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Programmed Multiple C-H Bond Functionalization of the Privileged 4-hydroxyquinoline Template

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Abstract: The introduction of substituents on bare heterocyclic scaffolds can selectively be achieved by directed C–H functionalization. However, such methods have only occasionally been used, in an iterative manner, to decorate various positions of a medicinal scaffold to build chemical libraries. We herein report the multiple, site selective, metal-catalyzed C–H functionalization of a "programmed" 4-hydroxyquinoline. This medicinally privileged template indeed possesses multiple reactive sites for diversity-oriented functionalization, of which four were targeted. The C-2 and C-8 decorations were directed by an *N*-oxide, before taking benefit of an *O*-carbamoyl protection at C-4 to perform a Fries rearrangement and install a carboxamide at C-3. This also released the carbonyl group of 4-quinolones, the ultimate directing group to functionalize position 5. Our study highlights the power of multiple C–H functionalization to generate diversity in a biologically relevant library, after showing its strong antimalarial potential.

Introduction

The confluence of chemical libraries and biological screenings holds huge promises for drug discovery. The development of medicinally relevant compound collections can be addressed by smart synthetic strategies,[1] while late-stage functionalization approaches provide a useful complement for library diversification.[2–4] Indeed, achievements empowered by transition-metal-catalysis[5] during the past two decades have permitted the site-selective C(sp^2)–H bond functionalization of aromatic and heteroaromatic scaffolds by the use of directing groups.[6–10] These methods allow diversity to be introduced on medicinal targets with minimal functional group manipulations. The concept was applied by Yu to the divergent C–H functionalization of the non-steroidal anti-inflammatory drug celecoxib, directed by a sulfonamide function present on the molecule.[11] Several methodology-driven C–H functionalizations then allowed the straightforward diversification of many pharmaceutical and biologically relevant substrates.[12] Overall, these approaches constitute a paradigm in diversity-oriented synthesis strategies, permitting the late-stage diversification of key pharmaceutical scaffolds.

However multiple C–H functionalizations have more rarely been used to decorate a bare heterocyclic template in an iterative manner, especially in the medicinal context. For example (Figure 1, top), multiple arylations were reported on thiazole *N*-oxide,[13] thiazoles,[14,15] azaindoles *N*-oxide,[16] imidazole,[17] 3-methoxythiophene,[18] imidazo[1,2-a]pyrazines,[19] or 3-acetylpyrrole.[20]

We report herein the programmed multiple C–H bond functionalization of the 4-hydroxyquinoline (**1**) pharmacophore. After introducing a carbamate and an *N*-oxide (**2**) for site-selectivity, this scaffold was successively decorated at positions 8, 2, 3 and 5 (Figure 1, bottom). Importantly, *4-hydroxy*quinoline-based substrates have rarely been addressed by methodological studies, despite significant interests. Compounds possessing the privileged 4-hydroxyquinoline core or its 4-

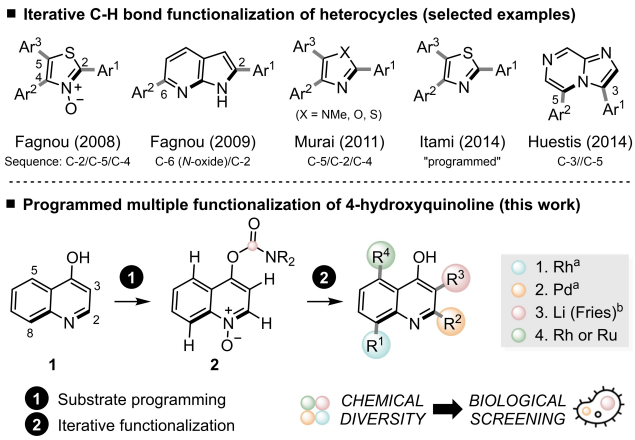

Figure 1. Divergent multiple C–H bond functionalization of heterocycles. *Notes:* [a] Steps can be inverted; [b] After *N*-oxide removal.

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quinolone tautomer have been associated to numerous activities,[21] especially in the field of cancer, infectious and parasitic, or cardiovascular diseases (Figure 2).[22] Some of them were taken as an inspiration for substituent choice during this work.

In 2009, Fagnou and co-workers reported the selective C-2 arylation of unsubstituted quinoline *N*-oxide, using the Pd-$(OAc)_2$/P(*t*Bu)$_2$Me·HBF_4 (1:1) catalytic system (5 mol%) in presence of an aryl bromide and K_2CO_3 in toluene at 110 °C.[24] In this seminal study, an excess of the *N*-oxide (3 equiv. relatively to ArBr) was used to maintain high yields. Numerous studies involving metal catalysis have demonstrated the efficiency of the C-2 functionalization of quinoline *N*-oxide to introduce aryl, alkenyl, alkyl, acyl groups or heteroatoms, using palladium, copper and rhodium catalysts.[25] However, these methods were rarely exemplified with an oxygenated substitution at C-4.[23a]

Alternatively, the *N*-oxide could serve as a directing group to functionalize position 8.[26,27] Shibata and Matsuo reported in 2014 the alkenylation of quinoline *N*-oxides in presence of the [Rh(cod)$_2$]OTf/DM-BINAP catalytic system (10 mol%) and diphenylalkyne.[28] This study was followed by numerous reports describing the introduction of aryl, alkyl, alkenyl, alkynyl, allyl, acyl, indolyl, halide, nitrogenated or other heteroatom groups using rhodium, iridium, ruthenium, palladium, or cobalt catalysis.[29] This field is rapidly growing but applications to 4-oxy-substituted quinoline substrates are still rare.[29c,l]

The C–H functionalization of position 3 by metal catalysis has been less frequently studied. The C-3 selective arylation of unsubstituted quinoline was first reported by Yu, using a $Pd(OAc)_2$/phenanthroline catalytic system in presence of aryl bromides.[30] Alternative strategies to functionalize position 3 used of the *ortho* lithiation of *O*-carbamates followed by a Fries rearrangement,[31] or that of *O*-phosphorodiamidates prior to the electrophile addition.[32] In principle, a carbamate group could also offer the possibility to direct an alkenylation at C-3, as done on electron-rich arenes in presence of cationic ruthenium(II) and an acrylate ester.[33]

With a 4-hydroxyl group, the C–H functionalization could be directed at position 5 by using [$RuCl_2$(p-cymene)]$_2$ or [Cp*$RhCl_2$]$_2$ in presence of alkynes, promoting an alkynylation[34] or an annulation,[35,36] respectively. Alkylations were also reported in presence of diazocarbonyl derivatives.[37] Finally, it is not surprising that the C–H functionalization of the two remote positions 6 and 7 are still poorly reported.[38] Recently Yu described a catalyst supporting a remote directing template allowing the functionalization of position 6.[39]

Considering this broad functionalization scope and the high medicinal potential of the quinoline ring, we envisioned a programmed approach for its multiple, divergent functionalization (Figure 1, bottom). Our strategy is centered on the putative 4-hydroxyquinoline *N*-oxide template, which bears two directing groups for the functionalization of positions 2/8 (the *N*-oxide group) and 3/5 (the 4-OH group). To avoid any interference between the two groups and take full benefits of the *N*-oxide as a directing group, the 4-hydroxyl was protected as a carbamate, which later offered the possibility to functionalize position 3 with a carboxamide by a Fries rearrangement. This step would also release the 4-OH directing group to further functionalize position 5. Overall, this approach offers a powerful mean to generate chemical diversity, whose significance will be demonstrated by the discovery of potent antimalarial compounds.

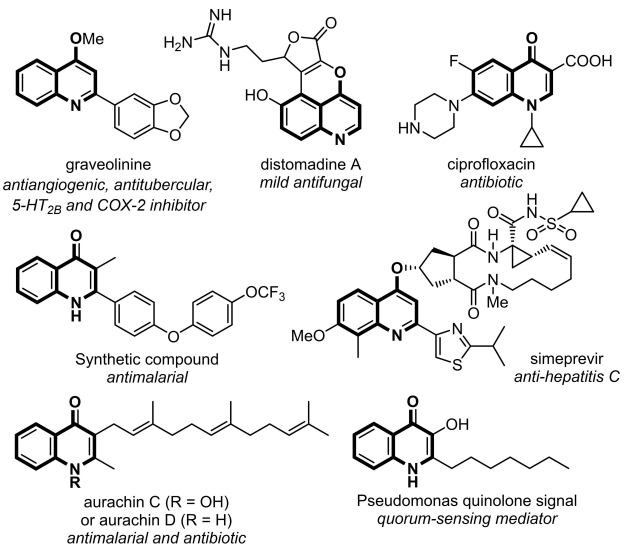
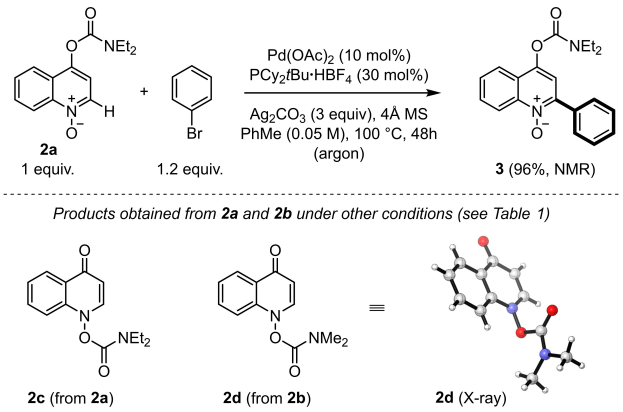


Figure 2. Examples of decorated 4-hydroxyquinoline and 4-quinolone structures with medicinal values, taken as an inspiration for this work.[23]

Results and Discussion

4-Hydroxyquinoline (**1**) was first converted into *N*-oxides **2a** and **2b** by carbamoylation in presence of diethyl and dimethyl carbamoyl chloride, respectively, followed by *N*-oxidation with *m*-chloroperbenzoic acid (see Scheme S1 in the supporting information).[24,31,40] The C-2 functionalization of **2a** was then attempted in presence of bromobenzene, targeting compound **3**. We tested variations of solvents, ligands, bases and the Pd/ligand ratio, all playing a critical role in the efficiency of the reaction. The best yield (96% by NMR) was obtained when employing 1.2 equivalent of PhBr and a catalytic amount of $Pd(OAc)_2$ (10 mol%) in presence of electron-rich phosphine ligand PCy_2*t*Bu (30 mol%, used as the HBF_4 salt according to Fu and Netherton[41]), Ag_2CO_3 (3 equiv) and 4 Å molecular sieves (MS) in dry toluene at 100 °C (Scheme 1). By contrast, under Fagnou's conditions (Table 1, entry 2),[24] no C-2 arylation was observed on substrate **2a**.[42] An undesired rearrangement product (*i.e.* 1-diethylcarbamyloxy-4(1*H*)-quinolone **2c**, Scheme 1) was instead isolated in 54% yield, resulting from the *O*-carbamyl migration onto the *N*-oxide,[43] together with the quinoline product (**S1**) resulting from the reduction of the *N*-oxide (10%). A similar rearrangement was observed with **2b**, providing suitable crystals for crystallographic confirmation of the rearranged structure (**2d**).[44]

Any variation from our successful condition (Table 1, entry 1) resulted in dropping yields. The use of phenyl iodide instead of phenyl bromide gave a satisfactory, yet lower, yield



Scheme 1. The C-2 functionalization of substrate **2a**. Structure of rearranged products **2c** and **2d**, including an X-ray crystallographic representation of **2d**.[44]

of 81% (entry 3). The absence of ligand or the use of bidentate ligands (entry 4) was unable to provide any quantifiable amount of product, while other phosphine ligands, including bulky and electron-rich ligands like P*t*Bu$_2$Me (used by Fagnou[24]) or P*t*Bu$_3$ (used by Schneider[23a]), proved less effective than PCy$_2$*t*Bu (entries 5, 6). Yields were affected by lowering the catalyst loading (entry 7) and changing the [Pd]/PR$_3$ ratio (entry 8). Furthermore, we show that Ag(I) cations are essential in this catalytic reaction, as the reaction in the presence of AgOAc instead of Ag_2CO_3 still proceeds in good yields (entry 9), but does not occur with K_2CO_3 (entry 10). Finally, arene solvents were preferred, especially toluene at an optimal substrate concentration of 0.05 M (entries 11–14). In addition, the use of 4 Å MS was necessary (3 Å MS could also be used), suggesting that traces of water are deleterious to the reaction (entry 15). Finally, performing the reaction under an air atmosphere decreased the yield to 44% (entry 16).

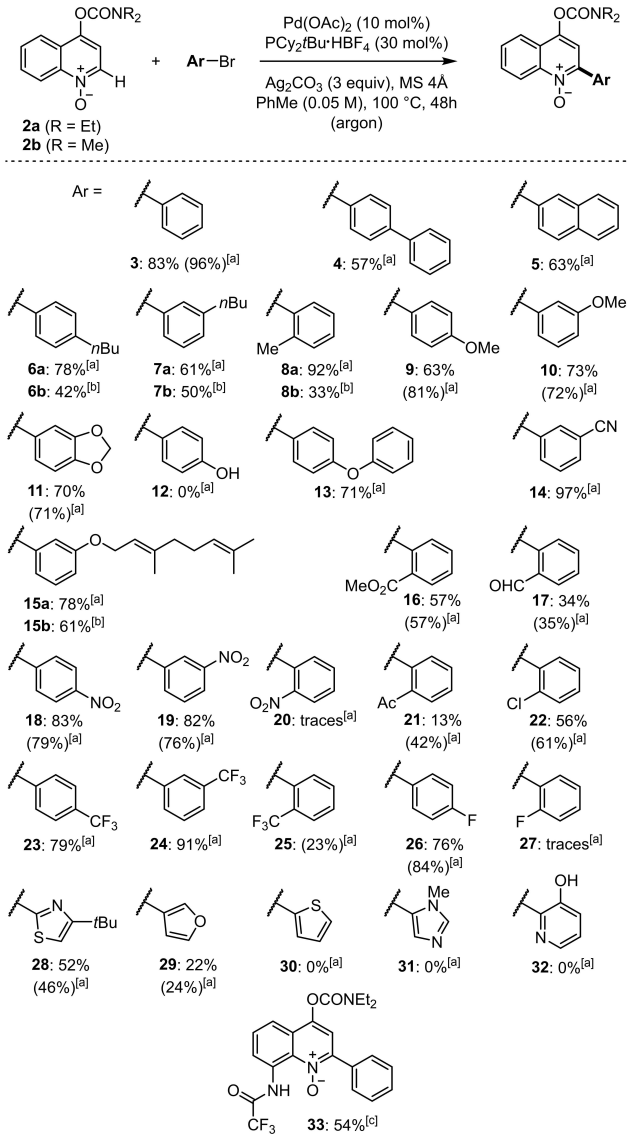
The mechanism of the Pd-catalyzed arylation of azine *N*-oxide has been thoroughly discussed in the literature. The acetate counter-anion could have an active role as a base during the palladium-catalyzed C–H activation, in a concerted metalation-deprotonation mechanism hypothesized by Fagnou.[45] The use of a *t*-butylphosphinepalladium(II) complex, by readily undergoing cyclometallation, could yet imply a cooperative palladium catalysis involving two distinct palladium complexes, as proposed by Hartwig on pyridine *N*-oxides.[46] Furthermore, as we found that Ag(I) salts are needed to achieve this functionalization, the silver cation could have an active role as a halide scavenger or as a catalyst for C–H activation, as discussed by Larrosa,[47] Sanford,[48] Hartwig,[49] or Houk.[50]

With these optimized conditions in hands, we evaluated the scope of this functionalization. It could be applied to a wide range of aryl donors (**3-26**, Scheme 2) including polyaromatic (**4**,**5**), electron-rich (**9**-**13**) or electro-deficient (**16**-**26**) substrates. Some of them were specifically chosen for biological purposes, when incorporating aryl or long-chain alkyl substituents sharing similarities with biologically relevant compounds (see Figure 2). Limitations were observed with arene containing free phenols (**12**), or heteroarenes like the 2-furyl (**29**), 2-thiophenyl (**30**), 4-(*N*-methyl)imidazole (**31**) or 2-(3-hydroxy)pyridyl (**32**) rings which were poorly or not reactive. However, a 2-thiazolyl substituent (**28**) could be introduced in 52% yield. *Ortho* substituents on phenyl rings were tolerated, except the most electron-deficient ones in **20** (NO_2), **25** (F), and **27** (CF_3). Remarkably, we were able to introduce an aryl group bearing an *O*-geranyl substituent, without losing the geranyl group and in a good yield of 78% (**15a**). The reaction was also possible

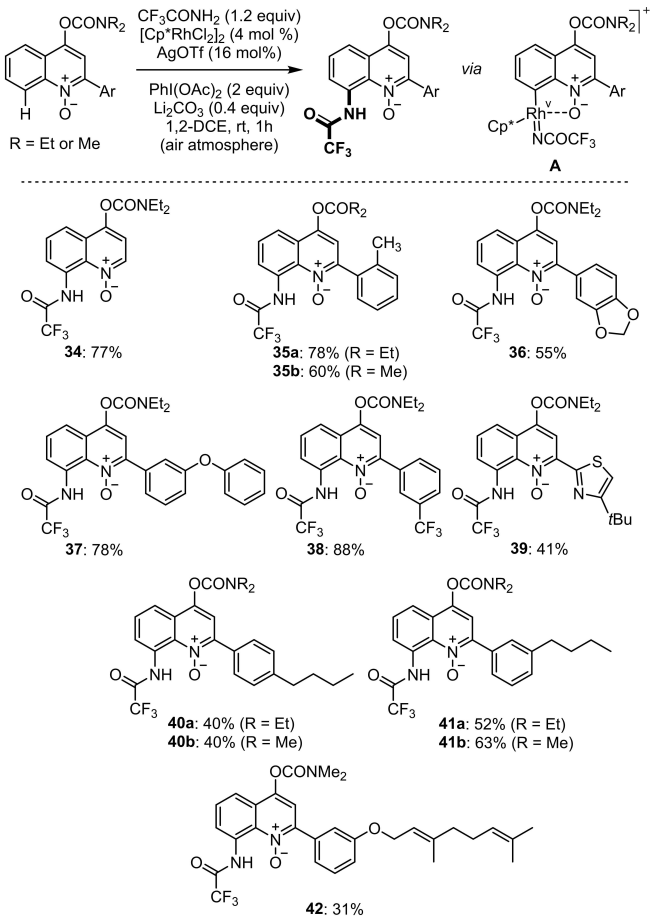
Table 1. Optimization of conditions for the C-2 functionalization of substrate **2a**.

Entry	Deviation from best conditions	Yield [%][a]
1	$Pd(OAc)_2$ (10 mol%), PCy$_2$tBu·HBF$_4$ (30 mol%), Ag_2CO_3 (3 equiv), 4 Å MS, PhMe (0.05 M), 100 °C, 48 h, under argon (best conditions, see Scheme 1)	96
2	Fagnou's conditions[24]: 3 equiv. of **2a**, $Pd(OAc)_2$ (5 mol%), P(tBu)$_2$Me·HBF$_4$ (5 mol%), K_2CO_3, PhMe (0.3 M), 110 °C	0[b]
3	PhI instead of PhBr	81
4	no ligand or Phen or Bbbpy[c] instead of PCy$_2$*t*Bu[d]	0[e]
5	ddpe, dppf, PCyPh$_2$, PPh$_3$, TFP or XantPhos[c] instead of PCy$_2$*t*Bu[d]	20-33
6	P*t*Bu$_2$Me,[d] P*t*Bu$_3$,[d] PCy$_3$,[d] or BINAP[c] instead of PCy$_2$*t*Bu[d]	37-66
7	2 or 5 mol% instead of 10 mol% of $Pd(OAc)_2$	42, 44
8	$Pd(OAc)_2$/PCy$_2$*t*Bu ratio: 1:1, 1:2 or 1:4 instead of 1:3	58, 69, 73
9	AgOAc instead of Ag_2CO_3	77
10	K_2CO_3 instead of Ag_2CO_3	0[e]
11	mesitylene, xylene instead of toluene	64, 75
12	1,2-DCE, PhCF$_3$ or DMF[c] instead of toluene	21-35
13	THF, 1,4-dioxane instead of toluene	38, 44
14	0.5 M, 0.25 M or 0.1 M instead of 0.05 M (toluene)	39, 55, 65
15	no 4 Å MS	0[e]
16	air instead of argon atmosphere	44

[a] ^{1}H NMR yields measured with dichloroethane as an internal standard. [b] Rearranged product **2c** was isolated in 54% yield, accompanied by 10% of corresponding quinoline product **S1**, from *N*-oxide reduction (see also Scheme S2 in the supporting information for details). [c] Abbreviations: BINAP: *rac*-2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene; 1,2-DCE: 1,2-dichloroethane; DMF: dimethylformamide; dppe: 1,2-Bis(diphenylphosphino)ethane; dppf: 1,1′-Ferrocenediyl-bis(diphenylphosphine); Phen: 1,10-Phenanthroline; TFP: Tris-(2-furyl)phosphine; XantPhos: 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene. [d] Used as the HBF$_4$ salt. [e] Entry 4: No reaction; Entry 10: **2c** observed in 68% yield, accompanied by 15% of *N*-oxide reduction; Entry 15: **2c** observed in 13% yield.



Scheme 2. C-2 functionalization of substrate **2a** (NMR yields in parentheses). Notes: [a] From **2a**. [b] From **2b**. [c] After [Rh]-catalyzed amidation at C-8.

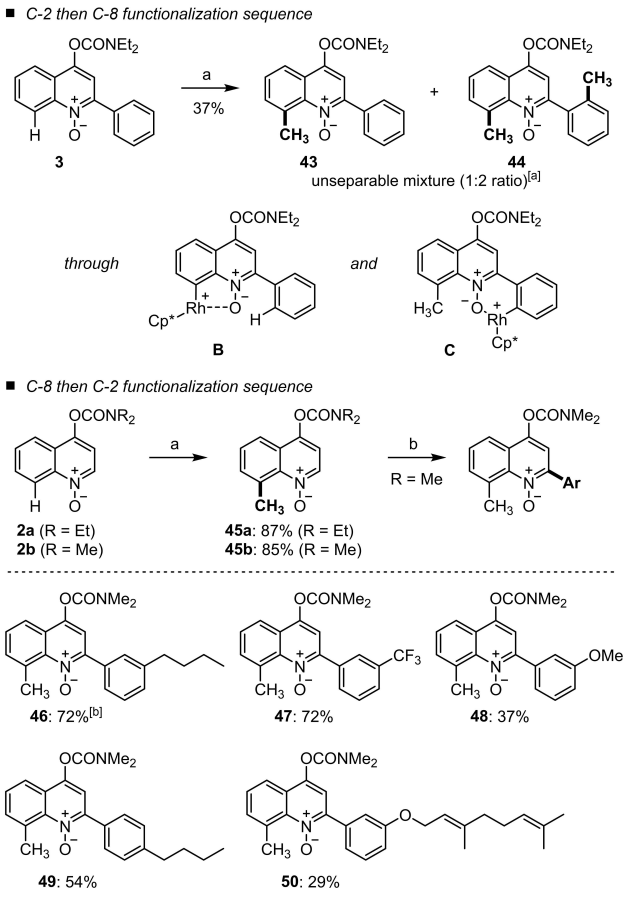


Scheme 3. Trifluoroamidation at C-8: method and scope.

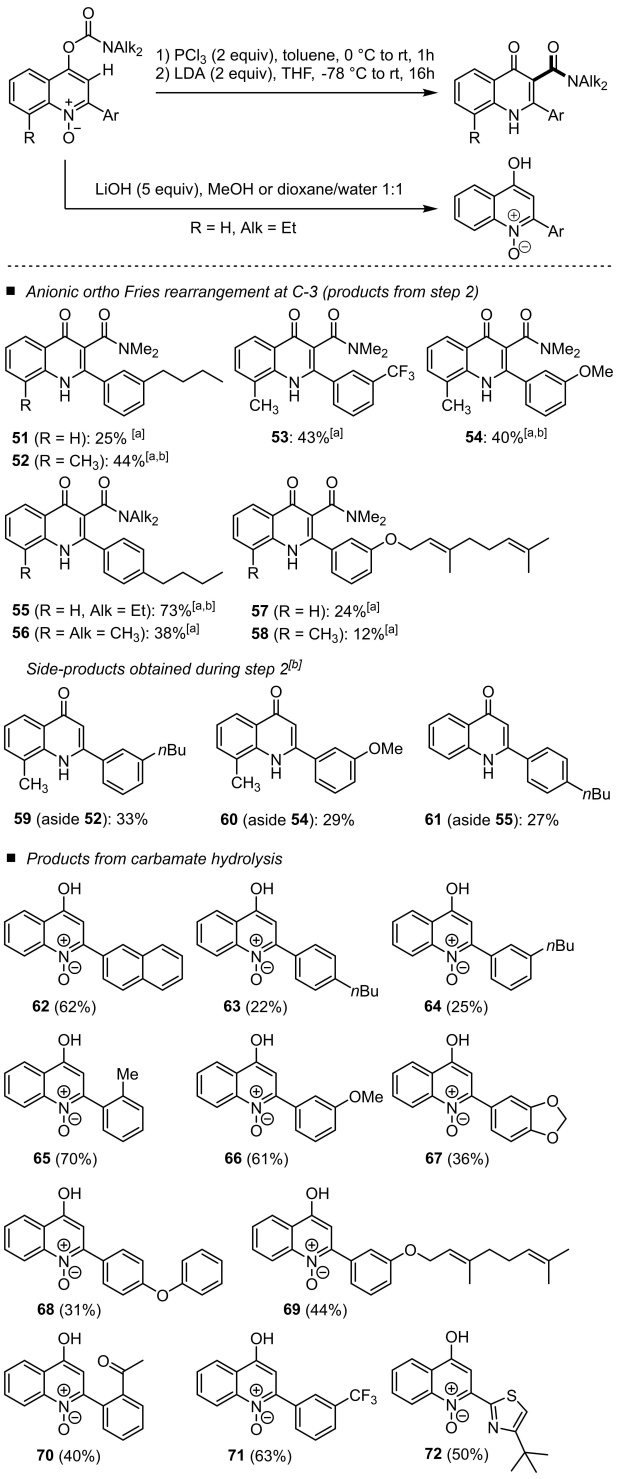
when an amide function was present in position 8 (**33**), or a methyl group in a multiple functionalization perspective (see discussion below). Concerning the influence of the carbamate group on the efficiency of the reaction, we observed that the diethyl carbamate (**2a**) gave generally better yields than the dimethyl carbamate (**2b**, mainly due to uncomplete conversion), giving products **6a**-**8a** or **6b**-**8b**, respectively. The diethyl carbamate should thus be preferred for this C-2 functionalization.

Next, we turned our attention to the functionalization of C-8, again directed by the *N*-oxide, focusing on readily affordable Rh(III)-catalyzed amidations and methylations (Scheme 3).[29c,n] We introduced a trifluoroacetamide group at C-8 by using Cui's oxidative conditions[29n] in presence of CF_3CONH_2 (1.2 equiv), PhI$(OAc)_2$ (2 equiv) and Li_2CO_3 (0.4 equiv), with $[Cp^*RhCl_2]_2$ (4 mol%) and AgOTf (16 mol%) as a catalytic system, in 1,2-DCE at room temperature. These conditions would involve the formation of an intermediary rhodium complex **A** (Scheme 3) following rhodium insertion and nitrene formation.[29n,51] After a successful attempt on substrate **2a** giving amide **34** in 77% yield, they were applied to 2-arylated substrates bearing 4-diethylcarbamoyloxy (**11**, **13**, **24**, **28**) and 4-dimethylcarbamoyloxy (**6b**, **7b**, **15b**) substituents, affording products (**35**–**42**). Geranylated substrate **42** was obtained with a lower yield of 31%, as expected owing to the sensibility of this aryl ether.

Alternatively, the methylation at C-8, expected from complex intermediate **B** (Scheme 4), was performed in presence of CH_3BF_3K (3 equiv), AgOAc (2 equiv) and a catalytic system composed of $[Cp^*RhCl_2]_2$ (10 mol%) and $AgSbF_6$ (20 mol%) in 1,2-dimethoxyethane at 65 °C, according to Liu.[29c] Substrate **3** gave mitigated results due to the undesired extra methylation observed at the *ortho* position of the 2-phenyl substituent, presumably through rhodium complex **C** although this assumption needs further investigation (Scheme 4). An inseparable mixture of both compounds **43** and **44** (1:2 ratio) was thus obtained in 37% yield (Scheme 4). This result suggested that our multiple C–H functionalization strategy should first target position 8, before the arylation of position 2. Consequently, the methylation was performed on quinoline *N*-oxide scaffolds **2a**



Scheme 4. Methylation at C-8. *Conditions:* a. CH_3BF_3K (3 equiv), $[Cp^*RhCl_2]_2$ (10 mol%), $AgSbF_6$ (20 mol%), AgOAc (2 equiv), DME, 65 °C, 16 h; b. ArBr (1.1 equiv), $Pd(OAc)_2$ (10 mol%), $PCy_2tBu{\cdot}HBF_4$ (30 mol%), Ag_2CO_3 (3 equiv), MS 4 Å, PhMe (0.05 M), 100 °C, 48 h (argon atmosphere). Note: [a] HPLC ratio (210 nm).



Scheme 5. Functionalization of position C-3 through the anionic Fries rearrangement, to give quinolones, and hydrolysis of the carbamate group to release 4-hydroxyquinolines. *Notes:* [a] Yields over two steps; [b] **52**, **54** and **55** were accompanied by hydrolysed products **59**, **60** and **61**, respectively.

and **2b** to furnish 8-methylquinoline derivatives **45a** and **45b** in 87% and 85% yields, respectively (Scheme 4). The next functionalization of position 2 was then performed on substrate **45b** under our previously optimized palladium-catalyzed arylation conditions, to furnish 2-aryl derivatives **46–50** in moderate to good yields (Scheme 4, condition b). The choice of **45b** instead of **45a** to make this functionalization was motivated by the next anionic Fries rearrangement, which was reputed to work well with *O*-dimethylcarbamyl derivatives, but not with their diethyl analogues.[31]

To perform the anionic *ortho* Fries rearrangement,[31,52,53] the *N*-oxide was first reduced in presence of PCl_3 (Scheme 5). Subsequently, the lithiation of position 3 in presence of LDA initiated the carbamoyl migration, providing quinolone products **51–56** in moderate to good yields (38-73%) over two steps. Only geranyl ethers **57** and **58** were obtained in lower yields due to substantial decomposition during the *N*-oxide reduction. Gratifyingly, compound **56** (R = Me) furnished crystals for X-ray analysis, showing the prevalence of the quinolone form in the solid state (Figure 3).[44] Incidentally, we attempted to use the *N,N*-dimethylcarbamate as a directing group for other C–H functionalization at C-3, but without success despite large condition screening (lithiation of *ortho* position 3 followed by addition of electrophiles,[53] or directed metal-catalyzed arylations[33]).[54] Overall, the Fries rearrangement finally pro-

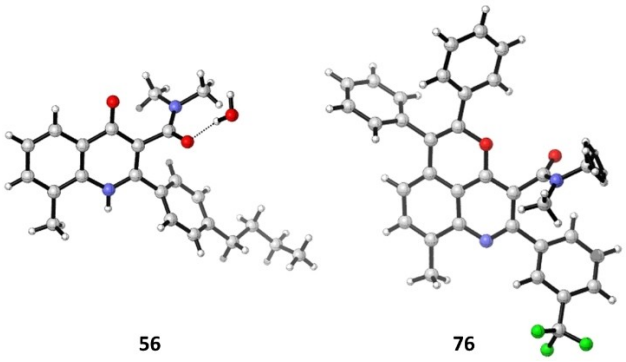
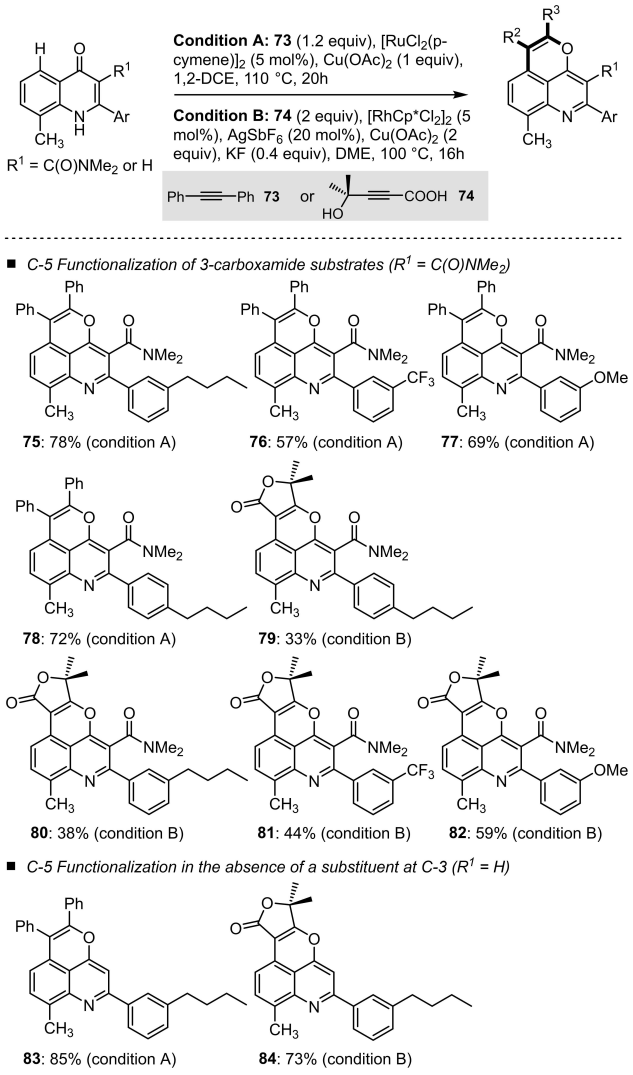


Figure 3. X-ray crystallographic structures of **56** and **76**. Compound **56** co-crystallized with a molecule of water. Compound **76** shows one disordered methyl group on the amide nitrogen (a mask was used during the refinement of structure **76**, removing the contribution of 42 electrons from the unit-cell content. This might correspond with a molecule of dichloromethane per formula unit. This disorder could not be treated in another way).[44]

vided a straightforward access to various substituted 4-quinolones bearing a carboxamide moiety at position 3, which are commonly found in biologically relevant compounds.[23c] Most importantly, this step also released the 4-oxo directing group that was necessary for the functionalization of position C-5. To complete this work and increase the diversity of compounds in view of biological investigations, the hydrolysis of diethylcarbamates was performed to provide 4-hydroxyquinoline *N*-oxide derivatives lacking the substitution at C-3 (**62**–**72**, Scheme 5).

Finally, an alkenylation of position C-5 was performed, in presence of alkynes, under rhodium or ruthenium catalysis (Scheme 6).[34–36,55] In fact, these reactions allowed an annulation with the adjacent 4-hydroxyl group, to give fused pyran ring systems **75**–**82**. The reaction with diphenylacetylene (**73**) was performed under the conditions defined by Patel,[35] in presence of $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), $Cu(OAc)_2$ (1 equiv) in 1,2-DCE at 110 °C, to give annulated compounds **75**–**78** in good yields generally ranging from 69 to 78%, except for CF_3-substituted substrate **53** giving **76** in 57% yield. This last product gave suitable crystals for X-ray crystallography (Figure 3).[44] Alternatively, the reaction with alkyne **74** was undertaken under conditions inspired by Shi's work[36] in presence of $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), $Cu(OAc)_2$ (2 equiv) and KF (0.4 equiv) in DME at 100 °C, providing lactones **79**–**82** in moderate yields ranging from 33 to 59% after purification. The selectivity was in accordance with the one described by Shi, as imposed by the steric hindrance of the *gem*-dimethyl group.[36] Interestingly these compounds are structurally related to distomadine natural products (Figure 2).[23b] In addition, in the absence of carboxamide substituent at position 3, the annulation reactions of 4-hydroxyquinoline substrate **59** performed well with both alkynes **73** and **74**, giving products **83** and **84** in 85 and 73% yields, respectively.

Overall, we show that the multiple C–H bond functionalization of a well-designed quinoline substrate is an efficient



Scheme 6. Functionalization of C-5 in presence of alkyne **73** or **74**, accompanied by the annulation with the 4-oxy group.

strategy to obtain a diverse collection of natural product- and drug-inspired compounds. Some of them are obviously structurally related to natural products like aurachin D, graveolinine, distomadine A, and the menaquinone analogues 2-alkyl-4-quinolones and their *N*-oxides, or to the heterocyclic core of sipremevir (Figure 2). Quinolone derivatives have been described as antimalarial compounds in many reports.[23d,e,56] More than 50 compounds of our collection were thus engaged in a screening against the parasite *Plasmodium falciparum*. First, we measured the percentage of growth inhibition of the chloroquine-resistant *P. falciparum* FcB1 strain by each compound at 10 μM and 1 μM (Table S24). These experiments showed that 33% of all compounds have a percentage of inhibition of the parasite above 75% at the concentration of 10 μM, and 7% at 1 μM (**57**, **61**, **69** and aurachin D that was available as a positive quinolone control from a previous study[23d]). These results show the prevalence of active compounds bearing a long lipophilic substituent on carbon 2, and the favorable effect of the free 4-

Table 2. Mean IC_{50} values (μM) of selected compounds on *Plasmodium falciparum* strains FcB1 and 3D7, and on the primary human fibroblast cell line AB943 (the selectivity index, SI, was calculated by dividing the IC_{50} obtained from human cell line AB943 by that from *P. falciparum* FcB1).

Compounds	FcB1[a]	3D7[a]	AB943[b]	SI
51	1.10	1.32	>100	>91
55	2.15	2.92	97	45
57	0.07	0.16	34.5	492
61	0.24	0.32	99	412
63	0.32	0.47	>100	>312
64	0.34	0.75	38.5	113
68	0.65	0.92	63	96
69	0.08	0.12	48	600
Aurachin D	0.09	0.21	>100	>1111
Chloroquine	0.048	0.011	25	520

[a] From quadruplicate values. [b] From duplicate values.

OH group on the antimalarial activity. Based on these data, 8 promising compounds were selected for IC_{50} evaluation on *P. falciparum* FcB1 and on the chloroquine-sensitive strain *P. falciparum* 3D7 (**51**, **55**, **57**, **61**, **63**, **64**, **68**, **69**, and aurachin D, all being 4-hydroxyquinoline *N*-oxides or 4-quinolones). In addition, the cytotoxicity of these compounds was evaluated on primary human fibroblast cell line AB943. The results are shown in Table 2.

These data first demonstrate that our compounds target both chloroquine-resistant and sensitive *P. falciparum* strains, mainly at submicromolar concentrations, despite slight differences indicating a better activity against the FcB1 strain. This observation suggests that the biological target of these compounds could be different from that of chloroquine. Indeed, being structural analogues of menaquinone, they are susceptible to target the mitochondrial electron transport chain,[23d] especially cytochrome B and type II NADH dehydrogenase.[56] Furthermore, it is striking that compounds **57** and **69**, like aurachin D, have the best activity, at low concentrations <0.1 μM. These compounds all share a crucial polyisoprenyl chain. Incidentally, the 2-aryl linker in **57** and **69** may also increase their metabolic stability.[56a] As for *n*-butyl-substituted derivatives (**51**, **55**, **61**, **63**, **64**), they are informative on the impact of the amide in position 3 and of the *N*-oxide on the activity. The presence of the amide seems to have a strong negative impact (**51** *vs.* **61**), while the *N*-oxide could have a limited positive influence (**61** *vs.* **63**). Finally, all compounds were poorly cytotoxic against the fibroblastic cell line AB943, resulting in high selectivity indexes, especially for compounds **57** (SI = 492), **69** (SI = 600) and aurachin D (SI = >1111). At the concentrations used to inhibit the parasites, these compounds could therefore have a limited toxicity on the human cells.

Conclusion

During this multiple functionalization approach, the 4-hydroxyquinoline scaffold was used as a valuable template to build a substantial chemical diversity in a minimum of steps. Comparatively, traditional approaches would have necessitated a dedicated synthetic route for each compound synthesized. Four positions were thus successfully functionalized, applying a programmed sequence on dedicated substrates **2a** and **2b**, taking benefit of two weakly coordinating directing groups. Two C–H functionalizations at C-2 and C-8 were first guided by the *N*-oxide. Then, after removal of the *N*-oxide, an anionic *ortho* Fries rearrangement of a 4-*O*-carbamyl moiety allowed the functionalization of position C-3, which released the 4-oxo group within the quinolone core. This was taken as a new directing group for the functionalization of position C-5. Taking into consideration the medicinal potential of this collection of quinoline and quinolone products, they were engaged in a biological screening against the agent of malaria, revealing compounds (**57**, **69**) with strong activities in the submicromolar range. In addition, the low cytotoxicity found on human cells revealed high selectivity indexes in favor of the antimalarial activity, demonstrating that these compounds hold promising properties for additional drug developments. This work shows that the multiple functionalization strategy, associated to substrate design, is a powerful mean to quickly generate biologically relevant libraries.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Antimalarial drugs · C–H bond functionalization · Compound library · Directing groups · Divergent synthesis

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[42] We checked that we could reproduce Fagnou's functionalization of quinoline *N*-oxide (3 equiv), successfully giving 89% yield of 2-phenylquinoline *N*-oxide in our hands (ref. [24]). Our conditions worked similarly on this substrate, giving 94% yield of product when 3 equiv. of substrate were used (vs. 60% with 1.1 equiv), suggesting our method could be general to quinoline substrates.

[43] This *O*-carbamyl rearrangement was not reported before, but Hammersmith and co-worker showed a related transformation of 4-(ethoxycarbonyloxy)quinoline *N*-oxides into 1-(ethoxycarbonyloxy)-4(1*H*)-quinolones (see ref. [40]). In fact, our rearrangement occurred spontaneously in trace amounts when substrates **2a** and **2b** were left in dichloromethane at room temperature for several hours. Surprisingly, it was not observed under our C-2 functionalization conditions.

[44] Deposition numbers 2069265 (for **2d**), 2042478 (for **56**) 2042479 (for **76**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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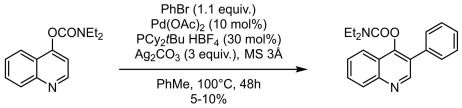

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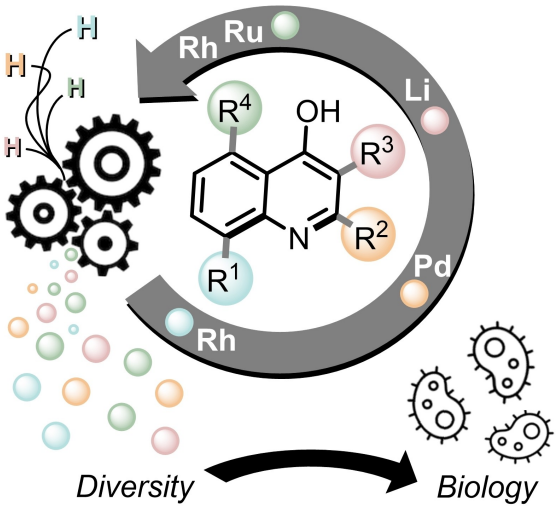

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The introduction of substituents on a "programmed" 4-hydroxyquinoline was selectively achieved by directed multiple C–H functionalizations. It could be decorated on four positions, successively at C-8, C-2, C-3 and C-5, three of which by using transition metal-catalyzed reactions. Our study highlights the power of multiple C–H functionalization to generate diversity in a biologically relevant library, after showing its strong antimalarial potential.