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Organic dye-photocatalyzed fluoroalkylation of heteroarene-*N*-oxide derivatives†

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The first direct C_{Het}–H perfluoroalkylation reaction of heteroaromatic-*N*-oxides has been achieved through a visible light-photocatalyzed reaction in the presence of commercially available perfluoroalkyl iodides R_F–I and base in DMF as solvent and Rose Bengal as organic photocatalyst. The reactions proceed in the absence of transition metals and can be scaled up. Through an acid-catalyzed transformation of the perfluoroalkylated-*N*-oxides thus obtained, the first direct syntheses of 2-(perfluoroalkyl)benzo[*f*][1,3]oxazepines are achieved. De-oxygenation of the resulting perfluoroalkylated heteroaromatic-*N*-oxides leads to high yielding and regioselective radical perfluoroalkylation protocols of heteroaromatic compounds. To the best of our knowledge, this is the first report on a direct method for perfluoroalkylation of pyridine-, quinoline-, and diazine-*N*-oxide derivatives.

Introduction

Heterocyclic *N*-oxides are known to possess relevant biological activity as anticancer, antibacterial, antihypertensive, antiparasitic, anti-HIV, anti-inflammatory, herbicidal, neuroprotective, and procognitive agents. A recent review article emphasizes the role of heterocyclic *N*-oxides as therapeutic compounds.[1] The *N*-oxide motif has been successfully utilized in a number of drug development protocols. For instance, minoxidil[2] (currently used for the treatment of any form of alopecia), otamixaban[3] (used for the management of acute coronary syndrome), Ancriviroc[4] (an HIV-1 entry inhibitor, known to be a noncompetitive allosteric antagonist of chemokine receptor CCR5), quindoxin, olaquindox, and carbadox[5a,b] (which have antibacterial properties) (Fig. 1) all have distinct identifiable clinical targets.

Homolytic aromatic substitution (HAS) of heteroaromatic-*N*-oxide derivatives has not been the subject of systematic studies in the literature.[5c–e] The *C*2 alkylation of pyridine-*N*-oxides has very recently been accomplished by photoredox catalysis as illustrated in Scheme 1.[6a] Other non-photocatalytic methods for the alkylation of heteroaromatic-*N*-oxides have also been reported.[6b–e] The thermal enantioselective counterpart alkylation of quinoline *N*-oxides with vinylarenes has also lately been carried out through the use of copper catalysis.[7] In the *N*-oxide-quinoline instance, however, the vinyl-substituted products do not retain the oxide functionality.

On the other hand, it has been well documented that the introduction of fluorinated functional groups R_F into heterocycles can bring about significant improvement of their lipophilicity, metabolic stability and bioavailability.[8a,b] There are few reports on the fluoroalkylation[8c–h] of pyridine-*N*-oxide derivatives (Py-NO). One such transformation employs perfluoroalkylsilanes[9] and affords perfluoroalkylated pyridine derivatives Py–R_F, where the *N*-oxide functionality aids in the

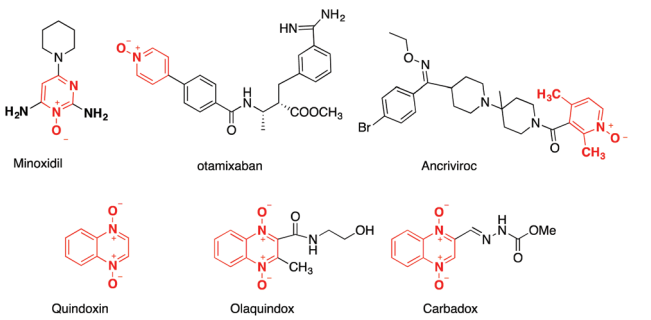
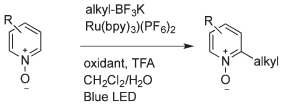


Fig. 1 Structures of minoxidil, otamixaban, ancriviroc, and antibacterial quinoxaline-*N*-dioxide derivatives.



Scheme 1 Alkylation of pyridine-*N*-oxide derivatives.

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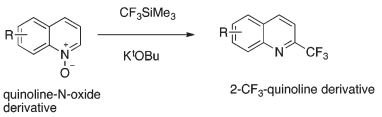
nucleophilic substitution of the ring but it is not conserved in the final product (Scheme 2).[10,11]

Indirect synthesis of fluoroalkylated pyridine-*N*-oxide derivatives has been accomplished through commodity chemicals, and Hansch-type syntheses from fluoroalkylated dicarbonyl compounds and ammonia.[12] In this last report,[12] the synthesis of 4-trifluoromethylpyridine-*N*-oxide is a precursor of the 4-trifluoromethylpyridine substrate with potential antitumor activity.

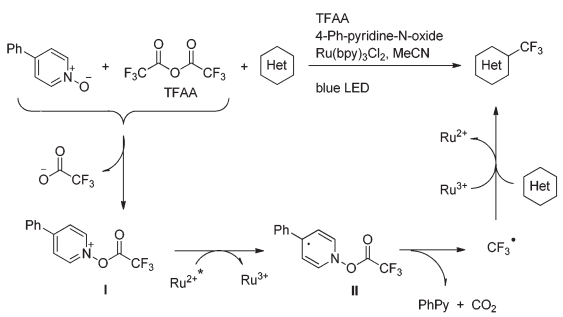
Another use of pyridine-*N*-oxides in the context of fluoroalkylation reactions has been as a conceptual alternative to direct carboxylate oxidation of trifluoroacetates/trifluoroacetic anhydrides (TFAAs) that provides access to CF_3 radicals capable of trifluoromethylating a number of (hetero)aromatic compounds.[13]

In this latter work[13] a complex is formed between TFAA and Py–O (**I**, Scheme 3) that is reduced by the excited photocatalyst to afford radical species **II**, which fragments into pyridine (PhPy), CO_2, and CF_3 radicals.

On the other hand, from the synthetic point of view, perfluoroalkylated pyridine derivatives can act as excellent electrophiles toward the addition of carbon nucleophiles,[14] affording substituted (perfluoroalkylated)pyridines under mild conditions, which renders these compounds potential precursors for mild nucleophilic substitutions of six-membered ring *N*-containing heteroaromatics.[15,16] However, to the best of our knowledge, no direct fluoroalkylation strategy has been informed toward the synthesis of fluoroalkyl-substituted heterocyclic-*N*-oxide derivatives. In this work, we present a mild and environmentally benign strategy for the synthesis of perfluoroalkyl-substituted pyridine-*N*-oxide derivatives and other perfluoroalkyl-heteroaromatic-*N*-oxides, employing an organic photocatalyst in the absence of transition metals, visible light and readily available perfluoroalkyl sources R_F–I. In this strategy, the *N*-oxide functionality is preserved in the perfluoroalkylated derivative final product.



Scheme 2 2-Trifluoromethyl-quinoline from the corresponding quinoline-*N*-oxide.



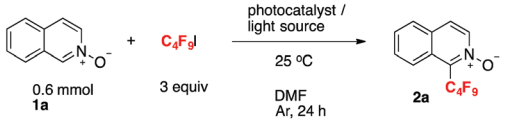
Scheme 3 Use of pyridine-*N*-oxides as CF_3 radical promoters.

Results and discussion

Taking into account the successful photocatalytic alkylation reaction of Py–NOs[6] (Scheme 1), we decided to explore photocatalytic protocols for the perfluoroalkylation counterpart reactions on these substrates, employing different photocatalysts, illumination sources, additives, and bases, according to Table 1.

The first photochemical studies of pyridine-*N*-oxides consisted of short-wavelength direct irradiations.[17,18] Thermal[19] and photoinduced[20a] electron transfer ET reactions between Py–NO and acceptors have been reported before generating the radical cations of Py–NO and the respective radical anions of acceptors. We therefore commenced our investigation by exploring the possibility of a high-energy photoinduced ET between isoquinoline-*N*-oxide[20b] **1a** and *n*-C_4F_9I,[21] in order to produce C_4F_9 radicals from the process. Under the reaction conditions of entry 1, Table 1, an unidentified mixture of polymeric material is obtained. When the concentration of *n*-C_4F_9I

Table 1 Optimization of reaction conditions. Reactions of isoquinoline-*N*-oxide **1a** (0.6 mmol) with *n*-C_4F_9I (3 equiv.) in DMF as solvent (or otherwise noted) (3 mL, Ar-deoxygenated), with vigorous constant stirring, under irradiation for 24 h (or otherwise noted) at 25 °C. Substitution product: 1-perfluorobutyl-isoquinoline-*N*-oxide **2a**



Entry	Additive	Photocatalyst/light source	Substitution % yield of **2**
1	—	—/LPL	—[a] <5[b]
2	TMEDA	—/CFL[c]	<5
3	Cs_2CO_3[d]	—/CFL[d]	<5
4	Cs_2CO_3[e]	Ir[dF(CF_3)ppy]$_2$(dtbpy))PF_6/ Blue LED[e]	77
5	Cs_2CO_3[f]	Eosin Y/CFL[f]	74
6	Cs_2CO_3[g]	Rose Bengal/CFL[g]	98
7	*p*-DNB,[g] Cs_2CO_3[h]	Rose Bengal/CFL[h]	<50
8	TEMPO,[h] Cs_2CO_3[i]	Rose Bengal/CFL[i]	<5
9	Cs_2CO_3[j]	Rose Bengal/—	—

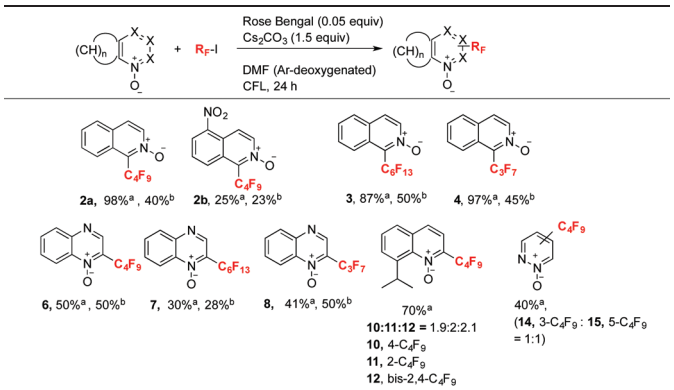
[a] Low pressure Hg lamp, LPL (20 Watt, $\lambda_{max.}$ = 254 nm). Quartz vessel used. The reaction is carried out in H_2O for 2 hours. No additive. Absorbance ratio of substrate/C_4F_9I equals 80 : 1. [b] *Idem* but ratio of substrate/C_4F_9I is 1 : 20. [c] Commercial fluorescent lamp (CFL), 20 Watt, is used, and TMEDA (1.5 equiv.). [d] CFL, 20 Watt, Cs_2CO_3 1.5 equiv. [e] Blue LED (5 Watt), (Ir[dF(CF_3)ppy]$_2$(dtbpy))PF_6, 0.01 equiv., Cs_2CO_3 (1.5 equiv.), 24 h. [Substrate] = 0.2 mmol. [f] CFL (40 Watt), Eosin Y (0.01 equiv.), Cs_2CO_3 (1.5 equiv.), 24 h. [g] Rose Bengal (0.05 equiv.)l as PC., Cs_2CO_3 1.5 equiv. [h] *p*-Dinitrobenzene. *p*-DNB (0.3 equiv.), Cs_2CO_3 1.5 equiv., RB (0.05 equiv.). [i] TEMPO (0.1 equiv.), Cs_2CO_3 1.5 equiv., RB (0.05 equiv.). [j] Dark reaction.

is increased (conditions a2.-[22]) a mixture of C_4F_9-substituted products is obtained in very low yield together with polymeric material. The reported visible light-activation of the electron donor acceptor (EDA) complex formed between R_F–I and an *N*,*N*′-tetramethylethylenediamine TMEDA, was also explored in order to produce R_F radicals that could effect ring substitution.[22b,c] Under these conditions (entry 2, Table 1), no substitution product is encountered. When TMEDA was changed to Cs_2CO_3 [23a–d] (entry 3, Table 1), the yield of substitution product was also very low.

When an organometallic photocatalyst PC is employed (*i.e.*: $[Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6]$) under blue light irradiation, a 77% yield of 1-perfluorobutyl-isoquinoline-*N*-oxide **2a** is obtained (entry 4, Table 1). Replacing the organometallic photocatalyst by the organic dye Eosin Y, a similar substitution yield (74% yield, entry 5, Table 1) of **2a** is observed (see Table S1† for redox potentials). Employing Rose Bengal (RB) as photocatalyst, the visible light irradiation reaction of **1a** in the presence of Cs_2CO_3 affords almost a quantitative yield of **2a** (98%, entry 6, Table 1). When Cs_2CO_3 is replaced by TMEDA, the RB-photocatalyzed reaction does not afford a substitution product. The reaction of **1a** (entry 7, Table 1) with 1,4-dinitrobenzene (a radical anion scavenger) affords less than 50% yield of the substitution product. When TEMPO (a radical scavenger, entry 8, Table 1) is added to the reaction mixture, very little product is encountered. This latter experiment seems to support the presence of radicals in the mechanism. Absence of light does not afford any product, with almost quantitative substrate recovery (entry 9, Table 1).

With the best reaction conditions in our hands (entry 6, Table 1), we have next examined a series of heteroaromatic-*N*-oxide derivatives and subjected them to the visible light-RB-photocatalyzed perfluoroalkylation reaction in order to study the scope, regioselectivity and electron demand/requirements of the substrates to undergo substitution with the R_F groups, according to Table 2.

Table 2 Perfluoroalkylation of heteroaromatic-*N*-oxide derivatives (0.6 mmol) in the presence of R_F–I (3 equiv.), Cs_2CO_3 (1.5 equiv.) in Ar-deoxygenated DMF as solvent (24 h) at 25 °C



[a] Yield obtained by ^{1}H NMR integration of crude reaction mixture after external standard added. [b] Isolated yields.

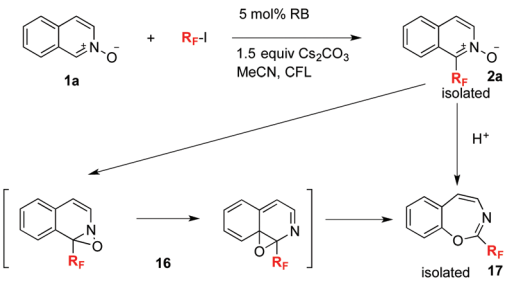
As demonstrated from Table 1, isoquinoline-*N*-oxide **1a** reacts under the RB-photocatalyzed protocol affording a quantitative yield of 1-perfluorobutyl-isoquinoline-*N*-oxide **2a** (Table 2). When 5-nitro-isoquinoline-*N*-oxide[23e] **1b** is allowed to react under conditions of Table 2 with C_4F_9–I, a 23% yield of 5-nitro-1-perfluorobutyl-isoquinoline-*N*-oxide **2b** is formed.

When **1a** is allowed to react with *n*-$C_6F_{13}I$, an 87% yield of 1-perfluorohexyl-isoquinoline-*N*-oxide **3** is obtained. Employing C_3F_7I as a fluoroalkylating source, a 97% yield of 1-perfluoropropyl-isoquinoline-*N*-oxide **4** is produced.

The reaction of quinoxaline-*N*-oxide **5** affords a 50% yield of 2-perfluorobutyl-quinoxaline-*N*-oxide **6** when *n*-C_4F_9I is employed. When *n*-$C_6F_{13}I$ is used instead as a fluoroalkyl source, a 30% yield of 2-perfluorohexylquinoxaline-*N*-oxide **7** is encountered. When **5** reacts under photocatalysis with C_3F_7I, a 41% yield of 2-perfluoropropylquinoxaline-*N*-oxide **8** is produced.

The reaction of 8-isopropyl-quinoline-*N*-oxide **9** affords a 70% yield of products substituted at the 4- and 2-positions (products **10** and **11**, respectively), along with a di-substituted product (product **12**), in a 1.9 : 2 : 2.1 ratio (Table 2). In order to clarify whether products **10–12** are primary photocatalytic products or arise from a consecutive reaction, we followed the photocatalytic formation of products **10–12** *versus* time (see Fig. S1†), demonstrating that the formation of product **12** comes at the expense of substitution of both products **10** and **11**. The photoreaction of pyridazine-*N*-oxide **13** affords a 40% yield of a 1 : 1 mixture of 3-perfluorobutylpyridazine-*N*-oxide **14** and 5-perfluorobutylpyridazine-*N*-oxide **15**. The photocatalyzed semi-large-scale reaction (2 mmol, see the ESI†) of **1a** renders 50% isolated and purified yield of **2a**, demonstrating the possibility for scaling-up protocols. Interestingly, when the isolated product **2a** is left overnight under silica gel, an acid-catalyzed-induced thermal rearrangement (see Experimental and ESI†) takes place, according to Scheme 4.

Rearrangements of heterocyclic *N*-oxides into (benzo)oxazepine rings have been reported and described before by Albini and other authors.[24] These rearrangements can easily occur photochemically[24a,d] or thermally.[24c] However, **17** (70% isolated yield, R_F = *n*-C_4F_9) is the first report of a perfluoroalkyl-substituted benzooxazepine re-arranged ring (*i.e.*: (perfluorobutyl)benzo[*f*][1,3]oxazepine **18**). Fig. 2 shows the distinctive ^{1}H NMR spectra of **2a** and **18**, where upfield resonance shifts



Scheme 4 Rearrangement of **2** into **17** through intermediates **16**.

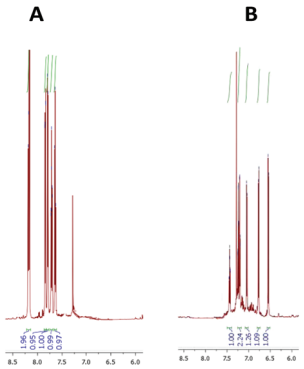


Fig. 2 A: ^{1}H NMR spectrum of **2a**. B: ^{1}H NMR spectrum of **18**.

of **18** as compared to **2a** indicate a loss of aromatic character (see the ESI† for the whole spectra). Given the high yield obtained for re-arranged **18**, this strategy can be regarded as a friendly alternative to the synthesis of 2-fluoroalkylated benzooxazepines.

We also subjected products **3** and **4** to the acid catalysis reaction (see the ESI†) and obtained products **19** and **20** in 58 and 77% yields, respectively (Scheme 5), according to a mechanism proposed in Scheme 4.

We carried out the deoxygenation reaction of product **2a** into 1-perfluorobutylisoquinoline **21** [25a] (ESI†) and at the same time the Rose Bengal-photocatalyzed perfluoroalkylation of isoquinoline **22** into **21** [25a] and then compared the regioselectivity and yield of the overall perfluoroalkylation reaction towards the synthesis of **21** starting from **1a** and from **22**, according to Scheme 6.

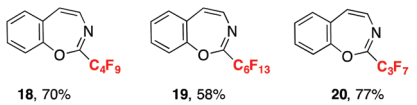
The overall yield of **21** starting from **1a** is 96%, whereas starting from **22** is exceedingly low (5%) as the reaction is poorly regioselective and also gives rise to perfluoroalkylated products at different ring positions. The higher activation of **1a** renders it a more appropriate substrate for the 1-regioselective perfluoroalkylation of the isoquinoline nucleus. The 2-hour reaction of **22** to yield **21** (Scheme 6) affords the same distribution of products as the 24-hour reaction, albeit with lower substrate conversion (see the ESI†). However, an alternative high-yielding perfluoroalkylation of quinoline at the 5-position has been reported in the literature through a radical cross-coupling reaction[18] and the 5-position-selective (per)fluoroalkylation of quinoline has also been informed.[25b] A very recent indirect fluoroalkylation strategy of isoquinoline at the 1-position has been disclosed through tandem radical cyclization of styryl-isocyanides.[25c]

We have next examined a series of simple pyridine-*N*-oxides substituted with electron donating or withdrawing groups and subjected them to the RB-photocatalyzed perfluoroalkylation reaction, in order to study the scope, regioselectivity and electron requirements of the substrates to undergo substitution with the R_F groups (Table 3).

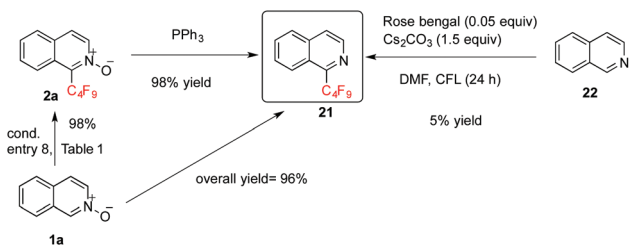
The visible-light photoreaction (RB-photocatalyzed) of 2-methylpyridine-*N*-oxide **23** with *n*-C_4F_9I gives 53% yield of 2-methyl-6-perfluorobutylpyridine-*N*-oxide **24** and 2-methyl-4-perfluorobutylpyridine-*N*-oxide **25** in 0.7 : 1 ratio. 3,5-Dimethylpyridine-*N*-oxide **26** affords a 48% yield of combined 3,5-dimethyl-2,4-bis-(perfluorobutyl)pyridine-*N*-oxide **27** and 3,5-dimethyl-2-perfluorobutylpyridine-*N*-oxide **28** in 1 : 0.3 ratio.

The Rose Bengal-photocatalyzed reaction of 3-methyl-pyridine-*N*-oxide **29** affords an overall low yield (9%) of substituted products at the 2-, 4-, and 6-positions with the C_4F_9 group (products **30–32**, respectively, Table 3).

When 4-methylpyridine-*N*-oxide **33** is made to react with *n*-C_4F_9I under RB-photocatalysis, a 30% yield of 4-methyl-2-perfluorobutyl-pyridine-*N*-oxide **34** (Table 3) is obtained as a

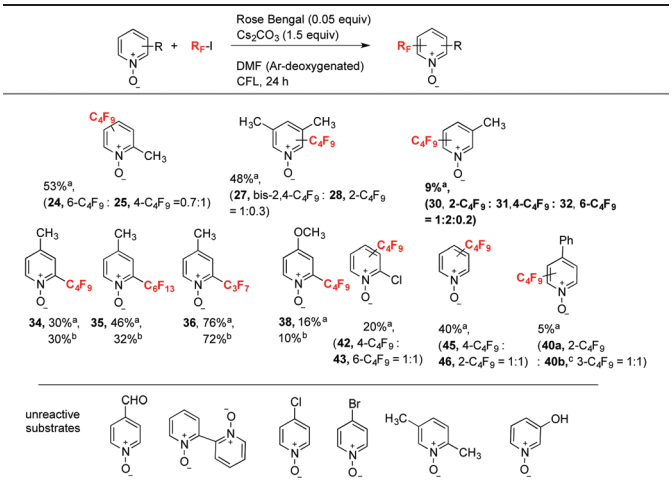


Scheme 5 Structures of fluoroalkylated benzooxazepine products **18**, **19**, and **20** from the acid-catalyzed transformation of **2**, **3**, and **4**.



Scheme 6 Overall ^{1}H NMR yields for the synthesis of 1-perfluorobutyl-isoquinoline **21** from **1a** as compared to the RB-photocatalyzed perfluoroalkylation of isoquinoline **22**.

Table 3 Photocatalyzed perfluoroalkylation of pyridine-*N*-oxides (0.6 mmol) in the presence of R_F–I (3 equiv.) and Cs_2CO_3 (1.5 equiv.) in Ar-deoxygenated DMF as solvent (24 h) at 25 °C



[a] Yields obtained by ^{1}H NMR integration of crude reaction mixtures after external standard added. [b] Isolated yields. [c] Product **40b** is a deoxygenated perfluoroalkylated product (*i.e.*: 3-perfluorobutyl-4-phenylpyridine).

single product. When **33** is subjected to reaction with *n*-$C_6F_{13}I$, a 46% yield of 2-perfluorohexyl-4-methylpyridine-*N*-oxide **35** is encountered. When C_3F_7I is made to react with **33** under reaction conditions from Table 2, a 76% yield of purified 2-perfluoropropyl-4-methylpyridine-*N*-oxide **36** is isolated.

4-Methoxypyridine-*N*-oxide **37** affords a low yield (16%) of 2-perfluorobutyl-4-methoxypyridine-*N*-oxide **38** when *n*-C_4F_9I is used. The radical C_4F_9 substitution of 4-phenylpyridine-*N*-oxide **39** (a core precursor of otamixaban[1]) gives a low yield (5%) of 2-perfluorobutyl-4-phenylpyridine-*N*-oxide **40a** and the deoxygenated product 3-perfluorobutyl-4-phenylpyridine **40b** in a 1 : 1 ratio. Apparently, the deoxygenation product **40b** is formed under the reaction conditions. 2-Chloropyridine-*N*-oxide **41** affords a 20% yield of isomers substituted at the 4-, and 6-positions (products **42** and **43**, respectively, in a 1 : 1ratio).

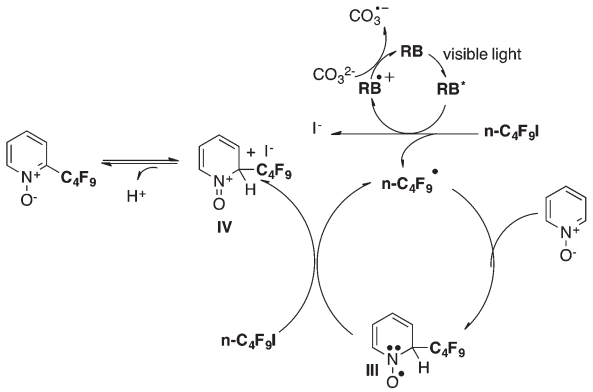
The unsubstituted pyridine-*N*-oxide **44** affords 2-perfluorobutylpyridine-*N*-oxide **45** and 4-perfluorobutylpyridine-*N*-oxide **46** in combined 40% isolated yield (in a 1 : 1 ratio). The vacant 4-position of Py–NO substituted with electron-donating groups is apparently the most reactive, followed by the 2-position (or 6-position), in agreement with classical polar substitutions. In electron-neutral pyridine-*N*-oxide **44**, both 2- and 4-positions are equally reactive.

The visible-light photoreaction (RB-photocatalyzed) of 4-formylpyridine-*N*-oxide **47** under the reaction conditions of Table 2 does not afford any substitution product. Use of other sacrificial donors (potassium oxalate[26]) or photocatalysts (anthraquinone-2-sulfonic acid[26] or Eosin Y) affords no substitution, probably due to the deactivation of the heteroaromatic nucleus and poor electron-availability.

The RB-photocatalyzed reaction of 2,2′-bipyridine-1,1′-dioxide **48**, 4-chloro-pyridine-*N*-oxide **49**, 2-bromo-pyridine-*N*-oxide **50** and 2,5-dimethylpyridine-*N*-oxide **51** failed to undergo substitution with R_F moieties under the conditions of Table 2. 3-Hydroxy-pyridine-*N*-oxide **52** also fails to undergo substitution by the C_4F_9 radical, probably on account of being in equilibrium with 1-hydroxypyridin-1-ium-3-olate,[27] which has a different electronic arrangement.

A reaction of isoquinoline-*N*-oxide, RB, and C_4F_9I in DMF was monitored by turning the lamp on and off at different intervals (Fig. S2†). This experiment reveals that the reaction is photocatalytic, and RB and light are needed through the entire reaction for the substitution product to accumulate.

We cautiously propose a radical mechanism (based on radical quenching experiments with TEMPO and *p*-DNB, entries 7,8, Table 1) where R_F radicals (R_F = C_4F_9, Scheme 7) are produced in an initiation event photocatalyzed by RB,[28] in an exergonic process (Table S1† for ΔG_{ET}). The excited triplet manifold of the photocatalyst is capable of reducing *n*-C_4F_9I to C_4F_9 radicals, and yields the radical cation of the photocatalyst (*i.e.*: $RB^{\bullet+}$) which in the presence of the carbonate ion is regenerated to the active catalyst species[23a] ($E\ CO_3^{\bullet-}/CO_3^{2-}$ = +1.23 ± 0.15 V, Table S1†). C_4F_9 radicals add to the Py–NO to afford the 2-perfluorobutyl-*N*-oxylpyridyl radical **III** (Scheme 7). Attempts to capture intermediate **III** in the presence of a H atom donor such as $(Me_3Si)_3SiH$ were unsuccessful. The three-electron π bonding intermediate **III** (2-perfluorobutyl-*N*-oxylpyridyl radical) undergoes an ET step to *n*-C_4F_9I, producing more C_4F_9 radicals and the 1-oxo-2-(perfluorobutyl)-1,2-dihydro-1λ⁴-pyridine cation **IV**, which by an ulterior proton transfer step (PT) to the base Cs_2CO_3 affords the C_4F_9-substituted pyridine-*N*-oxide. We are currently investigating the proposed mechanism through ESR spectroscopy and probe experiments.



Scheme 7 Proposed mechanistic pathway for the perfluoroalkylation of pyridine-*N*-oxide derivatives.

Experimental

For General considerations regarding substrates, reagents, solvents and compound characterization techniques, please see the ESI.†

Photocatalyzed reactions. General procedures

In a 3 mL-reaction vial provided with a screw-cap septum and microstirbar, 0.6 mmol of heteroaromatic-*N*-oxide substrate, 0.05 equivalents of photocatalysts (Rose Bengal or otherwise used), and 1.5 equivalents of Cs_2CO_3 are placed. Solvent DMF, 3 mL, is added and the mixture is de-oxygenated with a stream of dry Ar for 15 minutes. 3 equivalents of R_F–I (*n*-C_4F_9–I, *n*-C_6F_{13}–I, or C_3F_7–I) are then introduced through the septum with a microliter syringe. A brief deoxygenation with a slight stream of Ar is performed for an additional 3 minutes. The vessel is placed on a stir plate, and stirred vigorously for 24 h (at 22 °C) under constant illumination with a 60 Watt CFL (distance from the lamp: 3 cm, or 1 cm from a blue LED). After the reaction time elapsed, the mixture was extracted thrice with brine/$CHCl_3$, and the $CHCl_3$/DMF extracts evaporated *in vacuo*. The crude residues were analyzed using ^{1}H NMR, and an NMR integration of the product area is measured by use of an internal standard. The crude mixture was placed on a silica-gel preparative thin layer glass support, and eluted with $CHCl_3$: MeOH. In some cases, column chromatography was carried out instead of thin layer preparative silica-gel chromatography. The products reveal intensely under 254 nm-light illumination. The eluents were gathered, evaporated under

vacuum, and characterized using standard spectroscopic techniques (section VI, ESI†). Part of the product is complexed with the PC and remains absorbed inside the column or on the preparative thin layer chromatographic glass plate, as revealed by gathering the MeOH eluents, evaporated and characterized using ^{1}H NMR spectra. Isolated yields are based on mass obtained after purification protocols. NMR integration yields reflect the % of product(s) calculated with the aid of an external standard (benzotrifluoride for ^{19}F NMR spectra, and 1,3,5-trimethoxybenzene for ^{1} H NMR spectra).

Rearrangements of 1-perfluoroalkyl-isoquinoline-*N*-oxides into 2-(perfluoroalkyl)benzo[*f*][1,3]oxazepines 17

The 1-perfluoroalkyl-substituted-isoquinoline-*N*-oxides were isolated from the reaction mixtures, extracted thrice into $CHCl_3$/water, the organic layers gathered, dried over Na_2SO_4, and evaporated under vacuum. The crude reaction mixtures were mixed with powdered silica-gel (60-Mesh), chloroform added, and the solvent evaporated under vacuum. The 1-perfluoroalkyl-substituted -isoquinoline-*N*-oxides absorbed in the dried silica-gel were left for 48 h at room temperature in round bottom flasks. When time elapsed, the mixtures were solvent-extracted ($CHCl_3$) from the silica-mixture, concentrated and were chromatographed over preparative thin layer chromatographic glass plates employing $CHCl_3$/methanol as eluents. The fluorescent bands were scratched from the glass plates, collected, filtered off from $CHCl_3$, evaporated under vacuum and characterized using spectroscopic techniques (sections **VI** and **VII**, ESI†). The rearrangement reactions take place when products **2a–4** are left absorbed on silica-gel and do not arise from the secondary photochemical reaction (irradiation under prolonged reaction times) of products **2a–4**, as confirmed by 36-hour visible-light irradiation, purporting that formation of products **18–20** involves a dark (thermal acid-catalyzed) rearrangement.

For the photocatalyzed large scale reaction of isoquinoline-*N*-oxide **1a**, deoxygenation reaction of 1-perfluorobutyl-isoquinoline-*N*-oxide **2a** into 1-perfluorobutylisoquinoline **21**, synthesis of 5-nitro-isoquinoline-*N*-oxide **1b** and the Rose Bengal-photocatalyzed perfluoroalkylation of isoquinoline **22** see the ESI.†

Spectral characterization of compounds

1-Perfluorobutyl-isoquinoline-2-oxide **2a** (87 mg, 40%, ^{1}H NMR integrated yield: 98%). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 8.18 (1H, d, J = 8.7 Hz), 8.16 (1H, d, J = 7.1 Hz), 7.84 (1H, dd, J = 1.3, 8.1 Hz), 7.80 (1H, d, J = 7.0 Hz), 7.71 (1H, dt, J = 1.4, 7.0, 8.6 Hz), 7.64 (1H, t, J = 7.5 Hz). ^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 138.5, 133.8, 130.8, 129.2, 128.9, 128.5, 127.9, 127.2, 123.0. ^{19}F NMR (470.592 MHz, $CDCl_3$): δ (ppm): −80.65, −105.14, −119.52, −126.37. HRMS (ESI (+)): Mass calc. for $C_{13}H_6F_9NNaO$: 386.02034, found: 386.01979.

5-Nitro-1-perfluorobutyl-isoquinoline-2-oxide **2b** (56 mg, 23% isolated, ^{1}H NMR integrated yield: 25%). ^{1}H NMR: δ (ppm): 8.58 (1H, d, J = 7.6 Hz), 8.42 (1H, d, J = 9.0 Hz), 8.31 (1H, d, J = 7.8 Hz), 8.29 (1H, d, J = 7.7 Hz), 7.82 (1H, dd, J = 7.6, 9.0 Hz). ^{13}C NMR: δ (ppm): 146.51, 141.27, 133.95 (t, J = 25.9 Hz), 130.30, 129.56, 128.27, 125.00, 121.83, 120.61. ^{19}F NMR: δ (ppm): −80.53, −105.13, −119.61, −126.30. HRMS (ESI (+)): Mass calc. for $C_{13}H_6F_9N_2O_3$: 409.0156. Found: 409.0170. Mass cal. for $C_{13}H_5F_9N_2NaO_3$: 431.0156, found: 431.0167. A selective H–H decoupling experiment was performed in order to identify the doublet signals coupled to the resonance signal at 7.82 ppm (assigned to H7), this confirming that doublets at 8.42 ppm and 8.31 ppm are coupled to this triplet (*i.e.*: 7.82 ppm). A selective NOE experiment was also carried out in order to irrevocably identify the position of the nitro group on the aromatic ring, irradiating the doublet at 8.58 ppm (assigned to H4); an NOE was confirmed only with the signal at resonance 8.29 ppm (assigned to H3), supporting the 5-position of the nitro group in the ring.

1-Perfluorohexyl-isoquinoline-2-oxide **3** (139 mg, 50%, ^{1}H NMR integrated yield: 87%). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 8.15 (1H, d, J = 9.5 Hz), 8.14 (1H, d, J = 7.8 Hz), 7.81 (1H, d, J = 8.1 Hz), 7.77 (1H, d, J = 7.2 Hz), 7.68 (1H, t, J = 7.5 Hz), 7.60 (1H, t, J = 7.7 Hz). ^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 138.5, 133.7 (t, J = 24.0 Hz), 130.7, 128.8, 128.6, 128.4, 127.8, 127.2, 122.9 (t, J = 11.6 Hz). ^{19}F NMR (470.592 MHz, $CDCl_3$): δ (ppm): −80.99, −105.09, −118.75, −122.30, −122.53, −126.26. HRMS (ESI (+)): Mass calc. for $C_{15}H_7F_{13}NO$: 464.03201, found: 46403146, for: $C_{15}H_6F_{13}NNaO$: 486.01395, found: 486.01340.

1-Perfluoropropyl-isoquinoline-2-oxide **4** (85 mg, 45%, ^{1}H NMR integrated yield: 97%). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 8.17 (1H, d, J = 8.8 Hz), 8.15 (1H, d, J = 7.1 Hz), 7.84 (1H, d, J = 8.1 Hz), 7.79 (1H, d, J = 7.1 Hz), 7.71 (1H, td, J = 1.4, 8.6 Hz), 7.63 (1H, t, J = 7.5 Hz). ^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 138.4, 133.6 (t, J = 23.3 Hz), 130.8 (t, J = 1.9 Hz), 128.8, 128.6, 128.5, 127.9, 127.2, 122,9 (t, J = 11.5 Hz). ^{19}F NMR (470.592 MHz, $CDCl_3$): δ (ppm): −80.74, −105.81, −123.01. HRMS (ESI (+)): Mass calc. for $C_{12}H_7F_7NO$: 314,04159, found: 314.04104, for $C_{12}H_6F_7NNaO$: 336.02353, found: 336.02298.

2-Perfluorobutyl-quinoxaline-1-oxide **6** (108 mg, 50%, ^{1}H NMR integrated yield: 50%). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 8.92 (1H, s), 8.61 (1H, dd, J = 1.3, 8.7 Hz), 8.22 (1H, dd, J = 1.2, 8.4 Hz), 7.97 (1H, m, J = 1.4, 6.9, 8.7 Hz), 7.86 (1H, m, J = 1.3, 6.9, 8.5 Hz). ^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 146.4, 144.3 (t, J = 30 Hz), 138.0, 133.5, 131.2, 130.5, 129.6, 119.1. ^{19}F NMR (470.592 MHz, $CDCl_3$): δ (ppm): −80.67, −112.35, −120.30, −126.30. HRMS (ESI (+)): Mass calc. for $C_{12}H_6F_9N_2O$: 365.03364, found: 365.03309.

2-Perfluorohexyl-quinoxaline-1-oxide **7** (78 mg, 28%, ^{1}H NMR yield: 30%). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 8.92 (1H, s), 8.60 (1H, dd, J = 1.3, 8.7 Hz), 8.22 (1H, dd, J = 1.2, 8.5 Hz), 7.96 (1H, m, J = 1.4, 6.9, 8.4 Hz), 7.85 (1H, m, J = 1.3, 7.0, 8.6 Hz). ^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 146.3, 144.3 (t, J = 8.0 Hz), 138.0, 133.5, 131.2, 130.4, 129.6 (t, J = 25.1 Hz), 119.1. ^{19}F NMR(470.592 MHz, $CDCl_3$): δ (ppm): −80.83, −112.19, −119.48, −122.16, −122.56, −126.18. HRMS (ESI (+)): Mass calc. for $C_{14}H_6F_{13}N_2O$: 465.02725 found: 465.02725, for: $C_{14}H_5F_{13}N_2NaO$: 487.00920 found: 487.00865.

2-Perfluoropropyl-quinoxaline-1-oxide **8** (94 mg, 50%, ^{1}H NMR yield: 41%). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 8.92 (1H, s), 8.61 (1H, dd, J = 1.3, 7.4 Hz), 8.22 (1H, dd, J = 1.2, 8.5 Hz), 7.97 (1H, m, J = 1.4, 6.9, 8.4 Hz), 7.85 (1H, m, J = 1.3, 6.9, 8.5 Hz). ^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 146.4, 144.2, 137.9, 133.5, 131.2, 130.4, 129.4, 119.1. ^{19}F NMR (470.592 MHz, $CDCl_3$): δ (ppm): −80.83, −112.97, −123.70. HRMS (ESI (+)): Mass calc. for $C_{11}H_6F_7N_2O$: 315.03684, found: 315.03629.

4-Perfluorobutyl-8-isopropylquinoline-1-oxide **10** (34 mg, 15%, ^{1}H NMR yield: 12%). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 8.48 (1H, d, J = 6.6 Hz), 8.05 (1H, d, J = 8.7 Hz), 7.79 (1H, d, J = 7.4 Hz), 7.66 (1H, t, J = 8.1 Hz), 7.51 (1H, d, J = 6.7 Hz), 5.13 (1H, m, J = 6.8 Hz), 1.39 (6H, d, J = 6.8 Hz). ^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 145.2, 141.5, 136.3, 129.4, 129.3, 128.5, 123.2 (m, J = 4.2 Hz), 121.7 (t, J = 10.8 Hz), 121.2 (t, J = 23.2 Hz), 30.3, 24.8. ^{19}F NMR (470.592 MHz, $CDCl_3$): δ (ppm): −80.84, −105.32, −120.88, −125.58. HRMS (ESI (+)): Mass calc. for $C_{16}H_{13}F_9NO$: 406.08534, found: 406.08479, for $C_{16}H_{12}F_9NNaO$: 428.06729, found: 428.06674.

2-Perfluorobutyl-8-isopropylquinoline-1-oxide **11** (48 mg, 20%, ^{1}H NMR yield: 23%). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 7.75 (1H, dd, J = 1.5, 7.3 Hz), 7.72 (1H, dd, J = 1.5, 8.0 Hz), 7.70 (1H, d, J = 8.8 Hz), 7.64 (1H, t, J = 7.7 Hz), 7.54 (1H, d, J = 8.8 Hz), 5.07 (1H, h, J = 6.8 Hz), 1.37 (6H, d, J = 6.8 Hz). ^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 145.3, 143.6, 141.8, 133.2, 129.9, 128.6, 126.7, 124.6, 119.5 (t, J = 7.9 Hz), 30.1, 24.6. ^{19}F NMR (470.592 MHz, $CDCl_3$): δ (ppm): −80.53, −110.16, −118.12, −126.46. HRMS (ESI (+)): Mass calc. for $C_{16}H_{13}F_9NO$: 406.08534, found: 406.08492, for $C_{16}H_{12}F_9NNaO$: 428.06729, found: 428.06704.

2,4-bis(Perfluorobutyl)-8-isopropylquinoline-1-oxide **12** (88 mg, 24%, ^{1}H NMR yield: 25%). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 8.08 (1H, d, J = 8.6 Hz), 7.85 (1H, d, J = 7.4 Hz), 7.79 (1H, s), 7.75 (1H, t, J = 8.1 Hz), 4.83 (1H, h, J = 6.7 Hz), 1.38 (6H, d, J = 6.8 Hz). ^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 146.0, 143.1, 131.1, 129.7, 129.4, 123.3, 121.0, 120.3, 116.5, 30.5, 24.6. ^{19}F NMR (470.592 MHz, $CDCl_3$): δ (ppm): −80.55, −80.81, −105.41, −110.78, −118.70, −120.88, −125.54, −126.45. HRMS (ESI (+)): Mass calc. for $C_{20}H_{12}F_{18}NO$: 624.06315, found: 624.06260.

3-Perfluorobutylpyridazine-1-oxide **14** (30 mg, 15%, ^{1}H NMR yield: 20%). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 8.63 (1H, dd, J = 2.4, 4.5 Hz), 7.98 (1H, dd, J = 2.4, 8.2 Hz), 7.19 (1H, dd, J = 5.4, 8.2 Hz). ^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 152.8, 134.6 (t, J = 6.8 Hz), 114.6, 112.9, (t, J = 33.9 Hz). ^{19}F NMR (470.592 MHz, $CDCl_3$): δ (ppm): −80.64, −112.96, −119.62, −126.36. HRMS (ESI (+)): Mass calc. for $C_8H_3F_9N_2NaO$: 336.99994, found: 336.99978.

5-Perfluorobutylpyridazine-1-oxide **15** (32 mg, 16%, ^{1}H NMR yield: 20%). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 8.64 (1H, d, J = 3.1 Hz), 8.20 (1H, d, J = 6.7 Hz), 7.79 (1H, dd, J = 3.1, 6.9 Hz). ^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 148.4 (t, J = 7.1 Hz), 134.0, 132.1 (t, J = 7.1 Hz), 116.3 (t, J = 28.0 Hz). ^{19}F NMR (470.592 MHz, $CDCl_3$): δ (ppm): −80.90, −112.48, −122.62, −125.39. HRMS (ESI (+)): Mass calc. for $C_8H_3F_9N_2NaO$: 336.99994, found: 336.99939.

2-(Perfluorobutyl)benzo[f][1,3] oxazepane **18** (152 mg, 70%). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 6.55 (1H, d, J = 8.3 Hz), 6.77 (1H, d, J = 8.3 Hz), 7.05 (1H, d, J = 8.2 Hz), 7.20 (1H, dd, J = 1.8, 7.6 Hz), 7.24 (1H, dt, J = 1.1, 7.5 Hz), 7.44 (1H, dt, J = 1.8, 7.4 Hz). ^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 153.0, 143.3, 134.2, 132.0, 129.2, 128.1, 126.5, 125.0, 120.9. ^{19}F NMR (470.592 MHz, $CDCl_3$): δ (ppm): −80.91, −113.90, −122.17, −125.75. HRMS (ESI (+)): Mass calc. for $C_{13}H_6F_9NNaO$: 386.02034, found: 386.01982.

2-(Perfluorohexyl)benzo[f][1,3] oxazepine **19** (104 mg, 36%, ^{1}H NMR yield: 58%). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 7.44 (1H, td, J = 1.8, 7.2, 8.2 Hz), 7.24 (1H, td, J = 1.1, 7.5, 8.6 Hz), 7.20 (1H, dd, J = 1.8, 7.6 Hz), 7.04 (1H, d, J = 8.2 Hz), 6.77 (1H, d, J = 8.3 Hz), 6.55 (1H, d, J = 8.3 Hz). ^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 153.0, 141.4, 134.2, 132.0, 129.3, 129.2, 126.5, 125.0, 120.9. ^{19}F NMR (470.592 MHz, $CDCl_3$): δ (ppm): −80.85, −105.06, −118.71, −122.14, −122.46, −127.17. HRMS (ESI (+)): Mass calc. for $C_{15}H_7F_{13}NO$: 464.03201, found: 464.03146, for: $C_{15}H_6F_{13}NNaO$: 486.01395, found: 486.01340.

2-(Perfluoropropyl)benzo[f][1,3] oxazepine **20** (112 mg, 60%, ^{1}H NMR yield: 77%). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 7.45 (1H, td, J = 1.8, 7.2, 8.2 Hz), 7.25 (1H, td, J = 1.2, 7.5, 8.7 Hz), 7.22 (1H, dd, J = 1.8, 7.7 Hz), 7.05 (1H, d, J = 8.3 Hz), 6.78 (1H, d, J = 8.3 Hz), 6.55 (1H, d, J = 8.3 Hz). ^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 153.9, 144.3, 134.3, 132.0, 129.5, 129.2, 126.5, 125.0, 121.0. ^{19}F NMR (470.592 MHz, $CDCl_3$): δ (ppm): −80.47, −114.62, −125.70. HRMS (ESI (+)): Mass calc. for $C_{12}H_7F_7NO$: 314.04159, found: 314.04104, for $C_{12}H_6F_7NNaO$: 336.02353, found: 336.02298.

1-Perfluorobutyl-isoquinoline **21** (25 mg, 53%, ^{1}H NMR yield: 99%).[18] ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 8.70 (1H, d, J = 5.5 Hz), 8.40 (1H, d, J = 8.7 Hz), 7.97 (1H, dd, J = 1.2, 8.2 Hz), 7.90 (1H, d, J = 5.5 Hz), 7.80 (1H, dt, J = 1.0, 7.0, 8.1 Hz), 7.74 (1H, dt, J = 1.4, 8.6 Hz). ^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 146.1(t, J = 24 Hz), 141.0, 137.3, 130.6, 128.8, 127.7, 126.4, 124.9 (m, J = 4.5 Hz), 124.6. ^{19}F NMR (470.592 MHz, $CDCl_3$): δ (ppm): −80.91, −106.27, −121.02, −125.04.

6-Perfluorobutyl-2-methyl-pyridine-1-oxide **24** (21 mg, 21%, ^{1}H NMR yield: 22%). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 7.59 (1H, dd, J = 2.0, 8.1 Hz), 7.48 (1H, dd, J = 1.9, 7.8 Hz), 7.29 (1H, t, J = 7.8 Hz), 2.56 (3H, s). ^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 151.7, 139.0, 129.1, 124.3, 123.7, 17.6. ^{19}F NMR (470.592 MHz, $CDCl_3$): δ (ppm): −80.59, −110.52, −118.61, −126.48. HRMS (ESI (+)): Mass calc. for $C_{10}H_6F_9NNaO$: 350.02034, found: 350.01979.

4-Perfluorobutyl-2-methylpyridine-1-oxide **25** (56 mg, 30%, ^{1}H NMR yield: 32%). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 8.36 (1H, d, J = 6.8 Hz), 7.48 (1H, d, J = 2.6 Hz), 7.36 (1H, dd, J = 2.6, 6.9 Hz), 2.58 (3H, s). ^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 150.0, 139.7, 124.5, 121.6, 121.5, 17.9. ^{19}F NMR (470.592 MHz, $CDCl_3$): δ (ppm): −80.96, −112.12, −122.69, −125.49. HRMS (ESI (+)): Mass calc. for $C_{10}H_6F_9NNaO$: 350.02034, found: 350.01994.

(2,4-Diperfluorobutyl)-3,5-dimethylpyridine-1-oxide **27** (44 mg, 30%, ^{1}H NMR yield: 37%). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 8.06 (1H, s), 2.51 (3H, q, J = 4.5 Hz), 2.46 (3H, t, J = 4.8 Hz). ^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 141.4, 141.0, 139.4, 134.0, 124.5, 19.4, 16.5. ^{19}F NMR (470.592 MHz, $CDCl_3$): δ (ppm): −80.56, −80.75, −98.06, −103.43, −118.15, −119.84, −125.89, −126.32. HRMS (ESI (+)): Mass calc. for $C_{15}H_8F_{18}NO$: 560.03185, found: 560.03179.

2-Perfluorobutyl-3,5-dimethylpyridine-1-oxide **28** (14 mg, 7%, ^{1}H NMR yield: 11%). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 8.03 (1H, s), 6.96 (1H, s), 2.48 (3H, t, J = 5.6 Hz), 2.32 (3H, s). ^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 141.5, 139.5, 138.4, 138.5, 130.4, 20.5 (t, J = 8.7 Hz), 18.0. ^{19}F NMR (470.592 MHz, $CDCl_3$): δ (ppm): −80.57, −105.02, −118.90, −126.52. HRMS (ESI (+)): Mass calc. for $C_{11}H_9F_9NO$: 342.05404, found: 342.05349.

2-Perfluorobutyl-3-methylpyridine-1-oxide **30** (6 mg, 3%). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 8.19 (1H, bs); 7.29 (1H, t, J = 8.3 Hz); 7.15 (1H, d, J = 8.0 Hz); 2.53 (3H, t, J = 2.9 Hz). ^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 139.6, 139.5, 129.0, 127.2, 125.3, 20.3 (t, J = 0.06 Hz). ^{19}F NMR (470.592 MHz, $CDCl_3$): δ (ppm): −80.57, −105.34, −118.81, −126.51. HRMS (ESI (+)): Mass calc. for $C_{10}H_6F_9NNaO$: 350.02034, found: 350.01999.

4-Perfluorobutyl-3-methylpyridine-1-oxide **31** (36 mg, 18%). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 8.18 (2H, bs), 8.17 (2H, bs), 7.40 (1H, d, J = 7.3 Hz), 2.44 (3H, t, J = 2.9 Hz). ^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 141.3, 137.0, 136.7, 125.3, 124.4, 17.3. ^{19}F NMR (470.592 MHz, $CDCl_3$): δ (ppm): −80.91, −108.15, −121.90, −125.71. HRMS (ESI (+)): Mass calc. for $C_{10}H_6F_9NNaO$: 350.02034, found: 350 02001.

6-Perfluorobutyl-3-methylpyridine-1-oxide **32** (10 mg, 5%). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 8.16 (1H, s), 7.56 (1H, d, J = 8.3 Hz), 7.18 (1H, d, J = 8.3 Hz), 2.39 (3H, s). ^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 141.6, 140.2, 125.9, 125.6, 18.2. ^{19}F NMR (470.592 MHz, $CDCl_3$): δ (ppm): −80.64, −110.97, −119.31, −126.43. HRMS (ESI (+)): Mass calc. for $C_{10}H_6F_9NNaO$: 350.02034, found: 350.01996.

2-Perfluorobutyl-4-methylpyridine-1-oxide **34** (60 mg, 30%, ^{1}H NMR yield: 30%). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 8.20 (1H, d, J = 6.6 Hz), 7.47 (1H, d, J = 1.9 Hz), 7.26 (1H, dd, J = 2.4, 6.6 Hz), 2.44 (3H, s). ^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 145.8, 141.1, 136.4, 129.4, 127.1 (d, J = 7.4 Hz), 20.4. ^{19}F NMR (470.592 MHz, $CDCl_3$): δ (ppm): −80.62, −111.11, −119.09, −126.37. HRMS (ESI (+)): Mass calc. for $C_{10}H_6F_9NNaO$: 350.02034, found: 350.01989.

2-Perfluorohexyl-4-methylpyridine-1-oxide **35** (92 mg, 32%, ^{1}H NMR yield: 46%). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 8.19 (1H, d, J = 6.6 Hz), 7.47 (1H, d, J = 2.5 Hz), 7.27 (1H, dd, J = 2.6, 6.8 Hz), 2.44 (3H, s). ^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 147.8, 141.1, 136.2, 129.5, 127.0 (t, J = 7.4 Hz), 20.4. ^{19}F NMR (470.592 MHz, $CDCl_3$): δ (ppm): −80.78, −110.90, −118.23, −122.14, −122.45, −126.17. HRMS (ESI (+)): Mass calc. for $C_{12}H_7F_{13}NO$: 428.03201. Mass found: 428.03146. Mass calc. for $C_{12}H_6F_{13}NNaO$: 450.01395, found: 450.01340.

2-Perfluoropropyl-4-methylpyridine-1-oxide **36** (126 mg, 72%, ^{1}H NMR yield: 76%). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 8.18 (1H, d, J = 6.6 Hz), 7.46 (1H, d, J = 2.5 Hz), 7.26 (1H, dd, J = 2.5, 6.8 Hz), 2.43 (3H, s). ^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 140.9, 138.0 (t, J = 27.9 Hz), 136.0, 129.4, 126.8, 20.3. ^{19}F NMR (470.592 MHz, $CDCl_3$): δ (ppm): −81.03, −111.66, −122.45. HRMS (ESI (+)): Mass calc. for $C_9H_7F_7NO$: 278.04159, found: 278.04104.

2-Perfluorobutyl-4-methoxypyridine-1-oxide **38** (20 mg, 10%, ^{1}H NMR yield: 16%). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 8.22 (1H, d, J = 7.3 Hz), 7.18 (1H, d, J = 3.5 Hz), 7.00 (1H, dd, J = 3.4, 7.2 Hz), 394 (3H, s). ^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 156.7, 142.6, 114.8, 112.1, 56.5. ^{19}F NMR (470.592 MHz, $CDCl_3$): δ (ppm): −80.60, −110.86, −118.77, −126.34. HRMS (ESI (+)): Mass calc. for $C_{10}H_7F_9NO_2$: 344.03331, found: 344.03276.

2-Perfluorobutyl-4-phenyl-pyridine-1-oxide **40a** (9 mg, 4%). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 8.34 (1H, d, J = 6.8 Hz), 7.87 (1H, d, J = 2.7 Hz), 7.68 (1H, dd, J = 2.7, 6.7 Hz), 7.62 (2H, d, J = 7.3 Hz), 7.55 (2H, t, J = 7.0 Hz), 7.51 (1H, t, J = 7.3 Hz). ^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 141.8, 137.7, 135.4, 129.7, 129.5, 126.4, 126.2, 124.2 (t, J = 7.3 Hz), 114.0. ^{19}F NMR (470.592 MHz, $CDCl_3$): δ (ppm): −80.60, −111.01, −119.10, −126.30. HRMS (ESI (+)): Mass calc. for $C_{15}H_9F_9NO$: 390.05404, found: 390.05398.

3-Perfluorobutyl-4-phenyl-pyridine **40b** (2 mg, 1%). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 8.83 (1H, d, J = 5.0 Hz), 7.92 (1H, bs), 7.73 (1H, dd, J = 1.7, 5.1 Hz), 7.69 (2H, dd, J = 1.7, 6.7 Hz), 7.55 (2H, t, J = 6.9 Hz), 7.54 (1H, t, J = 6.9 Hz). ^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 150.5, 150.1, 136.9, 129.9, 129.4, 127.1, 124.2, 124.1, 120.3. ^{19}F NMR (470.592 MHz, $CDCl_3$): δ (ppm): −80.91, −114.08, −122.58, −125.62. HRMS (ESI (+)): Mass calc. for $C_{15}H_9F_9N$: 374.05913, found: 374.05858.

4-Perfluorobutyl-2-chloropyridine-1-oxide **42** (12 mg, 6%, ^{1}H NMR yield: 10%). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 8.44 (1H, d, J = 6.9 Hz), 7.73 (1H, J = 2.6 Hz), 7.41 (1H, dd, J = 2.6, 6.9 Hz). ^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 147.9, 140.8, 140.4, 125.4, 121.8. ^{19}F NMR (470.592 MHz, $CDCl_3$): δ (ppm): −80.90, −112.07, −122.51, −125.42. HRMS (ESI (+)): Mass calc. for $C_9H_4ClF_9NO$: 347.98377, found: 347.98364.

6-Perfluorobutyl-2-chloropyridine-1-oxide **43** (22 mg, 10%, ^{1}H NMR yield: 10%). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 7.70 (1H, dd, J = 2.6, 8.1 Hz), 7.62 (1H, dd, J = 2.0, 8.1 Hz), 7.31 (1H, t, J = 8.1 Hz).

4-Perfluorobutyl-pyridine-1-oxide **45** (10 mg, 10%, ^{1}H NMR yield: 20%). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 8.31 (2H, d, J = 6.9 Hz), 7.49 (2H, d, J = 7.1 Hz). ^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 139.7, 124.3. ^{19}F NMR (470.592 MHz, $CDCl_3$): δ (ppm): −80.63, −11.30, −119.19, −126.38. HRMS (ESI (+)): Mass calc. for $C_9H_5F_9NO$: 314.02274, found: 314.02221.

2-Perfluorobutyl-pyridine-1-oxide **46** (10 mg isolated 10%, ^{1}H NMR yield: 20%). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 8.29 (1H, d, J = 6.6 Hz), 7.68 (1H, dd, J = 2.1, 8.1 Hz), 7.47 (1H, ddd, J = 2.0, 6.6, 8.1 Hz), 7.36 (1H, t, J = 7.9 Hz). ^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 141.8, 139.2, 128.7, 128.6, 121.1. ^{19}F NMR (470.592 MHz, $CDCl_3$): δ (ppm): −80.94, −122.20, −122.71, −125.43. HRMS (ESI (+)): Mass calc. for $C_9H_5F_9NO$: 314.02274, found: 314.02219.

Conclusions

In summary, we have successfully achieved a convenient and environmentally benign method for the direct perfluoroalkylation of pyridine-, diazine-, and quinoline-*N*-oxide derivatives through visible light photocatalysis with the inexpensive laboratory dye Rose Bengal and commercially available R_F–I. These are the first examples of the direct synthesis of perfluoroalkyl-substituted heteroaromatic-*N*-oxides. The reactions proceeded in good yields, even in sub-gram scale. Also, a convenient strategy to access 2-(perfluoroalkyl)benzo[*f*][1,3]oxazepines is reported. As demonstrated in Scheme 5, the regioselectivity and yield of perfluoroalkylation reactions from heterocyclic *N*-oxides render these substrates as more convenient starting materials than their non-oxide heterocyclic analogs.

Conflicts of interest

We declare no conflicts of interest.

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Notes and references

1 A. M. Mfuh and O. V. Larionov, *Curr. Med. Chem.*, 2015, **22**, 2819.
2 G. R. Zins, *Clin. Dermatol.*, 1988, **6**, 132.
3 K. R. Guertin and Y. M. Choi, *Curr. Med. Chem.*, 2007, **14**, 2471.
4 (*a*) A. Palani, S. Shapiro, H. Josien, T. Bara, J. W. Clader, W. J. Greenlee, K. Cox, J. M. Strizki and B. M. Baroudy, *J. Med. Chem.*, 2002, **45**, 3143; (*b*) J. R. Tagat, S. W. McCombie, R. W. Steensma, S.-I. Lin, D. V. Nazareno, B. Baroudy, N. Vantuno, S. Xu and J. Liu, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 2143.
5 (*a*) A. R. English and C. M. Dunega, *Proc. Soc. Exp. Biol. Med.*, 1970, **133**, 398; (*b*) W. Suter, A. Rosselet and F. Knusel, *Antimicrob. Agents Chemother.*, 1978, **13**, 770; (*c*) C. Zhu, M. Yi, D. Wei, X. Chen, Y. Wu and X. Cui, *Org. Lett.*, 2014, **16**, 1840; (*d*) R. Kumar, I. Kumar, R. Sharma and U. Sharma, *Org. Biomol. Chem.*, 2016, **14**, 2613; (*e*) J.-P. Wan and Y. Jing, *Beilstein J. Org. Chem.*, 2015, **11**, 2209.
6 (*a*) W.-M. Zhang, J.-J. Dai, J. Xu and H.-J. Xu, *J. Org. Chem.*, 2017, **82**, 2059; (*b*) H. Andersson, F. Almqvist and R. Olsson, *Org. Lett.*, 2007, **9**, 1335; (*c*) G. Deng, K. Ueda, S. Yanagisawa, K. Itami and C.-J. Li, *Chem. – Eur. J.*, 2009, **15**, 333; (*d*) B. Xiao, Z.-J. Liu, L. Liu and Y. Fu, *J. Am. Chem. Soc.*, 2013, **135**, 616; (*e*) B. Yao, R.-J. Song, Y. Liu, J.-H. Li, M.-K. Wang, R.-Y. Tang, X.-G. Zhang and C.-L. Deng, *Adv. Synth. Catal.*, 2012, **354**, 1890–1896.
7 S. Yu, H. Leng Sang and S. Ge, *Angew. Chem., Int. Ed.*, 2017, **56**, 15896.
8 (*a*) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432; (*b*) *Fluorine in Medicinal Chemistry and Chemical biology*, ed. I. Ojima, Wiley-Blackwell, Chichester, 2009; (*c*) K. Matsuzaki, T. Hiromura, H. Amii and N. Shibata, *Molecules*, 2017, **22**, 1130; (*d*) H. Ji, H.-q. Ni, P. Zhi, Z.-w. Xi, W. Wang, J. j. Shi and Y.-m. Shen, *Org. Biomol. Chem.*, 2017, **15**, 6014; (*e*) B. Janhsen and A. Studer, *J. Org. Chem.*, 2017, **82**, 11703; (*f*) A. Prieto, R. Melot, D. Bouyssi and N. Monteiro, *ACS Catal.*, 2016, **6**, 1093; (*g*) J. Xie, T. Zhang, F. Chen, N. Mehrkens, F. Rominger, M. Rudolph and S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2016, **55**, 2934; (*h*) J. Xie, J. Li, T. Wurm, V. Weingand, H.-L. Sung, F. Rominger, M. Rudolph and A. S. K. Hashmi, *Org. Chem. Front.*, 2016, **3**, 841.
9 (*a*) T. Nishida, H. Ida, Y. Kuninobu and M. Kanai, *Nat. Commun.*, 2014, **5**, 3387; (*b*) M. Nagase, Y. Kuninobu and M. Kanai, *J. Am. Chem. Soc.*, 2016, **138**, 6103.
10 D. E. Stephens, G. Chavez, M. Valdes, M. Dovalina, H. D. Arman and O. V. Larionov, *Org. Biomol. Chem.*, 2014, **12**, 6190.
11 (*a*) Y. Kuninobu, M. Nagase and M. Kanai, *Angew. Chem., Int. Ed.*, 2015, **54**, 10263; (*b*) M. Makosza and R. Loska, *Z. Naturforsch., B: J. Chem. Sci.*, 2008, **63**, 363.
12 B. Jiang, X. N. Xiong and C. G. Yang, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 475.
13 J. W. Beatty, J. J. Douglas, R. Miller, R. C. Mcatee, K. P. Cole and C. R. J. Stephenson, *Chemistry*, 2016, **1**, 456.
14 W. Jo, J. Kim, S. Choi and S. H. Cho, *Angew. Chem., Int. Ed.*, 2016, **55**, 9690.
15 B. Lecointre, R. Azzouz and L. Bischoff, *Tetrahedron Lett.*, 2014, **55**, 1913.
16 (*a*) A. M. Starosotnikov, V. V. Nikol, A. N. Borodulya, V. V. Kachala, M. A. Bastrakov, V. N. Solkan and S. A. Shevelev, *Asian J. Org. Chem.*, 2016, **5**, 685; (*b*) L. Beutin, E. Preller and B. Kowalski, *Antimicrob. Agents Chemother.*, 1981, **20**, 336.
17 O. Buchardt, J. J. Christensen, C. Lohse, J. J. Turner and I. R. Dunkin, *J. Chem. Soc., Chem. Commun.*, 1977, 837.
18 J. W. Beatty, J. J. Douglas, R. Miller, R. C. Mcatee, K. P. Cole and C. R. J. Stephenson, *Chemistry*, 2016, **1**, 456.
19 (*a*) A. V. Ryzhakov, *Russ. J. Gen. Chem.*, 2001, **72**, 729; (*b*) A. V. Ryzhakov, O. O. Alekseeva and L. L. Rodina, *Russ. J. Org. Chem.*, 2000, **36**, 1039.
20 (*a*) Y. V. Geletii, V. V. Strelets, V. Y. Shafirovich and A. E. Shilov, *Heterocycles*, 1989, **28**, 677; (*b*) T. Endo, S. Saeki and M. Hamana, *Chem. Pharm. Bull.*, 1981, **29**, 3105.
21 S. Barata-Vallejo, M. Martín Flesia, B. Lantaño, J. E. Argüello, A. B. Peñéñory and A. Postigo, *Eur. J. Org. Chem.*, 2013, 998.

22 (*a*) M. Slodowicz, S. Barata-Vallejo, A. Vázquez, N. Sbarbati Nudelman and A. Postigo, *J. Fluorine Chem.*, 2012, **135**, 137; (*b*) T. Chen, Y. Guo, K. Sun, L.-Z. Wu, W.-Q. Liu, C. Liu, Y. Huang and Q.-Y. Chen, *Org. Chem. Front.*, 2018, **5**, 1045; (*c*) Y. Wang, J. Wang, G.-X. Li, G. He and G. Chen, *Org. Lett.*, 2017, **19**, 1442.

23 (*a*) Q. Guo, M. Wang, H. L. Liu, R. Wang and Z. Xu, *Angew. Chem., Int. Ed.*, 2018, **57**, 4747; (*b*) S. Barata-Vallejo, D. E. Yerien and Al Postigo, *Eur. J. Org. Chem.*, 2015, 7869; (*c*) S. P. Pitre, C. D. McTiernan and J. C. Scaiano, *Acc. Chem. Res.*, 2016, **49**, 1320; (*d*) L. Beutin, E. Preller and B. Kowalski, *Antimicrob. Agents Chemother.*, 1981, **20**, 336; (*e*) E. Ochiai Morio Ikehara, *J. Pharm. Soc. Jpn.*, 1953, **73**, 666.

24 (*a*) A. Albini, G. F. Bettinetti and G. Minoli, *Org. Synth.*, 1983, **61**, 98; (*b*) A. Albini, G. F. Bettinetti and G. Minoli, *Tetrahedron Lett.*, 1979, **39**, 3761; (*c*) T. Damiano, D. Morton and A. Nelson, *Org. Biomol. Chem.*, 2007, **5**, 2735; (*d*) O. Buchardt, C. L. Pedersen and X. Harri, *J. Org. Chem.*, 1972, **37**, 3592; (*e*) N. Hata and A. Yagi, *Chem. Lett.*, 1983, 309.

25 (*a*) H. Uno, S.-i. Okada and H. Suzuki, *J. Heterocycl. Chem.*, 1991, **28**, 341; (*b*) J. Xu, L. Qiao, B. Ying, X. Zhu, C. Shenb and P. Zhang, *Org. Chem. Front.*, 2017, **4**, 1116; (*c*) F. Ding, Y. Jiang, K. Lin and L. Shi, *Org. Biomol. Chem.*, 2018, **16**, 1812.

26 M. Rosario Torviso, D. Mansilla, S. Garcia, B. Lantaño, S. Barata-Vallejo and A. Postigo, *J. Fluorine Chem.*, 2017, **197**, 42.

27 G. N. Rodionova, R. E. Lokhov and K. M. Dyumaev, *Chem. Heterocycl. Compd.*, 1972, **8**, 876.

28 D. A. Armstrong, W. L. Waltz and A. Rauk, *Can. J. Chem.*, 2006, **84**, 1614.