Organocatalytic Electrophilic Arene Amination: Rapid Synthesis of 2-Quinolones

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ABSTRACT: For decades, the synthesis of 2-quinolones, a crucial structural motif in pharmaceuticals and agrochemicals, has relied heavily on costly noble metal complexes and structurally complex ligands. Despite considerable efforts from synthetic chemists, a mild, metal-free, environmentally friendly, and cost-effective approach has remained elusive. This study introduces a robust, metal-free synthetic platform that leverages an innovative organoiodine-catalyzed electrophilic arene C(sp^2)-H amination strategy to efficiently produce a wide range of new and modifiable 2-quinolones. Moreover, this study allows ready synthetic access to novel 8-aryl-substituted 2-quinolones, uncovering new chemical spaces with significant potential for medicinal applications.

INTRODUCTION: Quinolones represent a prolific class of heterocyclic scaffolds with widespread applications in pharmaceuticals, agrochemicals, and functional organic materials. Since the discovery of quinine in *Cinchona* in 1811, pharmaceutical interest has surged in its structural isomers, e.g., 4-quinolones and 2-quinolones. The clinical approval of nalidixic acid in 1967 for treating urinary tract infections marked a significant milestone, followed by the commercialization of various fluoroquinolones as potent broad-spectrum antibiotics targeting both Gram-positive and Gram-negative bacteria. Concurrently, 2-quinolones, structural analogs of 4-quinolones, gained prominence in the pharmaceutical industry. Clinically approved drugs such as Indacaterol, Procaterol, Repirinast, Rebamipide, Cilostamide, and Brexipiprazole exemplify their diverse therapeutic applications (Figure 1). [1-2] Additionally, 2-quinolones are found in several natural products[3] and are candidates for anti-cancer (e.g., tipifarnib [4]) and anti-viral (e.g., anti-HIV) drugs.[5] Moreover, they play a pivotal role in organic functional materials, including cationic metal sensors, luminescent materials, fluorescent pH probes, and π-electron acceptors in dye-sensitized solar cells. [6-8]

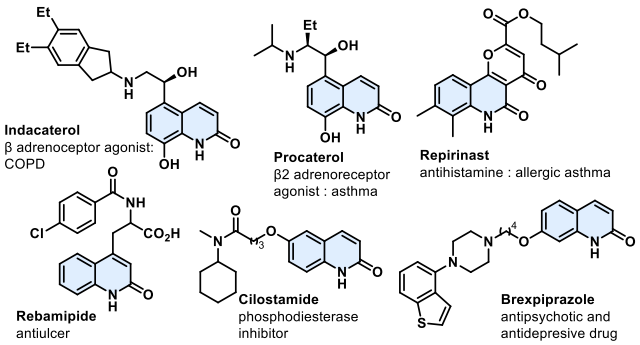
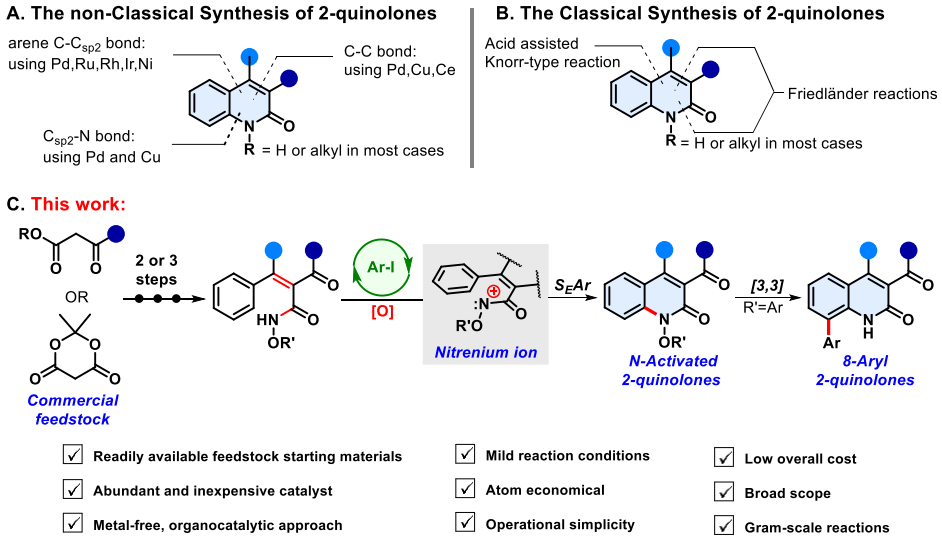


Figure 1: Clinically approved 2-quinolone based drugs.

Given the widespread application and economic impact of the 2-quinolone core, significant efforts have been made to develop synthetic strategies for its preparation.[9] Contemporary non-classical approaches predominantly rely on Pd-catalyzed cross-coupling and C–H activation methods.[10] These approaches saw substantial growth after R.F. Heck introduced the Pd-catalyzed two-component reaction, now known as the Heck reaction, in 1978.[11] While complexes of palladium remain the preferred catalysts, complexes of other transition metals such as copper (Cu), rhodium (Rh), ruthenium (Ru), silver (Ag), iridium (Ir), and nickel (Ni) have also been explored to improve overall efficiency (Scheme 1A). [12]

In the pursuit of an ideal synthetic strategy for a modifiable 2-quinolone core, the focus has shifted towards improving transition metal-free classical methods, notably modified Friedländer-type and Knorr-type reactions (Scheme 1B).[13-15] Unfortunately, strategies using basic mesoporous and bifunctional zeolite-catalyzed modified Friedländer reactions have faced limitations due to suboptimal yields at elevated temperatures.[16]

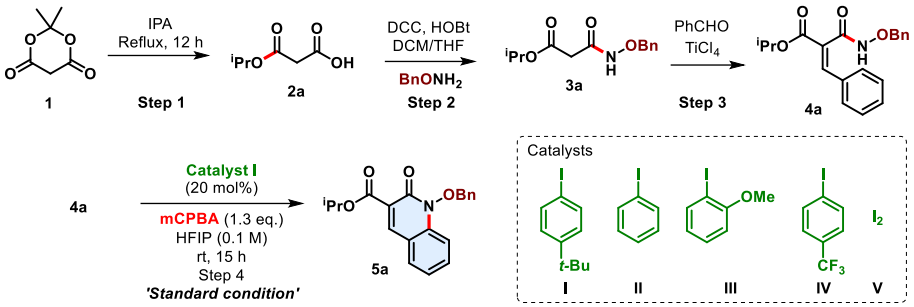
Despite considerable efforts, only a limited number of metal-free methods for accessing functionalized 2-quinolones have emerged. For instance, in 2014, Bui et al. reported a synthesis involving the condensation of 2-aminobenzophenones and acid chlorides under microwave irradiation.[17] Other notable contributions include Aksenov and Rubin's ring expansion strategy, Deng's DMAP-catalyzed cascade annulation, and Yu's independent discovery of a strong base-mediated lactamization approach using CO_2.[18-21] However, these advancements have primarily focused on accessing sparsely substituted 2-quinolone scaffolds, limiting their potential to enhance structural complexity. Consequently, only a handful of protocols are considered practical for route-scouting for 2-quinolones in medicinal applications, highlighting persistent challenges in synthesizing a 2-quinolone core from readily available chemical feedstock under mild, environmentally friendly, and cost-effective conditions.



Scheme 1: Evolution of the synthetic route of 2-quinolones

To address these challenges, a new, metal-free, organo-iodine-catalyzed C(sp^2)–N bond-forming strategy was developed for the efficient synthesis of easily modifiable *N*-activated 2-quinolones. This strategy leverages the catalytic generation of a key nitrenium ion intermediate, a highly reactive electrophilic nitrogen species, using a readily available organo-iodine catalyst in combination with an external oxidant. Nitrenium ions, characterized by a bivalent structure with a lone pair of electrons and a positive charge, are emerging electrophilic aminating agents used in C-N bond-forming reactions. [22-26] Furthermore, this study demonstrates the intriguing capability of *N*-aryloxy 2-quinolones to undergo a facile [3,3]-sigmatropic rearrangement, leading to the synthesis of novel 8-aryl-substituted 2-quinolones. This discovery opens avenues for exploring uncharted chemical spaces within the realm of 2-quinolones, showcasing significant potential for medicinal applications (Scheme 1C).

RESULTS AND DISCUSSION: Our synthetic efforts began with designing a concise route for preparing the crucial *N*-hydroxyacrylamide derivative **4a**, an essential substrate for the proposed organo-iodine-catalyzed electrophilic arene amination method. Starting with commercially available Meldrum's acid **1**, we converted it into the corresponding half ester **2a**. A subsequent amidation reaction produced the unsymmetrical ester amide **3a**, which underwent a straightforward Knoevenagel-type condensation with benzaldehyde to yield the desired substrate **4a** as an easily separable E/Z mixture (Table 1). Initial exploration of the key organo-iodine-catalyzed electrophilic arene C(sp^2)-H amination revealed that combining **4a** with catalyst **I** and *m*-CPBA in HFIP produced the expected *N*-activated 2-quinolone derivative **5a** with a promising 52% yield. This result provides proof-of-concept for our envisioned electrophilic arene amination strategy (Table 1, entry 1). [27]



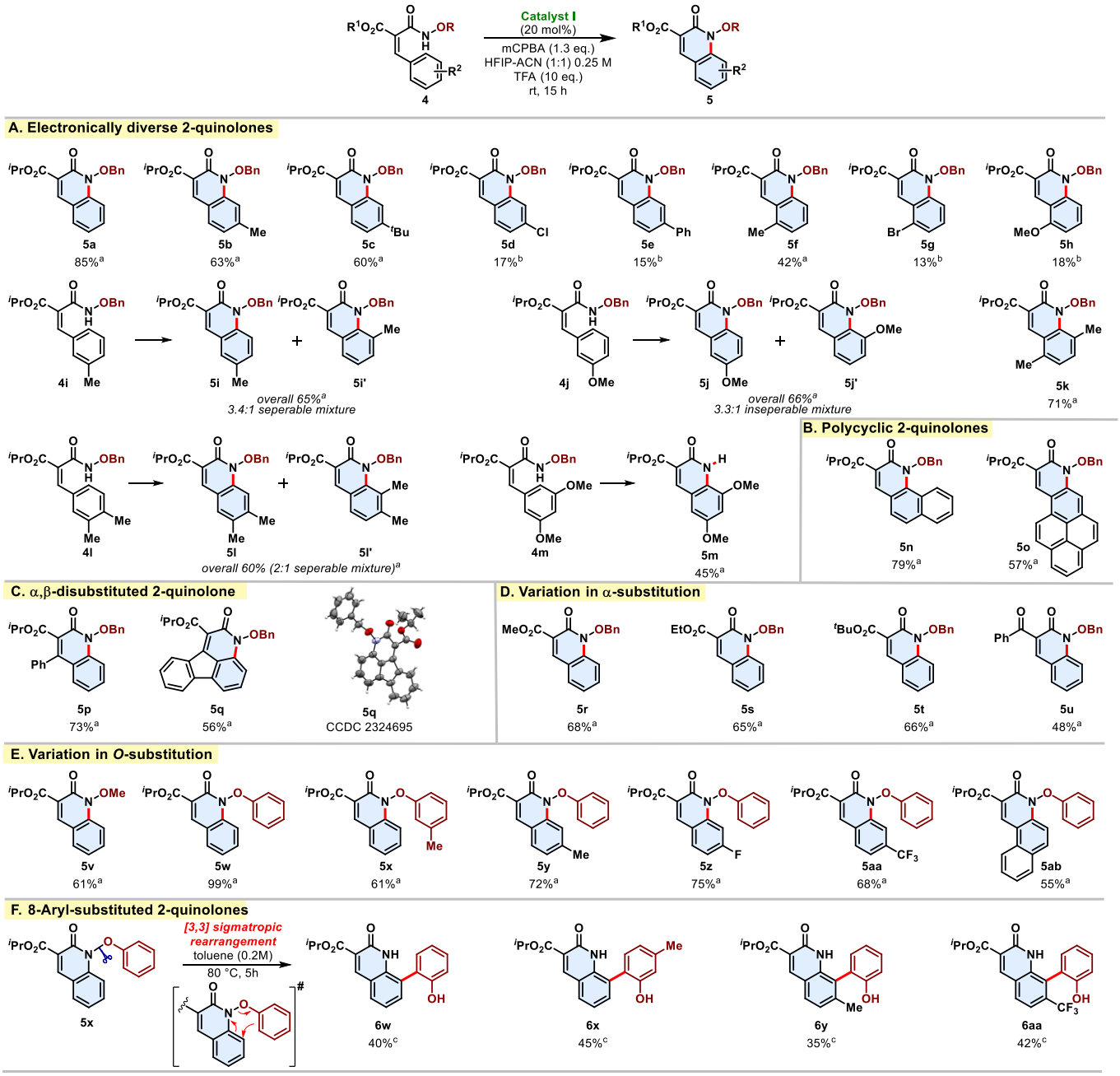
Entry[a]	Deviation from the standard condition (step 4)	Yield (%) of **5a**
1	none	52
2	Reaction without I	<5[b]
3	Reaction without mCPBA	<5[b]
4	TFE (0.1 M) instead of HFIP	51
5	ACN (0.1 M) instead of HFIP	46
6	HFIP (0.25 M)	69
7	TFE (0.25 M) instead of HFIP	60
8	HFIP-ACN (1:1) (0.25 M) instead of HFIP	70
9	TFE-ACN (1:1) (0.25 M) instead of HFIP	67
10	**II** instead of **I**; in HFIP-ACN (1:1) (0.25 M)	66
11	**III** instead of **I**; in HFIP-ACN (1:1) (0.25 M)	65
12	**IV** instead of **I**; in HFIP-ACN (1:1) (0.25 M)	64
13	**V** instead of **I**; in HFIP-ACN (1:1) (0.25 M)	9
14	AcOOH instead of mCPBA; in HFIP-ACN (1:1)	<5[b]
15	H_2O_2 instead of mCPBA; in HFIP-ACN (1:1) (0.25	<5[b]
16	AcOH (5.0 eq.) as additive; in HFIP-ACN (1:1)	51
17	TFA (5.0 eq.) as additive; in HFIP-ACN (1:1)	74
18	**TFA (10.0 eq.) as additive; in HFIP-ACN (1:1)**	**85**
19	$PhI(OAC)_2$ (1.0 eq.) instead of **I** and mCPBA	47

[a]Reactions carried out in 0.25 mmol scale. Compound **4a**, catalyst and oxidant were suspended in the given solvent followed by the addition of the additive and stirred at rt (25 °C) for 15 hrs. All given yields are isolated yields. [b] NMR yield.

Table 1: Optimization of the reaction conditions for the catalytic electrophilic amination step

Encouraged by our initial success, we conducted a comprehensive exploration of the critical electrophilic arene C(sp^2)-H amination reaction through various control experiments. In the absence of catalyst **I** and the external oxidant (mCPBA), we detected no product **5a**, underscoring the essential roles of both the aryl iodide catalyst and the oxidant in the electrophilic amination step (entries 2-3). Next, we focused on optimizing the reaction conditions by systematically screening solvents, catalysts, and oxidants. Solvent screening revealed that trifluoroethanol and acetonitrile were not advantageous compared to HFIP, as they did not improve the isolated yield for product **5a** (entries 4-5). Interestingly, increasing the dilution of the reaction medium enhanced the conversion (entries 6-7). The combination of HFIP and acetonitrile (1:1) emerged as the most effective reaction medium (entries 8-9). During the catalyst screening, we explored several electronically dissimilar aryl iodides (**II-IV**), but none demonstrated superior outcomes compared to catalyst **I** (entries 10-12). Using molecular iodine (I_2) in place of catalyst **I** resulted in a poor yield of only 9% for **5a** (entry 13). External oxidants other than mCPBA, such as peracetic acid ($MeCO_3H$) and hydrogen peroxide (H_2O_2), were unsuccessful in cyclizing substrate **4a** (entries 14-15). Brønsted acids were expected to enhance catalytic efficiency, therefore, we introduced acetic acid and trifluoroacetic acid (TFA) as additives (entries 16-17). Adding 5 equivalents of TFA proved beneficial, slightly improving the yield of **5a** to 74% (from 70% without the additive). Increasing the amount of TFA from 5 equivalents to 10 equivalents resulted in the optimal reaction conditions, yielding the desired 2-quinolone product **5a** in 85%

yield (entry 18). Additionally, employing stoichiometric amounts of hypervalent iodine reagent[28] instead of using the combination of *m*CPBA and catalyst **I** furnished product **5a** in only 47% isolated yield (entry 19).



[a] Unless noted otherwise, all catalytic electrophilic arene C(sp^2)-H amination reactions are carried out with *N*-hydroxy acrylamide **4** (0.5 mmol) in presence of catalyst **I** (20 mol%), mCPBA (1.3 equiv.), TFA (10.0 equiv.) and as a solution in HFIP-acetonitrile (1:1) mixture at rt for 15 hours. All yields are isolated yields of 2-quinolones **5** after flash column chromatography. [b] Reaction carried out for 24 hours. [c] [3,3] Sigmatropic rearrangement was carried out with 2-quinolone **5** (0.25 mmol) under heating at 80 °C for 5 hours in presence of toluene. All yields are isolated yields of compound **6** after flash column chromatography. See Supporting Information for detailed procedures.

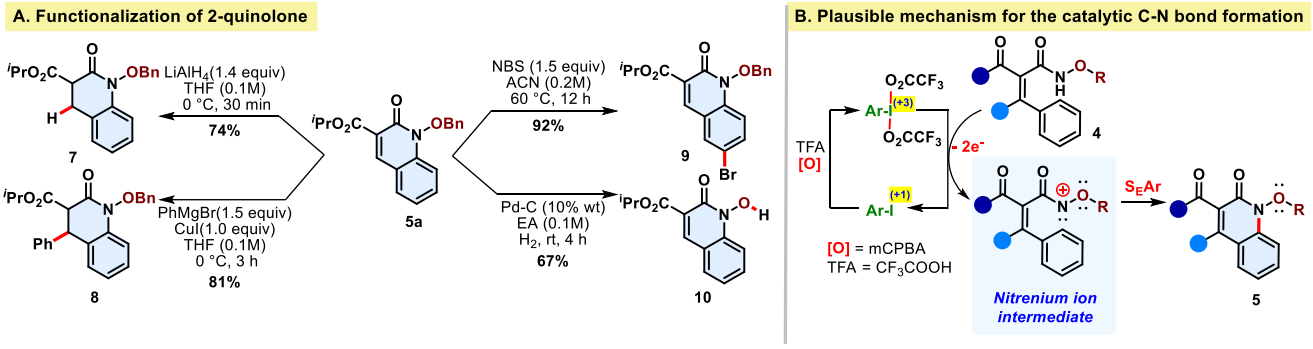
Scheme 2: Scope of *N*–activated 2-quinolones and novel 8-aryl-substituted 2-quinolones.

Having successfully optimized the reaction conditions for the key intramolecular electrophilic arene C(sp^2)-H amination step, we explored the scope and applicability of this innovative synthetic strategy to produce a structurally diverse library of *N*-activated 2-quinolones (Scheme 2). First, we prepared an electronically diverse collection of *N*-hydroxyacrylamide (**4**) substrates from readily available 1,3-dicarbonyl compounds in just two or three straightforward steps (See supporting information on page 4-7).[27] The *N*-hydroxyacrylamides **4** were then

converted to the corresponding 2-quinolones (Scheme 2A, **5a** to **5ac**; 29 examples) in moderate to good yields using the optimized cyclization conditions. Notably, electron-neutral (**4a-4c**, **4i** & **4k-4l**) and electron-rich β-aryl *N*-hydroxyacrylamides (**4j** & **4m**) cyclized more readily compared to their electron-deficient (**4d**, **4e**, **4g**) counterparts. Unsymmetrical *meta*-substituted β-aryl *N*-hydroxyacrylamides (**4i** & **4j**) yielded regioisomeric mixtures of the corresponding 2-quinolones (**4i** → **5i** & **5i'** as a separable mixture and **4j** → **5j** & **5j'** as an inseparable mixture) with overall yields of 65% and 66%, respectively. The substrate with a 3,4-di-Me-substituted β-aryl ring (**4l**) furnished a separable 2:1 regioisomeric mixture of 2-quinolones (**5l** & **5l'**) with an overall isolated yield of 60%. However, the substrate with the 3,5-di-methoxy-substituted β-aryl ring (**4m**) afforded 2-quinolone **5m** as a single regioisomer in which the *N*-O bond was cleaved. We also investigated the cyclization of two substrates (**4n** & **4o**) which had fused aromatic rings at their β-position, yielding completely new polycyclic *N*-activated 2-quinolones (Scheme 2B; **5n** & **5o**) in moderate to good yields. Additionally, two β,β-disubstituted *N*-hydroxyacrylamides (**4p** & **4q**), prepared via the condensation of benzophenone and fluorenone with unsymmetrical ester amide **3a**, efficiently underwent annulation, furnishing the corresponding highly substituted 2-quinolone **5p** and the novel tetracyclic 2-quinolone **5q** with isolated yields of 73% and 56%, respectively. The structure of **5q** was conclusively confirmed by SCXRD (Scheme 2C).

Shifting our focus, we explored different N-OR moieties in the cyclization precursors (**4**), synthesized from various *O*-substituted hydroxylamines. Substituting the *N*-benzyloxy group with *N*-methoxy group exhibited similar reactivity during the cyclization reaction (Scheme 2E; **5v**). Surprisingly, substrates featuring *N*-aryloxy groups showed enhanced reactivity during C–N bond formation, with *N*-phenyloxy phenylacrylamide (**4w**) producing the corresponding 2-quinolone **5w** in quantitative yield. Encouraged by this result, we prepared five cyclization substrates, each featuring both the *N*-phenyloxy group and an electronically diverse β-aryl ring (**4x**-**4ab**). Their cyclization under the optimized electrophilic amination conditions furnished the anticipated 2-quinolones (**5x**-**5ab**) in moderate to good yields.

Given the scarcity of *N*-activated 2-quinolones in existing literature and their untapped synthetic potential, we investigated the viability of a [3,3]-sigmatropic rearrangement for *N*-aryloxy 2-quinolones. This rearrangement was anticipated to facilitate the translocation of the aryloxy group from the *N*-center to the neighboring aryl ring (Scheme 2F). Remarkably, when compound **4w** was heated at 80 °C in toluene, we observed the formation of 8-aryl-substituted 2-quinolone **6w** in 40% yield. This powerful new transformation opened a previously unexplored chemical space within 2-quinolones. Encouraged by this breakthrough, we extended our exploration to similar *N*-aryloxy 2-quinolones (**5x**, **5y** & **5aa**). The results confirmed the generality of this newly developed [3,3]-sigmatropic rearrangement, yielding the anticipated novel 8-aryl-substituted 2-quinolones (Scheme 2F; **6x**, **6y** & **6aa**) in 45%, 35%, and 42% yields, respectively. This finding not only highlights the versatility of the transformation but also emphasizes its potential applicability for synthesizing diverse 8-aryl-substituted 2-quinolones.



Scheme 3: Functionalization of 2-quinolones and plausible mechanism for the catalytic C–N bond formation.

In our pursuit of expanding the modifiability of our 2-quinolones, we explored transformations targeting the embedded Michael acceptor in **5a**. Using $LiAlH_4$, we achieved a 1,4-reduction, yielding the dihydroquinolinone derivative **7** in 74% yield. Treating **5a** with an organocuprate derived from an aryl Grignard reagent (PhMgBr)

facilitated the formation of the β-phenyl substituted dihydroquinolinone derivative **8** in 81% yield. Bromination of **5a** with NBS produced a clean mono-brominated product, selectively brominating the activated fused phenyl ring *para* to the quinolone nitrogen atom, in 92% yield. Finally, catalytic hydrogenation in the presence of palladium on carbon induced a chemoselective *O*-debenzylation, leading to the formation of *N*-hydroxy 2-quinolone **10**. These representative functionalizations demonstrate the convenient modifiability of the 2-quinolone core obtained through this new synthetic platform. The facile incorporation of diverse functional groups paves the way for synthesizing more decorated 2-quinolone derivatives with tailored physical, chemical, and biological properties (Scheme 3A).

In our proposed mechanistic pathway, the key step involves an electrophilic arene C(sp^2)-H amination reaction catalyzed by an aryl iodide, leading to the formation of the final arene C(sp^2)–N bond. Control experiments demonstrated the essential roles of both the aryl iodide and the oxidant in the reaction (Table 1, entries 2-3). We propose that in the presence of stoichiometric amounts of *m*CPBA, the aryl iodide catalyst undergoes a two-electron oxidation to produce a hypervalent iodine species (in the +3 oxidation state), which then oxidizes the *N*-hydroxyacrylamide **4** into the corresponding nitrenium ion intermediate. The presence of 10 equivalents of trifluoracetic acid (TFA) was important to ensure good conversion and high yields – presumably via the formation of a bis-(trifluoroacetoxy)iodine(III) intermediate. Ultimately, the β-aryl ring of compound 4 undergoes an electrophilic aromatic substitution reaction (S_EAr), resulting in the formation of 2-quinolone **5**. Notably, the electron-deficient nature of the β-aryl ring, due to its attachment to a Michael acceptor, does not impede the success of the aromatic electrophilic substitution reaction. However, instances of low conversions observed in cases with β-aryl rings bearing electron-withdrawing groups (Scheme 2A; **5d**, **5e**, **5g**) support this mechanistic pathway (Scheme 3B).

CONCLUSION:

In conclusion, we have successfully established a robust synthetic platform that provides a facile route to a diverse array of both rare and new 2-quinolone scaffolds, with significant potential in medicinal chemistry applications. This achievement is made possible through the strategic application of the organo-iodide-catalyzed electrophilic amination reaction. Our newly developed strategy offers several advantages over previously reported classical and non-classical synthetic approaches:

1. The elimination of toxic and costly noble metals and ligands, marking a significant improvement over previous non-classical methods.

2. The successful utilization of abundant and environmentally friendly aryl iodide as an organocatalyst.

3. The use of commercially available feedstock chemicals as starting materials.

4. The avoidance of harsh reaction conditions and reagents, addressing a major drawback of classical methods.

5. The establishment of an operationally simple, cost-effective, and atom-economical alternative route for constructing easily modifiable N-activated 2-quinolones.

Furthermore, our exploration led to the discovery of novel 8-aryl-substituted 2-quinolones through a facile [3,3]-sigmatropic rearrangement. In summary, this work not only enables the preparation of 2-quinolones with increased molecular complexity but also introduces a new chemical space with great potential for applications in the pharmaceutical and agrochemical industries.

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