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Regiodivergent C5 & C8- visible light induced C-H functionalisation of quinolines under metal-, photosensitizer- and oxidant-free conditions

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Abstract. A general strategy towards C5 and C8 selective perfluoroalkylation of quinoline derivatives is described. This exceptionally mild radical transformation, compatible with a large panel of substrates, does not require any transition metal catalysts or oxidants. Outstandingly, visible light photoinduction using simple household bulbs, in absence of a photosensitizer, is a unique activation mode. Further importance of this reaction relays on its capacity to functionalise selectively both C5 and C8-quinoline positions. This transformation, perfectly fulfilling green-chemistry requirements, allows truly practical and straightforward access to a variety of unprecedented functionalised amino- and amidoquinolines skeletons, presenting attractive features for medicinal and agrochemical industry.

Keywords: quinoline; C-H functionalisation; visible light; perfluoroalkylation; photocatalysis

Quinoline, one of the most important *N*-heterocyclic aromatic compounds, is present in numerous natural products[1] and is largely exploited in both pharmaceutical and agrochemical industry. Quinoline-based compounds exhibit indeed anti-malarial, anti-bacterial, anti-fungal, anti-asthmatic, anti-hypertensive, anti-inflammatory, anti-tumoral and immune depressing properties.[2] Their applications as food colorants, pH indicators, OLED phosphorescent complexes and conjugate polymers, further underline their unique features. Thus the synthesis of complex quinoline-derived scaffolds by means of a late-stage functionalisation of simple, commercially available and inexpensive precursors is particularly tempting.[3] Due to the intrinsic reactivity of the heterocyclic moiety, a large panel of methods allowing C2, C3 and C4-quinoline functionalisation has been intensively studied (Figure 1A). Indeed, amongst others, C2-functionalisaton is commonly achieved *via* radical Minisci reaction,[4] while C3[5] and C4[6] diversification may account from metal-catalyzed transformations. In contrast, regioselective modifications of the carbocyclic ring have only recently received a great deal of attention. In particular, over the last two years, many research groups focused on selective C5 functionalisation of 8-amidoquinolines (Figure 1B). Commonly, transition metals such as copper,[7] nickel[8] or iron[9] have been employed to perform various C-X couplings,[10] under frequently harsh reaction conditions (high temperature, use of strong oxidants). Very recently, a few additional examples of metal-free transformations have been disclosed and a comparable reactivity can be achieved in the presence of strong oxidants like PIDA, PIFA or oxone, hampering their synthetic utility and versatility.[11] Indeed, the bicoordinating capacity of 8-amidoquinoline renders this substrate perfectly suited for remote C5-functionalisation but the same reaction using synthetically more attractive unprotected 8-aminoquinolines is much more challenging. Furthermore, direct couplings at C8-position are elusive. The rare selective transformations require expensive Ir- or Rh-based catalysts (Figure 1C)[12] and very sporadic radical couplings are low yielding and unselective.[13]

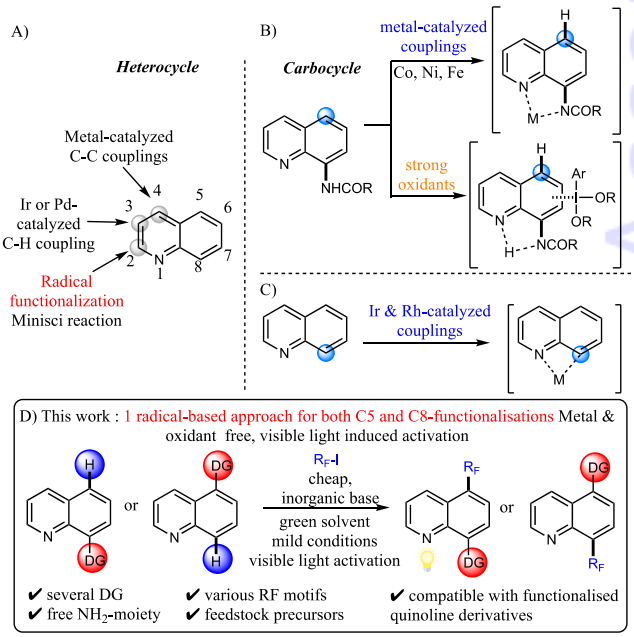

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Figure 1. Selective C-H functionalisation of quinolines.

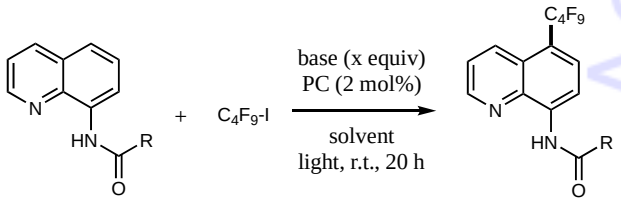
Following this analysis, we endeavored on designing an alternative, general approach, based on radical-type reactivity and suitable for both C5 and C8-selective C-H functionalisation of quinolines, under eco-compatible reaction conditions. The major challenge to undertake while targeting such transformation is therefore to overcome the intrinsic reactivity of the quinoline scaffold, orientating radical couplings at C2 position. Our working hypothesis surmised that a radical functionalisation of quinolines might be triggered towards carbocyclic ring by introducing a relevant substituent. Regardless position of the substituent, a similar type quinoline radical intermediate would be accessed and a subsequent oxidation would deliver the expected, regiosiomeric products. Regarding, on one hand, the relative stability of perfluoalkyl radicals ($R_F^{\cdot}$) and their convenient generation under visible-light irradiation, and on the other hand, unique biological properties of the fluorinated molecules, we have therefore chosen a perfluoroalkylation as a test reaction to develop the desired poly-regioselective functionalisation of quinolines.

We report herein an original synthetic route towards C5- and C8-perfluoroalkylated quinoline derivatives, unique molecular scaffolds with appealing features for pharmaceutical and agrochemical industry (Figure 1D).[14] This method implies exclusively visible-light photoactivation using simple household bulbs (simple "home-made" setup with commercially available two bulbs to insure convenience of this work), in absence of not only transition metals and oxidants but also a photosensitizer. Importantly, although several different strategies are already known to prepare fluorinated quinolines bearing the fluorine motifs at C2, C3 or C4 positions,[15] only very few pathways enabling installation of R_F motifs at C5 position has been described up to now. [11e],[16]-[19] Remarkably, synthesis of C8-perfluoroalkylated quinolines has been an uncharted field till this work. Finally, the use of polyfluoroalkane iodides further highlights the synthetic value of this reaction as such coupling partners bring not only the versatility (access to an array of scaffolds) but are also largely available and inexpensive fluorinated building blocks considered as raw materials.[20]

Our experimental work debuted by performing a coupling between *N*-(quinolin-8-yl)cyclopentanecarboxamide (**1A**) and nonafluoro-4-iodobutane (**2a**), in the presence of Ag_2CO_3 used as mild oxidant and iodine scavenger in DMAc and under irradiation with two household bulbs (Table 1, entry 1). The desired product was obtained albeit in low, 18% yield. Replacing Ag_2CO_3 by AgOAc and performing the reaction in DCM resulted in full conversion of **1A** with 85% yield of **3Aa** (entry 2), but significantly lower productivity was observed when employing other acetate source (entry 3). Despite its effectiveness, the use of a stoichiometric amount of silver salt obviously hampers the synthetic value of the reaction. Targeting, hence, a more eco-compatible transformation, we assumed that generation of the quinoline radicals should also be feasible via a photocatalytic process while using only a trace amount of a photosensitizer. Accordingly, the potency of an Ir-based photocatalyst (PC1: $[Ir\{dF(CF_3)ppy\}_2(dtbbpy]PF_6$) and an organic photocatalyst (PC2: Fukuzumi reagent: 9-mesityl-10-methylacridiniumperchlorate) to fulfil this role was investigated. A moderately efficient synthesis of **3Aa** was achieved when using PC1 together with K_2HPO_4 in MeOH or acetone but the desired product was isolated in 91% yields in mixed solvents (entries 4-6). The less expensive and more reliable organic photosensitizer (PC2) also performed quite well in combination with K_2CO_3 base and MeOH/acetone medium (entry 7). Unexpectedly, the reaction conducted in the absence of photosensitizer delivered **3Aa** in 82% yield (entry 8), but omission of the base or light irradiation (reaction in dark) completely suppressed the reactivity. Further improvement was reached with acetone as solvent. Noteworthy, unchanged outcome of the reaction in presence of extra pure K_2CO_3 supports the truly metal-free nature of this coupling (entry 9). Finally, the impact of the light source was investigated.[21] Only trace amount of the product was formed while using blue LED as a light source (entry 10) and a significantly lower efficiency of the coupling was observed while irradiating the reaction mixture with a single household bulb (entry 11). Furthermore, while using single light household bulb equipped with a cutoff $\lambda > 455$ nm filter, no reactivity was observed, whereas using $\lambda > 370$ nm filter, **3Aa** was delivered in 34% yield (entries 12-13).[22] Finally, high conversion of the starting material into the desired product could also be achieved while using UV-A irradiation although some degradation of the product was detected (entry 14, for details see SI).

For reasons of convenience and targeting a truly synthetically useful transformation, the following work was pursued using the standard setup with two 26W household bulbs.

Table 1. Optimisation of C5-functionalisation of **1A**.[a)]



1A (R = cyclopentane) **2a** **3Aa / 3Ba**
1B (R = Ph)

Entry	1	Base (x equiv)	Solvent	PC	Yield (%)[b]
1	1A	Ag_2CO_3 (1)	DMAc	-	18
2	1A	AgOAc (1.5)	DCM	-	85
3	1A	KOAc (1)	DCM	-	24
4	1A	K_2HPO_4 (2)	MeOH	PC1	66

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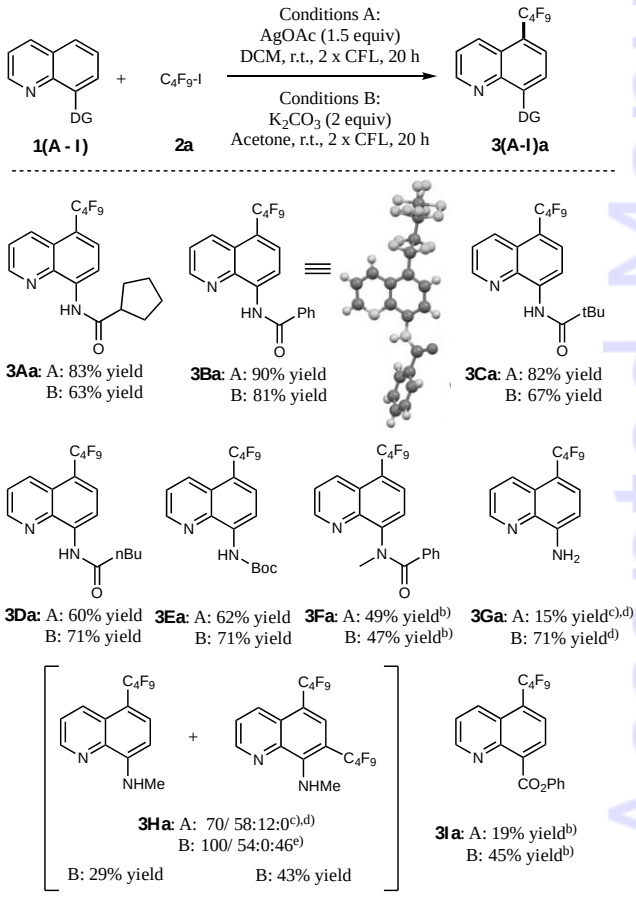
5	1A	K_2HPO_4 (2)	Acetone	PC1	79
6	1A	K_2HPO_4 (2)	Acetone/ MeOH	PC1	91
7	1A	K_2CO_3 (2)	Acetone/ MeOH	PC2	71
8	1A	K_2CO_3 (2)	Acetone/ MeOH	-	82, 6[c)]
9	1A	K_2CO_3 (2)	Acetone	-	89, 0,[d)] 93[e)]
10[f)]	1B	K_2CO_3 (2)	Acetone	-	traces
11[g)]	1B	K_2CO_3 (2)	Acetone	-	22
12[h)]	1B	K_2CO_3 (2)	Acetone	-	0
13[i)]	1B	K_2CO_3 (2)	Acetone	-	34
14[j)]	1B	K_2CO_3 (2)	Acetone	-	50

[a)] reaction Conditions: **1A** (0.1 mmol), **2a** (5 equiv), base (x equiv), PC (2 mol%), solvent (0.2 M), r.t., Ar_2, 2 × 26 W CFL for 20 h; [b)] GC yield with dodecane as internal standard; [c)] absence of base; [d)] reaction performed in dark at 37 °C; [e)] reaction performed with extra pure K_2CO_3; [f)] reaction performed using 23W Blue Led strips; [g)] reaction performed using 1 x 26W CFL; [h)] reaction performed using 1 x 26W CFL with filter $\lambda > 455$ nm; [i)] reaction performed using 1 x 26W CFL with filter $\lambda > 370$ nm; [j)] reaction performed using UV-A pen (λ = 315-400 nm; λ_{max} = 365 nm).

This optimisation study hence allowed us to define two types of reaction conditions to perform the desired coupling; **conditions A** implying use of the silver salt (AgOAc, 1.5 equivalent) in DCM and eco-compatible basic **conditions B** (K_2CO_3, 2 equivalents) in acetone. In both cases irradiation with two household bulbs is required. Although the superiority of conditions B fulfilling "green chemistry" principles over conditions A, the initial study of the reaction scope was undertaken using both protocols. As C5-functionalisation of quinolines is mainly limited to C8-amido-substituted compounds our aim was to establish a truly versatile system, prompt to tolerate an array of different directing group, both electron donating but also electron-withdrawing. We estimated therefore that comparison of both reaction conditions (Ag-mediated transformation and metal-free protocol) is crucial to delimitate their effectiveness for a panel of differently substituted quinoline derivatives.

Accordingly, the tolerance of the reaction towards various DG was explored (Table 2). The same regioselectivity was observed when using *N*-(quinolin-8-yl)benzamide (**1B**) and no functionalisation of the phenyl ring was evidenced[23] as confirmed by x-Ray analysis.[24] High yielding reactions and excellent C5-selectivity were also observed for *tert*-butyl (**1C**) and *n*-butyl (**1D**)-substituted amides. Functionalisation of the *N*-Boc protected 8-aminoquinoline (**1E**) occurred smoothly, delivering **3Ea** in 62% and 71% yield (under conditions A and B respectively). The secondary amide **1F** proved to be more challenging and regardless the conditions used **3Fa** was obtained in modest yield and as an inseparable mixture of regioisomers (C5 and C7). To further delimitate the scope of this methodology and regarding a limited number of C5-selective functionalisations of quinolines bearing diverse directing motifs, we pursued by examining the impact of the nature of the C8-substituents on the reaction. Remarkably, 8-aminoquinoline (**1G**) and ester-derived **1I** substrates, generally inefficient in C5-functionalisation, performed quite well under our basic protocol (71 and 45% yield respectively) whereas diminished yields were obtained under conditions A. These results demonstrate the outstanding potential and real synthetic value of our photocatalytic and green transformation. Secondary amine substrate **1H** turned out to be more challenging, as **3Ha** was isolated in only 29% yield along with diperfluoroalkylated derivative (43% yield) under conditions B. No selective functionalisation could be performed while using 8-hydroxy and 8-bromoquinolines, as well as unsubstituted quinoline and isoquinoline substrates.

Table 2. Substrate scope for 8-quinoline derivatives **1(A-I)**.[a)]



[a)] reaction conditions: Conditions A: **1(A-I)** (0.25 mmol), **2a** (5 equiv), AgOAc (1.5 equiv), DCM (0.2 M), r.t, Ar_2, 2 × 26 W CFL for 20 h; Condition B: **1(A-I)** (0.25 mmol), **2a** (5 equiv), K_2CO_3 (2 equiv), Acetone (0.2 M), r.t, Ar_2, 2 × 26 W CFL for 20 h; [b)] total yield of C_5 and C_7 for 40 h; [c)] GC yield; [d)] 1.2 equiv of **2a**; [e)] 5 equiv of **2a**.

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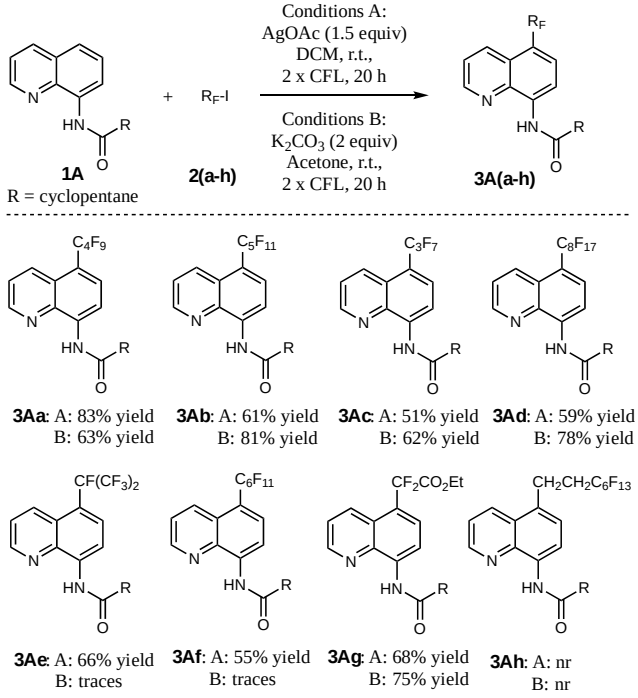
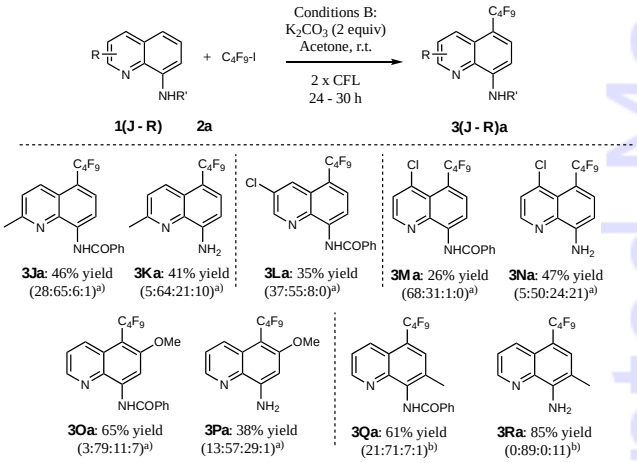
Subsequently, the tolerance of this transformation towards various perfluoroiodoalkanes **2** was explored (Table 3). The length of the polyfluorinated chain seems to have rather low impact on the reactivity, regardless reaction conditions used. Slightly lower yields were obtained while using C_3F_7-I (**2c**), probably due to its volatility. The more sterically demanding coupling partners such as 2-iodoheptafluoropropane **2e** and iodoperfluorocyclohexane **2f** performed well under conditions A (**3Ae**: 66% yield and **3Af**: 55% yield) but surprisingly, in the absence of AgOAc only trace amounts of products were formed. Rewardingly, a less activated ester-derived coupling partner **2g** underwent the reaction smoothly, delivering **3Ag** in 68% and 75% yield. This result is particularly attractive as the ester moiety is recognized as a convenient handle for post-modifications, paving the way towards several other fluorinated motifs.[25] Notably, no desired coupling was achieved when using an iodoalkane with no fluorine atom directly on the carbon generating the radical species (**2h**).

Table 3. Substrate scope for polyfluoroalkane iodides **2(a-h)**.



The synthetic value of the newly developed strategies strongly relies on their compatibility with more complex molecular scaffolds. This transformation occurs under extremely mild reaction conditions, hence seems perfectly suited for the late-stage functionalisation of more complex quinolines. Accordingly, the metal- and oxidant-free couplings of functionalised 8-amidoquinolines and unprotected 8-aminoquinolines were probed (Table 4).[26] Several substituents present at different positions of the heterocyclic scaffolds were well tolerated despite their clear impact on selectivity and efficiency. *N*-(2-methylquinoline-8-yl)benzamide (**1J**) was functionalised at C5 position with 65:6:1 (C_5:C_7:difunctionalisation) selectivity and the desired product was isolated in 46% yield. Although a slightly lower C5-selectivity was achieved for the corresponding 2-methylquinolin-8-amine **1K** (64:21:10), almost full conversion of the starting material was achieved in the presence of 1.2 equivalent of C_4F_9-I, hence delivering the regioisomerically pure **3Ka** in a comparable yield of 41%. Substitution of both 8-aminoquinoline and the corresponding amide in the positions 3 or 4 by a chlorine atom decreased the efficiency of the reaction. 3-chloro-8-amidoquinoline **1L** was converted into **3La** in 35% yield and its 4-chlorosubstituted congener delivered **3Ma** in 26% yield. A more synthetically useful reaction was however observed for the amine type substrate **1N** affording **3Na** in moderate 47% yield. Presence of the methoxy substituent at C6 position was quite well supported for the amide substrate **1O** (**3Oa** isolated in 65% yield). Besides, perfluoroalkylation of C7-methyl substituted quinolines worked better for the amino-quinoline delivering **3Ra** in high 85% yield.

Table 4. Functionalised 8-amido and 8-amino quinolines (**1J-R**)



a) GC conversion (unreacted SM:C5:C7:C5+C7); b) GC conversion (unreacted SM:C5:other regioisomer:difunctionalisation)

Regarding high reactivity of aminoquinoline substrate, we have subsequently accomplished double functionalisation of **1G** with two different perfluoroiodoalkanes (Scheme 1). Isolation of **4** in 63% yield over two steps further showcases the potential of this green and convenient synthetic pathway to build up polyfunctionalised quinoline scaffolds.

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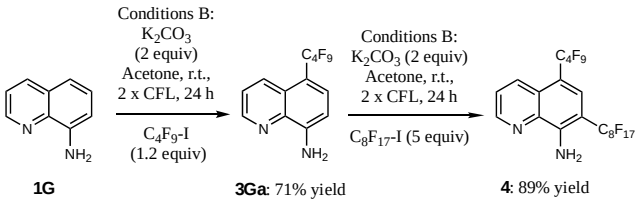
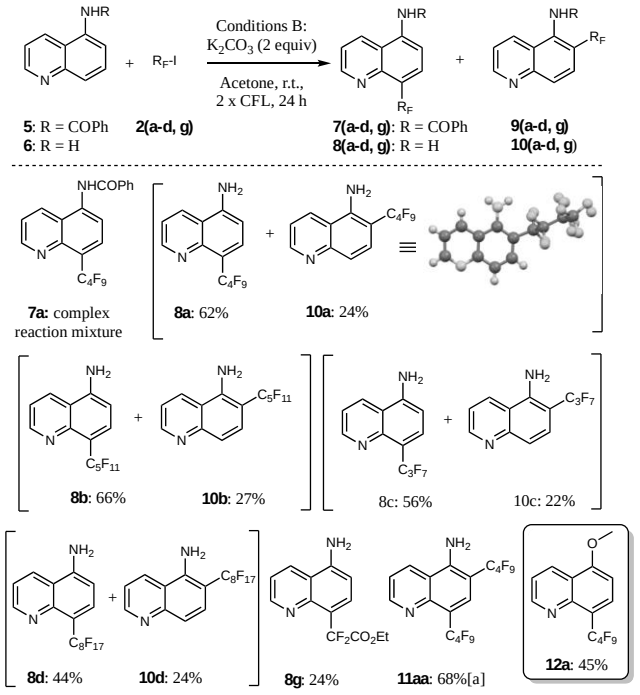


Scheme 1. Sequential functionalisation of 8-aminoquinoline (**1G**).

Following our initial purpose of designing a transformation allowing both, C5- and C8 couplings, we next explored the reaction of 5-amidoquinoline **5** and 5-aminoquinoline **6** using the basic protocol (conditions B). Although unselective coupling was observed for the amide **5**, the non-protected amine **6** underwent efficient C8-perfluoroalkylation using only 1.2 equivalent of **2a**, delivering **8a** in high yield (62%). Notably, minor C6-functionalised product **10a** could also be isolated in 24% yield (both regioisomers are separable by silica gel column).[27] **10a** was crystalized and the X-Ray analysis unambiguously confirm the regioselectivity. Encouraged by this first example of C8-quinoline perfluoroalkylation, we further enlarged the scope of this transformation using a few R_F coupling partners. Several unprecedented perfluoroalkylated quinolines have hence been prepared in synthetically useful yields (44 – 66%). Unfortunately, a somehow lower reactivity was observed while using the ester type iodoalkane **2g**. Likewise 8-aminoquinoline, its 5-substituted congener also undergoes bifunctionalisation while increasing the amount of the coupling partner and the reaction time. Accordingly, diperfluoroakylation of **6** took place and **11aa** was isolated in 68% yield. Notably, this protocol turned out to be equally compatible with OMe-type directing group installed at C5 position, hence delivering 5-OMe-8-perfluoroalkylated quinoline **12a** in 45% yield under basic conditions.

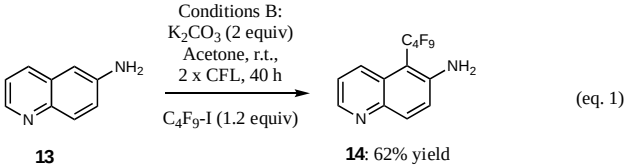
Table 5. Scope for the functionnalised 5-amido and 5-amino quinolines (**5, 6**)



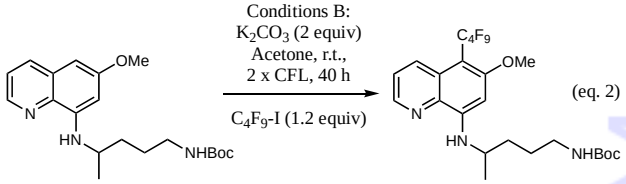
[a] 5 equiv of **2a**.

Further exceptional versatility of this reaction was demonstrated by performing the desired C-R_F coupling on C6-aminoquinoline **13,** delivering **14** in 62% yield (eq. 1).

Considering the simplicity of our transformation, its general effectiveness and tolerance towards several functionalised groups, this reaction establishes itself as an ideal tool for a late-stage diversification of complex molecular scaffolds. To exemplify this purpose, we embarked on perfluoroalkylation of Boc-protected (±)-primaquine derivative **15**, commercialised anti-malaria drug (eq. 2). Rewardingly, our methodology worked perfectly well, converting **15** into the desired product in 78% NMR yield. However, due to a tedious purification, **16** was isolated in moderate yield (69% yield with 88% purity and 44% yield with purity > 98%).



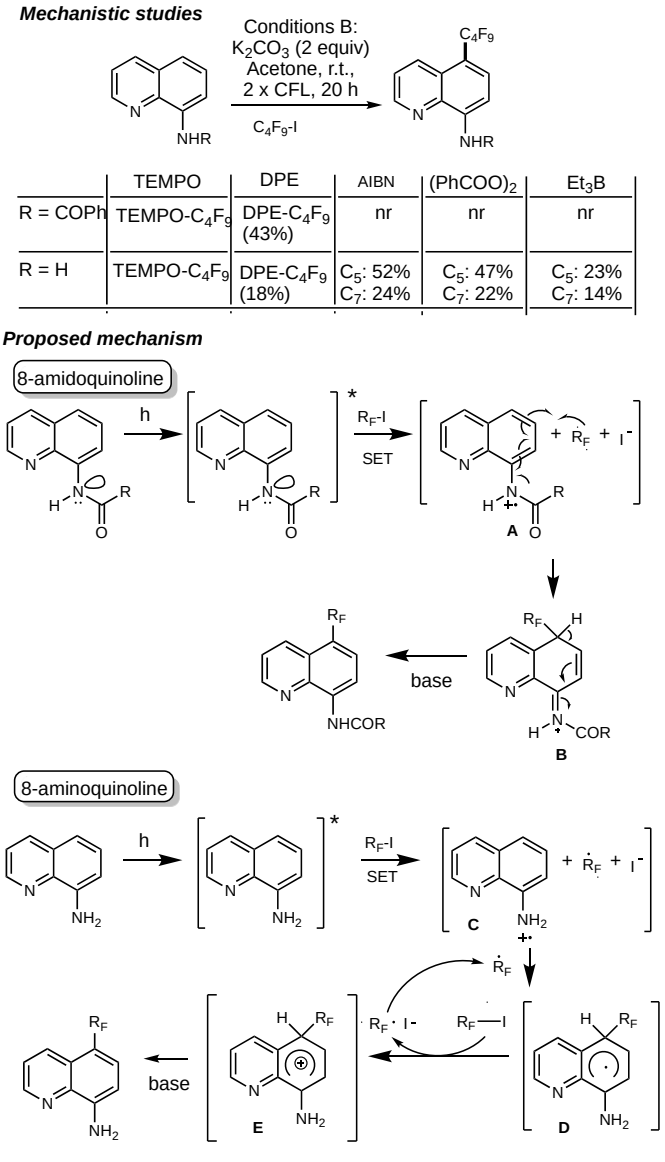
(eq. 1)



(eq. 2)

Finally, several mechanistic studies have been performed to elucidate the mechanism of this transformation using conditions B (for details see SI). The test reactions effectuated during the optimisation show unambiguously crucial role of the light and the experiments with cut-off filters (λ > 370 nm and λ > 455 nm) as well as UV-A lamp clearly suggest a particular importance of UV-A irradiation to allow the desired coupling. Optical absorption spectra of **1B** and **1G** (measured for λ = 330-430 nm for **1B** and λ = 330-500 nm for **1G**) indicate that both quinoline derivatives absorb light at λ < 370 nm (**1B**) and λ < 430 nm (**1G**). In contrast no absorption was observed for **2a** (for details see SI) and no change in UV-vis absorption spectra was detected while mixing **1B** or **1G** with **2a** in acetone. Accordingly, homolytic cleavage pathway of C_4F_9-I and intermediacy of photoactive EDA (electron donor-acceptor) aggregation between **1** and **2a** could be ruled out.[28] The radical character of this coupling was however confirmed by performing the standard reaction in the presence of TEMPO radical scavenger and 1,1-diphenylethylene (DPE) as a radical trapper (Scheme 2). For the 8-amidoquinoline, **3Aa** was not formed in a presence of both reactants but the adducts of R_F addition to TEMPO and DPE were detected. Likewise, no desired coupling product was formed when performing the reaction under "radical chain

type conditions" (presence of AIBN, benzoyl peroxide or triethylborane and heating at 70 °C). For 8-aminoquinoline **1G** adding TEMPO or DPE resulted in a formation of trapped species. In addition, rather unexpectedly, the reaction was effective while using three different typed of standard protocols implying radical chain reactions.



Scheme 2. Mechanistic studies.

In light of these mechanistic studies and precedents from the literature, the radical character of this metal-free transformation can be assumed and a possible divergent pathway for amide- and amine- substrates can be expected. In the case of 8-amidoquinoline derivatives, the presence of electron withdrawing group seems to render the substrate ineffective under classical radical-chain conditions and as the amido-quinoline substrate undergoes photoexcitation under irradiation, a single electron transfer (SET) mechanism could be envisioned. Such a scenario would imply: 1) generating of excited state **1B*** species under irradiation; 2) SET with R_F-I generating radical $R_F^{\cdot}$ and radical cation **A**; 3) radical addition providing intermediate **B**, followed by deprotonation yielding the desired product.

In contrast, the presence of the electron-donating amino group renders the quinoline core more prone to undergo radical chain reaction.[29] The reaction starts by 1) photoexcitation of the amino-quinoline **1G**; followed by 2) SET step between excited state **1G*** and **2a**, delivering $R_F^{\cdot}$ species (initiation of the process) and radical cation **C**; 3) addition of the two radical coupling partners affording **D**; 4) electron transfer from **D** to R_F-I to form oxidized cationic intermediate **E** together with $R_F^{\cdot}$ and I^- (formation of perfluoroalkyl radical further triggers the chain sequence); 5) formation of **3Ga** upon deprotonation. These mechanistic scenarios remain however highly speculative and further studies are currently undergoing.

In conclusion, an unprecedented and general strategy to access both C5- and C8-perfluoroalkylated quinolines is described. Remarkably, the reaction does not require any metal and/or oxidant and operates smoothly under extremely mild reaction conditions, using simple visible-light irradiation and green solvent. This coupling tolerates not only a range of functionalities on the amide moiety, but contrary to a majority of literature described protocols, is also compatible with non-protected amino-quinoline substrates, delivering an array of products. Consequently, to the best of our knowledge, it is the first general methodology allowing C5-perfluoroalkylation of both amido- and amino-quinolines. Remarkably, the same approach is also applicable for functionalisation of 5-aminoquinolines, yielding C8-coupling products. This protocol paves therefore the way towards a panel of new compounds with promising features for medicinal and agrochemical industry, as well as advanced material science, under truly green, mild and user-friendly reaction conditions.

Experimental Section

Typical procedure for perfluoroalkylation of quinoline substrates:

A 5 mL oven dried screw capped reaction tube was filled with amides (or) amines (1 equiv) and base (1.5 – 2 equiv), evacuated with vacuum-argon cycle for 5 times followed by the addition of perfluoroalkyl iodide (1.2 – 5 equiv) and solvent (0.2 M) under argon. The reaction tube was placed approximately 2 cm away from each 2*26 W CFL bulbs. The reaction mixture was stirred for the indicated time (20 – 40 h). After removal of the volatiles, the crude product was purified by column chromatography on silica gel. **Condition A:** Amide or amine (0.25 mmol, 1 equiv), R_F-I (1.25 mmol, 5 equiv for amides) or (0.3 mmol, 1.2 equiv for amines), AgOAc (0.375 mmol, 1.5 equiv) and DCM (1.25 mL, 0.2 M). **Condition B:** Amide or amine (0.25 mmol, 1 equiv), R_F-I (1.25 mmol, 5 equiv for amides) or (0.3 mmol, 1.2 equiv for amines), K_2CO_3 (0.5 mmol, 2.0 equiv) and Acetone (1.25 mL, 0.2 M).

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References

[1] For selected review see: S. Singh, G. Kaur, V. Mangla, M. K. Gupta, *Journal of Enzyme Inhibition and Medicinal Chemistry* **2015**, *30*, 492.

[2] a) S. M. A. Hussaini, *Expert Opin Ther Pat* **2016**, *26*, 1201; b) S. Kumar, S. Bawa and M. Gupta, *Mini-reviews in Medicinal Chemistry*, **2009**, ***9***, 1648.

[3] Selected recent reviews: a) T. Iwai and M. Sawamura, *ACS Catal.*, **2015**, *5*, 5031 ; b) S. M. Prajapati, K. D. Patel, R. H. Vekariya, S. N. Panchal and H. D. Patel, *RSC Advances*, **2014**, *4*, 24463; c) D. E. Stephens and O. V. Larionov, *Tetrahedron*, **2015**, *71*, 8683; d) G. A. Ramann and B. J. Cowen, *Molecules*, **2016**, *21*, 986.

[4] Selected recent review: a) M. A. J. Duncton, *Med. Chem. Commun.* **2011**, *2*, 1135.

[5] a) M. Ye, G.-L. Gao, A. J. F. Edmunds, P. A. Worthington, J. A. Morris, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 19090; b) P. Guo, J. M. Joo, S. Rakshit, D. Sames, *J. Am. Chem. Soc.* **2011**, *133*, 16338; c) B.-J. Li, Z.-J. Shi, *Chem. Sci.* **2011**, *2*, 488; d) M. Ye, G.-L. Gao, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 6964; e) J. Takagi, K. Sato, J. F. Hartwig, T. Ishiyama, N. Miyaura, *Tetrahedron Letters* **2002**, *43*, 5649.

[6] a) C.-C. Tsai, W.-C. Shih, C.-H. Fang, C.-Y. Li, T.-G. Ong, G. P. A. Yap, *J. Am. Chem. Soc*. **2010**, *132*, 11887 ; b) S. Yamamoto, Y. Saga, T. Andou, S. Matsunaga, M. Kanai, *Adv. Synth. Catal.* **2014**, *356*, 401; c) Y. Nakao, Y. Yamada, N. Kashihara, T. Hiyama, *J. Am. Chem. Soc*. **2010**, *132*, 13666.

[7] a) A. M. Suess, M. Z. Ertem, C. J. Cramer, S. S. Stahl, *J. Am. Chem. Soc.* **2013**, *135*, 9797; b) C. Xia, K. Wang, J. Xu, C. Shen, D. Sun, H. Li, G. Wang, P. Zhang, *Org. Biomol. Chem*. **2017**, *15*, 531; c) Y. Dou, Z. Xie, Z. Sun, H. Fang, C. Shen, P. Zhang, Q. Zhu, *ChemCatChem* **2016**, *8*, 3570; d) Y. Kuninobu, M. Nishi, M. Kanai, *Org. Biomol. Chem*. **2016**, *14*, 8092; e) H.-W. Liang, K. Jiang, W. Ding, Y. Yuan, L. Shuai, Y.-C. Chen, Y. Wei, *Chem. Commun.* **2015**, *51*, 16928 ; f) J.-M. Li, J. Weng, G. Lu, A. S. C. Chan, *Tetrahedron Letters* **2016**, *57*, 2121; g) H. Sahoo, I. Ramakrishna, M. Baidya, *ChemistrySelect* **2016**, *1*, 1949; h) H. Sahoo, M. K. Reddy, I. Ramakrishna, M. Baidya, *Chem. Eur. J.*, **2016**, *22*, 1592; i) S. Liang, G. Manolikakes, *Adv. Synth. Catal.* **2016**, *358*, 2371; j) H.-W. Liang, K. Jiang, W. Ding, Y. Yuan, L. Shuai, Y.-C. Chen, Y. Wei, *Chem. Commun.* **2015**, *51*, 16928; k) H. Sahoo, A. Mandal, J. Selvakumar, M. Baidya, *Eur. J. Org. Chem.* **2016**, 4321; l) J. Wei, J. Jiang, X. Xiao, D. Lin, Y. Deng, Z. Ke, H. Jiang, W. Zeng, *J. Org. Chem.*, **2016**, *81*, 946; m) L.-K. Jin, G.-P. Lu and C. Cai, *Org. Chem. Front.* **2016**, *3*, 1309; n) J. Chen, T. Wang, T. Wang, A. Lin, H. Yao, J. Xu, *Org. Chem. Front.* **2017**, *4*, 130; o) X. He, Y. Xu, L. Kong, H. Wu, D. Ji, Z. Wang, Y. Xu, Q. Zhu, *Org. Chem. Front.* **2017**, DOI 10.1039/C6QO00644B; p) J.-M. Li, Y.-H. Wang, Y. Yu, R. Wu, J. Weng, G. Lu, *ACS Catal.* **2017**, DOI 10.1021/acscatal.6b03671; for a recent example of heterogenous catalytic system see : q) C. Shen, J. Xu, B. Ying, P. Zhang, *ChemCatChem*, **2016**, *8*, 3560.

[8]H. Chen, P. Li, M. Wang, L. Wang, *Org. Lett.* **2016**, *18*, 4794.

[9] a) X. Cong, X. Zeng, *Org. Lett.* **2014**, *16*, 3716; b) T. Kino, Y. Nagase, Y. Ohtsuka, K. Yamamoto, D. Uraguchi, K. Tokuhisa, T. Yamakawa, *J. Fluorine Chem.* **2010**, *131*, 98.

[10] For a rare exmaple of C5-selective Pd-catalyzed functionalisation see : H.-Y. Xiong, D. Cahard, X. Pannecoucke, T. Besset, *Eur. J. Org. Chem.* **2016**, 3625.

[11] a) D. Ji, X. He, Y. Xu, Z. Xu, Y. Bian, W. Liu, Q. Zhu, Y. Xu, *Org. Lett.* **2016**, *18*, 4478; b) Y. Wang, Y. Wang, K. Jiang, Q. Zhang, D. Li, *Org. Biomol. Chem.* **2016**, ***14***, 10180; c) Z. Wu, Y. He, C. Ma, X. Zhou, X. Liu, Y. Li, T. Hu, P. Wen, G. Huang, *Asian J. Org. Chem.* **2016**, *5*, 724 ; d) Y. Wang, Y. Wang, Q. Zhang, D. Li, *Org. Chem. Front.* **2017**, doi : 10.1039/C6QO00730A; During submission of this paper a somehow related C5-perfluoroalkylation of 8-amidoquinolines using TMS-R_F coupling partners was disclosed: e) J. Xu, L. Qiao, B. Ying, X. Zhu, C. Shen, P. Zhang, *Org. Chem. Front*. **2017**, doi: 10.1039/C6QO00655H.

[12] a) S. Konishi, S. Kawamorita, T. Iwai, P. G. Steel, T. B. Marder, M. Sawamura, *Chem. Asian J.* **2014**, *9*, 434; b) J. Kwak, M. Kim, S. Chang, *J. Am. Chem. Soc.* **2011**, *133*, 3780.

[13] a) L. Strekowski, M. Hojjat, S. E. Patterson, A. S. Kiselyov, *J. of Heterocyclic Chem.* **1994**, *31*, 1413; b) R. Masciadri, M. Kamer, N. Nock, *Eur. J. Org. Chem.* **2003**, *2003*, 4286.

[14] For selected reviews see: a) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320; b) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 8315; c) C. Isanbor, D. O'Hagan, *J. Fluorine Chem.* **2006,** *127*, 303; d) V. Gouverneur, K. Seppelt, *Chem. Rev.* **2015**, *115*, 563; e) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* **2016**, ***116***, 422; f) A. M. Thayer, *Chem. Eng. News*, **2006**, *84*, 15.

[15] a) F. Aribi, E. Schmitt, A. Panossian, J.-P. Vors, S. Pazenok, F. R. Leroux, *Org. Chem. Front.* **2016**, *3*, 1392; b) J. Ichikawa, T. Mori, H. Miyazaki, Y. Wada, *Synlett* **2004**, *7*, 1219; c) H. Yanai, H. Mimura, K. Kawada, T. Taguchi, *Tetrahedron* **2007**, *63*, 2153; d) J. Han, L. Li, Y. Shen, J. Chen, H. Deng, M. Shao, X. Lu, H. Zhang, W. Cao, *Eur. J. Org. Chem.* **2013**, 8323; e) V. S. Gopinath, J. Pinjari, R. T. Dere, A. Verma, P. Vishwakarma, R. Shivahare, M. Moger, P. S. Kumar Goud, V. Ramanathan, P. Bose, M. V. S. Rao, S. Gupta, S. K. Puri, D. Launay, D. Martin, *Eur. J. Med. Chem*,

2013, *69*, 527; f) L. J. Allen, J. M. Muhuhi, D. C. Bland, R. Merzel, M. S. Sanford, *J. Org. Chem.* **2014**, *79*, 5827; g) A. Isobe, J. Takagi, T. Katagiri, K. Uneyama, *Org. Lett.* **2008**, *10*, 2657; h) K. B. McMurtrey, J. M. Racowski, M. S. Sanford, *Org. Lett.* **2012**, *14*, 4094; i) J. Ichikawa, Y. Wada, H. Miyazaki, T. Mori, H. Kuroki, *Org. Lett.* **2003**, *5*, 1455; j) R. D. Chambers, D. Holling, G. Sandford, H. Puschmann, J. A. K. Howard, *J. Fluorine Chem.* **2002**, *117*, 99; k) B.-C. Zhao, Q.-Z. Zhang, W.-Y. Zhou, H.-C. Tao, Z.-G. Li, *RSC Adv.* **2013**, *3*, 13106; l) S. A. El-Feky, H. K. Thabet, M. T. Ubeid, *J. Fluorine Chem.* **2014**, **161**, 87 ; l) H. Xie, J. Zhu, Z. Chen, S. Li and Y. Wu, *Synlett*, 2010, *17*, 2659 ; m) M. Soufyane, C. Mirand, J. Lévy, *Tetrahedron Letters* **1993**, *34*, 7737.

[16] For introduction of fluorine atom at C5 and/or C8 position see: I. I. Oleynik, V. D. Shteingarts, *J. Fluorine Chem.*, 1998, **91**, 25.

[17] For introduction of CF_3 moiety at C5 position see: ref. 7d, 7m, 7n, 9b, 11c; J. R. Ochola, M. O. Wolf, *Org. Biomol. Chem.* **2016**, *14*, 9088.

[18] For a rare example of introduction of CF_2R moiety at C5 position see : ref. 7m (3 examples) and 8 (2 examples). During preparation of this manuscript perfluoroalkylation using $TMSCF_3$,$TMSC_2F_5$ and $TMSC_3F_7$ has been reported; ref. 11e.

[19] Review on perfluoroalkylation of heteroaromatics: S. Barata-Vallejo, S. M. Bonesi, A. Postigo, *RSC Advances*, **2015**, **5**, 62498; for a general review on photocatalytic fluoroalkylation see: T. Chatterjee, N. Iqbal, Y. You, E. J. Cho, *Acc. Chem. Res.* **2016**, *49*, 2284.

[20] Selected reviews: a) P. M. Murphy, C. S. Baldwin, R. C. Buck, *J. Fluorine Chem.* **2012**, *138*, 3; b) G. G. Furin, *Russian Chem. Rev.* **2001**, *69*, 491; c) R. C. Buck, J. Franklin, U. Berger, J. M. Conder, I. T. Cousins, P. de Voogt, A. A. Jensen, K. Kannan, S. A. Mabury, S. P. van Leeuwen, *Integr Environ Assess Manag* **2011**, *7*, 513.

[21] For details see SI.

[22] The filters were chosen according to the absorption spectra of the coupling partners, for details see SI.

[23] X. Chen, Z. Tan, Q. Gui, L. Hu, J. Liu, J. Wu, G. Wang, *Chem. Eur. J.* **2016**, *22*, 6218.

[24] **3Ba:** CCDC 1536837. The crystallographic data are available free of charge from CCDC database.

[25] Selected examples concerning conversion of CF_2CO_2Et moiety see: a) K. Fujikawa, Y. Fujioka, A. Kobayashi, H. Amii, *Org. Lett.* **2011**, *13*, 5560; b) K. Fujikawa, A. Kobayashi, H. Amii, *Synthesis* **2012**, *44*, 3015; c) M.-C. Belhomme, T. Poisson, X. Pannecoucke, *J. Org. Chem.* **2014**, *79*, 7205.

[26] The impact of the light source of the efficiency of the perfluoroalkylation of 8-aminoquiniline was also investigated; for details see SI.

[27] **10a**: CCDC 1530956. The crystallographic data are available free of charge from CCDC database.

[28] a) J. Xie, J. Li, T. Wurm, V. Weingand, H.-L. Sung, F. Rominger, M. Rudolph, A. S. K. Hashmi, *Org. Chem. Front.* **2016**, *3*, 841; b) M. Silvi, E. Arceo, I. D. Jurberg, C. Cassani, P. Melchiorre, *J. Am. Chem. Soc.* **2015**, *137*, 6120.

[29] S. Barata-Vallejo, M. M. Flesia, B. Lantaño, J. E. Argüello, A. B. Peñéñory, A. Postigo, *Eur. J. Org. Chem.* **2013**, *2013*, 998.

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Regiodivergent C5 & C8- visible light induced C-H functionalisation of quinolines under metal-, photosensitizer- and oxidant-free conditions.

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