JOC The Journal of Organic Chemistry

Article

On-water Synthesis of 2-Substituted Quinolines from 2-Aminochalcones Using Benzylamine as the Nucleophilic Catalyst

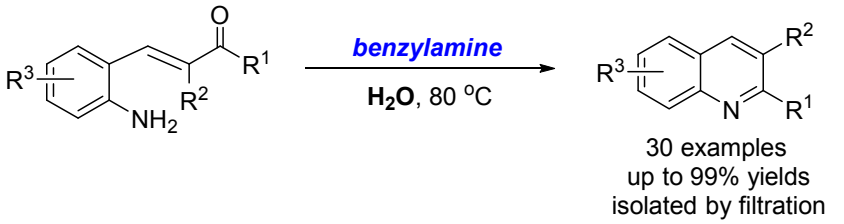
So Young Lee, and Cheol-Hong Cheon

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b01675 • Publication Date (Web): 08 Oct 2018

On-water Synthesis of 2-Substituted Quinolines from 2-Aminochalcones Using Benzylamine as the Nucleophilic Catalyst

So Young Lee and Cheol-Hong Cheon*

Department of Chemistry, Korea University, 145 Anam-ro, Seongbuk-gu, Seoul 02841, Republic of Korea, Phone: +82-2-3290-3147; Fax: +82-2-3290-3121; E-mail: cheon@korea.ac.kr



- simple operation	*- broad substrate scope*
- easy product isolation	*- good functional group tolerance*
- recycling of catalyst	*- scale-up synthesis*

Abstract

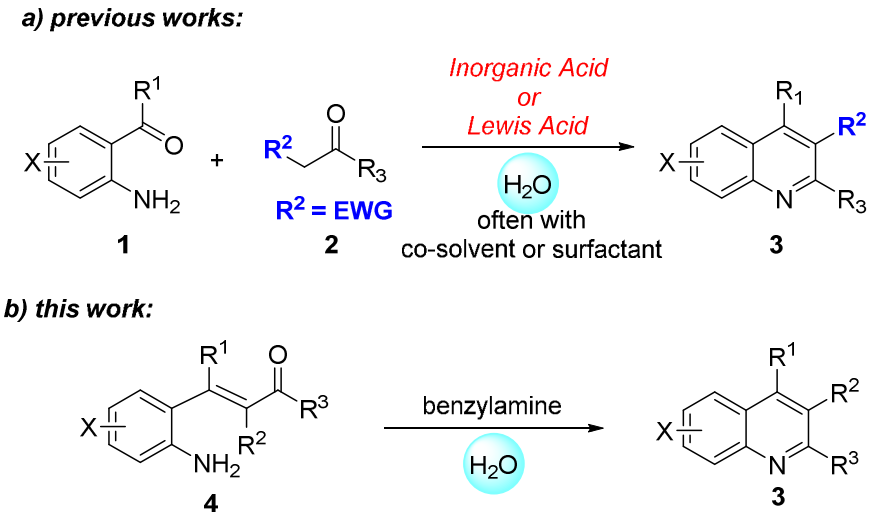
On-water synthesis of 2-substituted quinolines from 2-aminochalcone derivatives was developed using benzylamine as the nucleophilic catalyst. Various 2-aminochalcones could be applied to this protocol, and the desired 2-substituted quinoline products were isolated in excellent yields by simple filtration. Furthermore, we elucidated the role of benzylamine in this transformation and provided the detailed reaction mechanism. This protocol has several additional advantages, such as simple operation, broad substrate scope, good functional group tolerance, easy product isolation, recycling of the catalyst, and gram-scale synthesis.

Introduction

Water is an inexpensive, naturally abundant, safe, non-toxic, and environmentally benign solvent; hence, the development of novel organic reactions in aqueous media has attracted tremendous attention from the chemical community.[1,2] In addition, since many organic compounds are not soluble in water, the resulting products can be precipitated out from the aqueous reaction medium after the reaction. Consequently, the products can be easily isolated by simple filtration without tedious work-up and purification procedures. Ironically, solubility is considered a prerequisite for the reactivity of organic transformations. Therefore, the low solubility of organic compounds in water has triggered the development of several alternative approaches to increase the effectiveness of "aqueous reactions", such as the use of organic co-solvents, introduction of polar functional groups, and use of solubilizing materials for the starting materials. However, these methods often tend to diminish or even negate the advantages of water as the reaction medium over traditional solvents.[2a] Thus, it is highly desired to develop organic transformations in aqueous media with either no additives or readily available additives without specific treatments unless absolutely necessary.

Quinolines are important building blocks found in biologically active natural products, pharmaceuticals and materials science;[3] hence, considerable effort has been made to develop environmentally benign synthetic protocols for quinoline derivatives.[4] Along this line, several protocols have been developed for the synthesis of quinolines using water as the reaction medium.[5,6] However, most of the previous protocols are based on the Friedländer reaction, a condensation reaction between *ortho*-aminoaryl ketones or aldehydes **1** and ketones **2** having an active α-methylene unit, mostly, 1,3-dicarbonyl compounds (Scheme 1a).[5,6] In addition, these protocols generally require strong Brønsted acids or toxic transition metal-based Lewis acids to facilitate the formation of quinolines, which often leads to the poor functional group tolerance.[5] Furthermore, surfactants or ionic liquids would be employed as additives to

increase the solubility of the starting materials and/or catalysts in aqueous systems. However, in these approaches, either the additives and/or catalysts cannot be recycled, or additional steps are required to recover and recycle these additives.[6]



Scheme 1. Comparison of Previous Methods with Our Method for On-water Synthesis of Quinolines

Considering the limitations of the previous protocols for the synthesis of quinolines in aqueous media, it is highly desirable to develop organic transformations for the synthesis of quinolines in aqueous media using readily available catalysts/promotors without particular treatments. In this Article, we disclose the development of a novel protocol for the on-water synthesis of quinolines **3** from 2-aminochalcones **4** using benzylamine as the nucleophilic catalyst (Scheme 1b). Various 2-aminochalcone derivatives **4** could be applicable to this protocol, and the desired quinoline products **3** were obtained in excellent yields by simple filtration of the resulting quinolines from the reaction mixture. Mechanistic studies strongly suggested that this reaction would proceed though conjugate addition of benzylamine to 2-aminochalcones **4**, followed by condensation reaction between the amino and carbonyl group,

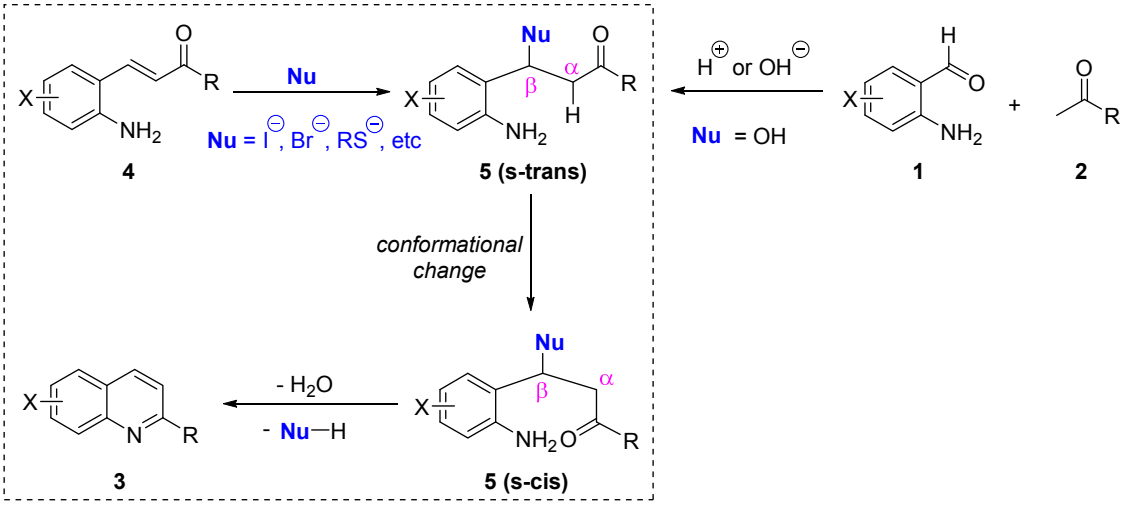
and subsequently elimination of benzylamine generating quinolines **3**. Furthermore, benzylamine could be recycled several times without any loss of its catalytic activity. Extremely simple operation, broad substrate scope, good functional group tolerance, and gram-scale synthesis are the additional advantages of this protocol.

Results and Discussion

Among the various quinoline derivatives, 2-substituted quinolines **3** have attracted considerable attention from the chemical community, since they not only exhibit interesting biological activities[7] but also serve as key building blocks in material sciences, for example, in organic light-emitting diodes (OLEDs)[8]. Thus, a great deal of effort has been made to develop new protocols toward the synthesis of 2-substituted quinolines **3**.[9] Among the various protocols developed, the dehydrative cyclization of 2-aminochalcones **4** is considered one of the most straightforward protocols for the synthesis of 2-substituted quinolines.[10-12] However, 2-aminochalcones **4** cannot be converted into the corresponding quinolines **3** because they exist in a stable (*E*)-configuration, where the amino group is positioned far away from the carbonyl group, preventing them from undergoing the condensation reaction.[13] Thus, most of the previous methods have been aimed to bring these two functional groups in a close position to react with each other by changing the stable (*E*)-configuration of the double bond to the unstable but reactive (*Z*)-configuration via the following approaches: either photoisomerization under UV and/or visible light,[10] chemical isomerization with a stoichiometric amount of iodine or selenium chloride in the presence of a base,[11] or chemical isomerization with a strong Brønsted acid[12].

Very recently, we developed a highly efficient protocol for the synthesis of 2-substituted quinolines **3** from 2-aminochalcones **4** in organic solvents using a nucleophile (Nu^-) as the catalyst (Scheme 2).[14] The nucleophile underwent conjugate addition to the α,β-

unsaturated carbonyl group in **4**, generating the corresponding saturated ketones **5**, in which the two amino and carbonyl groups could be positioned close enough to undergo condensation between these two functional groups through conformational change about the C_α-C_β single bond. Subsequent elimination of the nucleophile afforded **3** and the catalyst was regenerated. During the investigation of the reaction parameters in our previous studies,[14] water was found to promote this transformation, although it was not as efficient as other nucleophilic catalysts.[15] Furthermore, intermediate **5** (where Nu = OH), generated by the conjugate addition of water to ketone **4**, would be the same intermediate in the proposed mechanism of the Friedländer reaction; **5** could be formed by the addition of ketones **2** to 2-aminobenzaldehyde derivative **1**.[13] Thus, we investigated the conversion of **4** into **3** in water, where water would function as a nucleophilic catalyst.



Scheme 2. Working Hypothesis for On-Water Synthesis of Quinolines **3** from 2-Aminochalcones **4**.

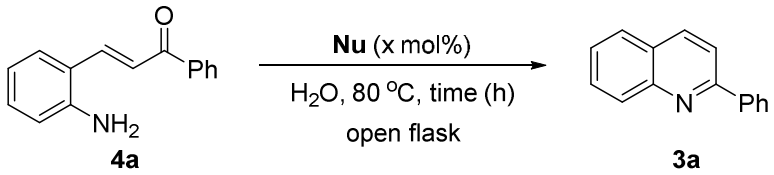
Based on the aforementioned idea, we investigated the possibility of synthesizing **3** from **4** in water (Table 1). Contrary to our expectation, when **4a** was subjected to dehydrative cyclization in water, quinoline **3a** was not formed and the starting material remained unreacted in the reaction mixture even after a long time (entry 1). We speculated that the

inefficiency of this transformation in water might be ascribed to the intrinsic low reactivity of water used as the nucleophilic catalyst under these conditions.[16] Thus, we decided to investigate a more nucleophilic reagent as the potential catalyst for this transformation in aqueous media. Since iodide was previously identified as the optimal nucleophilic catalyst in organic solvents,[14] we first explored the feasibility of using iodide as the potential catalyst for this transformation in water. However, the reaction did not proceed at all with iodide as a potential nucleophilic catalyst (entry 2). Since iodide is completely water-soluble, the effective concentration of iodide around **4a** in an aqueous system would be very low, which might be responsible for its poor efficiency as a nucleophilic catalyst in water. Thus, we explored several non-ionic nucleophiles as potential catalysts for this transformation. Fortunately, when using thiol, the desired quinoline **3a** was formed, albeit in low yield (entry 3). Encouraged by this result, we screened several different nucleophiles for this transformation (entries 4-6). Among the nucleophiles tested, benzylamine was the most efficient catalyst: with 10 mol% of benzylamine, **3a** was obtained in 67% yield (entry 5).

Next, we investigated the effect of an additional alkyl group on the nitrogen atom in benzylamine on this quinoline synthesis. Introduction of an alkyl group onto the nitrogen atom considerably decreased the catalytic efficiency of benzylamine; secondary benzylamine provided **3a** in low yield, while tertiary benzylamine did not furnish the product at all (entries 7 and 8). To further improve the yield of **3a**, the effect of the amount of benzylamine on this formation was examined and was found to have a beneficial influence on this transformation (entries 5, 9-11). Although the reaction did not complete with 10 mol% of benzylamine providing quinoline 3a in 67% even after 24 h (entry 5), the reaction proceeded to completion with more than 50 mol% of benzylamine and the rate of this reaction considerable increased with the amount of benzylamine (entries 9-11). Among the amount of benzylamine tested, we decided to use a stoichiometric amount of benzylamine as the optimal amount for this

transformation. Furthermore, we could easily isolate **3a** in quantitative yield by simple filtration from the reaction mixture (entry 10).

Table 1. Screening of Nucleophiles



4a **3a**

Entry	**Nu**	(mol%)	time (h)	yield[a] (%)
1	-	-	24	N.R.[b]
2	NaI	10	6	N.R.[b]
3	benzyl mercaptan	10	6	12
4	benzyl alcohol	10	6	N.R.[b]
5	benzylamine	10	6	67 (67)[c]
6	PPh_3	10	6	N.R.[b]
7	*N*-methylbenzylamine	10	6	9
8	*N,N*-dimethylbenzylamine	10	6	N.R.[b]
9	benzylamine	50	2.5	99
10	benzylamine	100	1	99 (99)[d]
11	benzylamine	200	0.5	99

[a] Yield was determined by ^{1}H NMR analysis of the crude mixture.

[b] No Reaction

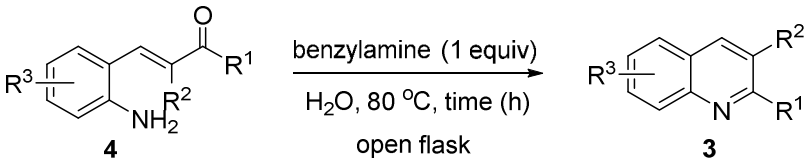
[c] The number in parenthesis indicated yield of **3a**.

[d] The number in parenthesis indicated isolated yield of **3a** by filtration.

With the optimized conditions (100 mol% benzylamine, H_2O, open flask, 80 ^oC) in hand, we investigated the substrate scope of 2-aminochalcones **4** in this transformation (Table 2). A variety of 2-aminochalcone derivatives **4** could be applied to this protocol, and the desired quinolines **3** were obtained in excellent yields (entries 1-15). The electronic effect of the aryl group (R^1) did not play a notable role in this transformation; the desired quinolines **3** were obtained in excellent yields, regardless of the electronic nature of the aryl group (R^1). Notably, that various functional groups were well-tolerated in this transformation. In particular, substrates bearing acid-sensitive functional groups such as acetals, silyl ethers, ethers and esters could be used in this protocol to furnish the desired quinolines **3** in excellent yields (entries 2, 7 and 9-11). In addition, this protocol could be applicable to 2-aminochalcones bearing fused aromatic and heteroaromatic moieties affording **3** in excellent yields (entries 16-19).

Next, the substituents (R^3) on the 2-aminophenyl ring were explored on the efficiency of this transformation (entries 20-26). The electronic effect and position of the substituent on the ring had little influence on the efficiency of this transformation. Thus, **3** could be obtained in excellent yields, regardless of the electronic nature and the relative position of the R^3 group. Furthermore, the protocol could be extended to the synthesis of quinolines bearing an alkyl group at the 2-position. When alkyl 2-aminostyryl ketones were subjected to the standard conditions, the desired products were obtained in high to excellent yields (entries 27-29).[17] Finally, this protocol was applied to the synthesis of 2,3-disubstituted quinolines; the reaction of α-substituted 2-aminochalcone **4ad** provided 2,3-disubstituted quinoline **3ad** in 97% yield (entry 30). Note that the resulting quinolines **3** could be easily isolated in pure form by either simple filtration for solid quinolines or simple extraction with ethyl acetate to remove benzylamine from the reaction mixture.[18]

Table 2. Substrate Scope



entry	3	R^1	R^2	R^3	time (h)	yield (%)
1	**3a**	Ph	H	H	1	99
2[a]	**3b**	4-$MeOC_6H_4$	H	H	1	99
3[a]	**3c**	4-MeC_6H_4	H	H	1	99
4	**3d**	4-FC_6H_4	H	H	2	94
5	**3e**	4-ClC_6H_4	H	H	1	99
6	**3f**	4-BrC_6H_4	H	H	1	99
7[a]	**3g**	4-$MeO_2CC_6H_4$	H	H	1	99
8[a]	**3h**	4-HOC_6H_4	H	H	5	99
9	**3i**	4-$THPOC_6H_4$	H	H	1	87
10	**3j**	4-$TBSOC_6H_4$	H	H	2	76 (23)[d]
11	**3k**	4-$TIPSOC_6H_4$	H	H	3	99
12[a]	**3l**	2-MeC_6H_4	H	H	2	99
13[a]	**3m**	3-MeC_6H_4	H	H	2	94
14[a]	**3n**	2-BrC_6H_4	H	H	1	99
15[a]	**3o**	3-BrC_6H_4	H	H	1	99
16[a]	**3p**	1-naphthyl	H	H	2	99
17[c]	**3q**	2-naphthyl	H	H	4	97
18	**3r**	2-furyl	H	H	3	98
19[a]	**3s**	2-thienyl	H	H	4	97
20[a]	**3t**	Ph	H	6-F	3	99

21[a]	**3u**	Ph	H	6-Cl	3	91
22[a]	**3v**	Ph	H	6-Br	3	99
23	**3w**	Ph	H	6-MeO	3	91
24[a]	**3x**	Ph	H	7-Br	3	99
25[a]	**3y**	4-$MeOC_6H_4$	H	6-MeO	5	99
26[b]	**3z**	Ph	H	6,8-Br_2	6	97
27	**3aa**	Methyl	H	H	3	67
28[a]	**3ab**	Isopropyl	H	H	4	83
29[b]	**3ac**	*tert*-Butyl	H	H	4	97
30	**3ad**	Ph	Me	H	24	97

[a] 3 Equivalents of benzylamine was used.

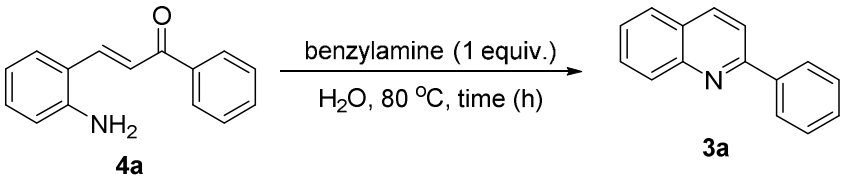
[b] 5 Equivalents of benzylamine was used.

[c] 5 Equivalents of *N*-methylbenzylamine was used.

[d] The TBS group was partly hydrolyzed during the reaction to afford **3h** in 23% yield.

With these excellent results in hand, we further attempted to demonstrate the advantage of this protocol. Since this transformation proceeded in a clean manner (without the formation of side products) and benzylamine should not be consumed after each transformation, we expected that the benzylamine solution would be effectively recycled (Table 3). To our delight, the benzylamine solution could be recycled more than 5 times, and **3a** was obtained in excellent yield even after 5 runs, although a slightly longer reaction time was required with each run.

Table 3. Recycle Studies [a]



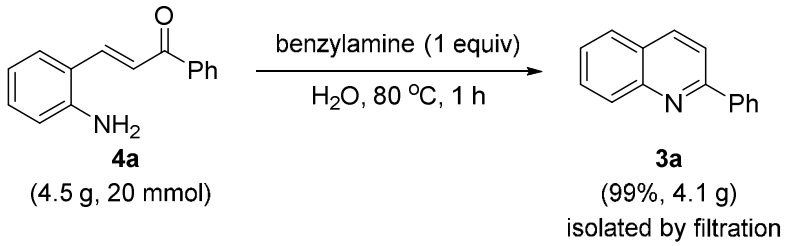
4a **3a**

entry	recycle run	time (h)	yield (%)[b]
1	0	1	99
2	1	3	99
3	2	4	99
4	3	4.5	99
5	4	5	99
6	5	5	57

[a] A 3.0 mL solution of aqueous benzylamine solution (0.10 M, i.e., 0.30 mmol of benzylamine in 3.0 mL of H_2O) was prepared. A suspension of **4a** (0.10 mmol) in the abovementioned benzylamine solution (1.0 mL) was heated to 80 °C in an open flask. After completion of the reaction, the reaction mixture was filtered and the solid collected was washed with the remaining solution of benzylamine (1.0 mL x 2) to provide **3a** in pure form without further purification. Then, the filtrate (the aqueous benzylamine solution) was re-used as the medium for the next reaction to test its catalytic efficiency.

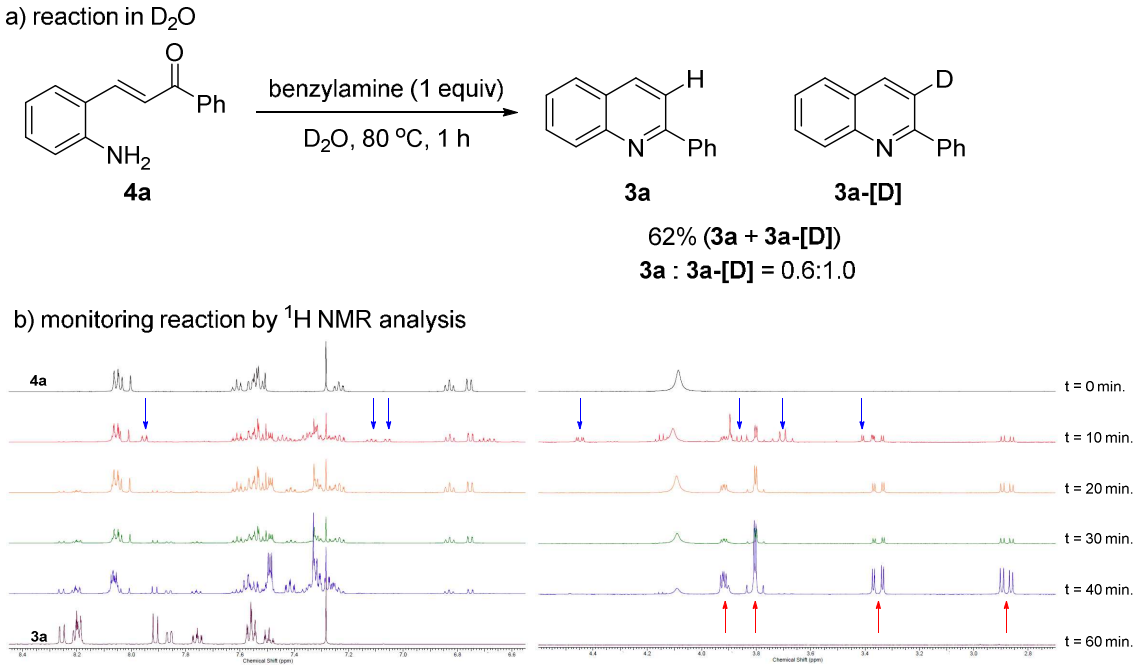
[b] Isolated yield of **3a** by filtration.

Next, we attempted to demonstrate the practicality of this protocol for a large-scale reaction (Scheme 3). To our delight, this transformation could be performed on a 20-mmol scale, and **3a** was obtained in 99% yield by simple filtration.



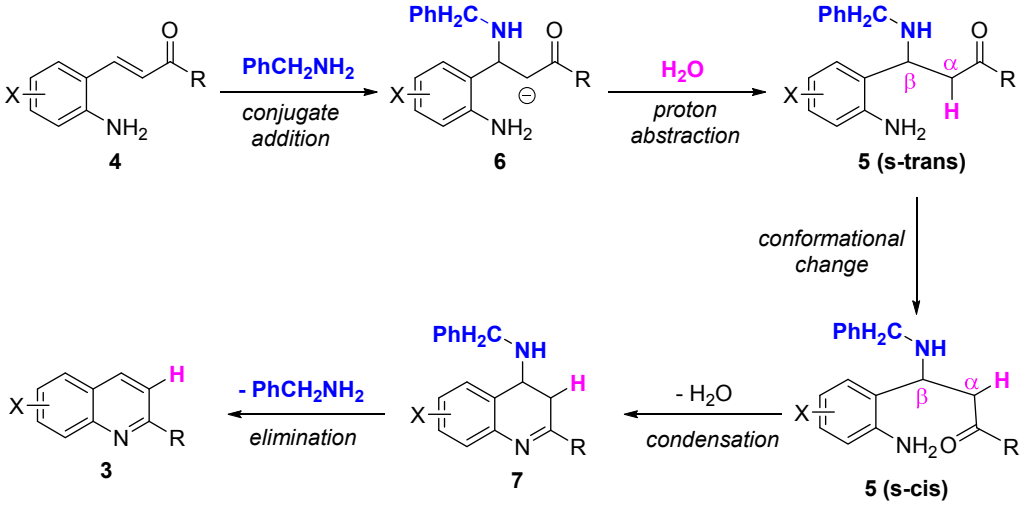
Scheme 3. Large-scale Synthesis of Quinoline **3a**

Finally, to get detailed insights into the reaction mechanism (see Scheme 2), particularly the role of benzylamine as a nucleophilic catalyst, for this transformation, several control experiments were carried out. We first carried out this transformation in D_2O as the reaction medium. When this transformation was performed in D_2O, the incorporation of the deuterium at the C-3 position of the quinoline ring was observed leading to a mixture of quinoline **3a** and its deuterated product **3a-[D]** in 62% yield with a ratio of 0.6 : 1.0 (Scheme 4a). This result indicated that benzylamine would undergo conjugate addition to **3** leading to enolate **6**, which abstracts proton from solvent. In addition, the more solid evidence for the reaction mechanism was found by monitoring this reaction with ^{1}H NMR analysis. When the mixture of **4a** and benzylamine was submitted to the standard conditions, we observed the formation of both benzylamine adduct **6a** (where Nu = $NHCH_2Ph$) and dihydroquinoline **7a** after 10 min. After 20 min, however, all peaks of the benzylamine adduct **6a** completely disappeared in ^{1}H NMR spectrum and only those from dihydroquinoline **7a** increased in the reaction mixture. As the reaction further proceeded, dihydroquinoline **7a** was gradually converted into the corresponding quinoline **3a**.[19] After 1 h, only quinoline **3a** was observed as the sole product in the reaction mixture (Scheme 4b).



Scheme 4. Controlled Experiments for Mechanistic Studies. Blue arrows indicate the peaks from benzylamine adduct **5a** and red arrows point out the peaks from dihydroquinoline **7a**.

Based on these experimental results, we proposed the reaction mechanism for this transformation (Scheme 5). Benzylamine undergoes conjugate addition to 2-aminochalcones **4** to form enolates **6**, which abstract proton from water to generate β-aminoketones **5**. Compounds **5** could undergo free rotation about the C_α-C_β bond leading to s-cis conformation. Under such a conformation, the two functional groups undergo condensation to generate dihydroquinoline **7**, which subsequently undergo the elimination of benzylamine to afford the desired quinoline **3**.



Scheme 5. Proposed Reaction Mechanism for Conversion of 2-Aminochalcones **4** to Quinolines **3** from using Benzylamine as the Nucleophilic Catalyst in Aqueous Medium

Conclusions

We have developed an on-water protocol for the synthesis of 2-substituted quinolines from 2-aminochalcones using benzylamine as the nucleophilic catalyst. This protocol was applicable to a variety of 2-aminochalcone derivatives, and the desired quinoline products were obtained in excellent yields by simple filtration. In addition, we provided a detailed reaction mechanism for this transformation by elucidating the role of benzylamine as the nucleophilic catalyst. Furthermore, the catalytic system could be recycled several times without significant loss of its activity. Extremely simple operation, broad substrate scope, large-scale synthesis and mild reaction conditions are additional advantages of this protocol. Further development of other organic transformations in the presence of a nucleophilic catalyst is underway in our laboratory, and the results will be reported in due course.

Experimental Section

General. Commercial grade reagents and solvents were used without further purification, unless otherwise noted. 2-Aminochalcone derivatives **4** were prepared by a literature protocol; aldol condensation of acetophenone derivatives with 2-nitrobenzaldehydes provided 2-nitrochalcones, and subsequent reduction of the nitro group into an amino group afforded the expected 2-aminochalcone derivatives **4**.[14] ^{1}H NMR and ^{13}C NMR spectra were recorded using 500 MHz and 125 MHz spectrometers, respectively. ^{1}H spectra were recorded using $CDCl_3$ or DMSO-d_6 as the solvent with chloroform ($CHCl_3$; δ = 7.26 ppm) or DMSO-d_6 (DMSO-d_6; δ 2.50 ppm) as the internal standard. ^{13}C spectra were obtained using $CDCl_3$ or DMSO-d_6 as the solvent with chloroform ($CDCl_3$; δ = 77.2 ppm) or DMSO-d_6 (DMSO-d_6; δ = 39.5 ppm) as the internal standard. The proton spectra are reported as follows: *δ* (position of proton, multiplicity, coupling constant *J*, number of protons). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (quintet), h (septet), m (multiplet) and br (broad). High-resolution mass spectra (HRMS) were recorded on a quadrupole time-of-flight mass spectrometer (QTOF-MS) with an electrospray ionization (ESI) source.

Synthesis of 2-Aminochalcone Derivatives 4. All previously unknown 2-aminochalcone derivatives (**4h**, **4i**, **4j**, and **4k**) were prepared from a suitable acetophenone derivative and 2-nitrobenzaldehyde by aldol condensation, followed by the reduction of a nitro group into an amino group.[14]

General Procedure for the Synthesis of 2-Aminochalcone Derivatives 4. To a mixture of a 2-nitrobenzaldehyde derivative (4.0 mmol, 1.0 equiv.), sodium hydroxide (16 mg, 0.40 mmol, 0.10 equiv.), and potassium carbonate (55 mg, 0.40 mmol, 0.10 equiv.) was added a relevant acetophenone derivative (4.0 mmol, 1.0 equiv.) at room temperature. The reaction mixture was stirred at room temperature and monitored by thin layer chromatography (TLC). After complete consumption of the 2-nitrobenzaldehyde, the reaction mixture was quenched with

H_2O and extracted with ethyl acetate. The organic layers were combined, dried over $MgSO_4$, and concentrated in vacuo. Recrystallization of the crude mixture in ethanol provided the corresponding (*E*)-2-nitrochalcone, which was directly subjected to the next reduction conditions.

To a solution of the resulting (*E*)-2-nitrochalcone derivative (2.5 mmol, 1.0 equiv.) in ethanol (25 mL) was added iron powder (70 mg, 13 mmol, 5.0 equiv.), followed by HCl (1.0 N, 1.3 mL, 1.3 mmol, 0.5 equiv.). The resulting mixture was vigorously stirred at 80 ^oC. After complete consumption of the (*E*)-2-nitrochalcone derivative, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a Celite pad. The filtrate was neutralized with saturated aqueous Na_2CO_3 solution, and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by recrystallization from a mixture of methylene chloride and hexanes to provide the desired (*E*)-2-aminochalcone derivative **4**.

(E)-2-Amino-4'-hydroxychalcone (**4h**)

Orange solid (0.24 g, 40% yield). R_f = 0.3 (ethyl acetate/hexanes = 1:1). ^1H NMR (500 MHz, DMSO-d_6, ppm): δ 8.03 (d, J = 8.7 Hz, 2H), 7.93 (d, J = 15.3 Hz, 1H), 7.67 (d, J = 7.0 Hz, 1H), 7.63 (d, J = 15.3 Hz, 1H), 7.09 (m, 1H), 6.88 (d, J = 8.5 Hz, 2H), 6.70 (d, J = 7.8 Hz, 1H), 6.57 (t, J = 7.5 Hz, 1H), 5.65 (s, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6, ppm): δ 159.1, 156.1, 147.6, 136.9, 129.7, 129.6, 128.8, 128.7, 127.7, 126.5, 125.8, 118.1, 115.6. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{14}NO_2$ 240.1019; found 240.1017.

(E)-2-Amino-4'-tetrahydro-2H-pyran-2-yloxychalcone (**4i**)

Yellow solid (0.52 g, 65% yield). R_f = 0.3 (ethyl acetate/hexanes = 1:5). ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 8.03 (m, 2H), 7.96 (d, J = 15.3 Hz, 1H), 7.52 (dd, J = 7.8, 1.4 Hz, 1H), 7.49

(d, J = 15.3 Hz, 1H), 7.20 (m, 1H), 7.13 (m, 2H), 6.80 (t, J = 7.5 Hz, 1H), 6.72 (dd, J = 8.1, 0.9 Hz, 1H), 5.54 (t, J = 3.1 Hz, 1H), 4.04 (br. s., 2H), 3.87 (dt, J = 10.7, 3.1 Hz, 1H), 3.64 (m, 1H), 2.02 (m, 1H), 1.90 (td, J = 7.5, 3.9 Hz, 2H), 1.71 (m, 2H), 1.62 (td, J = 8.6, 4.2 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, ppm): δ 188.9, 161.1, 146.2, 139.5, 131.9, 131.6, 130.8, 128.3, 122.0, 120.7, 119.0, 116.9, 116.2, 96.2, 62.2, 30.3, 25.2, 18.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{22}NO_3$ 324.1594; found 324.1593.

(E)-2-Amino-4'-tert-butyldimethylsilyloxychalcone (**4j**)

Yellow solid (0.35 g, 40% yield). R_f = 0.3 (ethyl acetate/hexanes = 1:5). ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 7.98 (m, 3H), 7.52 (dd, J = 7.9, 1.0 Hz, 1H), 7.49 (d, J = 15.4 Hz, 1H), 7.19 (m, 1H), 6.92 (m, 1H), 6.79 (t, J = 7.5 Hz, 1H), 6.72 (d, J = 8.1 Hz, 1H), 4.07 (br. s., 2H), 1.00 (s, 9H), 0.25 (s, 6H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, ppm): δ 188.8, 160.3, 146.2, 139.4, 131.9, 131.6, 130.8, 128.2, 121.9, 120.6, 120.2, 119.0, 116.9, 25.7, 18.4. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{28}NO_2Si$ 354.1884; found 354.1886.

(E)-2-Amino-4'-triisopropylsilyloxychalcone (**4k**)

Yellow solid (0.27 g, 27% yield). R_f = 0.3 (ethyl acetate/hexanes = 1:5). ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 7.97 (m, 3H), 7.51 (m, 2H), 7.19 (m, 1H), 6.96 (d, J = 8.7 Hz, 2H), 6.79 (t, J = 7.5 Hz, 1H), 6.72 (d, J = 8.1 Hz, 1H), 4.09 (br. s., 2H), 1.29 (m, 3H), 1.13 (m, 18H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, ppm): δ 188.7, 160.7, 146.3, 139.3, 131.6, 131.5, 130.8, 128.2, 121.9, 120.6, 120.0, 118.9, 116.8, 18.0, 12.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{34}NO_2Si$ 396.2353; found 396.2351.

General Procedure for the Synthesis of 2-Substituted Quinolines 3 (Table 2). To a suspension of (*E*)-2-aminochalcone derivative **4** (0.20 mmol) in water (2.0 mL) was added

benzylamine (21.8 μL, 0.20 mmol; 0.60 or 1.0 mmol was used for some substrates) at room temperature. The reaction mixture was warmed up to 80 ^{o}C and stirred at the same temperature in an open flask. After complete consumption of **4**, the reaction mixture was cooled to room temperature for precipitation. Then, the precipitate was collected by filtration and washed with water to remove benzylamine. After this simple filtration, the desired quinoline **3** was obtained in pure form without further purification. In the case of some liquid quinolines, the desired quinoline products were obtained by either simple extraction with ethyl acetate (**3k**, **3ac** and **3ad**) or purification by column chromatography on silica gel (**3aa** and **3ab**).

2-Phenylquinoline (**3a**)[14]

Purified by filtration from the reaction mixture. White solid (41 mg, 99% yield). R_f = 0.4 (ethyl acetate/hexanes = 1:10). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.23 (d, J = 8.5 Hz, 1H), 8.18 (m, 3H), 7.89 (d, J = 8.5 Hz, 1H), 7.84 (d, J = 7.9 Hz, 1H), 7.74 (m, 1H), 7.54 (m, 3H), 7.47 (m, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 157.5, 148.5, 139.9, 136.9, 129.9, 129.8, 129.5, 129.0, 127.7, 127.6, 127.3, 126.4, 119.2.

2-(4-Methoxyphenyl)quinoline (**3b**)[14]

Purified by filtration from the reaction mixture. Pale yellow solid (47 mg, 99% yield). R_f = 0.4 (ethyl acetate/hexanes = 1:7). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.19 (d, J = 8.5 Hz, 1H), 8.14 (m, 3H), 7.84 (d, J = 8.7 Hz, 1H), 7.81 (d, J = 8.1 Hz, 1H), 7.71 (ddd, J = 8.5, 6.9, 1.4 Hz, 1H), 7.50 (ddd, J = 8.0, 6.9, 1.1 Hz, 1H), 7.06 (m, 2H), 3.89 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 161.0, 157.0, 148.4, 138.8, 132.4, 129.7 (2C), 129.0, 127.6, 127.0, 126.0, 118.7, 114.4, 55.5.

2-(4-Methylphenyl)quinoline (**3c**)[14]

Purified by filtration from the reaction mixture. Pale yellow solid (44 mg, 99% yield). R_f = 0.4 (ethyl acetate/hexanes = 1:10). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.20 (d, J = 8.5 Hz, 1H), 8.17 (d, J = 8.4 Hz, 1H), 8.06 (d, J = 8.2 Hz, 2H), 7.87 (d, J = 8.5 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.72 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.51 (m, 1H), 7.34 (d, J = 8.1 Hz, 2H), 2.44 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 157.5, 148.4, 139.9, 139.6, 137.0, 136.8, 129.8, 129.7 (2C), 127.6, 127.2, 126.2, 119.0, 21.5.

2-(4-Fluorophenyl)quinoline (**3d**)[14]

Purified by filtration from the reaction mixture. Light green solid (42 mg, 94% yield). R_f = 0.4 (ethyl acetate/hexanes = 1:10). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.23 (d, J = 8.4 Hz, 1H), 8.16 (m, 3H), 7.83 (m, 2H), 7.73 (ddd, J = 8.4, 7.0, 1.5 Hz, 1H), 7.53 (ddd, J = 8.1, 6.9, 1.1 Hz, 1H), 7.21 (m, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 164.9, 163.0, 156.4, 148.4, 137.1, 136.0, 130.0, 129.8, 129.6, 129.5, 127.6, 127.2, 126.5, 118.8, 116.0, 115.8.

2-(4-Chlorophenyl)quinoline (**3e**)[14]

Purified by filtration from the reaction mixture. Pale yellow solid (48 mg, 99% yield). R_f = 0.4 (ethyl acetate/hexanes = 1:10). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.23 (d, J = 8.7 Hz, 1H), 8.16 (d, J = 8.5 Hz, 1H), 8.13 (m, 2H), 7.84 (m, 2H), 7.74 (dt, J = 7.7, 1.3 Hz, 1H), 7.55 (m, 1H), 7.50 (m, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 156.1, 148.4, 138.2, 137.1, 135.7, 130.0, 129.8, 129.1, 128.9, 127.6, 127.3, 126.6, 118.7.

2-(4-Bromophenyl)quinoline (**3f**)[14]

Purified by filtration from the reaction mixture. Pale yellow solid (57 mg, 99% yield). R_f = 0.4 (ethyl acetate/hexanes = 1:10). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.24 (d, J = 8.5 Hz, 1H),

8.16 (d, J = 8.4 Hz, 1H), 8.06 (m, 2H), 7.84 (m, 2H), 7.74 (ddd, J = 8.5, 6.9, 1.4 Hz, 1H), 7.66 (m, 2H), 7.55 (ddd, J = 8.0, 6.9, 1.1 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, ppm): δ 156.2, 148.4, 138.7, 137.1, 132.1, 130.0, 129.9, 129.2, 127.6, 127.4, 126.7, 124.1, 118.6.

2-(4-Methoxycarbonylphenyl)quinoline (**3g**)[14]

Purified by filtration from the reaction mixture. White solid (53 mg, 99% yield). R_f = 0.3 (ethyl acetate/hexanes = 1:7). ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 8.26 (m, 3H), 8.19 (m, 3H), 7.92 (d, J = 8.7 Hz, 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.76 (ddd, J = 8.5, 6.9, 1.4 Hz, 1H), 7.57 (ddd, J = 8.1, 6.9, 1.1 Hz, 1H), 3.97 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, ppm): δ 167.0, 156.1, 148.4, 143.8, 137.1, 130.7, 130.2, 130.0, 127.6 (2C), 127.5, 126.9, 119.0, 52.3.

2-(4-Hydroxyphenyl)quinoline (**3h**)[20]

Purified by filtration from the reaction mixture. Brown solid (44 mg, 99% yield). R_f = 0.3 (ethyl acetate/hexanes = 1:1). ^1H NMR (500 MHz, DMSO, ppm): δ 9.87 (s, 1H), 8.36 (d, J = 8.5 Hz, 1H), 8.14 (m, 2H), 8.05 (d, J = 8.7 Hz, 1H), 8.00 (d, J = 8.7 Hz, 1H), 7.94 (dd, J = 8.2, 1.0 Hz, 1H), 7.74 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.54 (ddd, J = 8.0, 6.9, 1.1 Hz, 1H), 6.92 (m, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, DMSO, ppm): δ 159.1, 156.1, 147.5, 136.9, 129.7, 129.6, 128.8, 128.7, 127.7, 126.5, 125.8, 118.1, 115.6.

2-(4-(Tetrahydro-2H-pyran-2-yl)oxyphenyl)quinoline (**3i**)

Purified by filtration from the reaction mixture. Brown solid (53 mg, 87% yield). R_f = 0.3 (ethyl acetate/hexanes = 1:10). ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 8.18 (d, J = 8.5 Hz, 1H), 8.13 (m, 3H), 7.84 (d, J = 8.5 Hz, 1H), 7.81 (dd, J = 8.1, 0.9 Hz, 1H), 7.71 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.50 (ddd, J = 8.0, 7.0, 1.1 Hz, 1H), 7.20 (m, 2 H), 5.53 (t, J = 3.2 Hz, 1H), 3.93 (ddd, J = 11.3, 9.9, 3.0 Hz, 1H), 3.64 (m, 1H), 2.04 (m, 1H), 1.91 (m, 2H), 1.71 (m, 2H), 1.63

(m, 1H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$, ppm): δ 158.4, 157.1, 148.4, 136.8, 133.2, 129.7(2C), 128.9, 127.6, 127.1, 126.1, 118.8, 116.8, 96.3, 62.2, 30.4, 25.3, 18.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{20}NO_2$ 306.1489; Found 306.1492.

2-(4-tert-Butyldimethylsilyloxyphenyl)quinoline (**3j**)[21]

Purified by filtration from the reaction mixture. Brown solid (51 mg, 76% yield). R_f = 0.3 (ethyl acetate/hexanes = 1:10). **3j**: ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.18 (d, J = 8.7 Hz, 1H), 8.14 (d, J = 8.5 Hz, 1H), 8.07 (m, 2H), 7.83 (d, J = 8.5 Hz, 1H), 7.81 (m, 1H), 7.71 (ddd, J = 8.5, 6.9, 1.4 Hz, 1H), 7.50 (m, 1H), 6.99 (m, 2H), 1.01 (s, 9H), 0.24 (s, 6H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$, ppm): δ 157.3, 157.2, 148.4, 136.8, 133.0, 129.7, 129.6, 129.0, 127.6, 127.0, 126.0, 120.7, 118.8, 25.8, 18.4. Compound **3h** (10 mg, 23%) was isolated by the extraction of the filtrate with ethyl acetate. Spectroscopic data were matched with the reported values.[20]

2-(4-Triisopropylsilyloxyphenyl)quinoline (**3k**)

Purified by extraction with ethyl acetate. Brown oil (76 mg, 99% yield). R_f = 0.3 (ethyl acetate/hexanes = 1:10). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.18 (d, J = 8.5 Hz, 1H), 8.13 (d, J = 8.5 Hz, 1H), 8.07 (m, 2H), 7.83 (d, J = 8.5 Hz, 1H), 7.80 (d, J = 7.5 Hz, 1H), 7.70 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.50 (ddd, J = 8.0, 6.9, 1.1 Hz, 1H), 7.02 (m, 2H), 1.30 (m, 3H), 1.14 (m, 18H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$, ppm): δ 157.7, 157.1, 148.4, 136.7, 132.6, 129.6, 128.9, 127.5, 127.0, 125.9, 120.4, 118.7, 18.0, 12.8. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{32}NOSi$ 378.2248; Found 378.2247.

2-(2-Methylphenyl)quinoline (**3l**)[14]

Purified by filtration from the reaction mixture. Brown solid (44 mg, 99% yield). R_f = 0.3 (ethyl acetate/hexanes = 1:10). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.22 (d, J = 8.4 Hz, 1H), 8.17 (d, J = 8.2 Hz, 1H), 7.87 (dd, J = 8.2, 1.1 Hz, 1H), 7.75 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.56 (m, 2H), 7.51 (m, 1H), 7.33 (m, 3H), 2.42 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 160.4, 147.9, 140.8, 136.2, 136.1, 131.0, 129.8 (2C), 129.6, 128.6, 127.6, 126.8, 126.5, 126.1, 122.5, 20.5.

2-(3-Methylphenyl)quinoline (**3m**)[14]

Purified by filtration from the reaction mixture. Brown solid (41 mg, 94% yield). R_f = 0.4 (ethyl acetate/hexanes = 1:10). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.22 (d, J = 8.5 Hz, 1H), 8.18 (d, J = 8.4 Hz, 1H), 8.01 (s, 1H), 7.92 (m, 1H), 7.88 (d, J = 8.5 Hz, 1H), 7.83 (dd, J = 8.1, 1.4 Hz, 1H), 7.73 (ddd, J = 8.4, 6.9, 1.4 Hz 1H), 7.53 (ddd, J = 8.0, 6.9, 1.1 Hz, 1H), 7.42 (t, J = 7.6 Hz, 1H), 7.29 (td, J = 7.6, 0.6 Hz, 1H), 2.49 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 157.6, 148.3, 139.7, 138.6, 136.8, 130.2, 129.8, 129.7, 128.8, 128.3, 127.5, 127.3, 126.3, 124.8, 119.2, 21.7.

2-(2-Bromophenyl)quinoline (**3n**)[14]

Purified by filtration from the reaction mixture. Yellow solid (57 mg, 99% yield). R_f = 0.3 (ethyl acetate/hexanes = 1:10). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.23 (d, J = 8.4 Hz, 1H), 8.18 (d, J = 8.5 Hz, 1H), 7.88 (d, J = 8.2 Hz, 1H), 7.76 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.71 (m, 2H), 7.64 (dd, J = 7.6, 1.8 Hz, 1H), 7.59 (td, J = 7.6, 1.1 Hz, 1H), 7.46 (td, J = 7.6, 1.1 Hz, 1H), 7.31 (td, J = 7.7, 1.7 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 158.9, 148.1, 141.8, 135.8, 133.4, 131.7, 130.1, 130.0, 129.8, 127.8, 127.7, 127.3, 127.0, 122.9, 122.0.

2-(3-Bromophenyl)quinoline (**3o**)[14]

Purified by filtration from the reaction mixture. Yellow solid (57 mg, 99% yield). R_f = 0.4 (ethyl acetate/hexanes = 1:10). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.36 (t, J = 1.8 Hz, 1H), 8.25 (d, J = 8.5 Hz, 1H), 8.17 (dd, J = 8.5, 0.8 Hz, 1H), 8.08 (dq, J = 7.8, 0.9 Hz, 1H), 7.85 (m, 2H), 7.75 (ddd, J = 8.5, 6.9, 1.5 Hz, 1H), 7.59 (ddd, J = 7.9, 2.0, 0.9 Hz, 1H), 7.55 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.40 (t, J = 7.9 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 155.7, 148.3, 141.7, 137.1, 132.3, 130.7, 130.4, 130.0, 129.9, 127.6, 127.4, 126.8, 126.1, 123.3, 118.7.

2-(1-Naphthyl)quinoline (**3p**)[14]

Purified by filtration from the reaction mixture. Brown solid (51 mg, 99% yield). R_f = 0.3 (ethyl acetate/hexanes = 1:10). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.30 (d, J = 8.4 Hz, 1H), 8.23 (m, 1H), 8.13 (m, 1H), 7.94 (m, 3H), 7.78 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.72 (m, 2H), 7.61 (m, 2H), 7.50 (m, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 159.5, 148.2, 138.8, 136.4, 134.1, 131.4, 129.9, 129.8, 129.3, 128.5, 127.9, 127.7, 127.1, 126.7 (2C), 126.1, 125.8, 125.5, 123.4.

2-(2-Naphthyl)quinoline (**3q**)[14]

Purified by filtration from the reaction mixture. Brown solid (50 mg, 97% yield). R_f = 0.4 (ethyl acetate/hexanes = 1:10). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.63 (d, J = 0.9 Hz, 1H), 8.38 (dd, J = 8.5, 1.8 Hz, 1H), 8.27 (d, J = 8.7 Hz, 1H), 8.23 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.5 Hz, 1H), 8.01 (m, 2H), 7.90 (m, 1H), 7.86 (d, J = 7.3 Hz, 1H), 7.76 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.54 (m, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 157.3, 148.5, 137.1, 137.0, 134.0, 133.7, 129.9 (2C), 129.0, 128.7, 127.9, 127.6, 127.4, 127.3, 126.9, 126.5, 125.2, 119.3.

2-(2-Furyl)quinoline (**3r**)[14]

Purified by filtration from the reaction mixture. Brown solid (38 mg, 98% yield). R_f = 0.3 (ethyl acetate/hexanes = 1:10). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.17 (d, J = 8.5 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 8.5 Hz, 1H), 7.78 (dd, J = 8.1, 1.2 Hz, 1H), 7.71 (ddd, J = 1.4, 6.9, 8.4 Hz, 1H), 7.63 (dd, J = 1.7, 0.8 Hz, 1H), 7.50 (ddd, J = 8.1, 6.9, 1.1 Hz, 1H), 7.22 (dd, J = 3.4, 0.7 Hz, 1H), 6.59 (dd, J = 3.4, 1.8 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 153.8, 149.1, 148.2, 144.2, 136.8, 130.0, 129.5, 127.7, 127.3, 126.3, 117.6, 112.3, 110.2.

2-(2-Thienyl)quinoline (**3s**)[14]

Purified by filtration from the reaction mixture. Yellow solid (41 mg, 97% yield). R_f = 0.3 (ethyl acetate/hexanes = 1:10). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.14 (d, J = 8.4 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 8.5 Hz, 1H), 7.78 (dd, J = 8.1, 1.2 Hz, 1H), 7.74 (dd, J = 3.7, 1.1 Hz, 1H), 7.70 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.48 (m, 2H), 7.16 ppm (dd, J = 5.0, 3.7 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 152.4, 148.2, 145.5, 136.7, 129.9, 129.4, 128.7, 128.2, 127.6, 127.3, 126.2, 126.0, 117.7.

6-Fluoro-2-phenylquinoline (**3t**)[14]

Purified by filtration from the reaction mixture. Pale yellow solid (45 mg, 99%). R_f = 0.4 (ethyl acetate/hexanes = 1:10). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.16 (m, 4H), 7.91 (d, J = 8.5 Hz, 1H), 7.54 (m, 2H), 7.48 (m, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 161.4, 159.5, 156.9 (2C), 145.5, 139.5, 136.3, 136.2, 132.3 (2C), 129.5, 129.0, 127.8 (2C), 127.6, 120.1, 119.9, 119.8, 110.7, 110.5.

6-Chloro-2-phenylquinoline (**3u**)[14]

Purified by filtration from the reaction mixture. Pale yellow solid (44 mg, 91% yield). R_f = 0.4 (ethyl acetate/hexanes = 1:10). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.15 (m, 3H), 8.11 (d, J = 9.0 Hz, 1H), 7.91 (d, J = 8.7 Hz, 1H), 7.82 (d, J = 2.3 Hz, 1H), 7.66 (dd, J = 8.9, 2.4 Hz, 1H), 7.54 (m, 2H), 7.48 (m, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 157.6, 146.7, 139.3, 135.9, 132.0, 131.4, 130.6, 129.7, 129.0, 127.8, 127.6, 126.2, 119.8.

6-Bromo-2-phenylquinoline (**3v**)[14]

Purified by filtration from the reaction mixture. Orange solid (57 mg, 99% yield). R_f = 0.4 (ethyl acetate/hexanes = 1:10). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.16 (d, J = 7.0 Hz, 2H), 8.13 (d, J = 8.9 Hz, 1H), 8.04 (d, J = 9.0 Hz, 1H), 7.99 (d, J = 2.0 Hz, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.79 (dd, J = 9.0, 2.1 Hz, 1H), 7.54 (m, 2H), 7.48 (m, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 157.8, 146.9, 139.3, 135.9, 133.2, 131.6, 129.7, 129.6, 129.0, 128.3, 127.6, 120.2, 119.9.

6-Methyoxy-2-phenylquinoline (**3w**)[14]

Purified by filtration from the reaction mixture. Pale yellow solid (43 mg, 91% yield). R_f = 0.3 (ethyl acetate/hexanes = 1:10). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.13 (m, 3H), 8.07 (d, J = 9.2 Hz, 1H), 7.84 (d, J = 8.5 Hz, 1H), 7.52 (m, 2H), 7.44 (m, 1H), 7.39 (dd, J = 9.2, 2.7 Hz, 1H), 7.10 (d, J = 2.7 Hz, 1H), 3.95 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 157.8, 155.2, 144.5, 139.9, 135.7, 131.3, 129.1, 129.0, 128.3, 127.4, 122.5, 119.4, 105.1, 55.7.

7-Bromo-2-phenylquinoline (**3x**)[14]

Purified by filtration from the reaction mixture. Pale yellow solid (57 mg, 99% yield). R_f = 0.3 (ethyl acetate/hexanes = 1:10). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.37 (s, 1H), 8.19 (d, J = 8.5 Hz, 1H), 8.16 (d, J = 7.6 Hz, 2H), 7.90 (d, J = 8.5 Hz, 1H), 7.70 (d, J = 8.5 Hz, 1H), 7.61

(d, J = 8.7 Hz, 1H), 7.54 (m, 2H), 7.48 (m, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, ppm): δ 158.3, 149.0, 139.3, 136.8, 132.2, 129.9, 129.8, 129.1, 128.9, 127.7, 125.9, 123.9, 119.4.

6-Methoxy-2-(4-methoxyphenyl)quinoline (**3y**)[14]

Purified by filtration from the reaction mixture. Brown solid (53 mg, 99% yield). R_f = 0.3 (ethyl acetate/hexanes = 1:8). ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 8.09 (m, 3 H), 8.03 (d, J = 9.2 Hz, 1H), 7.79 (dd, J = 8.5, 1.4 Hz, 1H), 7.36 (dd, J = 9.2, 2.7 Hz, 1H), 7.08 (d, J = 2.6 Hz, 1H), 7.04 (m, 2H), 3.94 (s, 3H), 3.88 (s, 3H) $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, ppm): δ 160.6, 157.5, 154.8 144.5, 135.6, 132.5, 131.1, 128.7, 127.9, 122.3, 119.0, 114.3, 105.2, 55.7, 55.5.

6,8-Dibromo-2-phenylquinoline (**3z**)[14]

Purified by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:10) as an eluent. Yellow solid (70 mg, 97% yield). R_f = 0.3 (ethyl acetate/hexanes = 1:10). ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 8.30 (m, 2H), 8.16 (d, J = 2.1 Hz, 1H), 8.12 (d, J = 8.5 Hz, 1H), 7.98 (d, J = 8.5 Hz, 1H), 7.95 (d, J = 2.1 Hz, 1H), 7.55 (m, 2H), 7.50 (m, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, ppm): δ 157.9, 144.0, 138.6, 136.4, 136.1, 130.2, 129.4, 129.1, 129.0, 127.8, 126.7, 120.1, 119.4.

2-Methylquinoline (**3aa**)[14]

Purified by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:10) as the eluent. White solid (19 mg, 67% yield). R_f = 0.3 (ethyl acetate/hexanes = 1:5). ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 8.03 (t, J = 9.7 Hz, 2H), 7.78 (m, 1H), 7.68 (m, 1H), 7.48 (t, J = 7.5 Hz, 1H), 7.29 (dd, J = 8.4, 1.2 Hz, 1H), 2.75 (d, J = 1.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, ppm): δ 159.2, 148.0, 136.3, 129.6, 128.8, 127.6, 126.6, 125.8, 122.2, 25.5.

2-Isopropylquinoline (**3ab**)[14]

Purified by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:10) as the eluent. Yellow oil (28 mg, 83% yield). R_f = 0.3 (ethyl acetate/hexanes = 1:10). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.09 (d, J = 8.5 Hz, 1H), 8.06 (d, J = 8.5 Hz, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.68 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.48 (ddd, J = 8.0, 6.9, 1.1 Hz, 1H), 7.35 (d, J = 8.5 Hz, 1H), 3.27 (td, J = 13.9, 6.9 Hz, 1H), 1.40 (d, J = 7.0 Hz, 6H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 167.8, 147.9, 136.5, 129.4, 129.1, 127.6, 127.1, 125.8, 119.3, 37.5, 22.7.

2-(tert-Butyl)quinoline (**3ac**)[10a]

Purified by extraction with ethyl acetate. Yellow oil (36 mg, 97% yield). R_f = 0.3 (ethyl acetate/hexanes = 1:10). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.08 (d, J = 8.2 Hz, 2H), 7.77 (d, J = 8.1 Hz, 1H), 7.67 (t, J = 7.5 Hz, 1H), 7.53 (d, J = 8.7 Hz, 1H), 7.48 (t, J = 7.4 Hz, 1H), 1.48 (s, 9H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 169.4, 147.5, 136.0, 129.5, 129.2, 127.4, 126.6, 125.8, 118.4, 38.3, 30.3.

3-Methyl-2-phenylquinoline (**3ad**)[14]

Purified by extraction with ethyl acetate. Orange oil (43 mg, 97% yield). R_f = 0.3 (ethyl acetate/hexanes = 1:10). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.13 (d, J = 8.5 Hz, 1H), 8.03 (s, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.66 (m, 1H), 7.59 (m, 2H), 7.51 (m, 3H), 7.44 (m, 1H), 2.47 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 160.6, 146.6, 140.8, 137.0, 129.4, 129.2, 129.0 (2C), 128.4, 128.3, 127.7, 126.9, 126.6, 20.7.

Recycle Studies of Benzylamine (Table 3)

A 3.0 mL solution of aqueous benzylamine solution (0.10 M, i.e., 0.30 mmol of benzylamine in 3.0 mL of H_2O) was prepared. A suspension of **4a** (0.10 mmol) in the abovementioned benzylamine solution (1.0 mL) was heated to 80 ^oC in an open flask. After completion of the reaction, the precipitate was collected by filtration and washed with the remaining benzylamine solution (1.0 mL × 2) to afford quinoline **3a** in pure form without further purification. The filtrate was tested for its catalytic activity by reusing it as the reaction media for the next reaction.

ORCID

Cheol-Hong Cheon: 0000-0002-6738-6193

Notes

The authors declare no competing financial interests.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Copies of NMR spectra for the products (PDF)

Acknowledgements

This work was supported by National Research Foundation of Korea (NRF) grants funded by the Korean Government (NRF-2015R1D1A1A01057200, NRF-2017M2A8A4018045 and NRF-20100020209). C.-H.C. thanks the financial support from an NRF grant funded by the Korean Government (NRF-2014-011165, Center for New Directions in Organic Synthesis).

References

1. For a seminal report on on-water synthesis, see: (a) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. "On-water": Unique Reactivity of Organic Compounds in Aqueous Suspension. *Angew. Chem. Int. Ed.* **2005**, *44*, 3275-3279. (b) A commentary on "On-water Synthesis": Klijin, J. E.; Engberts, B. F. N. Fast Reactions "On-water". *Nature* **2005**, *435*, 746-747.

2. For reviews on on-water synthesis, see: (a) Kitanosono, T.; Masuda, K.; Xu, P.; Kobayashi, S. Catalytic Organic Reactions in Water toward Sustainable Society. *Chem. Rev.* **2018**, *118*, 679-746. (b) Lipshutz, B. H. When Does Organic Chemistry Follow Nature's Lead and "Make the Switch"?. *J. Org. Chem.* **2017**, *82*, 2806-2816. (c) Chanda, A.; Fokin, V. V. Organic Synthesis "On-water". *Chem. Rev.* **2009**, *109*, 725-748.

3. For reviews on quinolines, see: (a) Musiol, R. An Overview of Quinoline as a Privileged Scaffold in Cancer Drug Discovery. *Expert. Opin. Drug Discov.* **2017**, *12*, 583-597. (b) Afzal, O.; Kumar, S.; Haider, M. R.; Ali, M. R.; Kumar, R.; Jaggi, M.; Bawa, S. A Review on Anticancer Potential of Bioactive Heterocycle Quinoline. *Eur. J. Med. Chem.* **2015**, *97*, 871-910. (c) Prajapati, S. M.; Patel, K. D.; Vekariya, R. H.; Panchal, S. N.; Patel, H. D. Recent Advances in the Synthesis of Quinolines: A Review. *RSC Adv.* **2014**, *4*, 24463-24476.

4. For a review on the synthesis of quinolines via green protocols, see: Batista, V. F.; Pinto, D. C. G. A.; Silva, A. M. S. Synthesis of Quinolines: A Green Perspective. *ACS Sustainable Chem. Eng.* **2016**, *4*, 4046-4078.

5. For selected examples of the preparation of quinolines in aqueous media, see: (a) Reddy, T. R.; Reddy, L. S.; Reddy, G. R.; Yarbagi, K.; Lingappa, Y.; Rambabu, D.; Krishna, G. R.; Reddy, C. M.; Kumar, K. S.; Pal, M. Construction of a Quinoline Ring via a 3-Component Reaction in Water: Crystal Structure Analysis and H-

bonding Patterns of a 2-Aryl Quinoline. *Green Chem.* **2012**, *14*, 1870-1872. (b) Shen, Q.; Wang, L.; Yu, J.; Liu, M.; Qiu, J.; Fang, L.; Guo, F.; Tang, J. Synthesis of Quinolines via Friedländer Reaction in Water and under Catalyst-Free Conditions. *Synthesis* **2012**, *44*, 389-392. (c) Das, B.; Jangili, P.; Kashanna, J.; Kumar, R. A. Organic Reactions in Water: A Distinct Approach for the Synthesis of Quinoline Derivatives Starting Directly from Nitroarenes. *Synthesis* **2012**, *20*, 3267-3270.

6. (a) Akbari, J.; Heydari, A.; Kalhor, H. R.; Kohan, S. A. Sulfuric Acid Functionalized Ionic Liquid in Combinatorial Approach, a Recyclable and Water Tolerant-Acidic Catalyst for One-Pot Friedländer Quinoline Synthesis. *J. Comb. Chem.* **2010**, *12*, 137-140. (b) Zolfigol, M. A.; Salehi, P.; Ghaderi, A.; Shiri, M. A Catalytic and Green Procedure for Friedländer Quinoline Synthesis in Aqueous Media. *Catal. Commun.* **2007**, *8*, 1214-1218. (c) Zolfigol, M. A.; Salehi, P.; Ghaderi, A.; Shiri, M.; Tanbakouchian, Z. An Eco-Friendly Procedure for the Synthesis of Polysubstituted Quinolines under Aqueous Media. *J. Mol. Catal. A: Chem.* **2006**, *259*, 253-258. (d) Wang, G.-W.; Jia, C.-S., Dong, Y.-W. Benign and Highly Efficient Synthesis of Quinolines from 2-Aminoarylketone or 2-Aminoarylaldehyde and Carbonyl Compounds Mediated by Hydrochloric Acid in Water. *Tetrahedron Lett.* **2006**, *47*, 1059-1063.

7. For a review on 2-substituted quinolines, see: Gopaul, K.; Shintre, S. A.; Koorbanally, N. A. A Review on the Synthesis and Anticancer Activity of 2-Substituted Quinolines. *Anticancer Agents Med. Chem.* **2015**, *15*, 631-646.

8. Zhou, Y.; Li, W.; Yu, L.; Liu, Y.; Wang, X.; Zhou, M. Highly Efficient Electrochemiluminescence from Iridium(□) Complexes with 2-Phenylquinoline Ligand. *Dalton Trans.* **2015**, *44*, 1858-1865.

9. For general methods for 2-substituted quinolines, see: (a) Berman, A., M.; Lewis, J. C.; Bergman, R. G.; Ellman, J. A. Rh(Ⅰ)-Catalyzed Direct Arylation of Pyridines and Quinolines. *J. Am. Chem. Soc.* **2008**, *130*, 14926-14927. (b) Korivi, R. P.; Cheng, C.-H. Nickel-Catalyzed Cyclization of 2-Iodoanilines with Aroylalkynes: An Efficient Route for Quinoline Derivatives. *J. Org. Chem.* **2006**, *71*, 7079-7082.

10. (a) Chen, X.; Qiu, S.; Wang, S.; Wang, H.; Zhai, H. Blue-Light-Promoted Carbon-Carbon Double Bond Isomerization and Its Application in the Syntheses of Quinolines. *Org. Biomol. Chem.* **2017**, *15*, 6349-6352. (b) Liao, H.-H.; Hsiao, C.-C.; Sugiono, E.; Rueping, M. Shedding Light on Brønsted Acid Catalysis – A Photocyclization-Reduction Reaction for the Asymmetric Synthesis of Tetrahydroquinolines from Aminochalcone in Batch and Flow. *Chem. Commun.* **2013**, *49*, 7953-7955. (c) Horaguchi, T.; Hosokawa, N.; Tanemura, K.; Suzuki, T. Photocyclization Reactions. Part 8 [1]. Synthesis of 2-Quinolone, Quinoline and Coumarin Derivatives Using *Trans*-*Cis* Isomerization by Photoreaction. *J. Heterocycl. Chem.* **2002**, *39*, 61-67.

11. (a) Okuma, K.; Seto, J.-I. Synthesis of Indoles, 3,1-Benzoxazines, and Quinolines from 2-Alkenylanilides and Active Seleniums. *Phosphorous Sulfur Silicon Relat. Elem.* **2010**, *185*, 1014-1020. (b) Okuma, K.; Yasuda, T.; Shioji, K.; Yokomori, Y. Novel Formation of 2-Arylquinolines and 1,3-Benzoxazines from 2-(1-Alkenyl)acylanilides and Active Halogens. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1824-1827.

12. (a) Chelucci, G.; Baldino, S. Synthesis of 4-Diphenylphosphanylmethyl- and 4-Phenylthiomethyl-1,4-methano-11,11-dimethyl-1,2,3,4-tetrahydroacridine: New N-P and N-S Camphor-Derived Chiral Ligands for Asymmetric Catalysis. *Tetrahedron: Asymmetry* **2006**, *17*, 1529-1536. (b) Chelucci, G.; Thummel, R. P. Sterically

Hindered Phenanthrolines: Synthesis of 1,7,7-Trimethyl[2.2.1]Bicycloheptano-[2,3-B]-L, 10-Phenanthroline from (+)-Camphor. *Synth. Commun.* **1999**, *29*, 1665-1669. (c) Love, B. E.; Ren, J. An Inthernational Journal for Rapid Communication of Synthetic Organic Chemistry. *Synth. Commun.* **1995**, *25*, 73-86.

13. Muchowski, J. M.; Maddox, M. L. Concerning the Mechanism of the Friedländer Quinoline Synthesis. *Can. J. Chem.* **2004**, *82*, 461-478.

14. Lee, S.; Jeon, J.; Cheon, C.-H. Synthesis of 2-Substituted Quinolines from 2-Aminostyryl Ketones Using Iodide as a Catalyst. *J. Org. Chem.* **2018**, *83*, 5177-5186.

15. Water was found to facilitate the formation of 2-phenylquinoline **3a** from 2-aminochalcone **4a**. No formation of **3a** was observed in 1,2-dichloroethane at 80 ^{o}C in the absence of water (i.e., in the presence of molecular sieves) after 24 h, whereas **3a** was obtained in 17% yield in the presence of water (i.e., in the absence of molecular sieves) under the same conditions.

16. Most of the Friedländer reactions in aqueous media required strongly acidic or strongly basic conditions to produce quinolines **3** via intermediates **5** (where X = OH). For details, see ref 13.

17. The yields of alkyl ketone substrates were much improved in aqueous media than in organic solvents. In our previous studies, 2-alkylquinolines **3aa** and **3ab** were obtained in 40% and 31% yields, respectively. However, the yields of these 2-alkylquinolines obtained by on-water synthesis were significantly improved as compared to those in our previous protocol (in an organic solvent).

18. Most of solid quinolines **3** are insoluble in water. Thus, the resulting quinolines **3** were precipitated out in the reaction mixture after the reaction was completed. Liquid

quinolines could be isolated in pure form by extraction with ethyl acetate, since benzylamine remains in aqueous layer during extraction.

19. Although we observed intermediates, **5a** and **7a**, in the reaction mixture by ^{1}H NMR analysis, all our attempts to isolate these intermediates failed; instead, chalcone **4a** and quinoline **3a** were isolated presumably because these intermediates are not stable and rapidly underwent elimination of benzylamine to provide **4a** and **3a**, respectively, during isolation. However, the existence of intermediate **7a** was further confirmed by mass analysis (HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for intermediate **7a** $C_{22}H_{21}N_2$ 313.1699; Found 313.1705).

20. Li, S.-M.; Huang, J.; Chen, G.-J.; Han, F.-S. $PdCl_2$(dppf)-Catalyzed In Situ Coupling of 2-Hydroxypyridines with Aryl Boronic Acids Mediated by PyBroP and the One-pot Chemo- and Regioselective Construction of Two Distinct Aryl–Aryl bonds. *Chem. Commun.* **2011**, *47*, 12840-12842.

21. Hyodo, I.; Tobisu, M.; Chatani, N. Catalytic Arylation of a C-H Bond in Pyridine and Related Six-Membered N-Heteroarenes Using Organozinc Reagents. *Chem. Asian J.* **2012**, *7*, 1357-1365.