The programmed multiple C–H bond functionalization of 4-hydroxyquinoline and its medicinal potential

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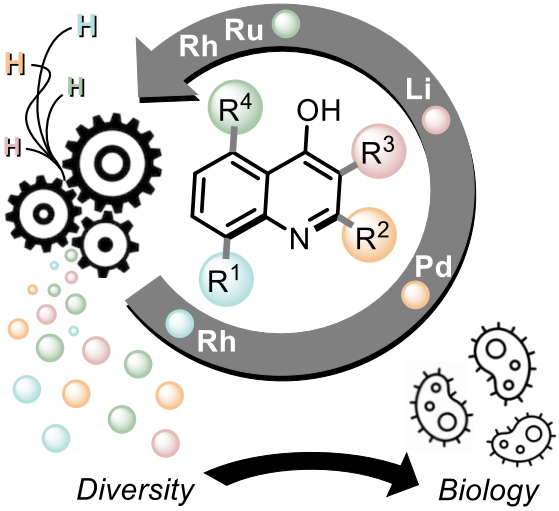


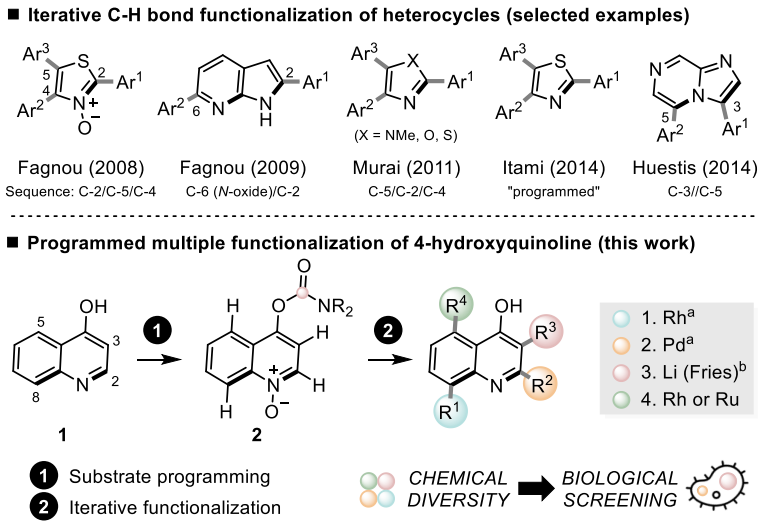
Abstract
The introduction of substituents on bare heterocyclic scaffolds can selectively be achieved by directed C–H functionalization. However, such methods have only occasionally been used, in an iterative manner, to decorate various positions of a medicinal scaffold to build chemical libraries. We 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.

Keywords
C–H bond functionalization, Quinoline, Diversity-oriented synthesis, Directing groups, Antimalarial drugs

Introduction

The confluence of chemical libraries and biological screenings holds huge promises for drug discovery. The development of medicinally relevant compound collections has been addressed by smart synthetic strategies[1] such as diversity-oriented synthesis (DOS),[2,3] biology-oriented and natural product-based synthesis,[4,5] function-oriented synthesis,[6] or fragment-based approaches,[7] which can be complemented by late-stage functionalization approaches.[8,9] Indeed, achievements empowered by transition-metal-catalysis[10] during the past two decades have permitted the direct site-selective C(sp^2)–H bond functionalization of aromatic and heteroaromatic scaffolds.[11,12,13,14,15] These methods allow diversity to be introduced on medicinal targets, with minimal functional group manipulations. The concept was initially 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.[16] Several methodology-driven divergent C–H functionalizations then allowed the straightforward diversification of many pharmaceutical and biologically relevant substrates.[17] Furthermore, the selectivity of C–H functionalizations can strongly be affected by reaction conditions, adding an experimental dimension to diversification.[18] Overall, these functionalization approaches constitute a paradigm in DOS strategies, permitting the late-stage diversification of key pharmaceutical scaffolds.

Multiple C–H bond functionalizations have however more rarely been used to decorate a bare heterocyclic template in an iterative manner, especially in the medicinal context. For example, multiple arylations were reported on thiazole *N*-oxide,[19] thiazoles,[20,21] azaindoles *N*-oxide,[22] SEM-protected imidazole,[23] 3-methoxythiophene,[24] imidazo[1,2-a]pyrazines,[25] or 3-acetylpyrrole[26] (Scheme 1, top).



Scheme 1. Approaches in divergent multiple C–H bond functionalization of heterocycles: representative examples (top) and this work (bottom). *Notes:* a. These steps can be inverted, depending on R^1 and R^2; b. After *N*-oxide removal.

We report the programmed divergent C–H bond functionalization of the 4-hydroxyquinoline (**1**) pharmacophore. After substrate design by introducing a carbamate and an *N*-oxide (**2**) for directed site-selectivity, this scaffold was successively decorated at positions 8, 2, 3 and 5 (Scheme 1, bottom). Importantly, before describing literature pillars used to set up this work, we must emphasize that there had been no development of C–H bond functionalization specifically designed for *4-hydroxy*quinoline-based substrates prior to this work, despite significant interests for this scaffold.[27] As a privileged structure,[28] we expected it promising for biological hit discovery, in addition to be suitable for multiple functionalization. Indeed, compounds possessing the 4-hydroxyquinoline core or its 4-quinolone tautomer have been associated to numerous activities, especially in the field of cancer, infectious and parasitic, or cardiovascular diseases (Figure 1).[29] Some of them were taken as an inspiration for substituent choice during this work.

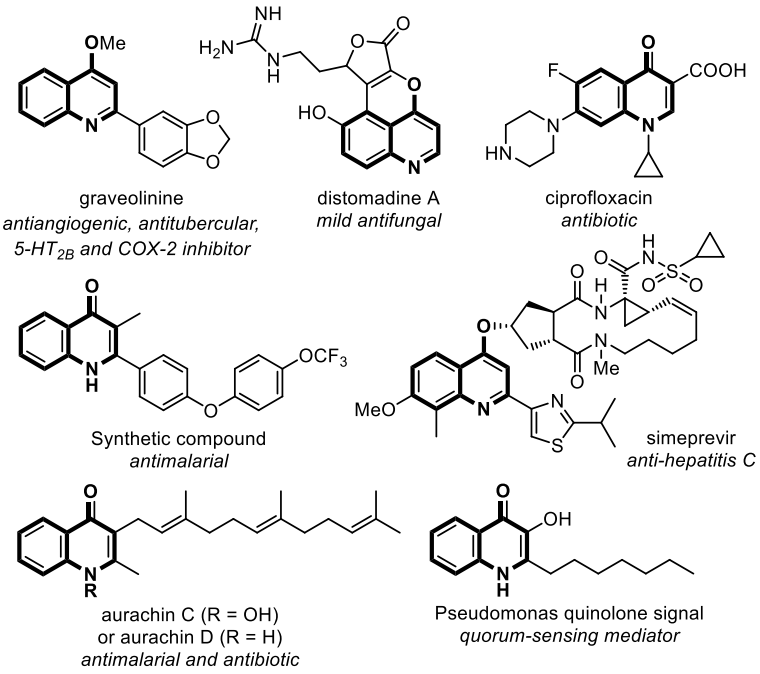


Figure 1. Examples of variously decorated 4-hydroxyquinoline and 4-quinolone structures with medicinal values, taken as an inspiration for this work.[30]

In 2009, Fagnou and co-workers reported the selective C-2 arylation of unsubstituted quinoline *N*-oxide, using the $Pd(OAc)_2/P(tBu)_2Me{\cdot}HBF_4$ (1:1) catalytic system (5 mol%) in presence of an aryl bromide and K_2CO_3 in toluene at 110°C.[31] In this seminal study, an excess of the *N*-oxide (3 equiv. relatively to ArBr) was necessary to maintain high yields. Related conditions were later applied by Schneider and co-workers to the synthesis of graveolinine, a 4-methoxyquinoline alkaloid (Figure 1), giving a moderate yield of the coupling product from an excess of the quinoline *N*-oxide substrate (4 equiv.) in presence of $Pd(OAc)_2/P(tBu)_3{\cdot}HBF_4$ (1:3).[30a] 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.[32] However, all these methods were only rarely exemplified with an oxygenated substitution at C-4.[30a,32q]

Alternatively, the *N*-oxide served as a directing group to functionalize position 8.[33] It was first reported in 2014 by Shibata and Matsuo as an alkenylation in presence of the $[Rh(cod)_2]$OTf/DM-BINAP catalytic system (10 mol%) and diphenylalkyne.[34] This study was followed by Chang's report on the iodination and amidation in presence of Rh(III) and Ir(III) catalysts, respectively, using *N*-iodosuccinimide and sulfonyl azides.[35] The same authors performed Rh(III)-catalyzed alkylations, alkynylations and amidation, in presence of diazoesters, alkynyl iodine(III) reagents and *N*-chlorocarbamates, respectively.[36] Several studies were later reported to introduce amide, amine, halide, aryl, alkyl, alkenyl, alkynyl, allyl, acyl or indolyl groups, using rhodium, iridium, ruthenium, palladium, or cobalt catalysts.[37] This field is rapidly growing but applications to 4-oxy-substituted quinoline substrates are still rare.[35,37e]

The C-H functionalization of position 3 has been less frequently achieved by metal catalysis. 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.[38] Other strategies to functionalize position 3 could use the lithiation of *O*-carbamates followed by a Fries rearrangement,[39] or that of *O*-phosphorodiamidates prior to the electrophile addition.[40] In principle, a carbamate group could also offer the possibility to direct the alkenylation at C-3, as done on electron-rich arenes in presence of cationic ruthenium(II) and an acrylate ester.[41]

With the 4-hydroxyl group, the C–H functionalization can be directed at position 5 by using $[RuCl_2(p\text{-cymene})]_2$ or $[Cp^*RhCl_2]_2$ in presence of alkynes, promoting alkynylation[42] or alkenylation and annulation,[43] respectively. Alkylations were also reported in presence of diazocarbonyl derivatives.[44] Finally, it is not surprising that the C–H

functionalization of the two remote positions 6 and 7 are still poorly reported.[45] Recently Yu described a catalyst supporting a remote directing template allowing the functionalization of position 6.[46]

Considering this broad functionalization scope and the high medicinal potential of the quinoline ring, we envisioned a programmed approach for its multiple, divergent functionalization (Scheme 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 with a medicinal perspective, as demonstrated at the end of the discussion with the discovery of promising antimalarial compounds.

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 (Scheme S1).[31,39,47] The functionalization of **2a** at position 2 was then attempted in presence of bromobenzene. We tested variations of solvents, ligands, bases and the Pd/ligand ratio, all playing a critical role in the efficiency of the reaction (Table 1). 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_2tBu (30 mol%, used as the HBF_4 salt according to Fu and Netherton[48]), Ag_2CO_3 (3 equiv.) and 4Å molecular sieves (MS) in dry toluene at 100 °C (entry 1). By contrast, under Fagnou's conditions (entry 2),[31,49] no C-2 arylation was observed on substrate **2a**, but an undesired rearrangement product in 54% yield resulting from the *O*-carbamyl migration onto the *N*-oxide (*i.e.* 1-diethylcarbamyloxy-4(1*H*)-quinolone **S3**, Scheme S2),[50] and the reduction product of the *N*-oxide (10%). A similar rearrangement was observed with **2b**, providing suitable crystals for crystallographic confirmation of the rearranged structure (see Supporting information).

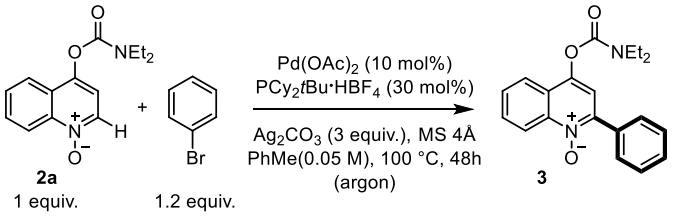
Any other variation from our successful conditions resulted in dropping yields. The use of phenyl iodide instead of phenyl bromide gave a satisfactory, yet lower, yield of 81% (entry 3). The absence of ligand or the use of bidentate ligands (entry 4) was unable to provide any quantifiable amount of product, while other phosphine ligands, including bulky and electron-rich ligands like $PtBu_2Me$ (used by Fagnou[31]) or $PtBu_3$ (used by Schneider[30a]), proved less effective than PCy_2tBu (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 (entry 11-14). In addition, the use of 4Å MS was necessary (3Å 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.[51] Alternatively, the use of a *t*-butylphosphine-palladium(II) complex, by readily undergoing cyclometallation, could imply a cooperative palladium catalysis involving two distinct palladium complexes, as proposed by Hartwig on pyridine *N*-oxides.[52] Finally, as we found that Ag(I) salts are needed to achieve this functionalization, the silver cation could act as a halide scavenger or as a catalyst for C-H activation, as discussed by Larrosa,[53] Sanford[54] and Hartwig.[55,56]

With these optimized conditions in hand, we evaluated the scope of this functionalization. It could be applied to a wide range of aryl donors (**3**-**26**, Figure 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 1). 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 when an amide function was present in position 8 (**33**), or a methyl group in a multiple functionalization perspective (see discussion below). As for the influence of the carbamate group on the efficiency of the reaction, we observed that the diethyl carbamate (**2a**) gave better yields than the dimethyl carbamate (**2b**, mainly due to uncomplete conversion), giving products **6a**-**8a** or **6b**-**8b**, respectively. The diethyl carbamate was thus preferred for this C-2 functionalization. To complete this work, after hydrolysis of the corresponding diethylcarbamate, 4-hydroxyquinoline *N*-oxide derivatives were obtained for biological screening (**S5**-**S16**, Scheme S3).

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



Entry	Deviation from standard conditions	Yield %[a]
1	none	96
2	Fagnou's conditions[50]: 3 equiv. of **2a**, $Pd(OAc)_2$ (5 mol%), $P(tBu)_2Me{\cdot}HBF_4$ (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_2tBu[d]	0[e]
5	ddpe, dppf, $PCyPh_2$, PPh_3, TFP or XantPhos[c] instead of PCy_2tBu[d]	20-33
6	$PtBu_2Me$,[d] $PtBu_3$,[d] PCy_3,[d] or BINAP[c] instead of PCy_2tBu[d]	37-66
7	2 or 5 mol% instead of 10 mol% of $Pd(OAc)_2$	42, 44
8	$Pd(OAc)_2$/PCy_2tBu 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 4Å MS	0[e]
16	air instead of argon atmosphere	44

[a] ^1H NMR yields measured with dichloroethane as an internal standard.
[b] Rearranged product **S3** was isolated in 54% yield, accompanied by 10% of the corresponding quinoline product (from the N-oxide reduction).
[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: **S3** observed in 68% yield, accompanied by 15% of *N*-oxide reduction; Entry 15: **S3** observed in 13% yield.

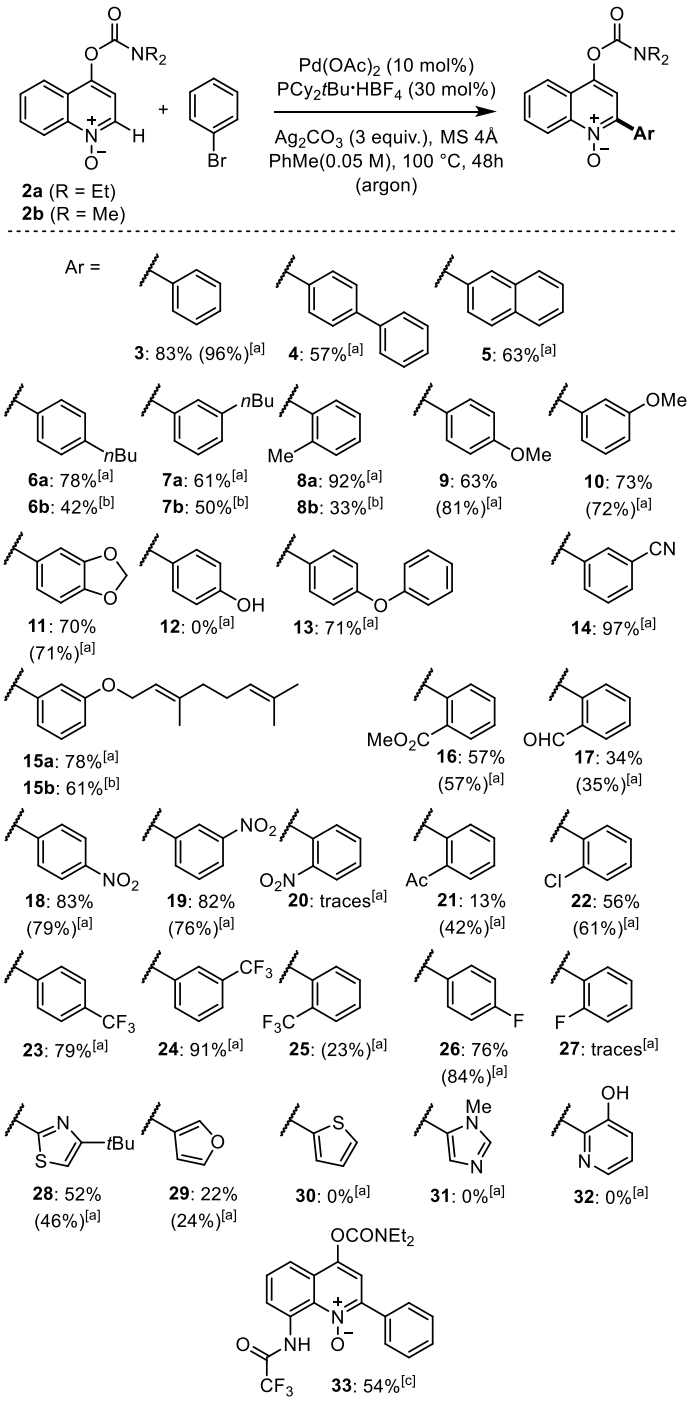
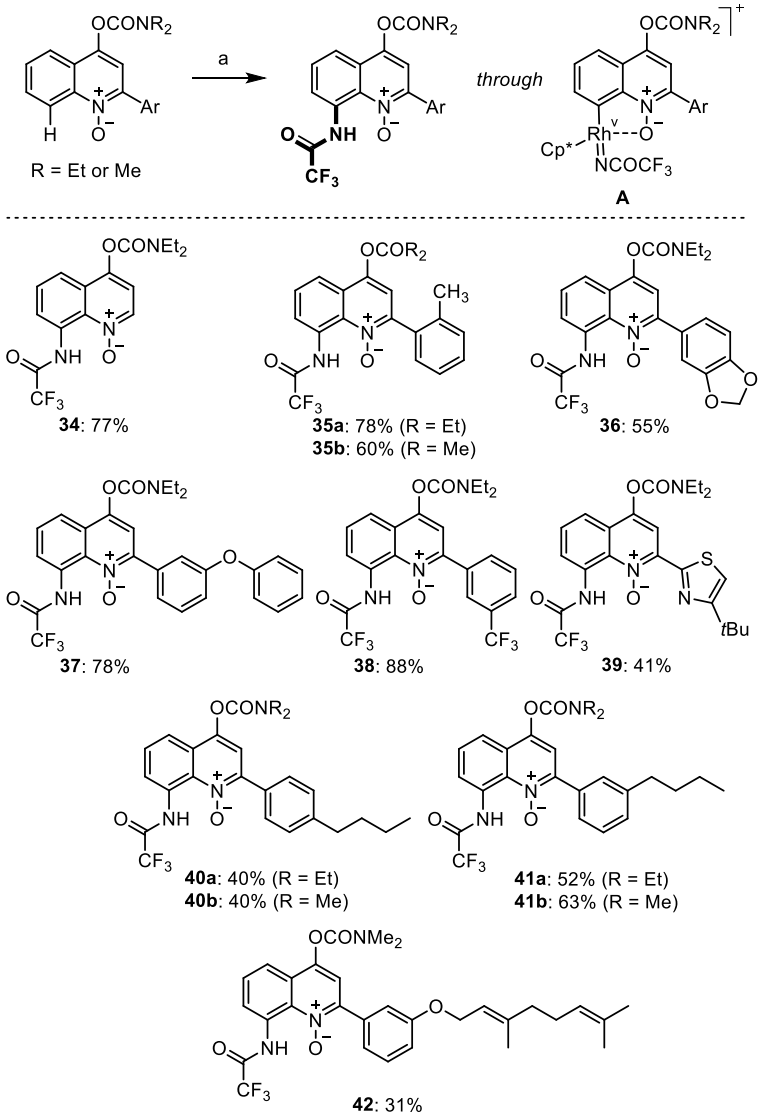


Figure 2. Functionalization of substrate **2a** at C-2 (NMR yields in parentheses). *Notes:* [a] From **2a**. [b] From **2b**. [c] After [Rh]-catalyzed amidation at C-8.

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 2).[37e,k] We introduced a trifluoroacetamide group at C-8 by using Cui's oxidative conditions[37k] in presence of CF_3CONH_2 (1.2 equiv.), $PhI(OAc)_2$ (2 equiv.) and Li_2CO_3 (0.4 equiv.), with $[RhCp^*Cl_2]_2$ (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 2)

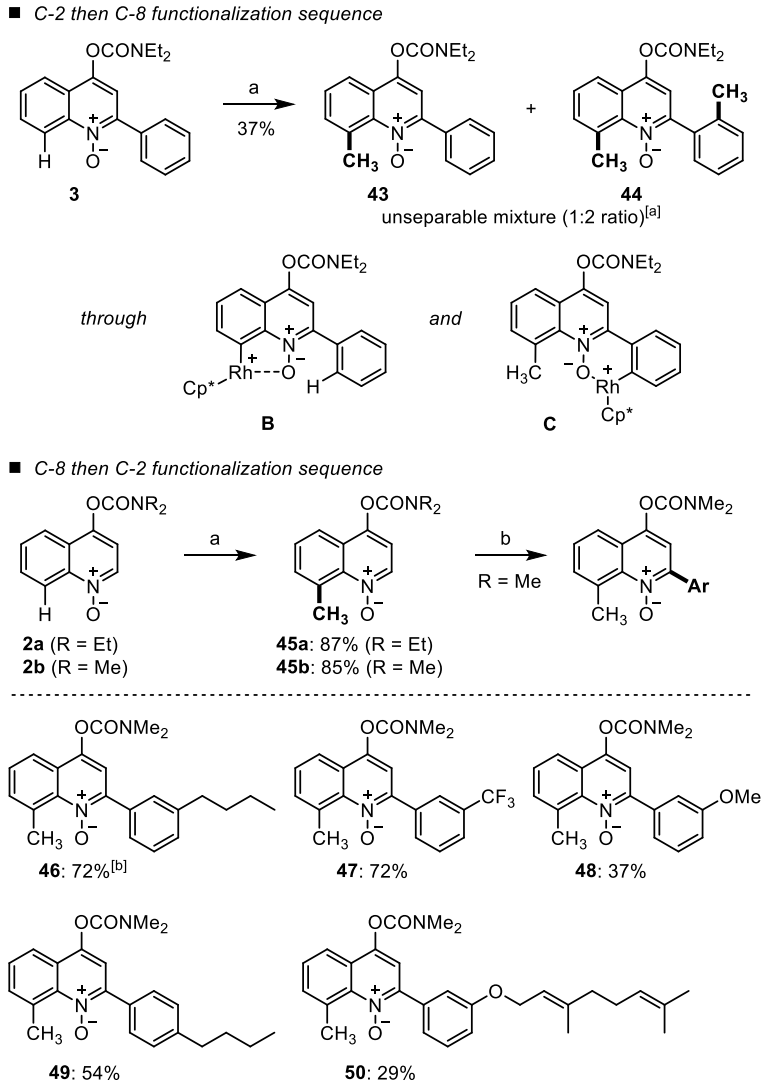
following rhodium insertion and nitrene formation.[37k,57] After a successful attempt on substrate **2a** giving amide **34** in 77% yield, they were applied to 2-arylated substrates bearing 4-diethylcarbamoyloxy (**11**, **13**, **24**, **28**) and 4-dimethylcarbamoyloxy (**6b**, **7b**, **15b**) substituents, 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.



Scheme 2. Amidation at C-8. *Condition:* a. CF_3CONH_2 (1.2 equiv.), $[RhCp^*Cl_2]_2$ (4 mol %), AgOTf (16 mol%), $PhI(OAc)_2$ (2 equiv.), Li_2CO_3 (0.4 equiv.), 1,2-DCE, rt, 1h (air atmosphere).

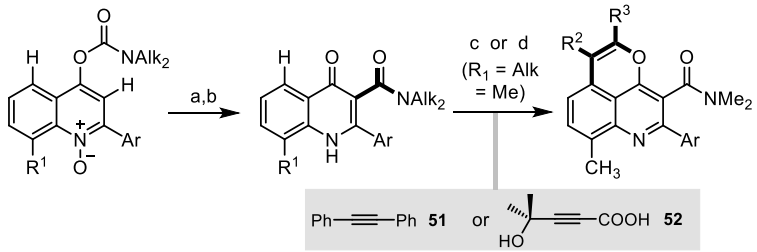
Alternatively, the methylation at C-8, expected from complex intermediate **B** (Scheme 3), was performed in presence of CH_3BF_3K (3 equiv.), AgOAc (2 equiv.) and a catalytic system composed of $[RhCp^*Cl_2]_2$ (10 mol%) and $AgSbF_6$ (20 mol%) in 1,2-dimethoxyethane at 65 °C, according to Liu.[37e] 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 3). An inseparable mixture of both compounds **43** and **44** (1:2 ratio) was thus obtained in 37% yield (Scheme 3). 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** 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 3, 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.[39]

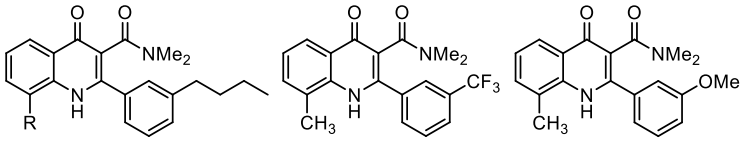


Scheme 3. Methylation at C-8. *Conditions:* a. CH_3BF_3K (3 equiv.), $[RhCp^*Cl_2]_2$ (10 mol %), $AgSbF_6$ (20 mol%), AgOAc (2 equiv.), DME, 65°C, 16h; b. ArBr (1.1 equiv.), $Pd(OAc)_2$ (10 mol%), $PCy_2tBu{\cdot}HBF_4$ (30 mol%), Ag_2CO_3 (3 equiv.), MS 4Å, PhMe (0.05 M), 100 °C, 48h (argon atmosphere). *Notes:* [a] HPLC ratio taken at 210 nm; [b] The corresponding rearrangement product from the carbamate migration onto the *N*-oxide was also observed in 5% yield.

To perform the anionic *ortho* Fries rearrangement,[39,58,59] the *N*-oxide was first reduced in presence of PCl_3 (Scheme 4). Subsequently, the lithiation of position 3 in presence of LDA initiated the carbamoyl migration, providing quinolone products **53**-**56** in moderate to good yields (38-73%) over two steps. Only geranyl ethers **57a** and **57b** were obtained in lower yields due to substantial decomposition during the *N*-oxide reduction. Gratifyingly, compound **56b** (R = Me) furnished crystals for X-ray analysis, showing the prevalence of the quinolone form in the solid state, co-crystalizing with a molecule of water (Figure 3).[60] 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,[59] or directed metal-catalyzed arylations[41,61]). Overall, the Fries rearrangement finally provided a straightforward access to various substituted 4-quinolones bearing a carboxamide moiety at position 3, which are commonly found in biologically relevant compounds.[30c] Most importantly, it also released the 4-oxo directing group needed for the functionalization of position C-5.



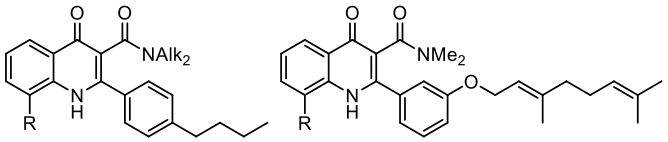
■ *Anionic ortho Fries rearrangement at C-3 (products from condition b)*



53a (R = H): 25% [a]
53b (R = CH_3): 44%[a,b]

54: 43%[a]

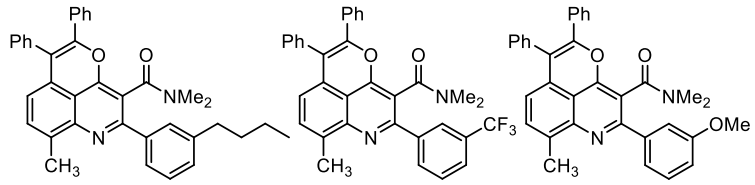
55: 40%[a,b]



56a (R = H, Alk = Et): 73%[a]
56b (R = Alk = CH_3): 38%[a]

57a (R = H): 24%[a]
57b (R = CH_3): 12%[a]

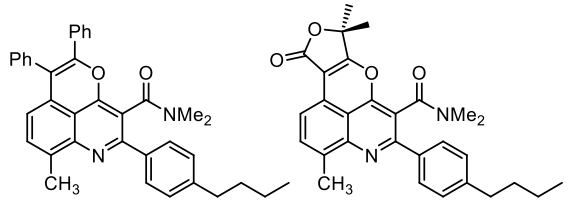
■ *C-5 Functionalization*



58: 78% (condition c)

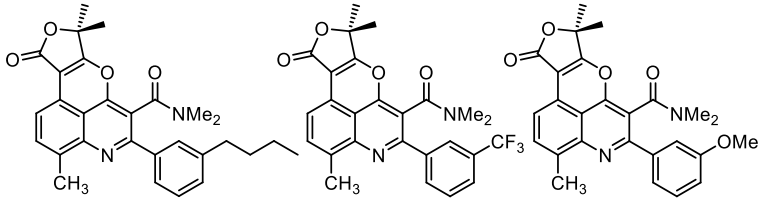
59: 57% (condition c)

60: 69% (condition c)



61: 72% (condition c)

62: 33% (condition d)[c]

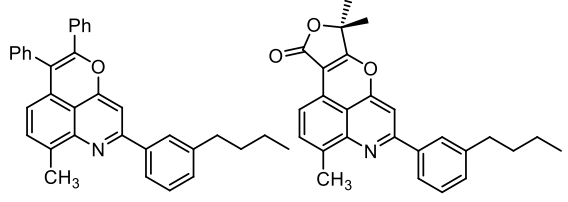


63: 38% (condition d)[c]

64: 44% (condition d)[c]

65: 59% (condition d)[c]

■ *C-5 Functionalization in the absence of a substituent at C-3*



66: 85% (condition c)

67: 73% (condition d)[c]

Scheme 4. Functionalization of positions C-3 and C-5. *Conditions:* a. PCl_3 (2 equiv.), toluene, 0 °C→rt, 1h; b. LDA (2 equiv.), THF, -78 °C→rt, 16h; c. **51** (1.2 equiv.), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), $Cu(OAc)_2$ (1 equiv.), 1,2-DCE, 110 °C, 20h; d. **52** (2 equiv.), $[RhCp^*Cl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), $Cu(OAc)_2$ (2 equiv.), KF (0.4 equiv.), DME, 100 °C, 16h. *Notes:* [a] Yields over two

steps; [b] **53b**, **55** and **56a** were accompanied by hydrolysis products **S17**, **S18** and **S19**, respectively; [c] Isolated compounds, formed in a 3.5:1 ratio with the other regioisomeric lactone.

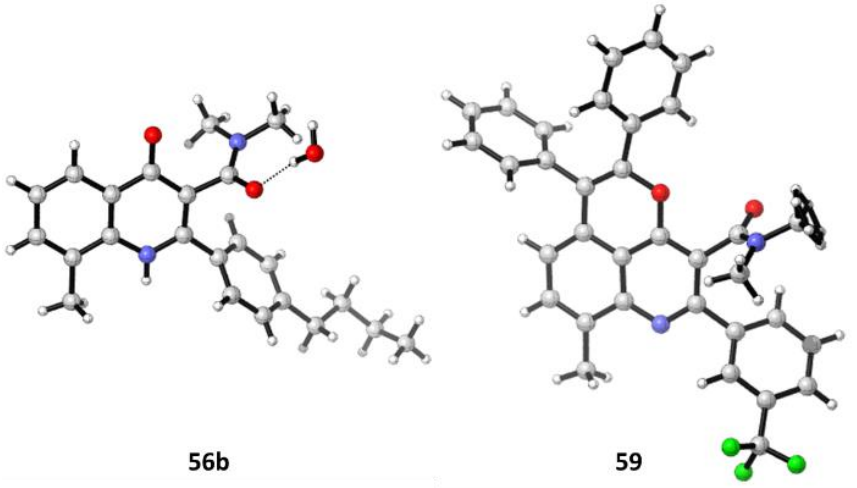


Figure 3. X-ray crystallographic structures of **56b** and **59**. Compound **56b** co-crystallized with a molecule of water. Compound **59** shows one disordered methyl group on the amide nitrogen (a mask was used during the refinement of structure **59**, removing the contribution of 42 electrons from the unit-cell content. This might correspond with a molecule of dichloromethane per formula unit. This disorder could not be treated in another way).[60]

To complete this functionalization program, we ended up with an alkenylation of position C-5 in presence of alkynes under rhodium or ruthenium catalysis.[42,43,62] In fact, these reactions allowed an annulation with the adjacent 4-hydroxyl group, to give fused pyran ring systems **58**-**65**. The reaction with diphenylacetylene (**51**) was performed under Patel's conditions,[43a] 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 **58**-**61** in good yields generally ranging from 69 to 78%, except for CF_3-substituted substrate **54** giving **59** in 57% yield. This last product gave suitable crystals for X-ray crystallography (Figure 3).[60] Alternatively, the reaction with dissymmetric alkyne **52** was undertaken under conditions inspired by Shi's work[43b] in presence of $[RhCp^*Cl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), $Cu(OAc)_2$ (2 equiv.) and KF (0.4 equiv.) in DME at 100 °C, providing lactones **62**-**65** in moderate yields ranging from 33 to 59% after separation from the minor regioisomeric lactones (3.5:1 ratio, major isomer drawn on Scheme 4). Interestingly these compounds are structurally related to natural product distomadines (Figure 1).[30b] In addition, in the absence of carboxamide substituent at position 3, the annulation reactions of 4-hydroxyquinoline substrate **S17** (see note b in Scheme 4 and the supporting information) performed well with both alkynes **51** and **52**, giving products **66** and **67** 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 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,[63] or to the heterocyclic core of sipremevir (Figure 1). Quinolone derivatives have been described as antimalarial compounds in many reports.[30d,32e,64] 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 (**57a**, **S12**, **S19** and aurachin D that was available as a positive quinolone control from a previous study[30d]). These results show the prevalence of active compounds bearing a long lipophilic substituent on carbon 2, and the favorable effect of the free 4-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 (**53a**, **56a**, **57a**, **S6**, **S7**, **S11**, **S12**, **S19** and aurachin D, all being 4-hydroxyquinoline *N*-oxides or 4-quinolones, see

Figure S4). In addition, the cytotoxicity of these compounds was evaluated on primary human fibroblast cell line AB943. The results are shown in Table 2.

Table 2. Mean IC_{50} values (µM) of selected compounds (see Figure S4) 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
53a	1.10	1.32	>100	>91
56a	2.15	2.92	97	45
57a	0.07	0.16	34.5	492
S6	0.32	0.47	>100	>312
S7	0.34	0.75	38.5	113
S11	0.65	0.92	63	96
S12	0.08	0.12	48	600
S19	0.24	0.32	99	412
Aurachin D	0.09	0.21	>100	>1111
Chloroquine	0.048	0.011	25	520

a. From quadruplicate values.
b. From duplicate values.

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,[30d] especially cytochrome B and type II NADH dehydrogenase.[64] Furthermore, it is striking that compounds **57a** and **S12**, 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 **57a** and **S12** may also increase their metabolic stability.[64a] As for *n*-butyl-substituted derivatives (**53a**, **56a**, **S6**, **S7**, **S19**), 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 (**53a** *vs.* **S19**), while the *N*-oxide could have a limited positive influence (**S6** *vs.* **S19**). Finally, all compounds were poorly cytotoxic against the fibroblastic cell line AB943, resulting in high selectivity indexes, especially for compounds **57a** (SI = 492), **S12** (SI = 600) and aurachin D (SI = >1111). At the concentrations used to inhibit the parasites, these compounds could therefore have a limited impact 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 (**57a**, **S12**) 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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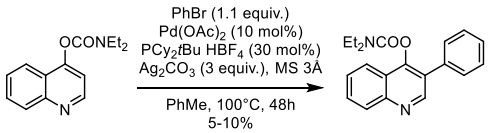
References

[1] O. O. Grygorenko, D. M. Volochnyuk, S. V. Ryabukhin, D. B. Judd, *Chem. Eur. J.* **2020**, *26*, 1196–1237.
[2] S. L. Schreiber, *Science* **2000**, *287*, 1964–1969.
[3] W. R. Galloway, A. Isidro-Llobet, D. R. Spring, *Nat. Commun.* **2010**, *1*, 80.
[4] S. Wetzel, R. S. Bon, K. Kumar, H. Waldmann, *Angew. Chem. Int. Ed.* **2011**, *50*, 10800–10826.
[5] M. Pascolutti, R. J. Quinn, *Drug Discov. Today* **2014**, *19*, 215-221.
[6] P. A. Wender, V. A. Verma, T. J. Paxton, T. H. Pillow, *Acc. Chem. Res.* **2008**, *41*, 40-49.
[7] D. E. Scott, A. G. Coyne, S. A. Hudson, C. Abell, *Biochemistry* **2012**, *51*, 4990–5003.
[8] T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal, S. W. Krska, *Chem. Soc. Rev.* **2016**, *45*, 546-576.
[9] J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960–9009.
[10] P. Gandeepan, T. Müller, D. Zell, G. Cera, S. Warratz, L. Ackermann, *Chem. Rev.* **2019**, *119*, 2192-2452.
[11] For an account on the "innate" and "guided" principles of C–H functionalization, see: T. Brückl, R. D. Baxter, Y. Ishihara, P. S. Baran, *Acc. Chem. Res.* **2012**, *45*, 826-839.
[12] S. R. Neufeldt, M. S. Sanford, *Acc. Chem. Res.* **2012**, *45*, 936-946.
[13] N. Kuhl, M. N. Hopkinson, J.Wencel-Delord, F. Glorius, *Angew. Chem. Int. Ed.* **2012,** *51*, 10236-10254.
[14] F. Zhang, D. R. Spring, *Chem. Soc. Rev.* **2014**, *43*, 6906-6919.
[15] C. Sambiagio, D. Schönbauer, R. Blieck, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes, M. Schnürch, *Chem. Soc. Rev.* **2018**, *47*, 6603-6743.
[16] H.-X. Dai, A. F. Stepan, M. S. Plummer, Y.-H. Zhang, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 7222-7228.
[17] See for example: (a) H. Sekizawa, K. Amaike, Y. Itoh, T. Suzuki, K. Itami, J. Yamaguchi, *ACS Med. Chem. Lett.* **2014**, *5*, 582-586; (b) M. Shang, M.-M. Wang, T. G. Saint-Denis, M.-H. Li, H.-X. Dai, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2017**, *56*, 5317–5321; (c) W. Ma, H. Dong, D. Wang, L. Ackermann, *Adv. Synth. Catal.* **2017**, *359*, 966–973; (d) S. Porey, X. Zhang, S. Bhowmick, V. K. Singh, S. Guin, R. S. Paton, D. Maiti, J. Am. Chem. Soc. 2020, 142, 3762-3774; (e) A. Benzai, X. Shi, F. Derridj, T. Roisnel, H. Doucet, J.-F. Soulé, *J. Org. Chem.* **2019**, *84*, 13135-13143; (f) F. Fumagalli, S. Warratz, S.-K. Zhang, T. Rogge, C. Zhu, A. C. Stückl, L. Ackermann, *Chem. Eur. J.* **2018**, *24*, 3984-3988; (g) G. G. Dias, T. A. do Nascimento, A. K. A. de Almeida, A. C. S. Bombaça, R. F. S. Menna-Barreto, C. Jacob, S. Warratz, E. N. da Silva Júnior, L. Ackermann, *Eur. J. Org. Chem.* **2019**, 2344–2353.
[18] For a review, see: L. Ping, D. S. Chung, J. Bouffard, S.-g. Lee, *Chem. Soc. Rev.* **2017**, *46*, 4299-4328.
[19] L.-C. Campeau, M. Bertrand-Laperle, J.-P. Leclerc, E. Villemure, S. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 3276-3277.
[20] F. Shibahara, E. Yamaguchi, T. Murai, *J. Org. Chem.* **2011**, *76*, 2680-2693.
[21] S. Tani, T. N. Uehara, J. Yamaguchi, K. Itami, *Chem. Sci.* **2014**, *5*, 123–135.
[22] M. P. Huestis, K. Fagnou. *Org. Lett.* **2009**, *11*, 1357-1360.
[23] J. M. Joo, B. B. Touré, D. Sames. J. Org. Chem. **2010**, *75*, 4911-4920.
[24] S. Yanagisawa, K. Ueda, H. Sekizawa, K. Itami, *J. Am. Chem. Soc.* **2009**, *131*, 14622-14623.
[25] B. M. Johnson, M. P. Huestis, *Eur. J. Org. Chem.* **2014**, 1589–1593.
[26] Y. Xu, L. Zhao, Y. Li, H. Doucet, *Adv. Synth. Cat.* **2013**, *355*, 1423-1432.
[27] T. Iwai, M. Sawamura, *ACS Catal.* **2015**, *5*, 5031−5040.
[28] (a) B. E. Evans, K. E. Rittle, M. G. Bock, R. M. DiPardo, R. M. Freidinger, W. L. Whitter, G. F. Lundell, D. F. Veber, P. S. Anderson, R. S. L. Chang, V. J. Lotti, D. J. Cerino, T. B. Chen, P. J. Kling, K. A. Kunkel, J. P. Springer, J. Hirshfieldt, *J. Med. Chem.* **1988**, *31*, 2235–2246; (b) M. E. Welsch, S. A. Snyder, B. R. Stockwell, *Curr. Opin. Chem. Biol.* **2010**, *14*, 347–361; (c) P. Schneider, G. Schneider, *Angew. Chem. Int. Ed.* **2017**, *56*, 7971–7974.
[29] For reviews on the quinoline pharmacophore, see: (a) C. Mugnaini, S. Pasquini. F. Corelli, *Curr. Med. Chem.* **2009**, *16*, 1746-1767; (b) V. R. Solomon, H. Lee, *Curr. Med. Chem.* **2011**, *18*, 1488-1508; (c) R. Musiol, *Expert Opin. Drug Discov.* **2017**, *12*, 583-597; (d) T. Idowu, F. Schweizer, *Antibiotics* **2017**, *6*, 26; (e) J. Fedorowicz, J. Sączewski, *Monatsh. Chem.* **2018**, *149*, 1199–1245.
[30] (a) Graveolinine: T. Rodrigues, D. Reker, J. Kunze, P. Schneider, G. Schneider, *Angew. Chem. Int. Ed.* **2015**, *54*, 10516–10520; (b) Distomadine A: A. N. Pearce, D. R. Appleton, R. C. Babcock, B. R. Copp, *Tetrahedron Lett.* **2003**, *44*, 3897-3899; (c) Ciprofloxacine: T. D. M. Pham, Z. M. Ziora, M. A. T. Blaskovich, *Med. Chem. Commun.* **2019**, *10*, 1719-1739; (d) Aurachin D: X.-W. Li, J. Herrmann, Y. Zang, P. Grellier, S. Prado, R. Müller, B. Nay, *Beilstein J. Org. Chem.* **2013**, *9*, 1551-1558; (e) Antimalarial compound: C. Pidathala, R. Amewu, B. Pacorel, Gemma L. Nixon, Peter Gibbons, W. David Hong, S. C. Leung, N. G. Berry, R. Sharma, P. A. Stocks, A. Srivastava, A. E. Shone, S. Charoensutthivarakul, L. Taylor, O. Berger, A. Mbekeani, A. Hill, N. E. Fisher, A. J. Warman, G. A. Biagini, S. A. Ward, P. M. O'Neill, *J. Med. Chem.* **2012**, *55*, 1831−1843; (f) Simeprevir: T.-I Lin, O. Lenz, G. Fanning, T. Verbinnen, F. Delouvroy, A. Scholliers, K. Vermeiren, Å. Rosenquist, M. Edlund, B. Samuelsson, L. Vrang, H. de Kock, P. Wigerinck, P. Raboisson, K. Simmen, *Antimicrob. Agents Chemother.* **2009**, *53*, 1377–1385.

[31] L.-C. Campeau, D. R. Stuart, J.-P. Leclerc, M. Bertrand-Laperle, E. Villemure, H.-Y. Sun, S. Lasserre, N. Guimond, M. Lecavallier, K. Fagnou, *J. Am. Chem. Soc.* **2009**, *131*, 3291–3306.
[32] (a) Arylation: H. C. Seung, J. H. Seung, S. Chang, *J. Am. Chem. Soc.* **2008**, *130*, 9254-9256; (b) L. Ackermann, S. Fenner, *Chem. Commun.* **2011**, *47*, 430-432; (c) Z. Wang, K. Li, D. Zhao, J. Lan, J. You, *Angew. Chem. Int. Ed.* **2011**, *50*, 5365-5369; (d) Heteroarylation: P. Xi, F. Yang, S. Qin, D. Zhao, J. Lan, G. Gao, C. Hu, J. You, *J. Am. Chem. Soc.* **2010**, *132*, 1822-1824; (e) Z. Wang, K. Li, D. Zhao, J. Lan, J. You, *Angew. Chem. Int. Ed.* **2011**, *50*, 5365-5369; (f) F. Gosselin, S. J. Savage, N. Blaquière, S. T. Staben, *Org. Lett.* **2012**, *14*, 862-865; (g) S. Liu, C. C. Tzschucke, *Eur. J. Org. Chem.* **2016**, 3509-3513; (h) S. P. Zucker, F. Wossidlo, M. Weber, D. Lentz, C. C. Tzschucke, *J. Org. Chem.* **2017**, *82*, 5616-5635; (i) Alkylation: Y. Tagawa, M. Nomura, H. Yamashita, Y. Goto, M. Hamana, *Heterocycles*, **1999**, *51*, 2385-2397; (j) B. Xiao, Z.-J. Liu, L. Liu, Y. Fu, *J. Am. Chem. Soc.* **2013**, *135*, 616–619; (k) Alkenylation: J. Wu, X. Cui, L. Chen, G. Jiang, Y. Wu, *J. Am. Chem. Soc.* **2009**, *131*, 13888–13889; (l) J. Ryu, S. H. Cho, S. Chang, *Angew. Chem. Int. Ed.* **2012**, *51*, 3677-3681; (m) A. Lehecq, K. Rousée, C. Schneider, V. Levacher, C. Hoarau, X. Pannecoucke, J.-P. Bouillon, S. Couve-Bonnaire, *Eur. J. Org. Chem.* **2017**, 3049-3054; (n) F. Roudesly, L. F. Veiros, J. Oble, G. Poli, *Org. Lett.* **2018**, *20*, 2346-2350; (o) V. V. Kouznetsov, L. Y. V. Méndez, C. E. P. Galvis, M. C. O. Villamizar, *New J. Chem.* **2020**, *44*, 12-19; (p) Acylation: R. Suresh, R. S. Kumaran, V. Senthilkumar, S. Muthusubramanian, *RSC Adv*. **2014**, *4*, 31685-31688; (q) Cyanation: Y. Tagawa, Y. Higuchi, K. Yamagata, K. Shibata, D. Teshima, *Heterocycles* **2004**, *63*, 2859-2862; (r) Amination, amidation: G. Li, C. Jia, K. Sun, *Org. Lett*. **2013**, *15*, 5198-5201; (s) G-H. Li, D-Q. Dong, Y. Yang, X-Y. Yu, Z-L. Wang, *Adv. Synth. Catal*. **2019**, *361*, 832-835.
[33] E. N. da Silva Júnior, G. A. M. Jardim, R. S. Gomes, Y.-F. Liang, L. Ackermann, *Chem. Comm.* **2018**, *5*4, 7398-7411.
[34] T. Shibata, Y. Matsuo, *Adv. Synth. Catal.* **2014**, *356*, 1516-1520.
[35] H. Hwang, J. Kim, J. Jeong, S. Chang, *J. Am. Chem. Soc.* **2014**, *136*, 10770–10776.
[36] (a) J. Jeong, P. Patel, H. Hwang, S. Chang, *Org. Lett.* **2014**, *16*, 4598–4601; (b) D. Gwon, H. Hwang, H. K. Kim, S. R. Marder, S. Chang, *Chem. Eur. J.* **2015**, *21*, 17200-17204.
[37] (a) Arylation: D. E. Stephens, J. Lakey-Beitia, G. Chavez, C. Ilie, H. D. Arman, O. V. Larionov, *Chem. Comm.* **2015**, 9507-9510; (b) D. E. Stephens, J. Lakey-Beitia, A. C. Atesin, T. A. Ateşin, G. Chavez, H. D. Arman, O. V. Larionov, *ACS Catal.* **2015**, *5*, 167−175; (c) K. Shin, S.-W. Park, S. Chang, *J. Am. Chem. Soc.* **2015**, *137*, 8584–8592; (d) G. E. M. Crisenza, E. M. Dauncey, J. F. Bower, *Org. Biomol. Chem.* **2016**, *14*, 5820-5825; (e) B. Wang, C. Li, H. Liu, *Adv. Synth. Catal.* **2017**, *359*, 3029–3034; (f) B. Ghosh, A. Biswas, S. Chakraborty, R. Samanta, *Chem. Asian J.* **2018***, 13*, 2388-2392; (g) J. Kim, K. Shin, S. Jin, D. Kim, S. Chang, *J. Am. Chem. Soc.* **2019**, *141*, 4137-4146; (h) J. Kim, S. Kim, D. Kim, S. Chang, *J. Org. Chem.* **2019**, *84*, 20, 13150–13158; (i) Y. Huang, X. Lv, H. Song, Y. Liu, Q. Wang, *Chin. Chem. Lett.* **2019**, doi: 10.1016/j.cclet.2019.11.028; (j) Amidation: S. Han, P. Chakrasali, J. Park, H. Oh, S. Kim, K. Kim, A. K. Pandey, S. H. Han, S. B. Han, I. S. Kim, *Angew. Chem. Int. Ed.* **2018**, *57*, 12737-12740; (k) C. You, T. Yuan, Y. Huang, C. Pi, Y. Wu, X. Cui, *Org. Biomol. Chem.* **2018**, *16*, 4728–4733; (l) A. K. Dhiman, S. S. Gupta, R. Sharma, R. Kumar, U. Sharma, *J. Org. Chem.* **2019**, *84*, 12871-12880; (m) Amination: A. Biswas, S. Sarkar, R. Samanta, *Chem. Eur. J.* **2019**, *25*, 3000-3004; (n) D.-Y. Li, Z.-L. Huang, P.-N. Liu, *Org. Lett.* **2018**, *20*, 2028-2032; (o) C. You, C. Pi, Y. Wu, X. Cui, *Adv. Synth. Catal.* **2018**, *360*, 4068-4072; (p) Alkenylation: R. Sharma, R. Kumar, U. Sharma, *J. Org. Chem.* **2019**, *84*, 2786-2797; (q) Acylation: X. Chen, X. Cui, Y. Wu, *Org. Lett.* **2016**, *18*, 3722-3725; (r) G. H. Li, D.-Q. Dong, X.-Y. Yu, Z.-L. Wang, *New J. Chem.* **2019**, *43*, 1667-1670; (s) Allylation: D. Kalsi, R. A. Laskar, N. Barsu, J. R. Premkumar, B. Sundararaju, *Org. Lett.* **2016**, *18*, 4198–4201; (t) Indolyl: E. Grenet, A. Das, P. Caramenti, J. Waser, *Beilstein J. Org. Chem.* **2018**, *14*, 1208-1214.
[38] M. Ye, G.-L. Gao, A. J. F. Edmunds, P. A. Worthington, J. A. Morris, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 19090–19093.
[39] J. M. Jacquelin, Y. Robin, A. Godard, G. Queguiner, *Can. J. Chem.* **1988**, *66*, 1135-1140.
[40] C. J. Rohbogner, S. Wirth, P. Knochel, *Org. Lett.* **2010**, *12*, 1984-1987.
[41] J. Li, C. Kornhaab, L. Ackermann, *Chem. Commun.* **2012**, *48*, 11343–11345.
[42] E. Tan, A. I. Konovalov, G. A. Fernández, R. Dorel, A. M. Echavarren, *Org. Lett.* **2017**, *19*, 5561-5564.
[43] (a) A. Banerjee, S. K. Santra, P. R. Mohanta, B. K. Patel, *Org. Lett.* **2015**, *17*, 5678−5681; (b) G. Liao, H. Song, X.-S. Yin, B.-F. Shi, *Chem. Comm.* **2017**, *53*, 7824-7827.
[44] K. Yan, B. Li, B. Wang, *Adv. Synth. Catal.* **2018**, *360*, 2113-2118.
[45] D. E. Stephens, O. V. Larionov, *Tetrahedron* **2015**, *71*, 8683-8716.
[46] H. Shi, Y. Lu, J. Weng, K. L. Bay, X. Chen, K. Tanaka, P. Verma, K. N. Houk, J.-Q. Yu, *Nature Chem.* **2020**, *12*, 399-404.
[47] A. Woschek, M. Mahout, K. Mereiter, F. Hammerschmidt, *Synthesis* **2007**, *10*, 1517-1522.
[48] M. R. Netherton, G. C. Fu, *Org. Lett.* **2001**, *3*, 4295-4298.
[49] We must point out that Fagnou's reaction could be reproduced on quinoline *N*-oxide (3 equiv.), giving 89% yield of 2-phenylquinoline *N*-oxide. 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.).
[50] 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. 47). 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.
[51] H.-Y. Sun, S. I. Gorelsky, D. R. Stuart, L.-C. Campeau, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *75*, 8180-8189.
[52] Y. Tan, F. Barrios-Landeros, J. F. Hartwig, *J. Am. Chem. Soc.* **2012**, *134*, 3683-3686.
[53] D. Whitaker, J. Burés, I. Larrosa, *J. Am. Chem. Soc.* **2016**, *138*, 8384-8387.
[54] M. D. Lotz, N. M. Camasso, A. J. Canty, M. S. Sanford, *Organometallics* **2017**, *36*, 165-171.
[55] S. Y. Lee, J. F. Hartwig, *J. Am. Chem. Soc.* **2016**, *138*, 15278-15284.
[56] See also: K. L. Bay, Y.-F. Yang, K. N. Houk, *J. Organomet. Chem.* **2018**, *864*, 19-25.
[57] Y. Park, Y. Kim, S. Chang, *Chem. Rev.* **2017**, *117*, 9247−9301.
[58] K. Fries, G. Finck, *Chem. Ber.* **1908**, *41*, 4271–4284.
[59] V. Snieckus, *Chem. Rev.* **1990**, *90*, 879–933.
[60] Crystallographic structures were deposited on the Cambridge Crystallographic Data Centre under CCDC numbers 2042478 for **56b** and 2042479 for **59**.
[61] When applying the conditions previously developed for C-2 functionalization (Table 1) to carbamate **2a**, we observed the formation of the corresponding 3-phenylquinoline in max. 5-10% yields. We were unable to improve this reaction.



[62] W. Ma, K. Graczyk, L. Ackermann, *Org. Lett.* **2012**, *14*, 6318–6321.
[63] D. Szamosvári, T. Böttcher, *Angew. Chem. Int. Ed.* **2017**, *56,* 7271-7275.
[64] (a) S. C. Leung, P. Gibbons, R. Amewu, G. L. Nixon, C. Pidathala, W. D. Hong, B. Pacorel, N. G. Berry, R. Sharma, P. A. Stocks, A. Srivastava, A. E. Shone, S. Charoensutthivarakul, L. Taylor, O. Berger, A. Mbekeani, A. Hill, N. E. Fisher, A. J. Warman, G. A. Biagini, S. A. Ward, P. M. O'Neill, *J. Med. Chem.* **2012**, *55*, 1844-1857; (b) T. Mogi, K. Matsushita, Y. Murase, K. Kawahara, H. Miyoshi, H. Ui, K. Shiomi, S. Ōmura, K. Kita, *FEMS Microbiol. Lett.* **2009**, *291*, 157–161; (c) A. Saleh, J. Friesen, S. Baumeister, U. Gross, W. Bohne, *Antimicrob. Agents Chemother.* **2007**, 1217–1222; (d) A. Nilsen, A. N. LaCrue, K. L. White, I. P. Forquer, R. M. Cross, J. Marfurt, *et al. Sci Transl Med.* **2013**, *5*7, 177ra37; (e) K. D. Lane, J. Mu, J. Lu, S. T. Windle, A. Liu, P. D. Sun, T. E. Wellems, *Proc. Natl. Acad. Sci. USA* **2018**, *115*, 6285–6290; (f) H. Ke, S. M. Ganesan, S. Dass, J. M. Morrisey, S. Pou, A. Nilsen, M. K. Riscoe, M. W. Mather, A. B. Vaidya, *PlosOne* **2019**, *14*, e0214023.