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# Photochemical Flow Synthesis of 3-Hydroxyazetidines

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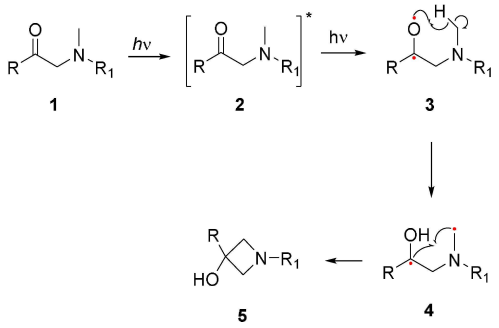
A photo-flow Norrish–Yang cyclisation has been devised that delivers 3-hydroxyazetidines in good yields. The high reproducibility and short residence times of the flow process enables easy scaling of the transformation allowing access to these valuable chemical entities at synthetically useful multi-gram scales. A systematic exploration of the constituent structural components was undertaken allowing an understanding of the reactivity and functional group tolerance of the transformation.

## 1. Introduction

Accessing new chemical space through the preparation of easily modified core templates has proven fertile ground in the discovery of new pharmaceutical and agrochemical leads. Often the core templates prepared are relatively rigid structures which allow medicinal chemists to more accurately model the interactions and make simple changes to further probe the important structural interactions to build up accurate pharmacophore maps. Over time, the knowledge gained by those working in the area has been distilled to establish key molecular descriptors and to generate sets of rules for characterizing and defining the characteristics of the small molecules and fragment-based libraries that correlate well with successful development.[1] Taking into account these charactoristics and in continuation of our investigations into how technology can be applied to help reduce synthetic challenges whilst leading to diversity and novelty in the compounds prepared,[2] we were attracted to the potential of accessing azetidines as building blocks through simple photochemical reactions.[3]

Azetidines represent an important heterocyclic class comprising valuable chemical and biological features synonymous with the structurally related β-lactams.[4] There general popularity is due to their small and highly geometrically configured structure that is very useful for exploring chemical space, making the azetidine ring a highly prized template. Consequently, they have been utilized widely as chemical analogues to several naturally occurring compounds[5] and are present in several pharmaceuticals (e.g. Cobimetinib, Delafloxacin, Azeinipidine, Penaresidin and Tebnicline). Among the possible synthetic approaches,[6] a interesting strategy to the 3-hydroxyazetidine ring is via a Norrish-Yang reaction, which in one guise, occurs via an excited state intermolecular cyclisation of a simple acyclic 2-amino ketone precursor **1** (Scheme 1). Following photochemical excitation involving a $n\rightarrow\pi^*$ transition (**1**→**2**), the transient intermediate oxygen centered radical **3** abstracts a proton from one of the available sites (normally due to geometrical factors this is the δ-proton relayed via a 6 membered cyclic transition state) leading to a new diradical intermediate **4** which can combine to form the cyclic product **5**.[7]




**Scheme 1.** Azetidine ring formation via the Yang reaction.

Although a small number of intramolecular Yang reactions leading to azetidine products have previously been reported in batch,[8] the true synthetic value of the transformation has not been fully exploited due to the photochemical processing conditions required. Often long reaction times and very dilute reaction conditions are necessary, delivering poor conversions and leading to low throughput, thus significantly restricting the synthetic value. Recently, much success has been achieved through transferring problematic or inefficient batch photochemical reactions into more dynamic flow based photochemical operations.[9] One of the main advantages offered by flow-photochemistry is that only small unit volumes are propagated through the small dimensional flow reactor channel(s) meaning a high and uniform incident photon flux can be achieved whilst avoiding the inherent thermal heating effects which accompany classical batch based photochemical set-ups. Furthermore, the continuous operation characteristic of a flow process allows for a more consistent and simple scale-up of the reaction by simply extending processing times.

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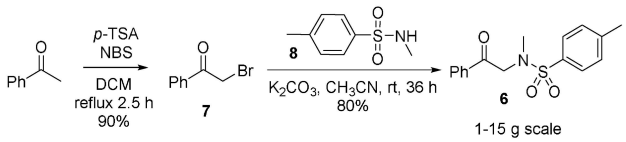
Herein, we report on the multi-gram scale synthesis of a series of 3-hydroxyazetidines under flow photochemical conditions.

## 2. Results and Discussion

We embarked upon the study of the Norrish-Yang reaction under flow conditions by evaluating the reaction of the basic sulfonamide **6** (Scheme 2) which had previously been shown to be a viable substrate for the reaction albeit at very small scale (30 mg).[10] Substrate **6** was readily synthesized in good yield by an overall simple synthetic sequence involving nucleophilic substitution of the corresponding α-bromoacetophenone (**7**) with *N*,*4*-dimethylbenzene sulfonamide (**8**). The starting material could therefore be readily prepared at multi-gram scale and was used to derive a general set of flow conditions based upon screening different light sources, solvents, photocatalysts, reagent concentration and residence times.




**Scheme 2.** Synthesis of the starting material **6**.

### 2.1. Light Source Screening

As an indication for the subsequent screening of the light sources, the absorption spectra for the starting material **6** was recorded and showed two different absorption bands;[11] a strong band around 250 nm pertaining to the π→π* transition and a weaker absorbance in the range of 280–320 nm relating to the synthetically desirable n→π* propagation, which would result in the eventual cyclisation reaction (Figure 1).

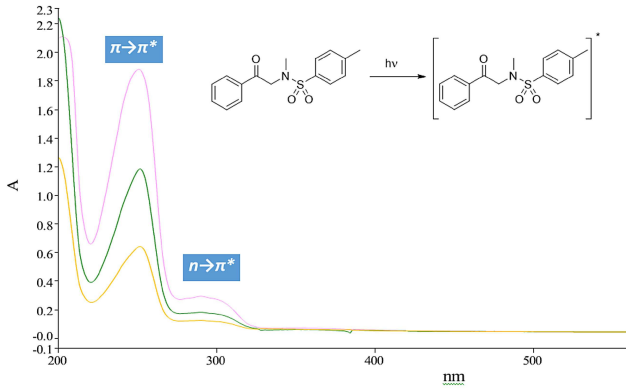



**Figure 1.** UV/Vis absorption spectra showing bands for the two main transitions of substrate **6**. Recorded in MeCN. Yellow (0.05 mM), green (0.1 mM) and pink (0.2 mM).

To perform the flow reaction screening, we utilised a commercially available Vapourtec UV-150 system based upon the E-series peristatic delivery unit.[12] A 0.15 M acetonitrile (solvent wavelength cut-off of 190 nm) stock solution of substrate **6** was passed at a specified flow rate into a 10 mL photoflow coil reactor and irradiated using a low pressure mercury lamp (150 W; 100% of the lamp power) fitted with a filter ('Gold' filter with transmission 415–250 nm; see SI for details). Encouragingly, at a flow of 1 mL/min (10 min residence time), 90% conversion and a 76% isolated yield following chromatographic purification was achieved. It should be noted that this specific flow rate represented an optimal productivity balancing the consumption of the starting material and its conversion to product against the occurrence of several by-products generated during extended irradiation (decomposition). In addition, it was found to be easier to purify samples comprising mainly residual starting material from incomplete consumption rather than driving the reaction to completion but subsequently having to separate the product from a complex mixture of multiple minor by-products. Indeed, at larger scales purification could be readily achieved by simple crystallisation of the incomplete reactions.

To evaluate the impact of the transmission window the reactor filter was changed to one with a narrower band ('Blue' filter transmission 310–400 nm) which removes most of the irradiation overlapping with the indicated n→π* transition. As anticipated, the detected conversion (1 mL/min; 10 min residence time) dropped dramatically to 10%, thereby confirming our premise and confirming the preferential filter selection ('Gold' transmission 415–250 nm). It should also be noted that using a simple quartz window ('Silver' filter, transmission 280–450 nm) that essential removes only the long wave IR bands led to substantial substrate decomposition even over very short residence times.

We next tested a selective low pressure Mercury lamp (7.8 W) which exhibits a peak emission at 310 nm. Under the previous standardized flow rate of 1 mL/min the reaction proceeded but with a much reduced conversion of 23% in accordance with the lower rated lamp power specification. Slowing the flow rate to 0.75, 0.5 or 0.25 mL/min enabled higher conversions of 34, 49 and 59% respectively to be achieved, indicating an essentially linear correlation with extended irradiation time. Of particular note was that these reactions were very clean showing only starting material and product. Unfortunately, we deemed the overall throughput would ultimately be too low with such a system as our challenge was to devise a system which could be used to perform larger preparative scale Norrish-Yang reactions. Consequently although showing high selectivity the low power system was deemed inadequate for our needs and we elected to revert to the original medium pressure lamp (150 W) for all further reactions.

In the hope of improving the transformation, we also evaluated the addition of a range of potential photocatalysts (e.g. diphenyl ketone, 2-methylthioxanthone and methylene blue at 10 and 40 mol%); however, none of the catalysts tested

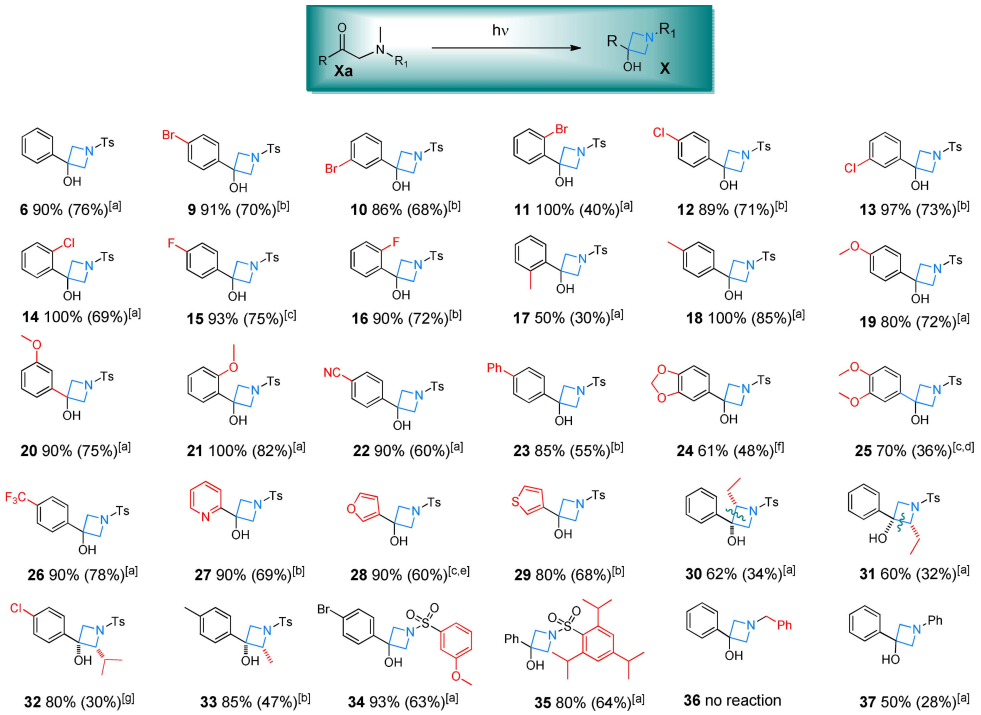



**Figure 2.** The expanded range of products prepared from the photo-flow Yang reaction. All reactions were performed at 1 and 5 mmol exploratory scales, results presented are the mean of at least 3 repeat runs at the 5 mmol scale. The % consumption of starting material and % isolated yields (in parentheses) are shown. NMR yields were determined for the crude products using an internal standard of 4-dimethylaminobenzonitrile. All isolated yields were in the range of −1→3% lower than the theoretical yield determined by NMR spectroscopy. [a] General flow conditions; 0.15 M solution of the starting material in acetonitrile, flow rate 1 mL/min (10 min residence time), reactor temperature 18–25 °C. [b] Concentration used was 0.075 M. [c] Solvent used was acetone. [d] Concentration used was 0.035 M. [e] Concentration used was 0.02 M. [f] A flow rate of 0.7 mL/min was used and the reactor temperature was 70 °C. [g] A flow rate of 0.5 mL/min was used.

showed any advantageous activity across a range of wavelengths for this particular transformation.

### 2.2. Solvent Screen

We next assessed a range of solvents evaluating them for solubility, absorption cut-off, impact on conversion and isolated yield. DMF, MeCN, THF and MeOH were all comparable, providing essentially equivalent results (~75% isolated yield). Acetone, although effective, gave a lower conversion (60%), which may be indicative of its absorption cut off of 330 nm and hence, competitive absorption. The chlorinated solvents $CHCl_3$ and DCM indicated some potential solubility issues and were therefore directly discounted. Ultimately, acetonitrile was selected as the primary solvent for convenience of evaporation (discounting DMF) and avoidance of potential radical side reactions, such as proton abstraction (THF and MeOH).[13]

### 2.3. Substrate Screening

The lack of any existing literature substrate studies and inconsistencies in the reaction conditions reported made it hard to generalize the synthetic scope or anticipate new reactivity based upon varying structural functionality. Therefore, we built a collection of functionalised starting materials for a systematic investigation. As previously outlined (Scheme 2), the general synthetic route entails a two-step process involving the bromination of the related acetophenone followed by substitution of the halogen with the sulfonamide unit **8**. Therefore by starting from the appropriately substituted ketones, a series of additional starting materials were prepared and their resultant solutions pumped through the photoreactor, allowing evaluation of their conversion into the related azetidinols (Figure 2).

Initially, the aromatic ring was enriched by the addition of bromine and chlorine substitution (Figure 2; **9**–**14**) as versatile handles for subsequent medicinal chemistry derivatisation. The 3 and 4 substituted compounds gave high conversions and were isolated in similarly high yield by column chromatography, indicating that their reactivity was not affected by a halogen substituent at either the *meta* or *para* positions. This was in contrast to the corresponding *ortho* substituted aromatics which although showing high starting material consumption gave significantly more decomposition and thus much lower isolated recoveries (Figure 2; **11** & **14**). We speculated this may be due to the *ortho* substituent imposing a steric impingement on the transition state thereby preventing planarity of the aromatic-carbonyl and thus affecting the electronics and desired absorption of the substrate (See section 5 of the SI for conformational modelling). To experimentally test this, we prepared and ran the corresponding methyl and fluoro substituted materials (Figure 2; **15**–**18**). Again, the differ-

ence in reactivity between the 2- and 4-methyl substituents was dramatic. Whereas, the 2- and 4-fluoro substituted reactants showed comparable reactivity as would be expected for the small orbital contracted fluoro group. These additional results indicated the observed effect was as hypothesised mainly steric in nature and not a direct electronic aspect of the potentially inductive halogens. This was further confirmed by assessing the methoxy series (Figure 2; **19**–**21**). The reactivity of which was essentially equivalent for each member, including the 2-methoxy substrate (Figure 2; **21**), which can preferentially orientate the methyl substituent to minimise steric interactions in the transition state and so easily achieve planarity (See section 5 of the SI for conformational modelling).

We next probed the installation of various π-donor and acceptor substituents as well as a trifluoromethyl functional group on the phenyl ring (Figure 2; **24**–**26**). It appears that strongly electron donating units diminish the reactivity as indicted by the dioxolane **24** and dimethoxy derivative **25**. Under the standard conditions (1 mL/min - 10 min residence time) only 22% conversion, equating to a 10% isolated yield of the corresponding azetidine **24** was obtained. However, wishing to demonstrate that the general conditions could be rapidly re-optimized (Table 1) in flow for poorly reacting

**Table 1.** Rapid reoptimization screen for product **24**.[a]

| Entry | Flow rate [mL/min] | Lamp power [%] | Temp. [°C] | Yield [%] |
|---|---|---|---|---|
| 1 | 1 | 90 | 18–25 | 10 |
| 2 | 0.7 | 90 | 18–25 | 20 |
| 3 | 0.5 | 90 | 18–25 | 15 |
| 4 | 0.7 | 90 | 49–52 | 22 |
| 5 | 0.7 | 90 | 70 | 48 |
| 6 | 0.7 | 90 | 80 | 39 |

[a] Reaction were performed at 0.15 M concentration in MeCN. At the higher temperatures indicated the photoreactor is more stable and easier to control the temperature at a specific set point.

substrates we were able to improve the conditions and enable an isolated yield of 48%. Of particular interest was an observed dependence on temperature in this reaction. Allowing the photo-reactor temperature to rise to 70 °C was accompanied by a steady but limited improvement in the yield. Although temperature has been shown to have a positive influence on other photochemical transformations, we, as well as others, are not able to fully account for this effect at this stage.[14] Indeed, this was in our case a seemingly localised effect as across the range of other substrates evaluated, the best yields were obtained at or below a temperature of 25 °C (note: the azetidine products show no thermal decomposition even at 100 °C over 1 h).

The same impact of strongly donating substituents on the phenyl ring was also clearly seen with the equivalent 3,4-dimethoxy substrate **25** which initially proved completely inert to the photo induced reaction under the standard condition and showed little benefit when tested with the newly derived conditions established for **24**. Interestingly, by changing the solvent, in this particular case to acetone, and using a lower flow rate (0.8 mL/min) we were able to achieve a modest 36% isolated yield of the cyclic product **25**. Of note, the addition of 30 mol% diphenyl ketone or acetone to the original acetonitrile solution had no impact on the transformation discounting a photo-catalysed process.

Overall the reactions to form products **24** and **25** highlight that the aryl electronic contributions do play an important role in the transformation. The implication is that high yields of the desired azetidinol can be attained when there is a good match between the light source and absorbance relating to the n→π* propagation. Significant electronic perturbation from strongly electron donating or assumedly withdrawing groups would be expected to shift the absorbance band and alter the transition to the reactive diradical **3**. Unfortunately, analysis of the UV spectra (See SI section 4) was not very revealing and did not allow any meaningful conclusions to be drawn. However, by comparing the $^{13}C$ chemical shift of the carbonyl signals for the electron rich aromatic starting materials **24a** (191.8 ppm) and **25a** (192.0 ppm) against the parent H substituted standard **6a** (193.8 ppm) it is clear some donation occurs which is associated with a diminished reactivity (**24** and **25**). Interestingly, during a wider analysis (see section 6 of the SI) we noted a general correlation that substrates with a carbonyl $^{13}C$ signal in the range of 196–193 generally showed good reactivity resulting in high isolated yields under the standard conditions (0.15 M in MeCN, 1 mL/min). In comparison compounds outside this range were typically much lower yielding but could often be improved by changing the processing conditions (i.e. flow rate, solvent or concentration). Although more data is required to confirm this observation, it may with the sophisticated predictive NMR packages currently available enable *in silico* design of idealised substrates for subsequent reaction.

Pleasingly, when expanding the substrate range, the direct replacement of the phenyl ring for other simple heteroaromatics (Table 1; **27**–**29**) was readily tolerated opening up the feasibility for exploring much greater structural diversity.

Next, we elected to explore the effect of further substitution on the carbon scaffold of the azetidine ring, consequently the additional substrates leading to compounds **30**–**33** were assembled and tested (Figure 2). Analysis of the crude products revealed that in each case the material produced was a single diastereoisomer with *syn* disposition of the corresponding hydroxyl and the alkyl groups as confirmed by COSY, NOE correlation experiments and by single crystal x-ray analysis. This observed selectivity is consistent with a predictive model based upon minimization of steric interactions in the ring forming transition state (Figure 3). It is apparent that by adding additional steric demands to the reaction in the form of these side chains the reaction becomes more challenging as expressed by the lower isolated yields (*cf.* compound **6** with **30**–**33**). Of particular interest was that steric factors were balanced as the regioisomeric starting materials leading to the equivalent products **30** and **31** were obtained in essentially identical conversion and isolated yield.

Having identified certain steric constraints which impact the reaction, we wished to explore the modification of the sulfonamide component of the system by an electron rich 3-

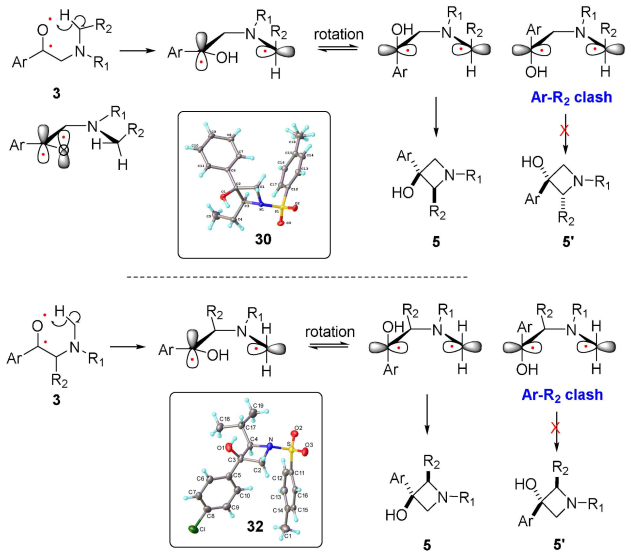
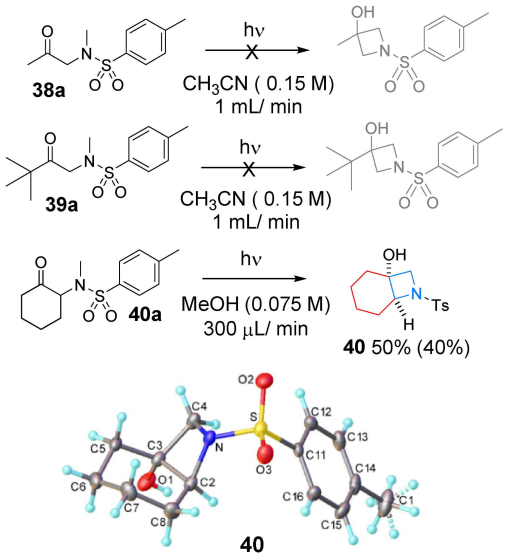



**Figure 3.** Ring closure transition states leading to *cis*-1-hydroxy-2-alkyl substituted products (**30**–**33**).




**Scheme 3.** Photochemical reaction of non-aromatic substrates.

methoxyphenyl and a bulky *tris*-2,4,6-isopropylphenyl ring (Figure 2; **34** & **35**). Both substrates were converted into the corresponding azetidinols under the standard condition without any appreciable difference in reactivity. This was in stark contrast with the simple benzyl substituted substrate which failed to yield any of the desired product **36** (Figure 2). Interestingly, removing the methylene group restored some of the reactivity allowing 28% of the corresponding product **33** to be isolated. Evidently an electron withdrawing group on the nitrogen helps increase the attached *N*-methyl C–H acidity enabling easier hydride abstraction via the proposed intermediate **3**, as well as stabilising the resultant radical formed (Scheme 1). This ultimately inspired us to consider other functional groups on the nitrogen which we will discuss below.

Our study has demonstrated that the photochemical process works generally for many aromatic ketones. In order to gauge how a non-aromatic structure responds to the flow process three aliphatic derivatives were prepared (Scheme 3). The methyl and *tert*-butyl derivatives were prepared by the standard sequence of bromination and substitution with sulfonamide **8** (Scheme 2), whereas the cyclohexanone derivative **40a** required a different approach as 2-bromocyclohexanone proved completely unreactive toward substitution by sulfonamide **8**. Compound **40a** was therefore prepared starting from the corresponding epoxide, which was ring opened and the intermediate alcohol subsequently oxidized (see SI for details).

The aliphatic sulfonamides (Scheme 3) were each subjected to the optimised flow conditions used previously (0.015 M, 1 mL/min 100% lamp power), compounds **38a** and **39a** showed no conversion whereas compound **40a** was converted into the related azetidine **40** but only in modest conversion and isolated yield. As the UV spectra for these compounds all possess a characteristic absorption in the correct region we expected these compounds would successfully react. Unfortunately, the lack of an aromatic ring seems to significantly affect the reactivity, possibly due to the diminished stability of the reactive intermediate **3**.[15] Indeed, even screening a wider range of conditions and solvents no sign of reactivity was ever seen. The fact that the substrate **40a** reacts at all is probably due to the more favourable locked geometric configuration which assists its cyclisation.

Having previously established that although an electron withdrawing substituent on the sulfonamide *N* was required for successful reaction (*cf* compounds **32** and **33**) there seemed to be some scope for variation in the functionality (*cf* compounds **6**, **9**, **34**, **35**). We therefore decided to explore some simplified amide groups and the synthetically more versatile Boc protection. Attempting the photocatalysed cyclisation using the standard flow condition despite indicating rapid consumption of the starting materials only resulted in low isolated yields of the corresponding cyclic products (<30%). Thus we embarked upon a reoptimisation which identified the solvent had a pronounced impact on the reaction process for these particular species (Table 2).

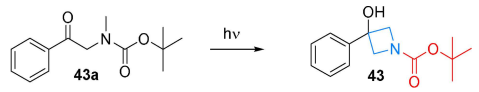
Adopting the newly determined condition the full range of substrates (acetyl, benzoyl and Boc species) were also proc-

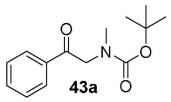
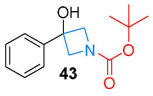
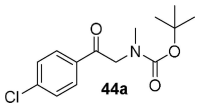
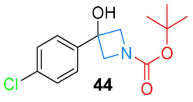
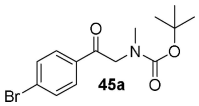
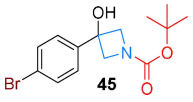
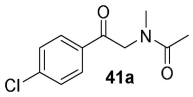
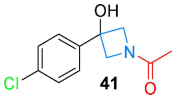
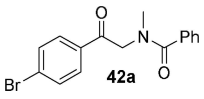
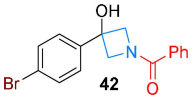
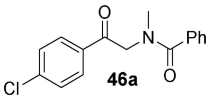
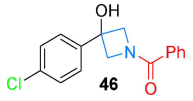
**Table 2.** Optimization of BOC derivative.[a]

| Solvent (Conc.) | T [°C] | Flow [mL/min] | Yield [%] |
|---|---|---|---|
| $CH_3CN$ (0.15 M) | 30 | 1 | 25 |
| $CH_3CN$ (0.037 M) | 30 | 1 | 30 |
| MeOH (0.15 M) | 30 | 1 | 62 |
| MeOH (0.15 M) | 30 | 0.7 | 62 |
| MeOH (0.15 M) | 40 | 1 | 63 |
| MeOH (0.075 M) | 40 | 1 | 69 |
| MeOH (0.037 M) | 40 | 1 | 71 |
| MeOH (0.037 M) | 40 | 0.8 | 71 |
| Acetone (0.037 M) | 40 | 1 | 52 |

[a] Performed with a lamp power of 100%.

**Table 3.** Synthesis of carbonyl derivatives.[a]




| Starting material | Product | Conversion (yield) |
|---|---|---|
|  |  | 100% (71%) |
|  |  | 100% (81%) |
|  |  | 100% (76%) |
|  |  | 100% (74%) |
|  |  | 91% (89%) |
|  |  | 90% (85%) |

[a] Performed with a lamp power of 100%, 0.037 M in MeOH at a reactor temperature of 40 °C.

essed and gave similar improved yields to the corresponding azetidine products (Table 3).

Having determined the general scope and some limitations to the reaction, we wished to demonstrate the robustness and scalability of the processing capabilities of working in flow through the scale up of the transformation. As such five compounds were selected to assess at larger scale production, namely products **6**, **9**, **12**, **19** and **33**. As an illustration compound **12** was directly scaled to 100 mmol (0.15 M concentration in MeCN equating to a required processing volume of 667 mL at 1 mL/min flow rate). In a single continuous run, this material required 11.5 hours of processing, including reactor washing. After solvent evaporation, the product could be more expediently isolated by trituration with cold $CHCl_3$ and following drying *in vacuo* furnished 20.3 g (60%). For larger processing volumes (i.e. **19** (64%) and **33** (40%) were achieved at 250 mmol), the mixture was conveniently processed intermittently during a standard working day (8 h), with the reactor flushed with MeCN each night and simply restarted in continuation the following day. In this way, it was trivial to prepare stock solutions of materials and thus generate multi-gram quantities of the products.

## 3. Conclusions

In conclusion, the Yang reaction has been studied in flow for the first time; starting from a sulfonamide derivative whereby the reactivity in batch was known. The reaction was optimized in a flow reactor showing a remarkable reduction in the reaction time from several hours (batch) to minutes. The initial substrate was progressively extrapolated in order to evaluate the effect of different substituents on the reactivity: initially both the aromatic ring and the sulfonamide fragments were functionalized, then the role of the substituent on the nitrogen was more closely assessed. Several *N*-carbonyl derivatives were subsequently assembled showing a good reactivity toward the cyclization, moreover the BOC protected azetidine particularly represents a valuable substrate giving the chance for deprotection and the use of the free nitrogen for further reactions. The reaction was also scaled up allowing the production of $>20$ g of product in under 12 h demonstrating the efficiency of the Yang reaction in flow as a valuable synthetic tool.

## Experimental Section

The photoreactions were investigated using a commercially available Vapourtec E series system with a UV 150 photochemical reactor unit equipped with a medium pressure mercury lamp (maximum of emission at 365 nm – see SI for output profile), three low pressure mercury lamps (254 nm (6.8 W), 310 nm (7.8 W), 370 nm (7.5 W)) and for conducting additional exploratory experiments 3 LED units (530 nm, 720 nm, 365 nm). The power of the medium pressure lamp could be controlled from 75 to 150 W while the 3 LED units have a total input power of 9 W and are rated between 30–40% efficient therefore providing an output of approximately 3 W. Moreover, 5 different filters can be installed around the medium pressure mercury lamp allowing a selection of different portions of the output radiation (See Table 1 in the SI). The flow reactor consists of a 10 mL FEP (fluorinated ethylene propylene) coiled tube housed in a closed body reactor with a temperature probe permitting monitoring of the reaction temperature and allowing moderation by an external cooling system gas (cylinder with dry ice coolant). A general temperature range of between −5 °C and 80 °C can be maintained.

### General Procedure for the Photocyclization

The α-aminoketone starting material **1** was dissolved in acetonitrile at the chosen concentration (typically 0.15 M), and the solution was pumped through the photoreactor at the given flow rate (typically 1 mL/min). The temperature of the reactor was kept between 20–25 °C using gas cooling. The outflow from the reactor was collected into a flask, and after solvent evaporation, it was purified by normal phase column chromatography (EtOAc/Hexane) or by trituration with cold $CHCl_3$. See the Supporting Information for further details.

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## Conflict of Interest

The authors declare no conflict of interest.

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