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Francis, D, Blacker, AJ orcid.org/0000-0003-4898-2712, Kapur, N orcid.org/0000-0003-1041-8390 et al. (1 more author) (2022) Readily Reconfigurable Continuous-Stirred Tank Photochemical Reactor Platform. Organic Process Research & Development, 26 (1). acs.oprd.1c00428. pp. 215-221. ISSN 1083-6160

https://doi.org/10.1021/acs.oprd.1c00428

A Readily-Reconfigurable Continuous-Stirred Tank Photochemical Reactor Platform

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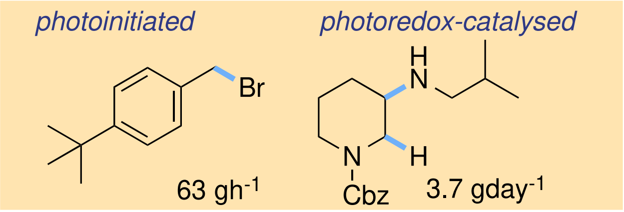
Graphical abstract:

- variable wavelength (365 or 460 nm)
- multiphasic reactions (solid/liquid, gas/liquid)
- facile telescoping with other reactions
- easily reconfigured for scale-out (1-5 reactors)



ABSTRACT. A new modular photochemical continuous-stirred tank reactor (CSTR) design is described, based upon the development of light-source units that can be fitted to the previously described fReactor CSTR platform. In addition to use in homogeneous photochemical reactions (e.g. photoredox-catalysed hydroamination), these units are especially well-suited to handling multiphasic mixtures, exemplified here in solid-liquid (Wohl-Ziegler bromination) and gas-liquid (photocatalytic oxidative decarboxylation) reactions. The use of slurries as input feeds allows for intensification of photochemical brominations, while the modular nature of the system facilitates simple integration of downstream reaction steps, exemplified here in a continuous synthesis of an intermediate for the anti-hypertensive drug valsartan.

Keywords. Continuous flow reactors, photochemistry, photoredox, multiphasic.

INTRODUCTION

Recent years have seen a huge growth in the application of photochemically-mediated synthetic transformations, driven in part by extensive developments in photoredox catalysis.[1] Well-documented issues with scaling photochemical reactions, especially around light penetration into larger reaction vessels, secondary photoreactions at extended reaction times, and control of thermal effects, have resulted in the widescale adoption of continuous flow photochemical reactors on laboratory scale[2] and, increasingly, on development and production scale.[3,4] The majority of reactor designs are based upon simple tubular reactors which deal well with homogeneous reactions. With multiphasic systems (liquid/liquid, gas liquid), segmented (slug) flow dominates under typical flow conditions.[5] Mixing is often used to enhance the rates of mass transfer through (for example) patterning or oscillations (either externally driven or as a result of internal chaotic flow) to modify the flow in the vicinity of the interface. Additionally, many real-life processes involve the input or formation of particulate materials (e.g. inorganic bases, poorly soluble reactants or reagents, insoluble salt by-products) and so a pressing need for photochemical reactors capable of handling solid/liquid biphasic systems has been identified.[6] Reports to date have included using immersion well reactors in semi-continuous recirculatory mode,[7] plate flow reactors combining oscillatory flow with static mixers,[8] and the use of continuous stirred tank reactors (CSTRs).[9] We recently described a modular, readily-reconfigurable miniature CSTR platform, the ‘fReactor’, which is capable of handling gas, liquid and solid multi-phasic mixtures and as a consequence of its low volume (offering potential for intense mixing) shows high mass transfer characteristics.[10] The general performance characteristics remove the requirement of specifying a reactor platform for a given combination of phases, and we subsequently demonstrated preliminary applications as a continuous flow photochemical reactor, combining good mass transport and a high surface area to volume ratio allowing for good light penetration..[11] Encouraged by this success, we now report the design, construction and application of an optimised photochemical reactor platform which combines the flexibility of multiple, small scale CSTRs (the fReactor platform) with dedicated LED-based photochemical modules to allow easy and safe operation within the laboratory environment.

RESULTS AND DISCUSSION

Reactor Design

Figure 1 shows the equipment layout, with the photo-modules sitting atop the conventional fReactor platform, which in turn sits on a standard laboratory stirrer hotplate. Syringe pumps are used to feed reactants into the fReactor platform, giving a broad selection of flowrates. Each photo-module contains a single wavelength LED: for this work, the LEDs used were either 365nm or 460nm with a nominal radiant light output of 4.3 W and 3.9W, respectively. The LED is positioned to direct the light through the glass window into the reactor (window diameter 15 mm, with a safety cutout installed so light output is cut if the unit is lifted from the fReactor). Cooling is effected through natural convection around each photo-module unit and can be enhanced with a small external fan. Extensive details of the single and multiphasic capabilities of the CSTRs are reported elsewhere;[9] briefly, each reaction vessel (PEEK material, volume 1.7ml) contains a single cross stirrer bar and is equipped with 4 standard ports accepting standard low pressure HPLC fittings, allowing for flexibility in connecting reactors to each other (1/8” OD FEP tubing) and to feed sources, sampling ports and instrumentation (e.g. thermocouples). Here, we connect the fReactors together in sequence (with a single or dual feed into the first reactor and output from the last) giving an improved residence time distribution when compared to a single larger reactor of equivalent total volume.[10] The fReactor platform sits on a standard stirrer-hotplate, which drives the cross-stirrer within each reactor and allows for heating if required.

Figure 1: Arrangement of the photo-flow modules on the individual CSTRs. Here, a complete set of five modules in series are shown.

Photochemical Reactions

(1) Wohl-Ziegler Bromination

We began our studies by investigating photochemically-initiated benzylic bromination using *N*-bromosuccinimide (NBS; the Wohl-Ziegler reaction), since this synthetically useful transformation has been the focus of many studies in continuous flow[12] (including for applications to the synthesis of pharmaceutical intermediates[12d,h]) and would provide a useful benchmark of performance for the reactors. We began by adopting conditions previously employed by Kappe for bromination in a Booker-Milburn-style[13] tubular reactor (coiled FEP tubing surrounding a 25W cool-white or 25W black-light lamp), namely a homogeneous solution of 1.05 equivalents of NBS to 0.5M methylarene (4-methylacetophenone in our initial work) in acetonitrile.[12g] Using reactors equipped with 365nm LEDs, we were pleased to find that the reaction gave good conversion to the brominated product, and that the conversion scaled effectively linearly with the number of reactors at constant overall residence time (t_{res} = 2.2 min), i.e. a five-fold faster flow-rate could be employed using five reactors versus one without negative impact on conversion (Figure 2).

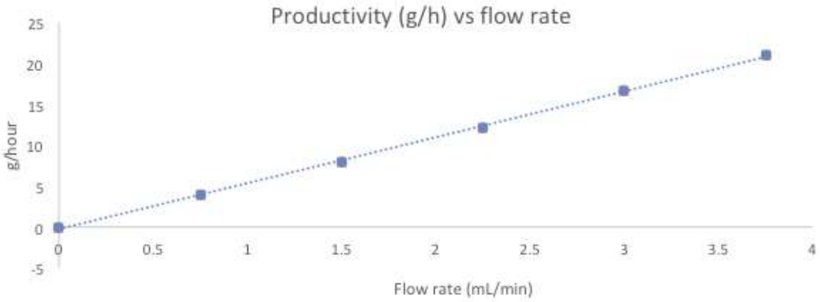
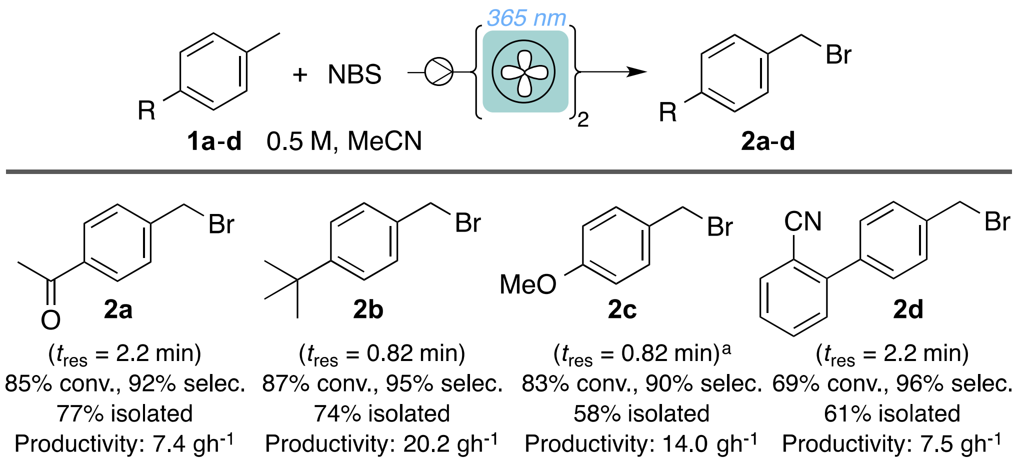


Figure 2. Linear response of productivity in benzylic bromination of **1a** to increased flow rate with scale-out of linked reactors (t_{res} = 2.2 min).

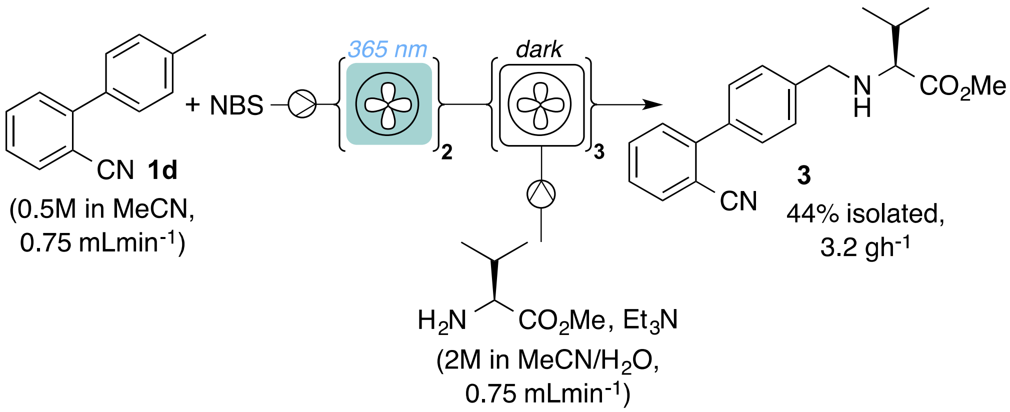
We chose to use two reactors in sequence to demonstrate the performance of the CSTRs in preparative reactions (Scheme 1). At a flow rate of 1.25 mLmin^{-1} **1a** gave an 85% conversion at steady-state, with good selectivity for monobrominated product **2a** (a small amount of 1,1-dibrominated product was also observed) leading to a 77% isolated yield (7.4 gh^{-1} productivity). The more electron-rich substrates **1b** and **1c** underwent faster reaction and similar conversions and selectivities to **1a** could be achieved at a higher flow rate of 4 mLmin^{-1}, leading to comparable isolated yields but much improved productivities (up to >20 gh^{-1}). In the case of 4-

methoxytoluene **1c**, it was found that a solvent switch to dioxane was required to prevent significant competition from electrophilic aromatic bromination.



Scheme 1 Wohl-Ziegler bromination using two sequential photochemical CSTRs. [a] reaction solvent = dioxane

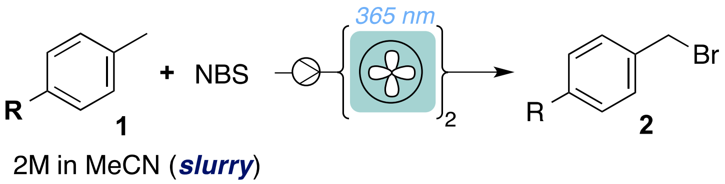
An advantage of the modular nature of the CSTR platform is the ease with which additional operations can be coupled with the photochemical transformation. We demonstrated this by coupling a benzylic bromination with a subsequent nucleophilic substitution step, following a sequence used in the synthesis of the anti-hypertensive drug valsartan (Scheme 2).[14] Thus, carrying out the benzylic bromination of toluene **1d** in our two-reactor configuration at a flow rate of 0.75 mLmin^{-1} gave a ca. 77% conversion to bromide **2d** at steady state, with excellent (98%) selectivity. The output from the photochemical modules was mixed with a feed of valine methyl ester and triethylamine at ambient temperature in aqueous acetonitrile in the third fReactor and pumped through a further two modules (giving a total of 3 non-irradiated modules) on the fReactor platform. This led to the formation of the substitution product **3** in an unoptimised 44% isolated yield, representing a productivity of 3.2 gh^{-1}.



Scheme 2 Synthesis of an intermediate for valsartan by telescoped photochemical bromination/nucleophilic substitution.

One of the advantages of CSTRs versus, for example, tubular reactors is the ease with which they can handle solid materials and slurries. As a demonstration of the potential of this, we investigated the intensification of the bromination reactions by carrying them out at concentrations higher than the solubility limit of NBS. Thus, pumping a four-fold more concentrated solution of the substrate toluenes **1a-d** through two photochemical reactor modules as a slurry with NBS led to generally similar steady-state conversions and selectivities to those observed in the homogeneous system but with greatly improved productivity (up to 63 gh^{-1}; Table 1). As far as we are aware these represent the highest productivities reported to date in continuous photochemical brominations using NBS as the bromine source.

Table 1. Biphasic photochemical benzylic brominations using slurries of NBS.



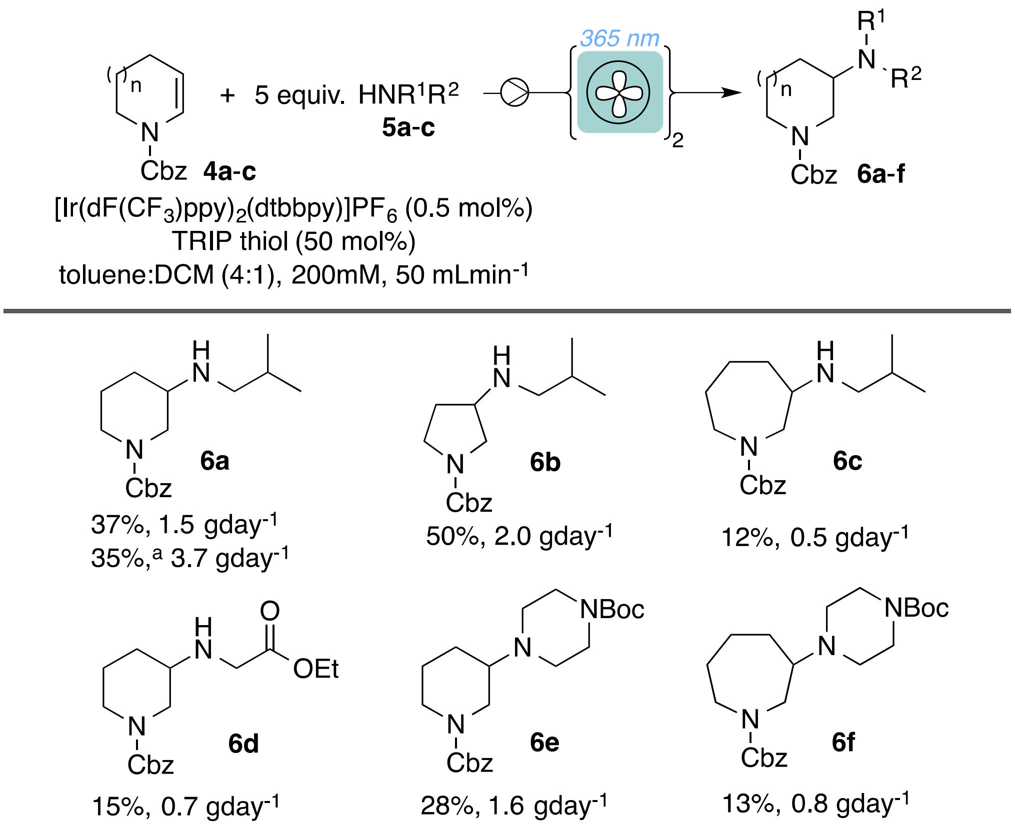
Entry	Product	t_{res} (min)	Conversion (%)	Selectivity (%)	Yield (%)[a]	Productivity (gh^{-1})
1	**2a**	2.6	81	87	65	20.8
2	**2b**	0.82	72	96	58	63.2
3[b]	**2c**	1.63	89	85	71	34.3
4[c]	**2d**	2.17	53	98	41	15.1

[a] isolated yield; [b] reaction solvent = dioxane; [c] substrate concentration 1.5M

(2) Photoredox-catalysed Hydroamination of Enecarbamates

We next wished to demonstrate applicability to a photoredox-catalysed process, and selected our recently-reported hydroamination of enecarbamates.[15] The discovery-scale batch reaction conditions represent a challenge for continuous processing, being dilute (50 mM in substrate), heterogeneous (partially insoluble photocatalyst at 2 mol%) and requiring long reaction times for completion (16 hours). We therefore undertook some optimisation studies in flow using photoflow modules operating at 365 nm (Supporting Information) using enecarbamate **4a** and isobutylamine **5a** as reactants, which allowed us to identify more intensive conditions for the continuous process. We reduced the catalyst loading to 0.5 mol%, to reduce both the cost and amount of insoluble material as we attempted to increase the reactant concentration. In neat toluene, the system still contained insoluble catalyst even at 50 mM substrate, and although the reactor is capable of handling the heterogeneous mixture we found that the process was more reproducible if a homogeneous solution was achieved, circumventing potentially uneven dosing of catalyst. Using 20% v/v THF/toluene led to a 50% conversion at 100 mM, but further intensification was not possible as the catalyst solubility limit in this solvent was reached. Using 20% dichloromethane/toluene allowed further intensification to 200 mM, and using two reactors in sequence at a flow-rate of 50 μLmin^{-1} (overall residence time ca. 1h), we were able to achieve a steady-state conversion to product **6a** of 42%, translating to a 37% isolated yield (85% based on recovered **4a**) and productivity equating to 1.5 gday^{-1} (Table 2). Five additional substrate combinations were examined, with >1.5 gday^{-1} productivities observed for **6b** and **6e**. As in the batch series, the reactions to form aminated azepanes such as **6c** and **6f** were rather sluggish, leading to low conversions – nevertheless, despite the low overall isolated yield these still returned 0.5 gday^{-1} quantities of material, which may be sufficient to progress e.g. discovery projects. To further boost the productivity, the formation of **6a** was carried out using five reactors in series, enabling an increase in flow rate to 125 μLmin^{-1}; we were pleased to find that the conversion and isolated yield remained essentially unchanged but the productivity was raised to ca. 3.7 gday^{-1}, a >50-fold increase in productivity over the standard batch reaction.

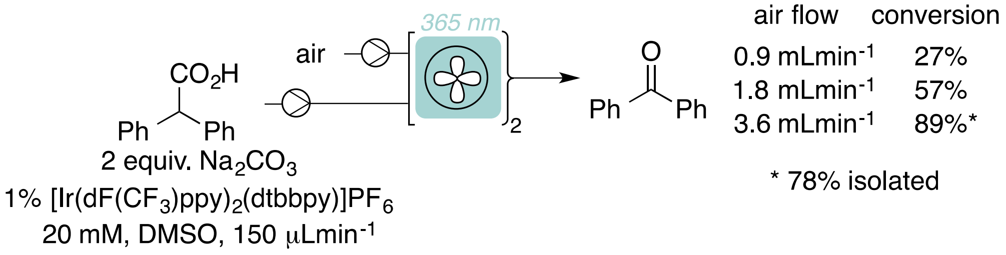
Table 2. Photoredox-catalysed hydroamination of enecarbamates in flow. [A]



[a] Isolated yields.

(3) Photoredox-catalysed Decarboxylative Oxidation (Biphasic Gas-Liquid Reaction)

The potential of the fReactor platform to handle gaseous reaction components has already been demonstrated in the context of a catalytic hydrogenation reaction,[10,16] and we also demonstrated the benzophenone-mediated aerobic benzylic oxidation of tetralin using our prototype photochemical reactor.[11] We wished to demonstrate the capabilities of the optimised reactor design in a biphasic gas-liquid process, and chose MacMillan's photoredox-catalysed decarboxylative oxidation of carboxylic acids.[17] For ease of operation, rather than the final optimised conditions described in that paper we adopted simplified conditions (alternative photocatalyst, no viologen salt additive and use of air rather than oxygen as the source of terminal oxidant). The substrate (1,1-diphenylacetic acid), catalyst and base were co-injected as a homogeneous solution, while air was added via a syringe pump. The conversion was found to be dependent upon the air flow-rate, indicating that the availability of dissolved oxygen was a limiting factor (Scheme 3). In a gas-liquid system within the fReactors, the volume above the midline of the inlet to the CSTR is filled with gas, with liquid sitting below it (although in practice the impeller creates a less defined interface). Consequently, the liquid phase occupies ca. 50% of the reactor. Based on this volume, at a liquid residence time of ca. 10 minutes using 2 reactors, an 89% conversion was achieved at a gas flow rate of 3.6 $\mathrm{mLmin^{-1}}$, corresponding to a 78% isolated yield of benzophenone. This is comparable to the 86% isolated yield obtained in MacMillan's optimised protocol, and represents a 5-fold more productive reaction (flow: 0.14 $\mathrm{mmolh^{-1}}$ product; batch: 0.43 mmol product in 16 hours equates to 0.026 $\mathrm{mmolh^{-1}}$) using reaction conditions that are simpler (additive-free) and safer (air vs. oxygen as terminal oxidant).



Scheme 3 Biphasic gas-liquid reaction: photoredox-catalysed decarboxylative oxidation of a carboxylic acid.

CONCLUSIONS

A new design for a modular photochemical continuous stirred tank reactor platform is described, based on our original 'fReactor' platform. The dedicated photo-units give a high radiant light output and offer easy and safe operation within the laboratory environment. The CSTRs equipped with the photoflow modules are capable of handling common process-relevant heterogeneous mixtures (solid/liquid, liquid/liquid and gas/liquid), thus widening the window of opportunity for novel photochemical reactions. In particular the ability to work above the solubility limit of individual reagents allows for highly productive reactions (up to 0.24 $kgL^{-1}h^{-1}$ in benzylic brominations), and integration with downstream chemical transformations is straightforward. The photochemical modules are now available commercially, along with the fReactor platform (www.asynt.com/product/freactor-photo-flow/). The ease-of-use and flexibility of CSTRs with demonstrably good productivity support the drive to create efficient and sustainable chemical processes.

EXPERIMENTAL SECTION

General Method for the Homogeneous Benzylic Brominations of Substituted Toluenes 1

A solution containing substituted toluene (500 mM) and *N*-bromosuccinimide (525 mM) was dissolved in the stated solvent. The mixture was taken up into a syringe and the fReactors purged with the mixture ensuring no air bubbles were present. The mixture was then injected *via* syringe pump at the specified flow rate, with reactor lights used being 365 nm. An aliquot was taken for analysis at steady state. The aliquot was concentrated *in vacuo* and the residue purified by column chromatography.

General Method for the Heteregeneous (Slurry) Benzylic Brominations of Substituted Toluenes 1

A solution of substituted toluene (2 M) was taken up into a syringe containing solid *N*-bromosuccinimide (2.1 M final concentration) and a magnetic stirrer bar. The reactors were then purged with the mixture ensuring no bubbles were present). The slurry mixture was injected with constant stirring at the specified flow rate, with reactor lights used being 365 nm. An aliquot was taken at steady state (after ca. 2 reactor volumes had been passed) and subject to analysis. The crude mixture was purified by flash chromatography to yield the pure benzylic bromide.

Methyl ((2'-cyano-[1,1'-biphenyl]-4-yl)methyl)-L-valinate 3

A solution of 4'-methyl-[1,1'-biphenyl]-2-carbonitrile (0.5 M) was taken up into a syringe containing *N*-bromosuccinimide (0.525 M final concentration) and a magnetic stirrer bar. The 5 sequential reactors (the first two of which were fitted with Photo Flow units, the final three of which were left as ‘dark’ reactors) were then purged with the mixture ensuring no bubbles were present. The mixture was injected to the first reactor with constant stirring at a rate of 0.75 mLmin^{-1}. A second syringe containing L-valine methyl ester and triethylamine (both 2M final concentration) was co-injected into the 3rd sequential reactor at a flow rate of 0.75 mLmin^{-1}. Once at steady state a 2 mL aliquot was taken from the output of the final reactor and immediately quenched with 1M HCl in dioxane. The reaction was diluted with ethyl acetate and extracted into 1M HCl (3 x 50 mL). The combined aqueous layers were basified using KOH pellets (pH ~10-14) and extracted into DCM (3 x 100 mL). The combined organics were dried over MgSO4 and concentrated *in vacuo*. The crude mixture was purified by column chromatography (0-2% methanol in DCM) to yield an off white solid (71 mg, 44%).

Spectral data matches that reported.[14] ^{1}H NMR (501 MHz, CDCl$_3$) δH 7.76 (1H, dd, *J* 7.8, 1.4), 7.64 (1H, td, *J* 7.8, 1.4), 7.53 – 7.50 (3H, m), 7.47 (2H, d, *J* 8.3), 7.43 (1H, td, *J* 7.6, 1.2), 3.90 (1H, d, *J* 13.4), 3.74 (3H, s), 3.65 (1H, d, *J* 13.4), 3.06 (1H, d, *J* 6.2), 1.95 (1H, app dh, *J* 13.5, 6.8), 0.98 (3H, d, *J* 7.2), 0.96 (3H, d, *J* 7.2). ^{13}C NMR (126 MHz, CDCl$_3$) δ 175.9, 145.5, 141.0, 137.0, 133.9, 132.9, 130.2, 128.8, 128.7, 127.6, 119.0, 111.4, 66.9, 52.3, 51.6, 31.9, 19.5, 18.8.

General Method for the Hydroamination of Cyclic Enecarbamates 4

A stock solution was prepared containing cyclic enecarbamate **4** (200 mM final concentration), amine (1 M final concentration), TRIP thiol (100 mM final concentration), [Ir{dFCF$_3$ppy}$_2$(bpy)]PF$_6$ (1 mM final concentration) in a 4:1 mixture of anhydrous toluene and DCM. The mixture was purged with nitrogen before being taken up into a syringe. The fReactor vessels were purged with the mixture, ensuring no air bubbles were present. The reactor lights (365 nm) were then turned on and the syringe was then placed in a syringe pump and run at the specified flow rate (µL/min). An aliquot was taken at steady state (after >2 reactor volumes) for analysis. The aliquot was concentrated *in vacuo*, redissolved with ethyl acetate (50 mL) and extracted with 1M HCl (3 x 50 mL). The acidic extracts were then basified with KOH pellets until pH12-14. The solution was then extracted with DCM (3 x 150 mL). Combined organics were dried over MgSO$_4$, concentrated *in vacuo* and isolated as colourless oils. For non-volatile amines, purification by flash chromatography was performed.

Photoredox-Catalysed Oxidative Decarboxylation

Diphenylacetic acid (20 mM final concentration) sodium carbonate (40 mM final concentration) and Ir[dFCF$_3$(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (0.1 mM final concentration) were suspended in dimethylsulfoxide. The mixture was stirred for 30 minutes before being taken up into syringe and injected at a rate of 150 μLmin^{-1}. Simultaneously a second syringe containing air was injected into the reactor at a rate of 3.6 mLmin^{-1}. A 10 mL aliquot was taken for analysis where the mixture was acidified with 1M HCl in and diluted with water (50 mL). The mixture was extracted with ethyl acetate (3 x 50 mL) and the combined organics washed with brine (5 x 50 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. The crude benzophenone product was purified by column chromatography resulting in a white solid (28 mg, 78%) whose properties matched an authentic sample.

ASSOCIATED CONTENT

Supporting Information.

The following file is available free of charge: full experimental procedures and compound characterisation data for **2a-d** and **6a-f** $^{1}H/^{13}C$ NMR spectra of all products.

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Author Contributions

The manuscript was written through contributions of all authors.

Note

The University of Leeds licenses the design of fReactors and photo-flow modules to Asynt Limited.

Funding Sources

EPSRC Impact Acceleration Account at the University of Leeds (EP/R511717/1) and the Royal Academy of Engineering for support of NKs Chair.

ACKNOWLEDGMENT

We thank Asynt Limited, Redbrick Molecular Limited and Sterling Pharma Solutions for useful discussions and support of this work.

ABBREVIATIONS

CSTR, continuous-stirred tank reactor; FEP, fluorinated ethylene propylene; HPLC, high-performance liquid chromatography; LED, light-emitting diode; NBS, *N*-bromosuccinimide; OD, outside diameter.

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