Iron-Catalyzed Tandem Reactions of Aldehydes, Terminal Alkynes, and Primary Amines as a Strategy for the Synthesis of Quinoline Derivatives

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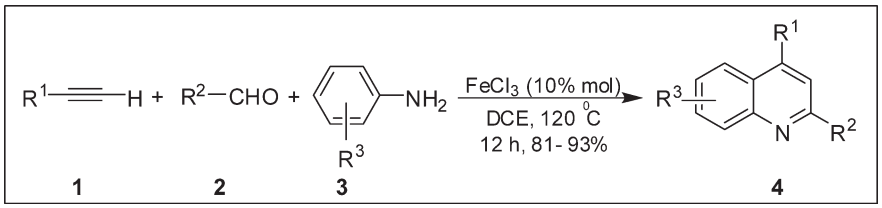

$FeCl_3$-catalyzed three-component tandem condensation/addition/cyclization/oxidation reactions of aldehydes, terminal alkynes, and primary amines have been developed. The processes can provide a diverse range of quinoline derivatives in good yields from simple starting materials. A possible reaction mechanism was proposed.

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INTRODUCTION

Iron salts as effective, alternative, and promising transition-metal catalysts have received much more attention in recent years because of their less expensive, readily available, and environmentally benign properties. During the last half decade, iron-catalyzed oxidation [1], hydrogenation [2], hydrosilylation [3], and carbon-carbon bond forming reactions have been intensively investigated [4–6]. Most recently, iron-catalyzed *S*-arylation of thiols [7], *N*-arylation of nitrogen nucleophiles [8], and *O*-arylation of phenols [9] with aryl halides, and A^3-coupling reaction of aldehyde, alkyne, and amine have been developed [10]. Because of interest for both the academic and the industrial community, it is desirable to expand the application scope of iron catalysts in organic transformations due to their unique and significant advantages.

One current important area of modern synthetic chemistry is the development of efficient practical methods that minimize the requisite time, cost, labour, resource management, and waste generation (atom economy) for the desired transformation [11]. Tandem reaction (several transformations in one synthetic operation) approach is recognized as a powerful method toward this goal, and only a single reaction solvent, workup procedure, and purification step may be required to provide a product that would otherwise have to be made over the course of several individual steps [12].

The quinoline nucleus is a prominent structural motif found in numerous natural products and synthetic compounds with important pharmacological and biological activities [13–15], and thus the development of efficient syntheses of highly functionalized quinoline derivatives has been the focus of most researches for many decades and continues to be an active and rewarding research area [16]. However, most of the existing methods suffer from the limited availability of substrates or require multistep procedures. During the course of our efforts directed toward the development of iron-catalyzed organic transformations, we found that treatment of aldehydes, primary amines, with terminal alkynes in the presence of $FeCl_3$ (10% mol) without any ligand and additive gave 2,4-disubstituted quinoline derivatives in good yields with high atom economy [17]. This reaction would proceed presumably through a tandem condensation/addition/cyclization/oxidation reactions with only water as the waste product (Scheme 1).

Scheme 1

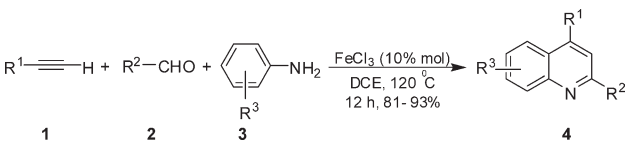
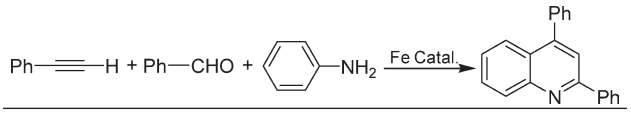


Table 1

Effect of solvent and iron source on the tandem reaction.[a]



Entry	Solvent	Fe source	Yield (%)[b]
a	Toluene	$FeCl_3$	71
b	Dioxane	$FeCl_3$	53
c	CH_3NO_2	$FeCl_3$	73
d	1,2-Dichloroethane	$FeCl_3$	93
			68[c]
e	1,2-Dibromoethane	$FeCl_3$	92
f	Ethylene glycol	$FeCl_3$	12
g	DMSO	$FeCl_3$	0
h	DMF	$FeCl_3$	0
i	1,2-Dichloroethane	$FeBr_3$	92
j	1,2-Dichloroethane	$FeCl_2$	82
k	1,2-Dichloroethane	$Fe(NO_3)_3$	Trace
l	1,2-Dichloroethane	$Fe_2(SO_4)_3$	Trace
m	1,2-Dichloroethane	Fe_2O_3	38
n	1,2-Dichloroethane	Fe powder	0
o[d]	1,2-Dichloroethane	$FeCl_3$	74
p[e]	1,2-Dichloroethane	$FeCl_3$	93

[a] Phenylacetylene (112 mg, 1.10 mmol), benzaldehyde (106 mg, 1.00 mmol), aniline (91 mg, 1.00 mmol), Fe source (0.01 mmol), solvent (2.0 mL) at 120°C for 12 h under an air atmosphere.
[b] Isolated yields.
[c] Under a nitrogen atmosphere.
[d] In the present of $FeCl_3$ (0.05 mmol).
[e] In the present of $FeCl_3$ (0.20 mmol).

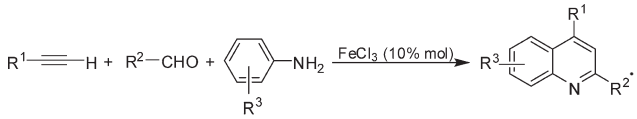
RESULTS AND DISCUSSION

Our initial investigation focused on the effect of solvent on the three-component tandem reactions of aldehydes, terminal alkynes, and primary amines. Several solvents were screened in a model reaction of phenylacetylene, benzaldehyde, and aniline, and a significant solvent effect was observed (Table 1). When the reactions were conducted in 1,2-dichloroethane and 1,2-dibromoethane under an air atmosphere, excellent yields of products (93%, 92%) were obtained. Use of toluene, nitromethane (CH_3NO_2), and dioxane as solvents led to lower yields of isolated products, and only 12% yield of the desired product was obtained while the reaction was performed in ethylene glycol. What surprised us was the reaction didn't work when DMSO and DMF were used as solvent (Table 1, entries **g** and **h**). It should be worth noting that 68% yield of the desired tandem product was isolated when the reaction was carried out under a nitrogen atmosphere (Table 1, entry **d**).

The effect of iron source on the tandem reaction was also explored. Among the tested iron sources, $FeCl_3$ and $FeBr_3$ proved to be the best choice (93% and 92% yields, respectively). $FeCl_2$ were inferior and generated the desired product in 82% yield, when Fe_2O_3 was used as catalyst, only 38% yield was obtained. However, $Fe(NO_3)_3$, $Fe_2(SO_4)_3$ or Fe powder (100 nm) was found to be inactive to the tandem reaction (Table 1, entries **i**–**n**).

Table 2

Synthesis of quinoline derivatives by $FeCl_3$-catalyzed tandem reaction.[a]



Entry	R^1	R^2	R^3	Yield[b] (%)
a	Ph	Ph	H	93
b	Ph	*p*-CH_3Ph	H	90
c	Ph	*p*-CH_3OPh	H	88
d	Ph	*p*-ClPh	H	87
e	Ph	*p*-BrPh	H	89
f	Ph	*m*-ClPh	H	85
g	Ph	*o*-ClPh	H	84
h	Ph	Ph	*p*-CH_3	91
i	Ph	Ph	*p*-CH_3O	83
j	Ph	Ph	*p*-Cl	92
k	Ph	Ph	*o*-CH_3	81
l	Ph	Ph	2,3-[b]-Ph	82
m	*p*-CH_3Ph	Ph	H	84
n	*p*-FPh	Ph	H	88
o	*p*-ClPh	Ph	H	89
p	*p*-PhPh	Ph	H	92

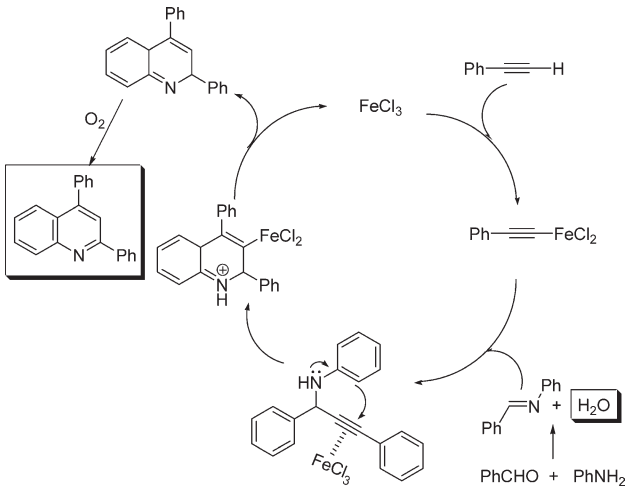
[a] Alkyne (1.10 mmol), aldehyde (1.00 mmol), amine (1.00 mmol), $FeCl_3$ (16 mg, 0.01 mmol), 1,2-dichloroethane (DCE, 2.0 mL) at 120°C for 12 h under an air atmosphere.
[b] Isolated yields.

With respect to the catalyst loading, 10 mol% of $FeCl_3$ was found to be optimal. When only 5 mol% of $FeCl_3$ was used, the desired product was isolated in 74% yield, and no significant improvement was observed with 20 mol% of Fe (Table 1, entries **o** and **p**). During the course of our further optimization of the reaction conditions, the reaction was generally completed within 24 h when it was performed at 120°C by using 10 mol% of $FeCl_3$ in the absence of any ligand and additive.

Under the optimized conditions, we extended our studies to different combinations of aldehydes, primary amines, and terminal alkynes, and the results are summarized in Table 2. Phenylacetylene and aniline were initially used as model substrates for exploring the aldehyde substrate scope. As can be seen from Table 2, benzaldehyde and substituted benzaldehydes with both electron-donating and electron-withdrawing functionalities, such as methoxy, methyl, bromo, and chloro groups, afforded the corresponding quinoline derivatives in good yields (Table 2, entries **a**–**g**). It seems that this reaction was not sensitive to steric effects (such as, 2-chlorobenzaldehyde giving the desired product in 84% yield), nor was it to electronic effects (Table 2, entries **c** *vs* **d**). However, when an aliphatic aldehyde (isobutyraldehyde) was subjected to the reaction, only 26% yield of the desired product was obtained. Then, we examined the scope of primary amine substrates, a combination of phenylacetylene-benzaldehyde-amine was chosen and various amines were surveyed. The results listed in Table 2 indicated that *p*-toluidine, *o*-toluidine, *p*-anisidine, and *p*-chloroaniline were good substrates for this tandem transformation, and high yields of the corresponding products were isolated under the optimized reaction conditions (Table 2, entries **h**–**k**). It was worthy noting that when 1-naphthylamine was used as substrate, the tandem reaction also underwent smoothly to give the corresponding quinoline derivative in 82% yield (Table 2, entry **l**). Subsequently, the scope of alkynes in this reaction was also investigated, and it was found that substituted phenylacetylenes, including *p*-methylphenylacetylene, *p*-chlorophenylacetylene, *p*-fluorophenylacetylene, and diphenylacetylene, were suitable substrates for this transformation, and the desired products were obtained in good yields (Table 2, entries **m**–**p**). Unfortunately, aliphatic alkynes were aborted in this process. Meanwhile, the reaction carried out in the presence of copper salt or oxide, such as CuCl, CuBr, CuI, or Cu_2O (0.10 equiv.) in $ClCH_2CH_2Cl$ was examined. However, no desired product was observed.

A possible mechanism of the $FeCl_3$-catalyzed one-pot tandem three-component reaction of aldehyde, alkyne, and amine was proposed in Scheme 2. The catalyst $FeCl_3$ probably possesses one terminal alkynyl groups because of the stability of Fe^{III} alkynyl ate complex. The

Scheme 2. Possible mechanism of iron-catalyzed tandem reaction of aldehyde, alkyne, and amine.



formed alkynyl ate complex underwent nucleophilic addition to imine formed *in situ* from aldehyde and primary amine to generate propargylamine. The triple bond of propargylamine could be activated by $FeCl_3$ as Lewis acid to promote an intramolecular nucleophilic attack by the *N*-substituted phenyl ring attached to the nitrogen. The resulting Fe^{III} vinyl ate complex subsequently underwent decomposition to give the dihydroquinoline intermediate and regenerate Fe^{III} catalyst for further reactions. In the presence of air oxygen, the generated dihydroquinoline could be further oxidized by O_2 to afford quinoline product. Comparing with the similar Au^{III}-catalyzed tandem transformation, the stronger Lewis acidity of $FeCl_3$ than $AuCl_3$ appears to be the main reason for the higher efficiency of this catalytic system [18].

CONCLUSIONS

In summary, we have developed an efficient, practical, and economic method for the synthesis of quinoline derivatives through a $FeCl_3$-catalyzed three-component tandem condensation/addition/cyclization/oxidation reactions with only water as the waste product. These processes can provide a diverse range of quinoline derivatives in good yields from simple starting materials. The method has advantages of broad substrate scope, simple operation, mild reaction conditions, and high effectiveness. Further studies on the synthetic application of iron as catalyst in organic synthesis are currently ongoing in our group.

EXPERIMENTAL

All ^1H NMR spectra were recorded at 400 MHz by Bruker FT-NMR spectrometers. Chemical shift are given as δ value

with reference to tetramethylsilane (TMS) as internal standard. The CHN analysis was performed on a Vario El III elementar. Products were purified by flash chromatography on 230–400 mesh silica gel, SiO_2. The chemicals were purchased from commercial suppliers (Aldrich and Shanghai Chemical Company, China) and were used without purification prior to use.

General experimental procedure for the tandem reaction. Under an air atmosphere, a 10 mL of sealable reaction tube equipped with a magnetic stir bar was charged with an aldehyde (1.00 mmol), amine (1.00 mmol), and the mixture was heated and stirred in an oil bath at 60°C for 1 h. Then $FeCl_3$ (16.2 mg, 0.10 mmol), alkyne (1.10 mmol) were added. The reaction mixture was then stirred in an oil bath at 120°C until the substrates were consumed completely (about 12 h), and then it was cooled to room temperature and the solvent was evaporated, the residue was purified by flash chromatography (hexane/AcOEt = 15:1) to afford the desired product.

2,4-Diphenylquinoline (4a) [19]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.26 (d, J = 8.45 Hz, 1H), 8.21–8.18 (m, 2H), 7.93–7.90 (m, 1H), 7.82 (s, 1H), 7.76–7.72 (m, 1H), 7.57–7.45 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.87, 149.20, 148.70, 139.56, 138.33, 130.03, 129.54, 129.35, 128.83, 128.56, 128.40, 127.58, 126.33, 125.73, 125.63, 119.38.

2-(4-Methylphenyl)-4-phenylquinoline (4b) [20]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, J = 8.45 Hz, 1H), 8.08 (d, J = 8.11 Hz, 2H), 7.86 (d, J = 8.48 Hz, 1H), 7.77 (s, 1H), 7.71–7.67 (m, 1H), 7.53–7.45 (m, 5H), 7.45–7.40 (m, 1H), 7.30 (d, J = 8.10 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.76, 148.97, 148.70, 139.35, 138.37, 136.70, 129.92, 129.49, 129.39, 128.50, 128.29, 127.39, 126.07, 125.60, 125.53, 119.38, 21.28.

2-(4-Methoxylphenyl)-4-phenylquinoline (4c) [21]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, J = 8.22 Hz, 1H), 8.17–8.15 (m, 2H), 7.87 (d, J = 8.35 Hz, 1H), 7.76 (s, 1H), 7.72–7.68 (m, 1H), 7.55–7.49 (m, 5H), 7.45–7.41 (m, 1H), 7.40–7.22 (m, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.76, 156.35, 148.96, 148.70, 138.42, 132.09, 129.80, 129.50, 129.42, 128.86, 128.52, 128.31, 125.92, 125.56, 125.53, 118.85, 114.15, 55.33.

2-(4-Chlorophenyl)-4-phenylquinoline (4d) [18]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, J = 8.45 Hz, 1H), 8.13–8.11 (m, 2H), 7.89–7.87 (m, 1H), 7.74 (s, 1H), 7.73–7.69 (m, 1H), 7.53–7.49 (m, 5H), 7.47–7.43 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.39, 149.30, 148.66, 138.14, 137.89, 135.47, 129.99, 129.63, 129.46, 128.92, 128.74, 128.56, 128.44, 126.47, 125.71, 125.60, 118.81.

2-(4-Bromophenyl)-4-phenylquinoline (4e) [18]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (m, 1H), 8.07–8.05 (m, 2H), 7.90–7.87 (m, 1H), 7.75 (s, 1H), 7.74–7.70 (m, 1H), 7.63–7.61 (m, 2H), 7.54–7.49 (m, 5H), 7.48–7.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.45, 149.34, 148.67, 138.36, 138.13, 131.89, 130.00, 129.66, 129.47, 129.03, 128.57, 128.45, 126.51, 125.75, 125.62, 123.89, 118.77.

2-(3-Chlorophenyl)-4-phenylquinoline (4f). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, J = 8.54 Hz, 1H), 7.98–7.96 (m, 1H), 7.76–7.71 (m, 2H), 7.70 (s, 1H), 7.57–7.47 (m, 7H), 7.42–7.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.25, 148.52, 147.95, 139.48, 137.91, 132.30, 131.64, 130.02, 129.98, 129.83, 129.56, 129.46, 128.52, 128.38, 127.12, 126.74, 125.62, 125.56, 122.94. Anal. Calcd. for $C_{21}H_{14}ClN$: C, 79.87; H, 4.47; N, 4.44. Found: C, 79.81; H, 4.51; N, 4.52.

2-(2-Chlorophenyl)-4-phenylquinoline (4g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31 (d, J = 8.29 Hz, 1H), 7.87 (s, 1H), 7.83–7.77 (m, 2H), 7.53–7.45 (m, 8H), 7.33 (t, J = 7.61 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.73, 149.66, 144.81, 138.95, 138.01, 134.27, 129.72, 129.60, 129.48, 128.84, 128.59, 128.55, 127.64, 127.12, 125.86, 124.77. Anal. Calcd. for $C_{21}H_{14}ClN$: C, 79.87; H, 4.47; N, 4.44. Found: C, 79.93; H, 4.55; N, 4.41.

6-Methyl-2,4-diphenylquinoline (4h) [22]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18–8.13 (m, 3H), 7.77 (s, 1H), 7.65 (s, 1H), 7.58–7.49 (m, 8H), 7.46–7.43 (m, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.98, 148.43, 147.30, 139.68, 138.57, 136.26, 131.76, 129.77, 129.52, 129.14, 128.78, 128.55, 128.27, 127.45, 125.66, 124.35, 119.42, 21.81.

6-Methoxyl-2,4-diphenylquinoline (4i) [23]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16–8.13 (m, 3H), 7.76 (s, 1H), 7.58–7.48 (m, 7H), 7.44–7.37 (m, 2H), 7.19 (d, J = 2.9 Hz,1H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.70, 154.56, 147.73, 144.80, 139.65, 138.64, 131.52, 129.30, 128.93, 128.75, 128.65, 128.30, 127.25, 126.57, 121.79, 119.63, 103.56, 55.38.

6-Chloro-2,4-diphenylquinoline (4j) [22]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18–8.15 (m, 3H), 7.86 (d, J = 2.36 Hz, 1H), 7.82 (s, 1H), 7.66–7.64 (m, 1H), 7.58–7.50 (m, 7H), 7.48–7.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.00, 148.39, 147.13, 139.11, 137.66, 132.14, 131.65, 130.40, 129.56, 129.39, 128.86, 128.77, 128.67, 127.48, 126.41, 124.43, 120.00.

2-Methyl-2,4-diphenylquinoline (4k) [24]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (d, J = 7.85 Hz, 2H), 7.81 (s, 1H), 7.70 (d, J = 8.54 Hz, 1H), 7.55–7.40 (m, 9H), 7.31 (t, J = 7.56 Hz, 1H), 2.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.85, 149.22, 147.64, 139.78, 138.89, 137.90, 129.56, 129.54, 129.20, 128.71, 128.43, 128.16, 127.44, 125.89, 125.62, 123.54, 118.58, 18.39.

2,4-Diphenylbenzo[h]quinoline (4l) [25]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.57 (d, J = 7.58 Hz, 1H), 8.33–8.31 (m, 2H), 7.87 (s, 1H), 7.78 (d, J = 8.00 Hz, 1H), 7.72–7.68 (m, 2H), 7.63–7.59 (m, 2H), 7.51–7.38 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.70, 148.88, 146.65, 139.60, 138.71, 133.49, 131.94, 129.59, 129.14, 128.71, 128.48, 128.17, 128.12, 127.51, 127.38, 127.18, 126.78, 125.14, 123.20, 122.75, 119.34.

2-Phenyl-4-p-tolylquinoline (4m) [26]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.26–8.24 (d, J = 8.63 Hz, 1H), 8.19–8.18 (m, 2H), 7.94 (q, J = 3.75 Hz, 1.2 Hz, 1H), 7.81 (s, 1H), 7.74–7.71 (m, 1H), 7.54–7.51 (m, 2H), 7.47–7.45 (m, 4H), 7.36 (d, J = 7.81 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.86, 149.26, 148.71, 139.62, 138.33, 135.39, 130.00, 129.46, 129.28, 128.81, 127.58, 126.23, 125.84, 125.69, 119.33, 21.31.

4-(4-Fluorophenyl)-2-phenylquinoline (4n) [27]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25–8.22 (m, 1H), 8.18–8.16 (m, 2H), 7.84–7.82 (m, 1H), 7.76 (s, 1H), 7.73–7.69 (m, 1H), 7.53–7.42 (m, 6H), 7.23–7.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.06, 161.60, 156.79, 148.74, 148.00, 139.44, 134.27, 134.23, 131.24, 131.15, 130.14, 129.56, 129.36, 128.79, 127.50, 126.41, 125.65, 125.28, 119.31, 115.70, 115.49.

4-(4-Chlorophenyl)-2-phenylquinoline (4o) [26]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25–8.23 (m, 1H), 8.23–8.16 (m,

2H), 7.84–7.81 (m, 1H), 7.76 (s, 1H), 7.74–7.70 (m, 1H), 7.54–7.43 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.82, 148.71, 147.80, 139.37, 136.69, 134.55, 130.81, 130.15, 129.64, 129.41, 128.82, 128.81, 127.50, 126.50, 125.42, 125.20, 119.20.

4-(Biphenyl-4-yl)-2-phenylquinoline (4p). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.26 (d, J = 8.36 Hz, 1H), 8.19 (d, J = 7.80 Hz, 2H), 7.95 (d, J = 8.40 Hz, 1H), 7.82 (s, 1H), 7.74–7.65 (m, 5H), 7.59 (s, 1H), 7.57 (s, 1H), 7.52–7.41 (m, 6H), 7.39–7.35 (t, J = 7.37 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.81, 148.77, 148.69, 141.21, 140.33, 139.53, 137.19, 130.08, 129.97, 129.50, 129.30, 128.87, 128.78, 127.60, 127.52, 127.21, 127.08, 126.32, 125.63, 125.54, 119.24. Anal. Calcd. for $C_{27}H_{19}N$: C, 90.72; H, 5.36; N, 3.92. Found: C, 90.81; H, 5.38; N, 3.81.

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