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Modular synthesis of cyclic β-difluoroamines†

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Fluorine-containing saturated nitrogen heterocycles are very attractive structures in medicinal and biological chemistry because fluorine can be used to tune conformation as well as key properties such as basicity and bioavailability. At present cyclic fluorinated amines are accessed using hazardous reagents such as DAST or by lengthy synthesis routes. Here we report a modular two-step synthesis of cyclic β-fluoroalkyl amines using a photoredox-catalysed cyclisation/hydrogen atom transfer reaction of bromodifluoroethylamines.

Fluorinated organic molecules underpin a range of scientific fields[1] and are used extensively in pharmaceutical and agrochemical research.[2] For example, fluorination of amines lowers their basicity and can also modulate acute toxicity and lipophilicity.[3–5] Given that saturated heterocyclic amines are very common in bioactive compounds, fluorine-containing analogues would be of significant value, particularly in the field of drug discovery.

Unfortunately, functionalised cyclic fluorinated amines are currently hard to access. They are generally synthesised through deoxydifluorination reactions using hazardous reagents (Fig. 1A) or lengthy Reformatsky-based sequences (Fig. 1B).[6–9] To address this problem we envisaged a two-step synthesis of cyclic β-fluoroalkyl amines using a photoredox-catalysed cyclisation reaction of bromodifluoroethylamines, prepared through a modular three-component coupling (Fig. 1C).[10] To the best of our knowledge, photoredox cyclisations[11,12] of this type have not been previously described as such reactions could be complicated by competing redox-triggered C–H functionalization reactions adjacent to nitrogen.[13] Related work has circumvented this problem by using redox inert sulfonamides[14,15] or amides[16–21] as cyclisation substrates, but subsequent deprotection or redox adjustments are then required to access synthetically useful products. Here we show that cyclisation of unprotected β-bromodifluoroalkyl amines prepared from readily available amines, aldehydes and carboxylic acids[22] is indeed possible resulting in a concise synthesis of cyclic β-fluoroalkyl amines (Fig. 1C).

We began our studies by screening conditions using model alkynyl amine substrate **3**, which was prepared by a three-component coupling using bromodifluoroacetic acid as the source of the bromodifluoromethyl group (Table 1).[10] We opted to use the strongly reducing $Ir(ppy)_3$ catalyst (−1.73 V *vs.* SCE) as a starting point and, gratifyingly, the desired cyclised product **4** was detected and no products arising from oxidation of the substrate or product were obtained (Table 1, entry 1). We then surveyed additional hydrogen atom sources and, while the Hantzsch ester (entry 2) and tris(trimethylsilyl)silane (TTMSS) (entry 3) were found to be poor, formic and acetic acid were superior (entries 4 and 5).

Optimal conditions (entry 6) were obtained using ten equivalents of triethylamine in combination with five equivalents of acetic acid. Increasing the concentration proved to be detrimental, as did the use of other photoredox catalysts ($Ir(ppy)_2$(dtbbpy), $Ru(bpy)_3Cl_2$, EosinY and 4CzIPN) as detailed in the ESI.†

We next conducted a further screen of conditions for the cyclisation of alkenyl amine **5** (Table 2). In this instance, the use of DIPEA as the base resulted in a moderately improved yield (44% *vs.* 38%, entries 1 and 2) for the transformation *vs.* triethylamine. Interestingly, for these substrates the addition of acetic acid was detrimental and only 10% of the product was obtained in this case (entry 3). Fortunately, TTMSS proved to be an excellent hydrogen atom donor for this substrate class (entry 4), with the desired compound **6** being obtained in a 97% yield.

Having optimised the reaction conditions for the cyclisation of alkyne- and alkene-containing tertiary amines, we explored

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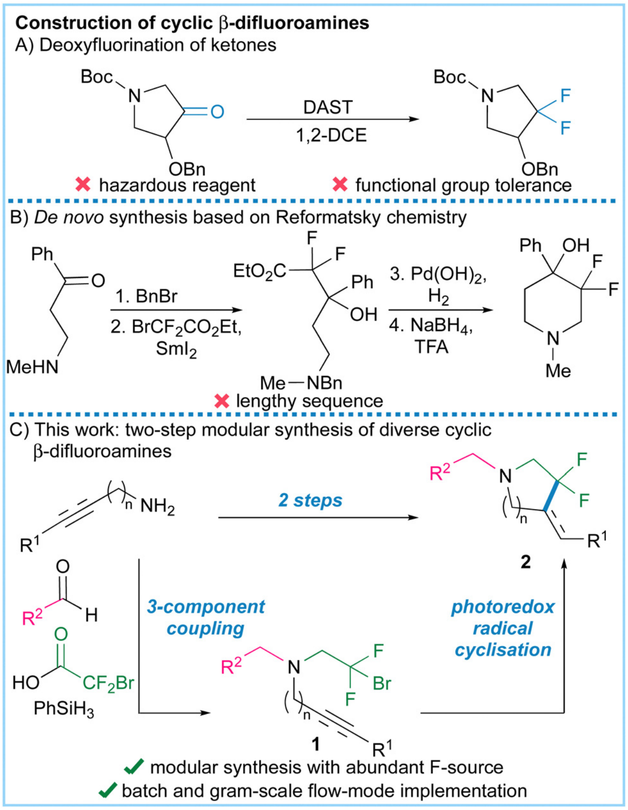
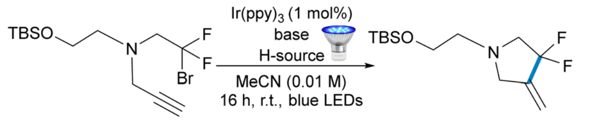


Fig. 1 Methods for the construction of difluorinated amines. (A) Deoxyfluorination of ketones. (B) Reformatsky chemistry using ethyl bromodifluoroacetate. (C) This work – a two-step modular amine synthesis using primary amines, aldehydes and bromodifluoroacetic acid as the fluorine source.

Table 1 Optimisation of alkynyl amine cyclisation

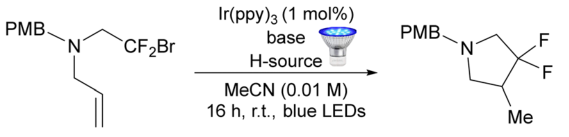


3 4

Entry	Base (equiv.)	H-source (equiv.)	Product yield[a]/%
1	Et_3N (10)	None	56
2	Et_3N (10)	Hantzsch ester (1.5)	7
3	Et_3N (10)	TTMSS (1.5)	12
4	Et_3N (10)	HCOOH (1.5)	71
5	Et_3N (10)	HCOOH (5.0)	77
6	Et_3N (10)	AcOH (5.0)	88

Reactions conducted on a 0.05 mmol scale. [a] Yield determined by ^{19}F NMR spectroscopy using trifluorotoluene as an internal standard.

Table 2 Optimisation of alkenyl amine cyclisation



5 6

Entry	Base (equiv.)	H-source (equiv.)	Product yield[a]/%
1	DIPEA (10)	None	44
2	Et_3N (10)	None	38
3	Et_3N (10)	AcOH (5.0)	10
4	DIPEA (10)	TTMSS (5.0)	97

Reactions conducted on a 0.05 mmol scale. [a] Yield determined by ^{19}F NMR spectroscopy using trifluorotoluene as an internal standard.

the scope of both photoredox cyclisation reactions (Fig. 2A and B). In all cases the yields were determined using ^{19}F NMR spectroscopy and after chromatographic purification (values in parentheses). Key findings were as follows.

Acyclic alkenes were successfully utilised as radical traps, with particularly high yields observed for products **9** and **10** where the cyclic radical intermediates are stabilised. This, however, was not crucial as products **6**, **13** and **14** derived from terminal alkenes substrates were obtained in good yield. The use of an endocyclic alkene afforded spirocyclic amine **11** in a good, isolated yield of 74%. Silyl-protected alcohols (**4**) are tolerated, as are free hydroxyl groups (**23**), carbamates (**22**), esters (**9** and **20**) and ketones (**10**). These products would be challenging to access using conventional nucleophilic fluorinating reagents such as DAST. Conformational restriction in the proline-derived substrate also promoted the desired cyclisation to give fluoroindolizidine **20**. Cyclisation of internal alkynes afforded products **24–28** with $E:Z$ ratios close to 50 : 50.

Having established the scope, we sought to further explore the practicality of the reaction. In particular, we were interested in scaling up the reaction and conducting deprotection/derivatisation sequences in order to generate novel building blocks.

Pleasingly, with no detriment to the yield, we were able to achieve a ten-fold scale-up of the batch reaction for the synthesis of **17** from 0.25 mmol to 2 mmol (Fig. 2C). Accounting for the presence of a PMB group in some of our substrates, we developed a cleavage protocol using 1-chloroethyl chloroformate, which gave **30** in a 69% isolated yield.

Our two-step protocol represents a very efficient method to access this pyrrolidine analogue and the calculated pK_aH and $\log P$ of **30** ($pK_aH = 15.1$, $\log P = 1.20$) *vs.* pyrrolidine ($pK_aH = 19.5$, $\log P = 0.77$)[23] indicate the impact fluorine has on key properties which can, in principle, modulate biological activity and metabolic stability. Next, the alkene in product **17** was transformed into tertiary alcohol **31** in 67% yield, *via* Mukaiyama hydration conditions, thereby demonstrating the versatility of the alkene handle and providing a new method to access the difluorohydrin motif previously generated through Reformatsky chemistry (Fig. 1B). In order to obtain still larger quantities of product **17**, we developed a flow-chemistry platform (Fig. 2C) which allowed us to prepare over 9 g of **17** with a productivity of 101 g day^{-1}. In principle this method can be applied to access multigram quantities of any of the products described above.

Finally, we investigated the mechanism of the cyclisation reactions (Fig. 3). Given that $Ir(ppy)_3$ has a reduction potential of −1.73 V *vs.* SCE and taking into account mechanistic

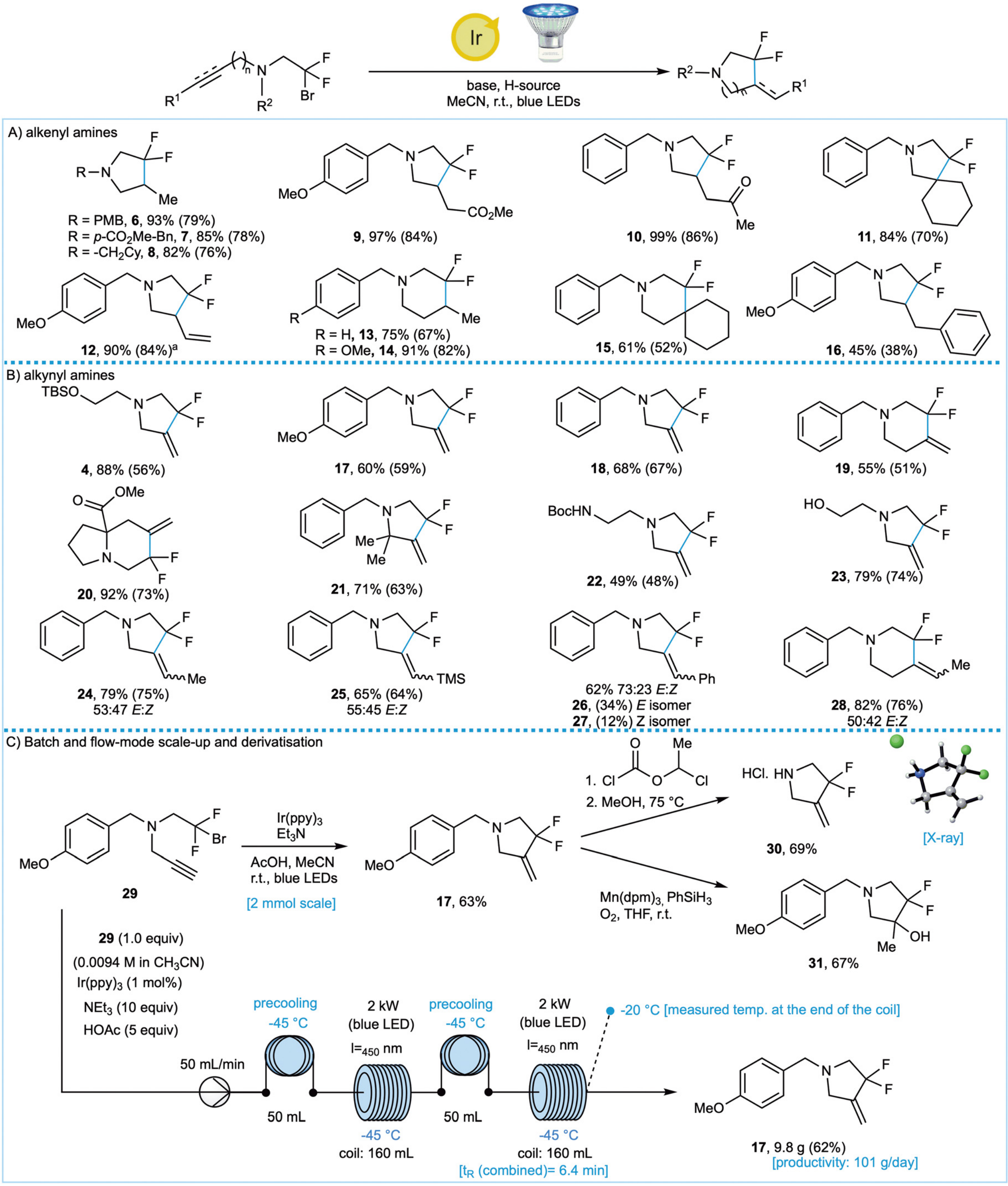


Fig. 2 Photoredox radical cyclisation of alkenyl and alkynyl amines. [a] Reaction conditions: (A) alkenyl amine cyclisation – $Ir(ppy)_3$ (1 mol%), DIPEA (10 equiv.), TTMSS (5 equiv.), MeCN (0.01 M), r.t., blue LED irradiation; (B) alkynyl amine cyclisation – $Ir(ppy)_3$ (1 mol%), Et_3N (10 equiv.), acetic acid (5 equiv.), MeCN (0.01 M), r.t., blue LED irradiation; PMB deprotection – 1-chloroethyl chloroformate (1.1 equiv.), 1,2-DCE (0.4 M), 90 °C, 2 h, then MeOH (1.0 M), 75 °C, 1 h; Mukaiyama hydration – $Mn(dpm)_3$ (5 mol%), $PhSiH_3$ (2 equiv.), O_2 (1 atm), THF (0.2 M), r.t., 24 h. Yields were determined by NMR spectroscopy *vs.* internal standard (1,3-benzodioxole or trifluorotoluene); yields of isolated material after chromatography are given in parentheses. [a] DIPEA (20 equiv.), TTMSS (2 equiv.). (C) Batch and flow-mode scale-up reactions.

investigations into cyclisations of un-activated alkyl iodides,[24] an oxidative quenching cycle is likely to be operating. We propose that irradiation of the catalyst forms the excited Ir(III)* complex which then reduces the bromodifluoroalkyl starting material **1** by single electron transfer to give radical **32** and the corresponding Ir(IV) species. Intramolecular radical addition is favoured under our dilute conditions to give cyclic radical **33**, which is then able to participate in hydrogen atom transfer with multiple donors (*vide infra*).

We examined other possible reactions of radical **32** using QM calculations (see ESI†) and large barriers were obtained for the potentially competitive 1,4-HAT and 1,6-HAT pathways as

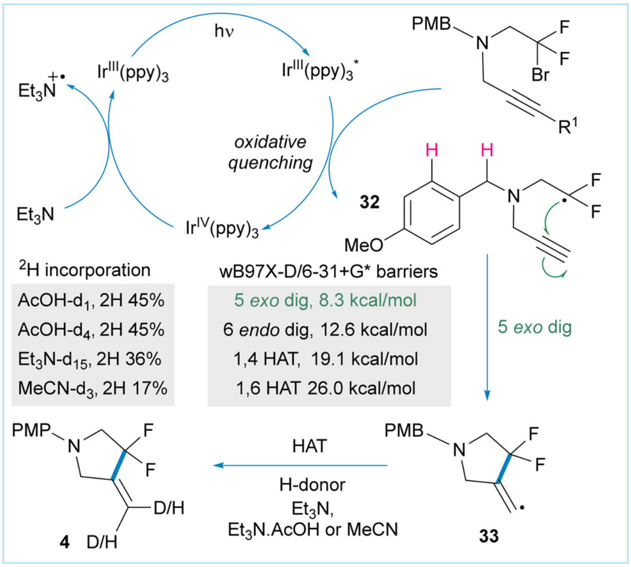


Fig. 3 Proposed catalytic cycle based on control experiments, deuterium quenching and quantum chemical calculations.

well as the 6-*endo* cyclisation. The *exo*-cyclisation has a barrier of 8.3 kcal mol^{-1} (Fig. 3) which is consistent with related processes.[25] Possible C–H functionalisation products arising from oxidation of either the amine substrate or product were absent. This is due to the negative inductive effect of the β-difluoro group which substantially alters the redox potential of both compounds, thereby preventing C–H functionalisation adjacent to nitrogen.

Next, we carried out a series of deuterium-incorporation studies in which all possible H atom sources were systematically exchanged with their ^2H counterparts. This revealed that Et_3N, AcOH and MeCN were all competent hydrogen atom donors (Fig. 2 and ESI†) for the HAT reaction of intermediate **33**.

A series of control experiments (see ESI†) confirmed that the reaction does not proceed in the absence of light, nor in the absence of tertiary amine base.

The reaction does proceed (albeit in lower yield – 56% for **4**) in the absence of acetic acid which suggests that triethylamine can act as an electron and hydrogen atom donor in this process.

In summary, we have demonstrated a mild and efficient visible-light-mediated intramolecular cyclisation reaction of bromodifluoroalkyl amines. In two-steps, complex fluorinated nitrogen-containing heterocycles are generated using a carboxylic acid as the source of fluorine.

R. M. D., N. G. C. and M. A. G. designed the experiments. N. G. C. carried out the experiments and collected the data. R. M. D. carried out the computational calculations. R. M. D. and N. G. C. analysed the data. R. M. D. and N. G. C. drafted the manuscript. S. A. P. determined the crystal structure of compound **30**. P. M. and O. P. carried out flow chemistry. All the authors approved the final version of the manuscript for submission.

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Data availability

The experimental and computational data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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