL) were added, solution was degassed for 5 min and irradiated with blue light for 43 h. This yielded a colourless oil, methyl 6-(2-(1-((benzyloxy)carbonyl)-4-((ethoxycarbonothioyl)thio)piperidin-4-yl)ethyl)picolinate **4b** (35.5 mg, 0.071 mmol, 19%).
LCMS showed no production of **3a**.

Table 2, Entry 3. [Ir{dF(CF$_3$)ppy}$_2$(dtbpy)]PF$_6$, DLP and CSA Methyl 6-(((ethoxycarbonothioyl)thio)methyl)picolinate **1b** (100 mg, 0.369 mmol, 1.00 eq), [Ir{dF(CF_3)ppy}$_2$(dtbpy)]PF_6 (2.07 mg, 1.84 µmol, 0.005 eq), DLP (30 mg, 0.074 mmol, 0.20 eq) and CSA (85.6 mg, 0.369 mmol, 1.00 eq) were added to a vial and placed under nitrogen. Benzyl 4-methylenepiperidine-1-carboxylate **2** (0.19 mL, 0.921 mmol, 2.50 eq) and DMSO (1 mL) were added were added, solution was degassed for 5 min and irradiated with blue LEDs for 23 h. This yielded 1'-benzyl 2-methyl 6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidine]-1',2-dicarboxylate **3a** (41.3 mg, 0.109 mmol, 30 % yield).

Table 2, Entry 4. [Ir{dF(CF$_3$)ppy}$_2$(dtbpy)]PF$_6$ and CSA Methyl 6-(((ethoxycarbonothioyl)thio)methyl)picolinate **1b** (110 mg, 0.405 mmol, 1.00 eq), [Ir{dF(CF_3)ppy}$_2$(dtbpy)]PF_6 (2 mg, 1.78 µmol, 0.005 eq) and CSA (90 mg, 0.387 mmol, 0.96 eq) were added to a vial and placed under nitrogen. Benzyl 4-methylenepiperidine-1-carboxylate **2** (0.19 mL, 0.915 mmol, 2.30 eq) and DMSO (1 mL) were added, solution was degassed for 5 min and irradiated with blue light for 24 h. This yielded 1'-benzyl 2-methyl 6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidine]-1',2-dicarboxylate **3a** (31.2 mg, 82.0 µmol, 20% yield) and methyl 6-(2-(1-((benzyloxy)carbonyl)-4-((ethoxycarbonothioyl)thio)piperidin-4-yl)ethyl)picolinate **4b** (17.7 mg, 0.035 mmol, 9%).

Table 2, Entry 5. [Ir{dF(CF$_3$)ppy}$_2$(dtbpy)]PF$_6$ (2 mol%) and CSA Methyl 6-(((ethoxycarbonothioyl)thio)methyl)picolinate **1b** (98.8 mg, 0.364 mmol, 1.00 eq), [Ir{dF(CF_3)ppy}$_2$(dtbpy)]PF_6 (8.17 mg, 7.28 µmol, 0.02 eq) and CSA (85 mg, 0.365 mmol, 1.00 eq) were added to a vial and placed under a nitrogen. Benzyl 4-methylenepiperidine-1-carboxylate **2** (0.19 mL, 0.915 mmol, 2.50 eq) and DMSO (1 mL) were added, solution was degassed for 5 min and irradiated with blue light for 18 h. This yielded 1'-benzyl 2-methyl 6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidine]-1',2-dicarboxylate **3a** (36.3 mg, 95.4 µmol, 26% yield).

Table 2, Entry 6. [Ir{dF(CF$_3$)ppy}$_2$(bpy)]PF$_6$ and CSA Methyl 6-(((ethoxycarbonothioyl)thio)methyl)picolinate **1b** (100 mg, 0.368 mmol, 1.00 eq), [Ir{dF(CF_3)ppy}$_2$(bpy)]PF_6 (1.86 mg, 1.84 µmol, 0.005 eq) and CSA (85.6 mg, 0.368

mmol, 1.00 eq) were added to a vial and placed under a nitrogen. Benzyl 4-methylenepiperidine-1-carboxylate **2** (0.19 mL, 0.921 mmol, 2.50 eq) and DMSO (1 mL) were added, solution was degassed for 5 min and irradiated with blue light for 18 h. This yielded 1'-benzyl 2-methyl 6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidine]-1',2-dicarboxylate **3a** (35.6 mg, 93.6 µmol, 25% yield).

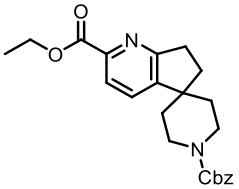
Table 2, Entry 7. $[Ir\{dF(CF_3)ppy\}_2(bpy)]PF_6$ (2 mol%) and CSA Methyl 6-(((ethoxycarbonothioyl)thio)methyl)picolinate **1b** (101.5 mg, 0.374 mmol, 1.00 eq), $[Ir\{dF(CF_3)ppy\}_2(bpy)]PF_6$ (7.5 mg, 7.43 µmol, 0.020 eq) and CSA (86.9 mg, 0.374 mmol, 1.00 eq) were added to a vial and placed under a nitrogen. Benzyl 4-methylenepiperidine-1-carboxylate **2** (0.19 mL, 0.921 mmol, 2.50 eq) and DMSO (1 mL) were added, solution was degassed for 5 min and irradiated with blue light for 46 h. This yielded 1'-benzyl 2-methyl 6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidine]-1',2-dicarboxylate **3a** (17.6 mg, 46.2 µmol, 12% yield).

Table 2, Entry 8. $[Ir\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$ and CSA (2 equiv) Methyl 6-(((ethoxycarbonothioyl)thio)methyl)picolinate **1b** (100 mg, 0.369 mmol, 1.00 eq), $[Ir\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$ (8.27 mg, 7.37 µmol, 0.02 eq) and CSA (171.2 mg, 0.737 mmol, 2.00 eq) were added to a vial and placed under a nitrogen. Benzyl 4-methylenepiperidine-1-carboxylate **2** (0.19 mL, 0.921 mmol, 2.50 eq) and DMSO (1 mL) were added, solution was degassed for 5 min and irradiated with blue light for 23 h. This yielded 1'-benzyl 2-methyl 6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidine]-1',2-dicarboxylate **3a** (36.4 mg, 95.7 µmol, 26% yield).

Table 2, Entry 9. $[Ir\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$ and MeCN Methyl 6-(((ethoxycarbonothioyl)thio)methyl)picolinate **1b** (100.00 mg, 369 µmol, 1.00 eq), CSA (86 mg, 369 µmol, 1.00 eq), and $[Ir\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$ (8.3 mg, 7.37 µmol, 0.02 eq,) were added to a microwave vial and placed under nitrogen. After this, Benzyl 4-methylenepiperidine-1-carboxylate **2** (0.19 mL, 921 µmol, 2.50 eq) and acetonitrile (1 mL) were added, and the solution was degassed for 5 min and irradiated with blue light for 24 h. This yielded 1'-benzyl 2-methyl 6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidine]-1',2-dicarboxylate **3a** (44.8 mg, 118 µmol, 32 % yield).

Table 2, Entry 10. Kessil® A160WE Tuna Blue lamp colour set to 0% rather than 100% Methyl 6-(((ethoxycarbonothioyl)thio)methyl)picolinate **1b** (104 mg, 0.383 mmol, 1.00 eq), $[Ir\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$ (8.6 mg, 7.67 µmol, 0.02 eq) and CSA (85 mg, 0.366 mmol, 0.96 eq) were added to a vial and placed under a nitrogen. Benzyl 4-methylenepiperidine-1-carboxylate **2** (0.20 mL, 0.963 mmol, 2.50 eq) and DMSO (1 mL) were added, solution was degassed for 5 min and irradiated with blue light for 24 h. This yielded 1'-benzyl 2-methyl 6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidine]-1',2-dicarboxylate **3a** (43 mg, 0.11 mmol, 28% yield), (96% purity).

Synthesis of 1'-benzyl 2-ethyl 6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidine]-1',2-dicarboxylate (3b)

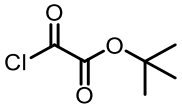


1'-Benzyl 2-ethyl 6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidine]-1',2-dicarboxylate (3b) (Table 1, entry 4). Ethyl 6-(((ethoxycarbonothioyl)thio)methyl)picolinate (176 mg, 0.616 mmol, 1.00 eq) **1c** was dissolved in ethyl acetate (2 mL). DLP (368 mg, 0.924 mmol, 1.50 eq) and CSA (143 mg, 0.616 mmol, 1.00 eq) were added to a microwave vial and placed under nitrogen. Following this, the solution of ethyl 6-(((ethoxycarbonothioyl)thio)methyl)picolinate **1c** in ethyl acetate was added, followed by benzyl 4-methylenepiperidine-1-carboxylate **2** (0.320 mL, 1.54 mmol, 2.50 eq) and was heated to reflux for 2 h. After

this time, the solution was cooled to room temperature and concentrated under reduced pressure to give a yellow oil. MeCN (5 mL) and potassium carbonate (255 mg, 1.85 mmol, 3.00 eq) were added to the oil and vigorously stirred for 1 h. The solid was filtered and the filtrate was concentrated under reduced pressure to give a brown oil. The product was purified using flash column chromatography on a silica column (24 g) using eluent cyclohexane:ethyl acetate (50-100% ethyl acetate). The relevant fractions were combined, and these were concentrated under reduced pressure to give a colourless oil, 1'-benzyl 2-ethyl 6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidine]-1',2-dicarboxylate **3b** (139 mg, 0.352 mmol, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.97 (d, 1H, *J* 7.9 Hz), 7.52 (d, 1H, *J* 7.9 Hz), 7.42-7.31 (m, 5H), 5.18 (s, 2H), 4.48 (q, 2H, *J* 7.4 Hz), 4.19 (br s, 2H), 3.16 (t, 2H, *J* 7.6 Hz), 3.07 (br t, 2H, *J* 12.6 Hz), 2.16 (t, 2H, *J* 7.6 Hz), 1.79 (br t, 2H, *J* 12.8 Hz), 1.59 (br d, 2H) (overlap with water peak), 1.43 (t, 3H, *J* 7.1 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm); 165.4, 165.2, 155.3, 147.6, 147.5, 136.7, 130.9, 128.5, 128.0, 127.9, 123.6, 67.2, 61.8, 44.9, 41.0, 36.1, 32.4, 31.7, 14.4.

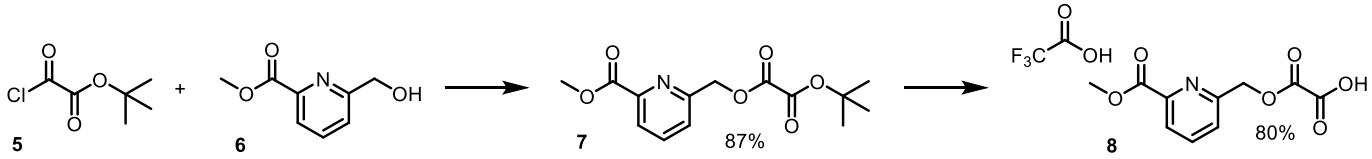
Oxalate-ester based reactions

Synthesis of *tert*-butyl 2-chloro-2-oxoacetate



***tert*-Butyl 2-chloro-2-oxoacetate (5).** Oxalyl dichloride (1.864 mL, 21 mmol, 1.00 eq) and diethyl ether (10 mL) were added to a purged round-bottomed flask. This was cooled to 0 °C and 2-methylpropan-2-ol (2.065 mL, 21 mmol, 1.00 eq) in diethyl ether (5 mL) was added and stirred for 30 min. The solution was heated to room temperature and stirred for 18 h. The resulting solution was concentrated under reduced pressure yielding a pale-yellow oil, *tert*-butyl 2-chloro-2-oxoacetate **5** (1.91 g, 10.77 mmol, 51% yield). The product was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.59 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm); 157.8, 157.4, 84.3, 27.7.

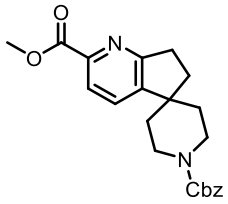
Synthesis of 2-((6-(methoxycarbonyl)pyridin-2-yl)methoxy)-2-oxoacetic acid trifluoroacetic acid salt (8)



Telescoped synthesis of 2-((6-(methoxycarbonyl)pyridin-2-yl)methoxy)-2-oxoacetic acid trifluoroacetic acid salt (8) *via tert*-butyl ((6-(methoxycarbonyl)pyridin-2-yl)methyl) oxalate (7). A solution of *tert*-butyl 2-chloro-2-oxoacetate **5** (0.318 mL, 2.15 mmol, 1.20 eq) in DCM (4.5 mL) was added to a purged microwave vial containing methyl 6-(hydroxymethyl)picolinate **6** (305 mg, 1.83 mmol, 1.00 eq), DMAP (23 mg, 0.19 mmol, 0.10 eq), triethylamine (0.5 mL, 3.60 mmol, 2.00 eq) and DCM (4.5 mL) at 0 °C. The resulting yellow solution was heated to room temperature and stirred for 17 h. The solution was purged with saturated ammonium chloride (6 mL) and the organic layers were separated, and the aqueous layer was washed with DCM (8 mL). The combined organic layers were concentrated under reduced pressure yielding an orange oil, *tert*-butyl ((6-(methoxycarbonyl)pyridin-2-yl)methyl) oxalate **7** (495 mg, 1.60 mmol, 1.00 eq). DCM (3 mL) was added to the orange oil followed by 2,2,2-trifluoroacetic acid (TFA) (1 mL, 13.1 mmol, 8.20 eq) which was added dropwise. The reaction was concentrated under a high flow of nitrogen yielding a brown oil, 2-((6-(methoxycarbonyl)pyridin-2-yl)methoxy)-2-oxoacetic acid trifluoroacetic acid salt **8** (452 mg, 1.28 mmol, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.17-8.14 (m, 1H), 7.98 (t, 1H, *J* 7.8 Hz), 7.69-7.66 (m, 1H), 5.54 (s,

2H), 4.02 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -75.8; FTIR (neat) $\tilde{\nu}_{max}$ (cm^{-1}) 2959 (broad), 1733, 1619, 1529, 1440, 273, 1167, 1138, 1093, 968, 826, 797, 760, 718, 700, 673, 602, 474.; HRMS (ESI-TOF) *m/z* Calcd. for $C_{10}H_{10}NO_6$ [M+H$^+$] requires 240.0503. Found [M+H$^+$] 240.0511.

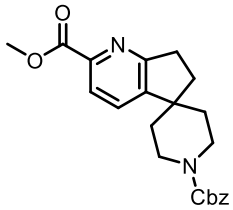
Synthesis of 1'-benzyl 2-methyl 6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidine]-1',2-dicarboxylate (3a)



1'-Benzyl 2-methyl 6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidine]-1',2-dicarboxylate (3a). 2-((6-(methoxycarbonyl)pyridin-2-yl)methoxy)-2-oxoacetic acid trifluoroacetic acid salt **8** (100 mg, 0.207 mmol, 1.00 eq) and PIFA (150 mg, 0.349 mmol, 1.70 eq) were added to a microwave vial placed under nitrogen. Benzyl 4-methylenepiperidine-1-carboxylate **2** (0.129 mL, 0.620 mmol, 3.00 eq) and MeCN (3 mL) were added, and the solution was degassed for 5 min. Following this the solution was irradiated with blue LEDs for 46 h. The solution was concentrated under reduced pressure giving a brown oil. The crude product was purified by FCC on silica (40 g silica cartridge) and was eluted with cyclohexane:ethyl acetate (10-100% ethyl acetate) yielding a colourless oil, 1'-benzyl 2-methyl 6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidine]-1',2-dicarboxylate **3a** (7.4 mg, 0.02 mmol, 9% yield). Analytical data as above.

Bromide-Based Reactions

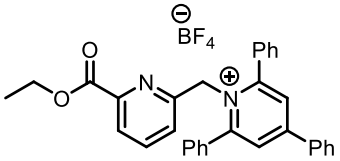
Synthesis of 1'-benzyl 2-methyl 6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidine]-1',2-dicarboxylate (3a)



1'-Benzyl 2-methyl 6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidine]-1',2-dicarboxylate (3a). Methyl 6-(bromomethyl)picolinate **9** (109 mg, 0.474 mmol, 1.00 eq) and potassium peroxydisulfate (250 mg, 0.925 mmol, 2.00 eq) were added to a microwave vial placed under nitrogen. Benzyl 4-methylenepiperidine-1-carboxylate **2** (0.246 mL, 1.184 mmol, 2.50 eq) and N-ethyl-N-isopropylpropan-2-amine (DIPEA) (0.330 mL, 1.90 mmol, 4.00 eq) were added followed by DMSO (3 mL) and water (1 mL). The solution was heated to 70 °C and stirred for 3 h. The resulting solution was cooled to room temperature and diluted with water (15 mL) and ethyl acetate (15 mL). The orange organic layer was separated, and the aqueous layer was washed with ethyl acetate (2 x 15 mL). The organic layers were combined, washed with brine (15 mL), dried with $MgSO_4$ and concentrated under reduced pressure yielding a brown oil. The crude product was purified by FCC on silica (40 g silica cartridge) and was eluted with cyclohexane:ethyl acetate (10-100% ethyl acetate) yielding a colourless oil, 1'-benzyl 2-methyl 6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidine]-1',2-dicarboxylate **3a** (14.3 mg, 0.048 mmol, 8% yield) (95% purity). Analytical data as above.

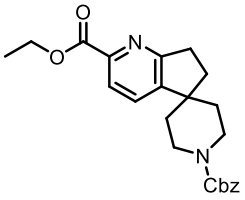
Katritzky Salt-Based Reactions

Synthesis of 1-((6-(ethoxycarbonyl)pyridin-2-yl)methyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (10)



1-((6-(Ethoxycarbonyl)pyridin-2-yl)methyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (10). Ethyl 6-(aminomethyl)picoline hydrochloride (164 mg, 0.757 mmol, 1.20 eq) was added to a round bottom flask followed by ethanol (2.5 mL) and triethylamine (0.105 mL, 0.757 mmol, 1.20 eq) – this was stirred for 30 min. Then 2,4,6-triphenylpyrylium tetrafluoroborate (250 mg, 0.631 mmol, 1.00 eq) was charged and the solution was heated to reflux for 4 h. After 4 h the solid was filtered and washed with ethanol (25 mL) followed by diethyl ether (25 mL) removing unreacted 2,4,6-triphenylpyrylium and the liquors were concentrated under reduced pressure yielding a yellow solid. This was purified by FCC on silica (40 g cartridge) and was eluted with DCM:acetone (from 10-30% acetone) yielding 1-((6-(ethoxycarbonyl)pyridin-2-yl)methyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate **10** (237 mg, 0.424 mmol, 67% yield) (57% yield from an average of 4 reactions). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.96 (s, 2H), 7.92 (dd, 1H, *J* 7.7, 0.9 Hz), 7.86-7.82 (m, 2H), 7.69 (br d, 3H, *J* 6.9 Hz), 7.61-7.39 (m, 11H), 6.70 (dd, 1H, *J* 7.8, 1.0 Hz) 5.85 (s, 2H), 4.40 (q, 2H, *J* 7.1 Hz), 1.39 (t, 3H, *J* 7.1 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 164.4, 157.7, 156.0, 153.4, 147.8, 137.8, 134.0, 132.9, 132.2, 130.8, 129.8, 129.1, 128.9, 128.1, 126.0, 124.9, 124.2, 61.8, 58.7, 14.2; ^{19}F NMR (376 MHz, DMSO-d_6) δ (ppm) -148.4; FTIR (neat) $\tilde{\nu}_{max}$ (cm^{-1}) 3064, 2979, 1719, 1621, 1598, 1565, 1495, 1446, 1368, 1348, 1314, 1247, 1176, 1144, 1049, 914, 891, 761, 699, 646, 591, 520; HRMS (ESI-TOF) *m/z* Calcd. for $C_{32}H_{27}N_2O_2^+$ [M^+] requires 471.2072. Found [M^+] 471.2061.

Synthesis of 1'-benzyl 2-ethyl 6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidine]-1',2-dicarboxylate (3b)



1'-benzyl 2-ethyl 6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidine]-1',2-dicarboxylate (3b).

Method 1 – use of a photocatalyst. 1-((6-(ethoxycarbonyl)pyridin-2-yl)methyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate **10** (144 mg, 0.258 mmol, 1.00 eq) and $[Ir(dtbpy)(ppy)_2]PF_6$ (6.4 mg, 7.00 μmol, 2.70 mol%) were charged to a microwave vial, which was backfilled with nitrogen 3 times. Benzyl 4-methylenepiperidine-1-carboxylate **2** (0.14 mL, 0.674 mmol, 2.60 eq) and N,N-dimethylacetamide (DMA) (1.5 mL) were added and the reaction mixture was degassed for 5 min. The sample was irradiated with blue LEDs for 47 h. (After 44 h, triethylamine (0.054 mL, 0.387 mmol, 1.50 eq) was added). The brown solution was washed with ethyl acetate (30 mL), water (20 mL) and brine (20 mL). The organic layer was concentrated under reduced pressure yielding a brown oil. The crude product was purified by FCC on silica (40 g silica cartridge) and was eluted with cyclohexane:ethyl acetate (0-100% ethyl acetate) yielding , 1'-benzyl 2-ethyl 6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidine]-1',2-dicarboxylate **3b** (5.8 mg, 0.014 mmol, 5% yield) (93% purity). Analytical data as above.

Method 2 – EDA complex

Table 3, Entry 1. DMA. CSA (114.8 mg, 0.494 mmol, 2.00 eq), 1-((6-(ethoxycarbonyl)pyridin-2-yl)methyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate **10** (150 mg, 92% wt., 0.247 mmol, 1.00 eq) and Hantzsch ester **HE**

12(125.2 mg, 0.494 mmol, 2.00 eq) were added to a vial and placed under nitrogen. Benzyl 4-methylenepiperidine-1-carboxylate **2** (0.128 mL, 0.618 mmol, 2.50 eq) and DMA (2 mL) were added, and the solution was degassed for 5 min. The solution was irradiated with blue light for 18 h.
LCMS showed no production of desired product.

Table 3, Entry 2. H_2O:MeCN (1:1) CSA (76.5 mg, 0.330 mmol, 2.00 eq), 1-((6-(ethoxycarbonyl)pyridin-2-yl)methyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate **10** (100 mg, 92% wt., 0.165 mmol, 1.00 eq) and Hantzsch ester **HE 12**(85 mg, 0.336 mmol, 2.00 eq) were added to a vial and placed under nitrogen. Then benzyl 4-methylenepiperidine-1-carboxylate **2** (0.09 mL, 0.412 mmol, 2.50 eq), water (1 mL) and acetonitrile (1 mL) were added, and the solution was degassed for 5 min and irradiated with blue light for 24 h. The solution was quenched with saturated potassium carbonate (3 mL) and the solution was extracted with diethyl ether (2 x 10 mL). The organic layers were combined and concentrated under reduced pressure to give a red crude oil. The product was purified using FCC on silica (24 g cartridge) using eluent gradient cyclohexane:ethyl acetate (20-80% ethyl acetate). The relevant fractions were combined and concentrated under reduced pressure to give a colourless oil, 1'-benzyl 2-ethyl 6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidine]-1',2-dicarboxylate **3b** (26.6 mg, 0.066 mmol, 40% yield) (98% purity)

Table 3, Entry 3. MeCN **CSA** (128 mg, 0.551 mmol, 2.10 eq), 1-((6-(ethoxycarbonyl)pyridin-2-yl)methyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate **10** (150 mg, 0.269 mmol, 1.00 eq) and Hantzsch ester **HE 12** (127 mg, 0.501 mmol, 2.00 eq) were added to a microwave vial and placed under nitrogen. Benzyl 4-methylenepiperidine-1-carboxylate **2** (0.139 mL, 670 mmol, 2.50 eq) and acetonitrile (2 mL) were added, and the mixture was degassed for 5 min and irradiated with blue light for 48h. The solution was quenched with saturated potassium carbonate (3 mL) and diluted with water (10 mL) and extracted with diethyl ether (3 x 10 mL). The organic layers were combined and concentrated under reduced pressure to give an orange oil. The product was purified using FCC on silica (24 g cartridge) using eluent cyclohexane:ethyl acetate (20-90% ethyl acetate). The relevant fractions were combined and concentrated under reduced pressure to give a pale yellow oil, 1'-benzyl 2-ethyl 6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidine]-1',2-dicarboxylate **3b** (66.3 mg, 0.16 mmol, 59%) (95% purity) (47% yield for an average of 3 reactions (59%, 38% and 43%)).

Table 3, Entry 4. H_2O **CSA** (123 mg, 0.529 mmol, 2.00 eq), 1-((6-(ethoxycarbonyl)pyridin-2-yl)methyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate **10** (148 mg, 0.264 mmol, 1.00 eq) and Hantzsch ester **HE 12** (134 mg, 0.529 mmol, 2.00 eq) were added to a microwave vial and placed under nitrogen. Benzyl 4-methylenepiperidine-1-carboxylate **2** (0.139 mL, 671 mmol, 2.50 eq) and water (2 mL) were added, and the mixture was degassed for 5 min and irradiated with blue light for 47 h. The solution was quenched with saturated potassium carbonate (2 mL) and extracted with diethyl ether (3 x 10 mL). The organic layers were combined, washed with brine (20 mL) and concentrated under reduced pressure to give a yellow oil. The product was purified using FCC on silica (24 g cartridge) using eluent cyclohexane:ethyl acetate (20-80% ethyl acetate). The relevant fractions were combined and concentrated under reduced pressure to give a pale yellow oil, 1'-benzyl 2-ethyl 6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidine]-1',2-dicarboxylate **3b** (4.4 mg, 0.010 mmol, 4%) (85% purity).

Table 3, Entry 5. MeCN without CSA and HE 1-((6-(ethoxycarbonyl)pyridin-2-yl)methyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate **10** (100 mg, 0.180 mmol, 1.00 eq) was added to a microwave vial and placed under nitrogen. Benzyl 4-methylenepiperidine-1-carboxylate **2** (0.093 mL, 448 mmol, 2.50 eq) and MeCN (1.34 mL) were added, and the mixture was degassed for 5 min and irradiated with blue light for 24 h.
LCMS showed no production of desired product.

Table 3, Entry 6. MeCN and CSA **CSA** (83 mg, 0.358 mmol, 2.00 eq) and 1-((6-(ethoxycarbonyl)pyridin-2-yl)methyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate **10** (100 mg, 0.180 mmol, 1.00 eq) were added to a

microwave vial and placed under nitrogen. Benzyl 4-methylenepiperidine-1-carboxylate **2** (0.093 mL, 448 mmol, 2.50 eq) and MeCN (1.34 mL) were added, and the mixture was degassed for 5 min and irradiated with blue light for 24 h. The solution was concentrated under reduced pressure to give a pale-yellow oil. The product was purified using FCC on silica (24 g cartridge) using eluent cyclohexane:ethyl acetate (20-90% ethyl acetate). The relevant fractions were combined and concentrated under reduced pressure to give a pale yellow oil, suspected salt, therefore sodium bicarbonate (5 mL) was extracted with ethyl acetate (3 x 10 mL). The organic layers were concentrated under reduced pressure to give an orange oil. This was further purified using MDAP, acidic reverse phase purification, the relevant fractions were combined and concentrated under reduced pressure to give a clear oil, 1'-benzyl 2-ethyl 6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidine]-1',2-dicarboxylate **3b** (33.2 mg, 0.08 mmol, 45%) (95% purity) (50% yield average over 2 reactions (45% and 55%).

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Supplementary Material

Copies of ^{1}H, ^{13}C and ^{19}F NMR are available in the supplementary material associated with this manuscript.

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34. In several publications reporting photocatalysed C-C bond formation between KS and alkenes, low level background reaction in the absence of catalyst was noted: Jiang, X.; Zhang, M.-M.; Xiong, W.; Lu, L.-Q.; Xiao, W.-J. *Angew. Chem. Int. Ed.*, **2019**, *58*, 2402-2406.
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Yang, Z.-K.; Xu, N.-X.; Wang, C.; Uchiyama, M. *Chem. Eur. J.*, **2019**, *25*, 5433-5439.
https://doi.org/10.1002/chem.201900886
Importantly, the KS used in these studies were structurally distinct from **10**. A KS leading to a more stabilised radical, such as **10**, might display a higher photo-lability.
35. KS **10** was observed to slowly decompose under light irradiation in the presence of CSA. Although overall conversion after 48h was low (2% isolated yield of triphenylpyridine **16** alongside unreacted **10**), this might be sufficient to initiate a chain reaction leading to full conversion of **10**.