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Synthesis of 2-Substituted Quinolines from 2-Aminostyryl Ketones Using Iodide as a Catalyst

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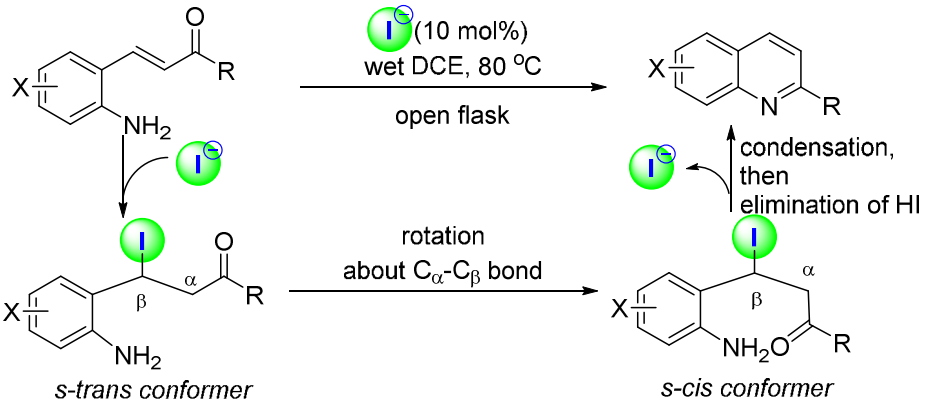


Abstract: A new protocol for the synthesis of 2-substituted quinolines from 2-aminostyryl ketones has been developed using iodide as a nucleophilic catalyst. Conjugate addition of iodide to 2-aminostyryl ketones yielded the corresponding β-iodoketones, which could have a conformation where the amino and carbonyl groups are proximal through free rotation about the C_α-C_β single bond. Subsequent condensation between the amino and carbonyl groups followed by elimination of hydrogen iodide provided the corresponding quinolines, with regeneration of the iodide catalyst.

Introduction

Since quinolines are privileged scaffolds found in a number of biologically active natural products and are used in pharmaceuticals and materials science, numerous quinoline derivatives bearing a different substituent(s) at specific positions have been prepared.[1] Among the various quinoline derivatives developed, 2-substituted quinolines are particularly important as they are not only associated with a wide range of biological properties such as antimalarial and antitumor activity,[2] but are also used as key building blocks in materials science (Figure 1).[3] Consequently, a great deal of efforts have been devoted to the development of new protocols for the synthesis of 2-substituted quinolines.[4-6]

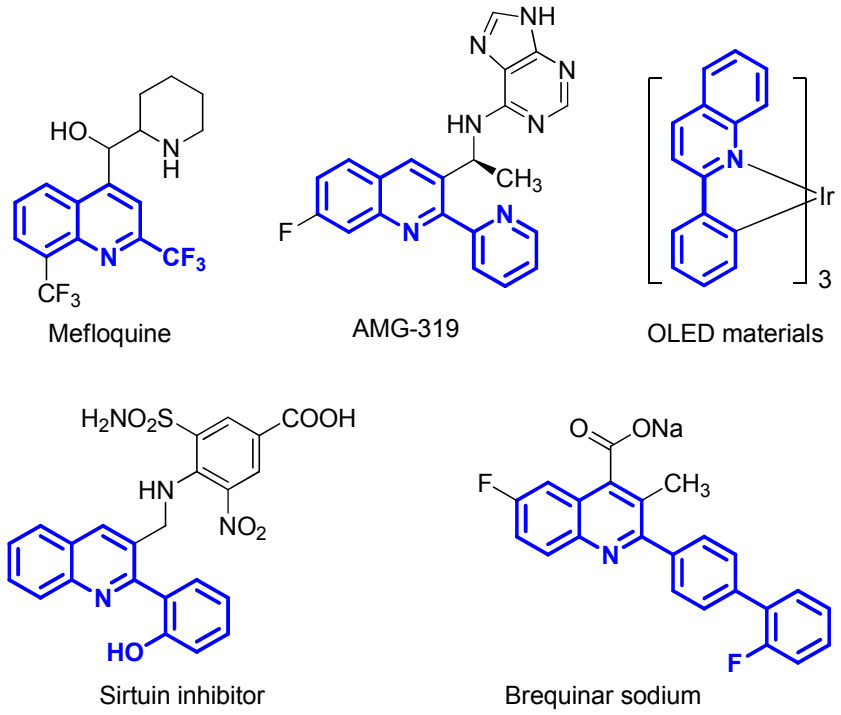
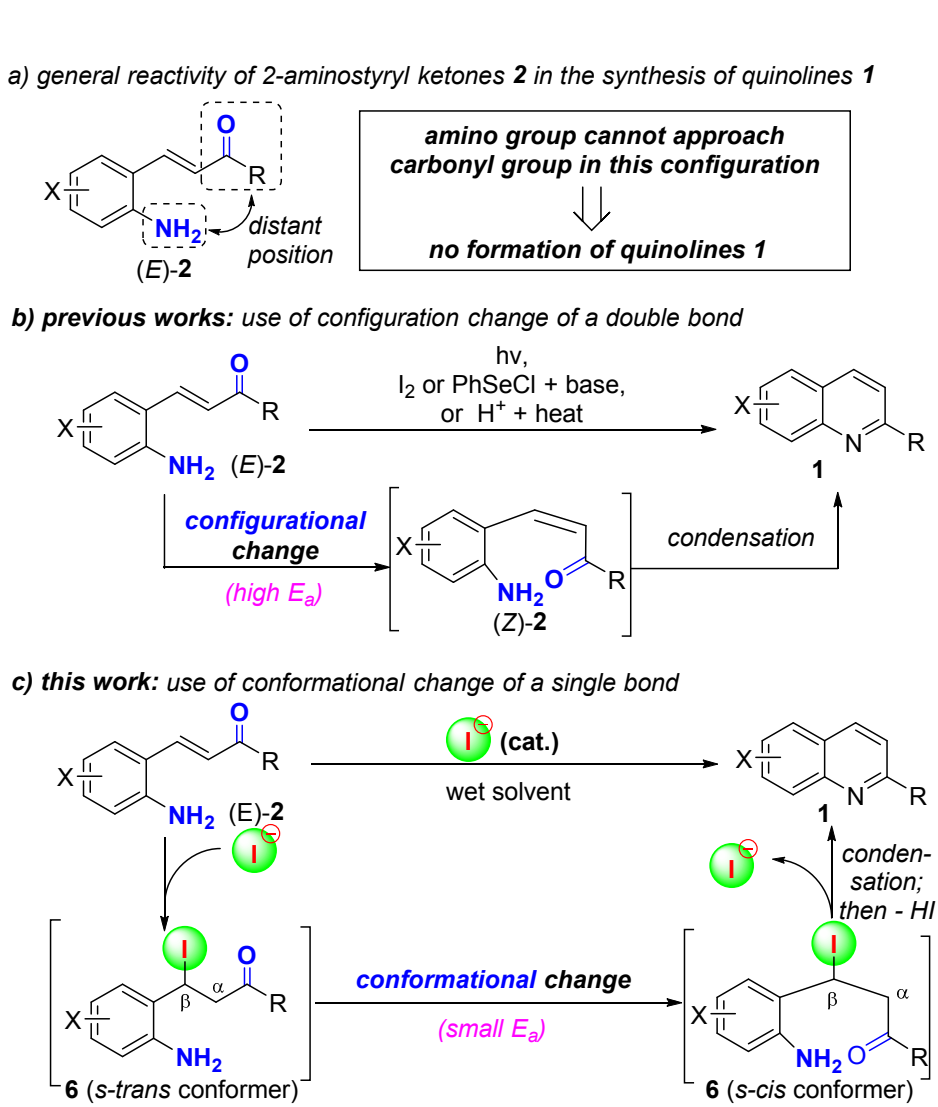


Figure 1. Representative Quinoline Derivatives Carrrying a Substituent at the 2-Position

One important approach for the synthesis of 2-substituted quinolines **1** is through the dehydrative cyclization of 2-aminostyryl ketone derivatives **2** (Scheme 1).[6] However, in general, the conversion of 2-aminostyryl ketones **2** to quinolines **1** is unlikely to take place,

because ketones **2** exist in the stable (*E*)-configuration, where the amino group cannot approach the carbonyl group to undergo the condensation reaction (Scheme 1a).[7] Thus, most previous methods have exploited the conversion of the stable, but unreactive (*E*)-configuration of **2** into the unstable, but reactive (*Z*)-configuration, where the two amino and carbonyl groups are located in a close position, using either photoisomerization, a stoichiometric amount of I_2 or PhSeCl in the presence of a base, or a strong acid under reflux conditions (Scheme 1b).[6] However, considering the importance of 2-substituted quinoline derivatives **1**, the development of efficient and operationally simple and convenient synthetic protocols to access these scaffolds still remains a highly pursued target in both academia and industry.



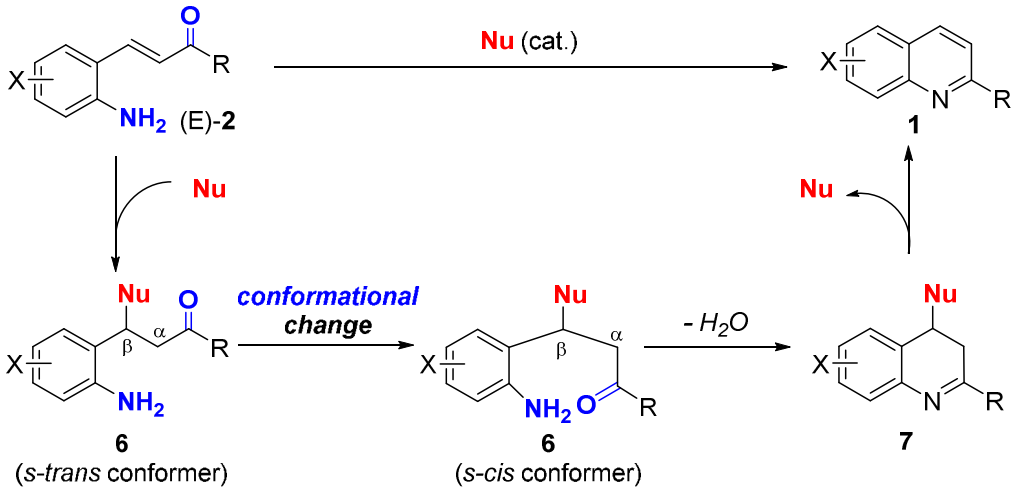
Scheme 1. (a) General Reactivity of 2-Aminostyryl Ketones **2** and (b-c) Comparison of Previous and Present Methods for the Synthesis of Quinolines **1** from Ketones **2**

Herein, we describe the development of a novel approach toward the synthesis of 2-substituted quinolines **1** from 2-aminostyryl ketones **2** using tetrabutylammonium iodide (TBAI) as a nucleophilic catalyst (Scheme 1c).[8] Iodide underwent conjugate addition to **2**, leading to the corresponding β-iodoketones **6**, which could adopt the *s-cis* conformation where the amino and carbonyl groups can be proximally located via free rotation about the C_α-C_β single bond. Subsequent condensation between these two groups followed by the elimination of hydrogen iodide provided the corresponding quinolines **1** and iodide was

regenerated as the nucleophilic catalyst. Various 2-aminostyryl ketones **2** could be applicable to this protocol and the desired quinoline products **1** were obtained in excellent yields. Furthermore, the resulting quinoline products **1** could be directly subjected to other transformations without isolation of quinoline products **1**. Broad substrate scope, no need of any special equipments and a stoichiometric amount of reagents, and extremely simple operation will be other features of this transformation.

Result and Discussions

Since the proximity of the amino and carbonyl groups in ketones **2** is the prerequisite for the success of this protocol,[7,9] we attempted to find an alternative and more efficient way to promote this transformation. Particularly, we noticed that the energy barrier for the free rotation about a C-C single bond (around 6 kcal·mol^{-1}) is significantly smaller than that for the *E*/*Z* isomerization of a C-C double bond (around 65 kcal·mol^{-1}).[10] Based on this energy consideration, we envisioned that the amino and carbonyl groups could be brought into proximity with a much lower energy cost if the double bond in ketones **2** could be converted into a single bond. One way to accomplish this is the use of a nucleophile capable of conjugate addition to the α,β-unsaturated carbonyl moiety present in ketones **2** (Scheme 2). The nucleophile could convert α,β-unsaturated ketones **2** into the corresponding saturated ketones **6** via conjugate addition of the nucleophile, and the saturated ketones **6** could adopt the *s-cis* conformation where the amino and carbonyl groups can be proximally located via free rotation about the C_α-C_β single bond. Subsequent condensation between these two groups followed by the elimination of the nucleophile from the resulting dihydroquinolines **7** could provide the corresponding quinolines **1**, with a regeneration of the catalyst.



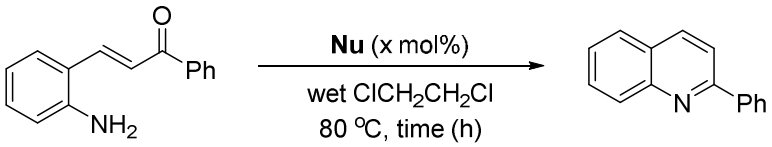
Scheme 2. Working Hypothesis

With this working hypothesis in mind, we first explored various nucleophiles as a possible catalyst in this transformation (Table 1). It was found that a nucleophile significantly facilitated this transformation; no formation of the desired product **1a** was observed in the absence of a nucleophile (entry 1), while the desired product **1a** was obtained in 88% yield when 2-aminostyryl phenyl ketone **2a** was treated with a stoichiometric amount of benzylamine (entry 2) . With these interesting results in hand, other amine sources were tested as the nucleophilic catalyst in this transformation. Aromatic amine could be used as the nucleophilic catalyst leading to the desired product **1a** in 79% yield (entry 3), whereas sterically hindered bulky secondary amine did not provide **1a** (entry 4). According to our working hypothesis in Scheme 2, a nucleophile could be regenerated after the quinoline formation, and thus, the same transformation was attempted to be performed with 10 mol% of benzylamine. Unfortunately, however, with a 10 mol% of benzylamine the quinoline product **1a** was obtained only in 34% yield (entry 5). Next, several other nucleophiles were tested as a catalyst in this transformation (entries 5-8). The nucleophilicity of a catalyst was found to have a strong influence on this transformation. Alcohol did not catalyze this reaction at all (entry 6), but more nucleophilic thiol and phosphine afforded the desired product **1a** in moderate to good yield (entries 7 and 8).

Since a catalyst should be a good nucleophile to undergo facile conjugate addition to 2-aminostyryl ketone **2** and be a good leaving group from intermediate **7** leading to the quinoline product **1a**, a halide was next explored as a catalyst in this transformation (entries 9-11). Gratifyingly, when the reaction was carried out in the presence of a catalytic amount of TBAI, the desired product **1a** was obtained in quantitative yield after 12 h (entry 9). However, less nucleophilic halides, such as bromide and chloride, provided **1a** in 66% and 54% yields, respectively (entries 10 and 11). Furthermore, other nucleophiles, such as hydroxide and

alkoxide, were tested as a catalyst in this quinoline synthesis (entries 12 and 13). However, these nucleophilic anions failed to act as a nucleophile; either no reaction or the formation of side product was observed with these nucleophiles. Since iodide provided the desired product **1a** in the highest yield among the nucleophiles tested, iodide was selected as the optimal nucleophilic catalyst for further investigation.

Table 1. Screening of Nucleophiles



2a **1a**

entry	**Nu**	(mol%)	time (h)	yield[a] (%)
1	-	-	24	N.R.[b]
2	benzylamine	100	12	88
3	p-anisidine	100	12	79
4	diisopropylamine	100	12	N.R.[b]
5	benzylamine	10	12	34
6	benzyl alcohol	10	12	N.R.[b]
7	benzyl mercaptan	10	12	80
8	triphenylphosphine	10	12	65
9	TBAI	10	12	>99
10	TBABr	10	12	66
11	TBACl	10	12	54
12	NaOH	10	12	side reaction[c]
13	NaOMe	10	12	N.R.[b]

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

[b] No Reaction

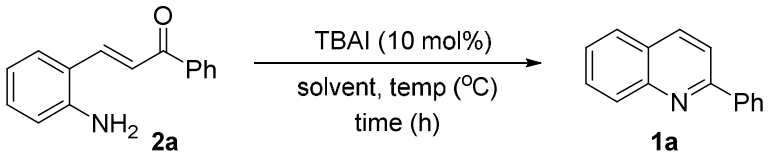
[c] Several unidentifiable products were formed.

With iodide as the optimal nucleophilic catalyst in this transformation, we further investigated other reaction parameters in this transformation (Table 2). Interestingly, water was found to play a crucial role in this transformation (entries 1 and 2). When the reaction was performed with 10 mol% of iodide in the absence of water (i.e., in the presence of molecular sieves), the yield of **1a** significantly decreased and the starting material **2a** remained unreacted even after a long reaction time (entry 2).[11] Furthermore, the reaction atmosphere was found to slightly influence the efficiency of this transformation. When the reaction was performed under an argon atmosphere, quinoline **1a** was obtained in lower yield than in the reaction in an open flask (entries 1 and 3). Thus, the transformation was carried out in an open flask in the further investigations.

Next, the effect of the reaction medium on this transformation was investigated (entries 1, 4−9), indicating that the choice of reaction medium had a considerable influence on the efficiency of this transformation. The reaction in 1,2-dichloroethane (DCE) provided the desired product **1a** in quantitative yield within 12 h (entry 1), whereas the use of other solvents afforded **1a** in very low yield and a considerable amount of the starting material **2a** remained unreacted in the reaction mixture (entries 4−9). Finally, the effect of the reaction temperature on this transformation was investigated and was found to have a beneficial effect on the reaction rate (entries 1, 10−14). The reaction performed below 60 ^{o}C proceeded slowly to provide the desired product **1a** in no or low yield (entries 10−12), while the reactions went to completion at the temperature above 80 ^{o}C (entry 3 vs. entries 13 and 14). Although the

reaction proceeded slightly faster above 80 °C, 80 °C was selected as optimal for the simple operation of this protocol.[12]

Table 2. Optimization of Reaction Conditions



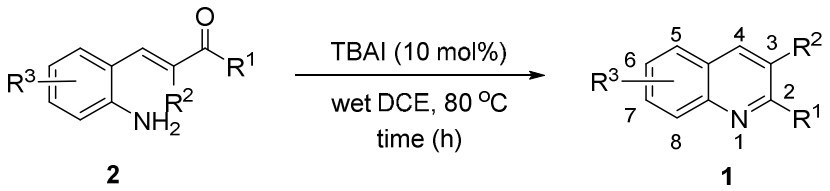
entry	solvent	temp (°C)	time (h)	yield[a] (%)
1	$ClCH_2CH_2Cl$	80	12	>99
2[b]	$ClCH_2CH_2Cl$	80	12	trace
3[c]	$ClCH_2CH_2Cl$	80	12	71
4	MeOH	80	24	17
5	EtOH	80	24	17
6	toluene	80	12	7
7	1,4-dioxane	80	12	7
8	CH_2Cl_2	80	24	12
9	$CHCl_3$	80	24	trace
10	$ClCH_2CH_2Cl$	rt	12	trace
11	$ClCH_2CH_2Cl$	40	12	trace
12	$ClCH_2CH_2Cl$	60	12	18
13[d]	$ClCH_2CH_2Cl$	90	11	97
14[d]	$ClCH_2CH_2Cl$	100	10	98

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

[b] Reaction was performed in the presence of 4 Å molecular sieves.

[c] Under an argon atmosphere.

Table 3. Substrate Scope



2 **1**

Entry	**1**	R^1	R^2	R^3	time (h)	yield (%)
1	**1a**	Ph	H	H	12	99
2	**1b**	4-$MeOC_6H_4$	H	H	16	83
3	**1c**	4-MeC_6H_4	H	H	17	93
4	**1d**	4-FC_6H_4	H	H	11	96
5	**1e**	4-ClC_6H_4	H	H	14	99
6	**1f**	4-BrC_6H_4	H	H	15	99
7	**1g**	4-$MeO_2CC_6H_4$	H	H	10	99
8	**1h**	2-MeC_6H_4	H	H	21	95
9	**1i**	3-MeC_6H_4	H	H	20	89
10	**1j**	2-BrC_6H_4	H	H	13	97
11	**1k**	3-BrC_6H_4	H	H	13	98
12	**1l**	1-naphthyl	H	H	13	99
13	**1m**	2-naphthyl	H	H	15	99
14	**1n**	2-furyl	H	H	15	96
15	**1o**	2-thienyl	H	H	11	98
16	**1p**	Ph	H	6-F	13	99
17	**1q**	Ph	H	6-Cl	15	96
18	**1r**	Ph	H	6-Br	15	99

19	**1s**	Ph	H	6-OMe	11	87
20	**1t**	4-$MeOC_6H_4$	H	6-OMe	11	95
21[a]	**1u**	Ph	H	7-Br	20	94
22[b]	**1v**	Ph	H	6,8-Br_2	20	82
23	**1w**	Ph	Me	H	10	80
24	**1x**	Methyl	H	H	12	40
25[a]	**1y**	Isopropyl	H	H	12	31

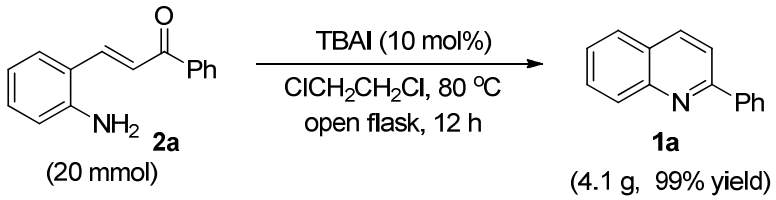
[a] 20 mol% TBAI was used.

[b] 40 mol% TBAI was used.

With these optimized reaction conditions (10 mol% of TBAI, wet DCE, open flask, 80 ^oC) in hand, the substrate scope of ketones **2** was further investigated in this transformation (Table 3). Various 2-aminostyryl aryl ketones **2** could be applied in this protocol to afford the 2-aryl substituted quinolines **1** (entries 1−11). The electronic effect of the aryl group slightly affected this transformation (entries 1-7); the ketones **2** bearing an electron-deficient aryl group provided the desired products **1** in slightly better yields than those with electron-rich aryl groups. Furthermore, the position of the substituent on the aryl group in ketones **2** had little influence on the efficiency of this transformation (entries 3, 6, and 8−11). The desired products **1** were obtained in excellent yields regardless of the position of the substituent on the aryl ring. Furthermore, 2-aminostyryl ketones carrying fused aromatic and heteroaromatic moieties were tolerated in this transformation, and the desired products **1** were obtained in excellent yields (entries 12−15).

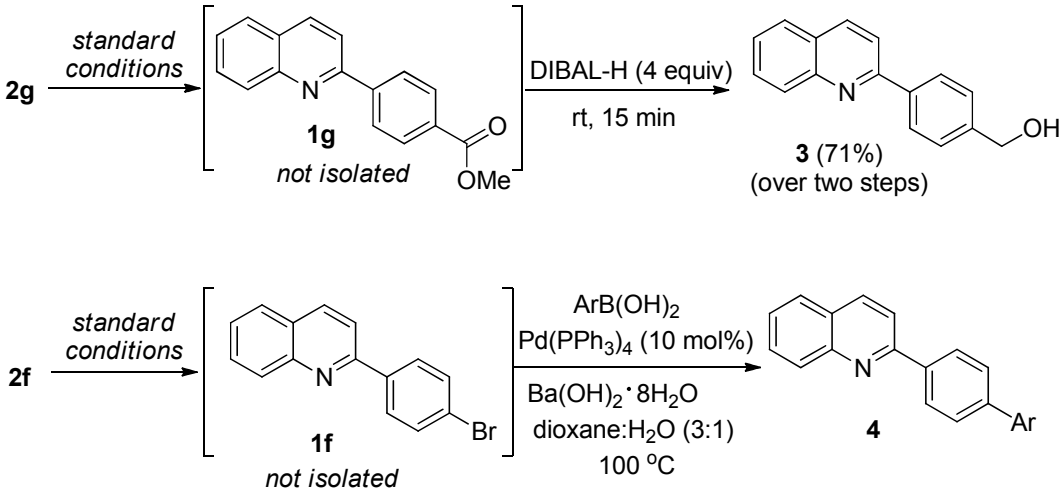
The effect of the substituent on the 2-aminophenyl ring in ketones **2** was further explored on the efficiency of this transformation (entries 16−22). When several 2-aminostyryl ketones derivatives **2** bearing a different substituent were subjected to the standard conditions,

the desired disubstituted quinoline products **1** were obtained in excellent yields regardless of the electronic nature of the substituent (entries 16-20). Next, the position of a substituent on the phenyl ring in 2-aminostyryl scaffold was further investigated and was found to have little effect on this transformation (entries 18, 21 and 22). A substrate bearing a substituent on the vinyl moiety in the 2-aminostyryl group was also applicable in this protocol, and the desired 2,3-disubstituted quinoline **1w** was obtained in high yield (entry 23). Unfortunately, however, this protocol was limited for application to ketones **2** carrying aliphatic groups; the desired quinoline products **1** were obtained in only moderate yields and rather complex mixtures were obtained (entries 24 and 25).



Scheme 3. A Gram-Scale Transformation

To test the practicality of the developed method, the transformation was carried out on the gram-scale (Scheme 3). When 20 mmol of **2a** was subjected to the standard conditions, the desired product **1a** was obtained in quantitative yield. Notably, after completion of this transformation, **1a** could be easily isolated by removal of TBAI through simple aqueous extraction.



	4a	4b	4c
Ar	C_6H_5	4-$MeOC_6H_4$	4-$F_3CC_6H_4$
yield (%)[a]	91	73	65

[a] two-step yield from **2f**

Scheme 4. Direct Transformation of Quinolines

With these results in hand, we further attempted to demonstrate the versatility of this protocol (Scheme 4). Particularly, since this protocol required no additional reagents except TBAI, and the reaction proceeded very cleanly without the formation of any other side-products, attempts were made to develop a one-pot protocol where the resulting quinoline products **1** were directly subjected to other transformations without their complete isolations. First, quinoline **3** bearing a 4-hydroxymethylphenyl group could be prepared by reduction of the ester moiety in quinoline **1g** to an alcohol in the same reaction mixture. Reaction of **2g** under the standard conditions followed by direct reduction of the resulting quinoline **1g** with DIBAL in the same pot at room temperature afforded quinoline **3** in 72% yield over two steps. Furthermore, several biaryl substituted quinolines **4**[13] could be prepared through the direct Suzuki-Miyaura reaction of quinoline **1f** without its complete isolation. The treatment of ketone **2f** with TBAI provided **1f**, and without complete isolation of **1f**, the crude mixture was

subjected to Suzuki-Miyaura reactions with several aryl boronic acids to provide the expected biaryl substituted quinolines **4** in good to high yields over two steps.[14]

Conclusions

In conclusion, a new protocol was developed for the synthesis of 2-substituted quinolines from 2-aminostyryl ketones using iodide as a nucleophilic catalyst. Conjugate addition of iodide to 2-aminostyryl ketones **2** led to β-iodoketones **6**, which could adopt the *s-cis* conformation via free rotation about the C_α-C_β bond. In this conformation, intramolecular imine formation between the carbonyl and the amino groups followed by elimination of HI provided the desired 2-substituted quinolines **1**. Various 2-substituted quinolines **1** could be prepared from the corresponding ketones **2** in excellent yields. Furthermore, the utility of this transformation was demonstrated by direct application of the resulting quinolines to other transformations without prior isolation. Further application of this protocol to the synthesis of other important quinoline compounds are currently underway in our laboratory and will be reported in due course.

Experimental Section

General. All reactions were carried out in an oven-dried glassware in an open flask, unless otherwise noted. Except as otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin layer chromatography (TLC) using pre-coated silica gel glass plates (0.25 mm) with F254 indicator. Visualization was accomplished by UV light (254 nm), with a combination of potassium permanganate and/or phosphomolybdic acid solution as an indicator. Flash column chromatography was performed using silica gel 60 (230 – 400 mesh). Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise

noted. Commercial grade reagents and solvents were used without further purification. 2-Nitrobenzaldehydes and all methyl ketones were purchased from commercial suppliers and used without further purification. 2-Aminostyryl ketone derivatives **2** were prepared by a protocol reported in the literature through aldol condensation of methyl ketone derivatives with 2-nitrobenzaldehydes followed by the reduction of a nitro group into an amino group.[15a,b] ^{1}H NMR and ^{13}C NMR spectra were recorded at 500 MHz and 125 MHz spectrometers, respectively. Tetramethylsilane (δ: 0.0 ppm) and a residual NMR solvent (either $CDCl_3$ (δc: 77.16 ppm) were used as internal standards for ^{1}H NMR and ^{13}C NMR spectra, respectively. 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) in electrospray ionization (ESI) mode as ionization method.

All unknown 2-aminostyryl ketones (**2g**, **2h**, **2i**, **2j**, **2p**, **2t**, **2v** and **2y**) were prepared from methyl ketone derivatives and 2-nitrobenzaldehydes via a modified method reported in the literature procedure.[15a,b]

Synthesis of 2-aminostyryl ketone derivatives 2

To a mixture of a 2-nitrobenzaldehyde derivative (4.0 mmol), sodium hydroxide (16 mg, 0.40 mmol) and potassium carbonate (55 mg, 0.40 mmol) was added a methyl ketone derivative (4.0 mmol) at 25 ^{o}C. The reaction stirred for 30 min at room temperature. After complete consumption of the 2-nitrobenzaldehyde derivative, the reaction mixture was quenched by the addition of H_2O and extracted with ethyl acetate. The organic layer was combined, dried over $MgSO_4$, and concentrated in vacuo. The crude mixture was purified by recrystallization with ethanol to provide the desired (*E*)-2-nitrostyryl ketone as a pale yellow solid in about 60-70%

yield. To a solution of the resulting (*E*)-2-nitrostyryl ketone derivative (2.5 mmol) in ethanol (25 mL) was added iron powder (70 mg, 13 mmol), followed by HCl (1.0 N, 1.3 mL/ 1.3 mmol), and the resulting mixture was virgorously stirred at 80 ^{o}C. After complete consumption of the (*E*)-2-nitrostyryl ketone derivative, the reaction mixture was cooled to room temperature, diluted with ethyl acetate and filtered through a Celite pad. The filtrate was washed with saturated Na_2CO_3 aqueous solution and the aqueous phase was extracted with ethyl acetate. The combinded organic phases were dried over $MgSO_4$, and concentrated in vacuo. The crude material was purified by recrystallization with a mixture of methylene chloride and hexanes to provide the desired (*E*)-2-aminostyryl ketone **2**.

(E)-2-Aminophenylstyryl 4-Methoxycarbonylphenyl Ketone (**2g**)

Compound **2g** was obtained as an orange solid (0.42 g, 60%) after purification by recrystallization with methylene chloride and hexanes. R_f= 0.3 (ethyl acetate/hexanes = 1:5). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.15 (d, J = 8.2 Hz, 2H), 8.05 (d, J = 8.1 Hz, 2H), 8.01 (d, J = 15.4 Hz, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.46 (d, J = 15.4 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 6.80 (t, J = 7.6 Hz, 1H), 6.73 (d, J = 8.1 Hz, 1H), 4.11 (br. s., 2H), 3.96 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 189.9, 166.5, 146.6, 141.9, 141.1, 133.6, 132.2, 130.0, 128.4, 128.3, 121.4, 120.0, 119.1, 117.0, 52.6. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{15}NO_3Na$ 304.0944; Found 304.0944.

(E)-2-Aminophenylstyryl 2-Methylphenyl Ketone (**2h**)

Compound **2h** was obtained as a yellow solid (0.39 g, 65%) after purification by recrystallization with methylene chloride and hexanes. R_f= 0.3 (ethyl acetate/hexanes = 1:5). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.70 (d, J = 15.7 Hz, 1H), 7.53 (d, J = 7.0 Hz, 1H), 7.46 (d, J = 7.9 Hz, 1H), 7.38 (m, 1H), 7.28 (d, J = 7.3 Hz, 2H), 7.19 (m, 1H), 7.10 (d, J = 15.7 Hz,

1H), 6.78 (t, J = 7.6 Hz, 1H), 6.70 (d, J = 8.1 Hz, 1H), 4.02 (br. s., 2H), 2.48 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, ppm): δ 196.1, 146.2, 140.9, 139.3, 137.1, 131.9, 131.5, 130.6, 128.2 (2C), 126.2, 125.6, 120.0, 119.0, 116.9, 20.5. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{15}NONa$ 260.1046; Found 260.1048.

(E)-2-Aminophenylstyryl 3-Methylphenyl Ketone (**2i**)

Compound **2i** was obtained as a yellow solid (0.39 g, 66%) after purification by recrystallization with methylene chloride and hexanes. R_f = 0.3 (ethyl acetate/hexanes = 1:5). ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 7.98 (d, J = 15.4 Hz, 1H), 7.84 (s., 2H), 7.51 (m, 2H), 7.40 (s., 2H), 7.21 (t, J = 7.6 Hz, 1H), 6.81 (t, J = 7.4 Hz, 1H), 6.73 (d, J = 8.1 Hz, 1H), 4.06 (br. s., 2H), 2.45 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, ppm): δ 190.6, 146.3, 140.0, 138.6, 138.5, 133.7, 131.8, 129.1, 128.6, 128.3, 125.8, 122.1, 120.5, 119.1, 116.9, 21.6. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{15}NONa$ 260.1046; Found 260.1047.

(E)-2-Aminophenylstyryl 2-Bromophenyl Ketone (**2j**)

Compound **2j** was obtained as a yellow solid (0.48 g, 63%) after purification by recrystallization with methylene chloride and hexanes. R_f = 0.3 (ethyl acetate/hexanes = 1:5). ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 7.67 (d, J = 9.8 Hz, 1H), 7.64 (d, J = 1.7 Hz, 1H), 7.43 (m, 3H), 7.33 (dt, J = 7.6, 1.8 Hz, 1H), 7.20 (t, J = 7.6 Hz, 1H), 7.05 (d, J = 15.9 Hz, 1H), 6.79 (t, J = 7.6 Hz, 1H), 6.71 (d, J = 8.1 Hz, 1H), 3.98 (br. s., 2H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, ppm): δ 194.5, 146.3, 141.9, 141.5, 133.6, 132.2, 131.6, 129.5, 128.6, 127.6, 125.8, 120.0, 119.6, 119.2, 117.0. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{12}BrNONa$ 323.9994; Found 323.9994.

(E)-2-Amino-5-Fluorophenylstyryl Phenyl Ketone (**2p**)

Compound **2p** was obtained as a yellow solid (0.40 g, 67%) after purification by recrystallization with methylene chloride and hexanes. R_f = 0.3 (ethyl acetate/hexanes = 1:5). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.03 (d, J = 7.5 Hz, 2H), 7.92 (d, J = 15.3 Hz, 1H), 7.60 (m, 1H), 7.52 (m, 2H), 7.47 (d, J = 15.3 Hz, 1H), 7.24 (dd, J = 9.5, 2.9 Hz, 1H), 6.95 (dt, J = 8.3, 2.9 Hz, 1H), 6.68 (dd, J = 8.9, 4.9 Hz, 1H), 3.92 (br. s., 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 190.0, 157.3, 155.4, 142.6, 138.9, 138.2, 133.1, 128.8, 128.6, 122.8, 121.3, 118.9, 118.8, 118.2, 118.1, 113.5, 113.3. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{12}FNONa$ 264.0795; Found 264.0793.

(E)-2-Amino-5-Methoxyphenylstyryl 4-Methoxyphenyl Ketone (**2t**)

Compound **2t** was obtained as a red solid (0.46 g, 65%) after purification by recrystallization with methylene chloride and hexanes. R_f = 0.3 (ethyl acetate/hexanes = 1:5). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.04 (d, J = 8.7 Hz, 2H), 7.95 (d, J = 15.3 Hz, 1H), 7.47 (d, J = 15.4 Hz, 1H), 7.05 (d, J = 2.7 Hz, 1H), 6.99 (d, J = 8.7 Hz, 2H), 6.85 (dd, J = 8.7, 2.7 Hz, 1H), 6.69 (d, J = 8.7 Hz, 1H), 3.89 (s, 3 H), 3.80 (s, 5 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 188.7, 163.5, 152.9, 140.4, 139.3, 131.3, 130.9, 122.2, 121.6, 118.7, 118.5, 114.0, 112.0, 56.0, 55.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{18}NO_3$ 284.1281; Found 284.1282.

(E)-2-Amino-3,5-dibromophenylstyryl Phenyl Ketone (**2v**)

Compound **2v** was obtained as a yellow solid (0.66 g, 69%) after purification by recrystallization with methylene chloride and hexanes. R_f = 0.3 (ethyl acetate/hexanes = 1:5). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.03 (m, 2H), 7.85 (d, J = 15.3 Hz, 1H), 7.62 (m, 1H), 7.60 (m, 1H), 7.57 (d, J = 2.1 Hz, 1H), 7.53 (m, 2H), 7.48 (d, J = 15.3 Hz, 1H), 4.54 (br. s., 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 189.6, 142.6, 138.1, 137.9, 136.3, 133.4,

129.6, 128.9, 128.7, 124.3, 122.9, 111.4, 109.9. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{11}Br_2NONa$ 401.9100; Found 401.9093.

(E)-2-Aminophenylstyryl Isopropyl Ketone (**2y**)

Compound **2y** was obtained as yellow oil (0.28 g, 60%) after purification by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:6) as an eluent. R_f= 0.3 (ethyl acetate/hexanes = 1:5). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.78 (d, J = 15.7 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.18 (m, 1H), 6.77 (m, 2H), 6.71 (d, J = 7.9 Hz, 1H), 3.98 (br. s., 2H), 2.87 (td, J = 13.8, 6.9 Hz, 1H), 1.18 (d, J = 6.9 Hz, 6H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, ppm): δ 203.8, 146.1, 137.8, 131.5, 128.2, 124.4, 120.2, 119.1, 116.9, 40.0, 18.6. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{15}NONa$ 212.1046; Found 212.1045.

General procedure for the synthesis of 2-substituted quinoline derivatives 1 (Table 2).

To a solution of (*E*)-2-aminostyryl ketone derivative **2** (0.20 mmol) in 1,2-dichloroethane (2.0 mL) was added tetrabutylammonium iodide (7.4 mg, 0.020 mmol) at room temperature. The reaction mixture was stirred at 80 ^{o}C in an open flask and monitored by TLC. After complete consumption of compound **2**, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. Then the crude reaction mixture was quenched with water, and extracted with and ethyl acetate. The organic layer was combined, dried over $MgSO_4$, and concentrated. Even after extraction, the crude mixture was generally pure enough to use without further purification. If necessary, the crude mixture was purified by short flash column chromatography on silica to provide the desired product **1**.

2-Phenylquinoline (**1a**)

Compound **1a** was obtained as a white solid (41 mg, 99%) after purification by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:6) as an eluent. Spectroscopic data were matched with the reported values.[16] 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 = 8.1 Hz, 1H), 7.74 (t, J = 7.6 Hz, 1H), 7.54 (t, J = 7.2 Hz, 3H), 7.48 (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 (**1b**)

Compound **1b** was obtained as a pale yellow solid (44 mg, 83%) after purification by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:6) as an eluent. Spectroscopic data were matched with the reported values.[16] R_f = 0.4 (ethyl acetate/hexanes = 1:7). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.19 (d, J = 8.7 Hz, 1H), 8.15 (m, 3H), 7.84 (d, J = 8.5 Hz, 1H), 7.81 (dd, J = 8.1, 1.1 Hz, 1H), 7.71 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.50 (ddd, J = 8.0, 6.9, 1.1 Hz, 1H), 7.05 (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 (**1c**)

Compound **1c** was obtained as a pale yellow solid (40 mg, 93%) after purification by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:6) as an eluent. Spectroscopic data were matched with the reported values.[16] 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 (**1d**)

Compound **1d** was obtained as a light green solid (43 mg, 96%) after purification by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:6) as an eluent. Spectroscopic data were matched with the reported values.[16] 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 (**1e**)

Compound **1e** was obtained as a pale yellow solid (48 mg, 99 %) after purification by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:6) as an eluent. Spectroscopic data were matched with the reported values.[16] 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 (**1f**)

Compound **1f** was obtained as a pale yellow solid (58 mg, 99%) after purification by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:6) as an eluent. Spectroscopic data were matched with the reported values.[16] 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{^{1}H} 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-Methyoxycarbonylphenyl)quinoline (**1g**)

Compound **1g** was obtained as a white solid (54 mg, 99%) after purification by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:6) as an eluent. Spectroscopic data were matched with the reported values.[17] R_f = 0.3 (ethyl acetate/hexanes = 1:7). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.26 (m, 3H), 8.20 (m, 3H), 7.92 (d, J = 8.5 Hz, 1H), 7.86 (dd, J = 8.1, 1.2 Hz, 1H), 7.76 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.57 (ddd, J = 8.0, 6.9, 1.1 Hz, 1H), 3.97 (s, 3H). ^{13}C{^{1}H} 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-(2-Methylphenyl)quinoline (**1h**)

Compound **1h** was obtained as a brown solid (42 mg, 95%) after purification by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:6) as an eluent. Spectroscopic data were matched with the reported values.[18] 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 = 8.5 Hz, 1H), 7.87 (dd, J = 8.1, 1.2 Hz, 1H), 7.74 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.56 (m, 2H), 7.50 (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 (**1i**)

Compound **1i** was obtained as a brown solid (39 mg, 90%) after purification by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:6) as an eluent. Spectroscopic data were matched with the reported values.[16] 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 (**1j**)

Compound **1j** was obtained as a yellow solid (55 mg, 97%) after purification by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:6) as an eluent. Spectroscopic data were matched with the reported values.[16] 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 (**1k**)

Compound **1k** was obtained as a yellow solid (56 mg, 98%) after purification by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:6) as an eluent. Spectroscopic data were matched with the reported values.[18] 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). $^{13}C\{^1H\}$ 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 (**1l**)

Compound **1l** was obtained as orange oil (53 mg, 99%) after purification by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:6) as an eluent. Spectroscopic data were matched with the reported values.[19] R_f = 0.3 (ethyl acetate/hexanes = 1:10). ^1H 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). $^{13}C\{^1H\}$ 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 (**1m**)

Compound **1m** was obtained as a brown solid (54 mg, 99%) after purification by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:6) as an eluent. Spectroscopic data were matched with the reported values.[18] R_f = 0.4 (ethyl acetate/hexanes = 1:10). ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 8.63 (d, J = 0.9 Hz, 1H), 8.38 (dd, J = 8.6, 1.8 Hz, 1H), 8.27 (d, J = 8.4 Hz, 1H), 8.23 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.7 Hz, 1H), 8.01 (m, 2H), 7.91 (m, 1H), 7.86 (dd, J = 8.1, 1.2 Hz, 1H), 7.76 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.54 ppm (m, 3 H). $^{13}C\{^1H\}$ 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 (**1n**)

Compound **1n** was obtained as a brown solid (46 mg, 96%) after purification by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:6) as an eluent. Spectroscopic data were matched with the reported values.[17] 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 (**1o**)

Compound **1o** was obtained as a yellow solid (42 mg, 98%) after purification by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:6) as an eluent. Spectroscopic data were matched with the reported values.[6a] 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 (**1p**)

Compound **1p** was obtained as a pale yellow solid (44 mg, 99%) after purification by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:6) as an eluent. Spectroscopic data were matched with the reported values.[18] 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 (**1q**)

Compound **1q** was obtained as a pale yellow solid (46 mg, 96%) after purification by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:6) as an eluent. Spectroscopic data were matched with the reported values.[18] 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 (**1r**)

Compound **1r** was obtained as an orange solid (57 mg, 99%) after purification by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:6) as an eluent. Spectroscopic data were matched with the reported values.[20] 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 (**1s**)

Compound **1s** was obtained as a pale yellow solid (41 mg, 87%) after purification by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:6) as an eluent. Spectroscopic data were matched with the reported values.[20] 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.

6-Methoxy-2-(4-methoxyphenyl)quinoline (**1t**)

Compound **1t** was obtained as orange oil (50 mg, 95%) after purification by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:5) as an eluent. Spectroscopic data were matched with the reported values.[21] R_f = 0.3 (ethyl acetate/hexanes = 1:8). ^{1}H 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{^{1}H} 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.

7-Bromo-2-phenylquinoline (**1u**)

Compound **1u** was obtained as a pale yellow solid (53 mg, 94%) after purification by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:6) as an eluent. Spectroscopic data were matched with the reported values.[18] 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{^{1}H} 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.

6,8-Dibromo-2-phenylquinoline (**1v**)

Compound **1v** was obtained as orange oil (60 mg, 82%) after purification by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:6) as an eluent. Spectroscopic data were matched with the reported values.[22] R_f = 0.3 (ethyl acetate/hexanes = 1:10). ^{1}H 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{^{1}H} 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.

3-Methyl-2-phenylquinoline (**1w**)

Compound **1w** was obtained as orange oil (35 mg, 80%) after purification by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:6) as an eluent. Spectroscopic data were matched with the reported values.[18] 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.

2-Methylquinoline (**1x**)

Compound **1x** was obtained as a white solid (12 mg, 43%) after purification by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:6) as an eluent. Spectroscopic data were matched with the reported values.[6a] R_f = 0.3 (ethyl acetate/hexanes = 1:5). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.03 (t, J = 9.7 Hz, 2H), 7.77 (d, J = 8.1 Hz, 1H), 7.68 (m, 1H), 7.48 (m, 1H), 7.29 (dd, J = 8.4, 1.2 Hz, 1H), 2.75 (d, J = 1.2 Hz, 3H). ^{13}C{^{1}H} 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 (**1y**)

Compound **1y** was obtained as yellow oil (13 mg, 37%) after purification by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:6) as an eluent. Spectroscopic data were matched with the reported values.[23] 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), 8.05 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.68 (ddd, J = 8.4, 7.0, 1.3 Hz, 1H), 7.48 (m, 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.

Synthesis of 2-(4-Hydroxymethylphenyl)quinoline (3)

To a solution of *(E)*-2-aminostyryl ketone derivative **2g** (0.30 mmol) in 1,2-dichloroethane (3.0 mL) was added TBAI (11 mg, 0.030 mmol) at room temperature. The reaction mixture was stirred at 80 ^{o}C in an open flask and monitored by TLC. After complete consumption of compound **2g**, the reaction mixture was cooled to room temperature and to it was added DIBAL-H in THF solution (1.0 M, 3.0 mL, 3.0 mmol) at room temperature. The reaction mixture was stirred at room temperature and monitored by TLC. After complete consumption of compound **1g**, the crude mixture was quenched with water, and extracted with dichloromethane. The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (ethyl acetate:hexanes = 1:2) to afford alcohol **3** as a white solid (51 mg, 0.22 mmol, 72%). Spectroscopic data were matched with the reported values.[24] 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), 8.19 (d, J = 8.5 Hz, 1H), 8.14 (d, J = 6.7 Hz, 2H), 7.87 (d, J = 8.5 Hz, 1H), 7.83 (d, J = 8.1 Hz, 1H), 7.74 (t, J = 7.6 Hz, 1H), 7.52 (m, 3H), 4.77 (s, 2H). ^{13}C{^{1}H} NMR (125 MHz,

$CDCl_3$, ppm): δ 157.2, 148.4, 142.3, 139.0, 137.0, 129.9, 129.8, 127.9, 127.6, 127.4, 127.3, 126.5, 119.1, 65.1.

General procedure for the synthesis of compound 4

To a solution of *(E)*-2-aminostyryl ketone derivative **2f** (0.10 mmol) in 1,2-dichloroethane (1.0 mL) was added TBAI (3.7 mg, 0.010 mmol) at room temperature. The reaction mixture was stirred at 80 ^oC in an open flask and monitored by TLC. After complete consumption of compound **2f**, the reaction mixture was concentrated. A crude mixture of 2f was re-dissolved in a mixture of dioxane (0.75 mL) and H_2O (0.25 mL) and to it were added $ArB(OH)_2$ (0.11 mmol), $Pd(PPh_3)_4$ (12 mg, 0.010 mmol) and $Ba(OH)_2.8H_2O$ (47 mg, 0.15 mmol). The reaction mixture was monitored by TLC, and after complete consumption of compound **1f**, the crude mixture was quenched by 1.0 N HCl and extracted by water and dichloromethane. The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (ethyl acetate:hexanes = 1:8) to afford **4**.

2-(4'-Biphenyl)quinoline (**4a**)

Compound **4a** was obtained as a white solid (26 mg, 91%) after purification by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:8) as an eluent. Spectroscopic data were matched with the reported values.[17] R_f= 0.3 (ethyl acetate/hexanes = 1:10). ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 8.26 (m, 3H), 8.19 (d, J = 8.4 Hz, 1H), 7.94 (d, J = 8.5 Hz, 1H), 7.84 (dd, J = 8.2, 1.1 Hz, 1H), 7.75 (m, 3H), 7.69 (dd, J = 8.3, 1.1 Hz, 2H), 7.54 (ddd, J = 8.0, 6.0, 1.1 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 7.39 (m, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, ppm) δ 157.0, 148.5, 142.2, 140.7, 138.7, 136.9, 129.9, 129.8, 129.0, 128.1, 127.7 (2 C), 127.6, 127.4, 127.3, 126.4, 119.0.

2-(4'-Methoxy-4-biphenyl)quinoline (**4b**)

Compound **4b** was obtained as a yellow solid (22 mg, 73%) after purification by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:8) as an eluent. Spectroscopic data were matched with the reported values.[13a] R_f = 0.3 (ethyl acetate/hexanes = 1:10). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.24 (m, 3H), 8.18 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 8.5 Hz, 1H), 7.84 (m, 1H), 7.73 (m, 3H), 7.62 (m, 2H), 7.53 (ddd, J = 8.1, 6.9, 1.1 Hz, 1H), 7.02 (m, 2H), 3.88 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, ppm) δ 159.6, 157.1, 148.5, 141.8, 138.1, 136.9, 133.2, 129.9, 129.8, 128.3, 128.1, 127.6, 127.3, 127.2, 126.4, 119.0, 114.5, 55.5.

2-(4'-(Trifluoromethyl)-4-biphenyl)quinoline (**4c**)

Compound **4c** was obtained as a white solid (23 mg, 65%) after purification by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:8) as an eluent. R_f = 0.3 (ethyl acetate/hexanes = 1:10). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.30 (m, 2H), 8.27 (d, J = 8.4 Hz, 1H), 8.19 (d, J = 8.4 Hz, 1H), 7.94 (d, J = 8.5 Hz, 1H), 7.86 (m, 1H), 7.77 (m, 5H), 7.73 (m, 2H), 7.55 (ddd, J = 8.0, 6.9, 1.1 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 156.7, 148.5, 144.3, 140.7, 139.6, 137.1, 130.0, 129.9, 128.3, 127.9, 127.7, 127.6, 127.4, 126.6, 126.0, 125.9, 119.0, 29.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{15}F_3N$ 350.1157; Found 350.1151.

Associated Content

Supporting Information

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Notes

The authors declare no competing financial interests.

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12. Because the boiling point of DCE is 84 ^{o}C, the solvent evaporated from the reaction mixture at temperatures above 90 ^{o}C. Thus, the solvent was frequently added to the reaction mixture or a condenser was used when the temperature was above 90 ^{o}C to keep a sufficient amount of the solvent in the reaction mixture.

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