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$FeCl_3$-Mediated One-Pot Cyclization–Aromatization of Anilines, Benzaldehydes, and Phenylacetylenes under Ball Milling: A New Alternative for the Synthesis of 2,4-Diphenylquinolines

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A straightforward and efficient method has been developed for the solvent-free synthesis of 2,4-diphenylquinolines via a one-pot reaction of anilines, benzaldehydes, and phenylacetylenes promoted by $FeCl_3$ under solvent-free mechanochemical ball milling. Using this protocol, a series of 2,4-diphenylquinolines were synthesized in good to excellent yield (74–95%) just by washing the resulting reaction mixture with water and recrystallizing in $EtOH/H_2O$ without any extraction or column chromatography work-up.

Keywords: Quinoline; Ball milling; Ferric trichloride; One-pot; Solvent free.

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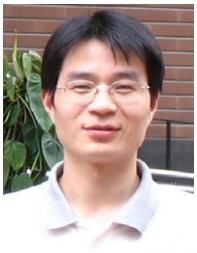

INTRODUCTION

Quinoline is a common heterocyclic scaffold in many natural and synthetic compounds of medicinal and biological significance. Consequently, there has been growing attention and interest in the development of synthetic methods for quinoline derivatives bearing diverse substitution patterns.[1] Since Skraup reported the synthesis of quinoline in 1880 for the first time,[2] a large number of synthetic methods have been extensively developed and well documented, including the use of various new catalysts, reaction media, physical conditions, multicomponent or cascade synthetic strategy, and so on.[3] Conceptually, these methods can be classified into two approaches (Figure 1): the first one relates to the use of the aromatic amine as the nucleophilic component providing nitrogen as the C—C—N unit (a), and the second one employs the ortho-substituted anilines as the C—C—C—N unit (b).[4]

Forthrightly, most of them are efficient enough, but there are still some disadvantages such as harsh reaction conditions, extended reaction times, limited availability of the starting materials, tedious work-up procedures, and the use of expensive catalysts or environmentally harmful solvents. Keeping in view the importance of the quinoline scaffold in pharmaceutical and synthetic chemistry, it is necessary to circumvent these problems by developing more convenient and efficient methods. A powerful alternative is to perform these reactions under ball milling, a novel solvent-free technique that has been contributing more and more to the efficient promotion of various organic transformations.[5,6] This technique can provide high mechanical energy and high local concentration of the reactants,

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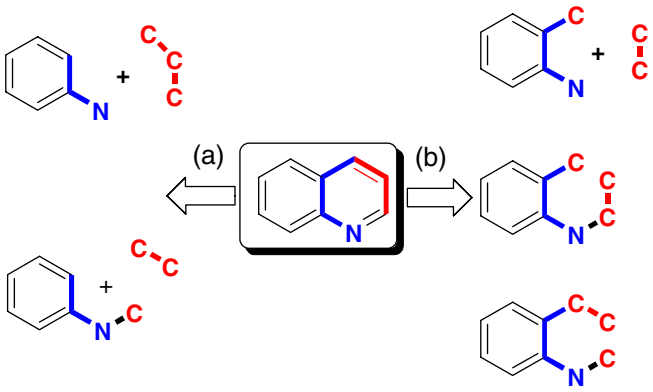


Fig. 1. Common synthetic strategies towards quinolone.

and thus may be more suitable for multicomponent reactions.

On the other hand, $FeCl_3$ is a highly attractive Lewis acid catalyst for construction of various heterocycles from an environmental and economic point of view.[7] We therefore envisaged that synergies arising from the combined use of ball milling and $FeCl_3$ could lead to an efficient method for the synthesis of quinolines. In continuation of our efforts to develop new solvent-free methods for the synthesis of nitrogen-containing compounds using the ball milling technique,[8] we report here a straightforward and practical one-pot synthesis of 2,4-diphenylquinolines via cyclization–aromatization of anilines, benzaldehydes, and phenylacetylenes catalyzed by $FeCl_3$ under ball milling.

RESULTS AND DISCUSSION

Before the formal synthesis of 2,4-diphenylquinolines, we first selected the cyclization–aromatization of phenylacetylene with *in situ* generated imine from 4-methoxylaniline and 3-nitrobenaldehyde as the model reaction to screen an optimal catalyst (Table 1).

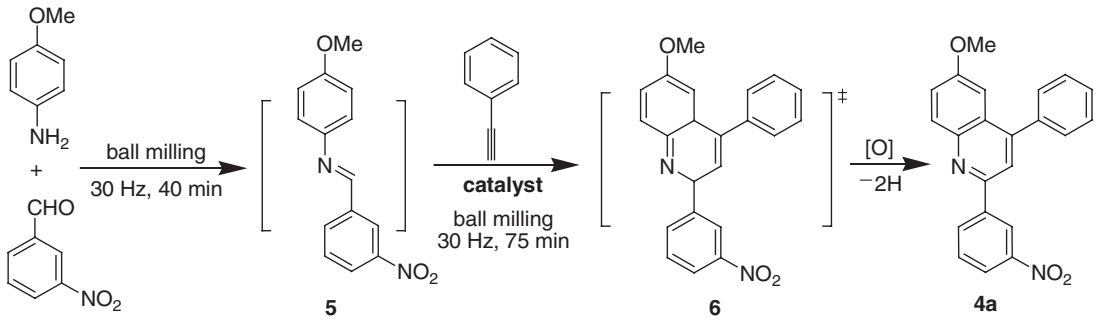
As shown in Table 1, we attempted various Lewis acids and Brønsted acids that have been widely employed in the traditional synthesis of quinoline derivatives. The experimental results demonstrated that relatively weak Lewis acids and Brønsted acids work too inefficiently or cannot work at all for the transformation of imine **5** into dihydroquinoline **6** even when a large excess of them was employed (entry 12–20). Strong Lewis acids such as $ZnCl_2$, $AlCl_3$, $FeCl_3$, and $BF_3{\cdot}OEt_2$ promoted the addition–cyclization reaction of imine **5** with phenylacetylene very smoothly to generate dihydroquinoline **6** (entry 1–11) even in the presence of a catalyst (entry 2, 4, 9, 11). In contrast, $FeCl_3$ shows the best efficiency. Although dihydroquinoline **6** can be easily oxidized into the corresponding quinoline **4a** in the presence of air, the reaction system used here was sealed and thus mostly suffered from inadequate oxidant. Therefore, the generated dihydroquinoline **6** was converted into quinoline **4a** to a very poor extent with the aid of the air in the reaction vessel. But when using enough $FeCl_3$, this conversion was almost completely accomplished (entry 5–7) because of its strong oxidizing ability.

These results, together with the effects to be described later from different substituents in the anilines, benzaldehydes, and phenylacetylene for formation of various 2,4-diphenylquinolines, can be well understood from the reaction mechanism (Scheme 1). Although there are some minor controversies, it can still be outlined as shown in Scheme 1 based on the current experimental results and together with comprehensive analysis and evaluation in various reports. Initially, the intermediate **A** was formed by coordination of Fe(III) with phenylacetylene **3** and imine **5,** which was *in situ* generated from aniline **1** and benzaldehyde **2**.[9] Then, the addition of the alkyne to the imine forms the propargylamine intermediate **B**,[10] in which the triple bond is activated by Fe(III) to undergo an intramolecular hydroarylation through the aniline aromatic-ring nitrogen,[7a,11] resulting in the Fe(III) vinylate complex **C**.[12] The intermediate **C** subsequently undergoes decomposition to regenerate Fe(III) for next catalytic cycle and gives dihydroquinoline **6**,[13] which would be further oxidized into quinoline **4** in the presence of excessive Fe(III) and air. It should be pointed out that we did not detect the propargylamine **B** in the reaction mixture, which may imply that the formation of intermediate **B** and the subsequent hydroarylation reaction involve a cooperative process.

Considering its easy availability, low price, sustainability, nontoxicity, and environmentally friendly nature,[14] we next selected $FeCl_3$ to clarify the generality of substrate scope by using various aldehydes, alkynes, and amines for the synthesis of various 2,4-diphenylquinolines. The results are summarized in Table 2.

As shown in Table 2, a wide range of structurally diverse benzaldehydes, phenylacetylenes, and anilines

Table 1. Screening of optimal condition for the synthesis of 6-methoxy-2-(3-nitro-phenyl)-4-phenyl-quinoline (**4a**) under ball milling[a]

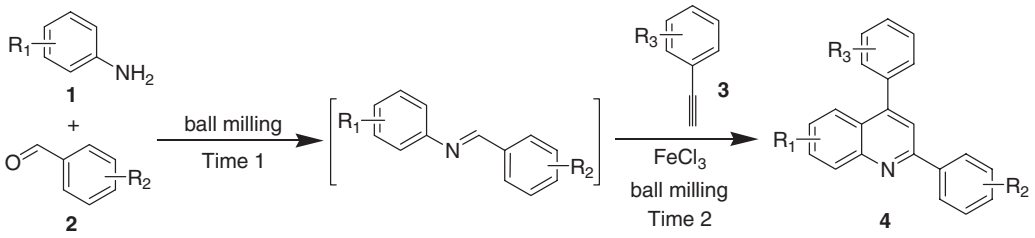


Entry	Catalyst (equiv.)	Conversion of **5** (%)[b]	Yield for **6** (%)[c]	Yield for **4a** (%)[c]
1	$ZnCl_2$ (2.5)	94	73	18
2	$ZnCl_2$ (0.25)	90	70	18
3	$AlCl_3$ (2.5)	96	74	19
4	$AlCl_3$ (0.25)	94	72	18
5	$FeCl_3$ (2.5)	>99	Not detected	93
6	$FeCl_3$ (2.0)	>99	Trace	92
7	$FeCl_3$ (1.5)	>99	<5	87
8	$FeCl_3$ (1.0)	>99	30	64
9	$FeCl_3$ (0.25)	94	63	27
10	$BF_3{\cdot}Et_2O$ (1.25)	97	73	18
11	$BF_3{\cdot}Et_2O$ (0.25)	93	70	17
12	$Mn(OAc)_3$ (2.5)	<5	Trace	Trace
13	$Co(OAc)_2$ (2.5)	<5	Trace	Trace
14	$Cu(OTf)_2$ (2.5)	21	Trace	12
15	$Cu(OAc)_2$ (2.5)	16	Trace	10
10	$CuCl_2$ (2.5)	<5	Trace	Trace
16	DDQ (2.5)	<5	Not detected	Trace
17	CuI (2.5)	<5	Trace	Trace
18	TsOH (2.5)	35	15	17
19	CF_3SO_3H (2.5)	38	17	18
20	TFA (2.5)	39	18	16

[a] Reactions were carried out with 4-methoxylaniline (1.0 mmol), 3-nitrobenaldehyde (1.0 mmol), phenylacetylene (1.25 mmol) and catalyst under ball milling at room temperature.
[b] Rapidly determined by GC-MS analysis on the sample solution from prompt extraction of the reaction mixture.
[c] Rapidly determined by GC-MS analysis on the sample solution from prompt extraction of the reaction mixture and calculated according to 4-methoxylaniline.

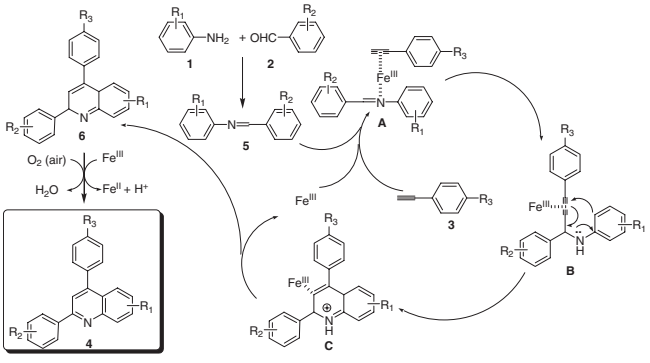
gave the corresponding quinolines in good to excellent yields. The structure of all the synthesized compounds was confirmed by ^1H NMR, ^{13}C NMR, and high-resolution mass spectrometry. In general, different functional groups such as Me, OMe, F, Cl and NO_2 are tolerated, and the reactions get completed within 2–3 h. The role and high efficiency of ball milling is expected from the high mechanical energy causing local high pressure, friction, shear strain, and so on.[5c,15] In contrast, reactions in which anilines bearing strong electron-donating substituents and phenylacetylenes/benzaldehydes containing strong electron-withdrawing substituents proceeded more smoothly, thus resulting in relatively higher yields. This result can be reasonably interpreted according to the mechanism in Scheme 1, in which the electron-donating group in aniline and the electron-withdrawing group in phenylacetylene or benzaldehyde may facilitate the intramolecular nucleophilic

Table 2. Synthesis of 2,4-diphenyl-quinolines **4** via imino Diels–Alder and aromatization of *in situ* generated imine (from anilines **1** and benzaldehydes **2**) with phenylacetylene **3** under ball milling[a]



Entry	R_1	R_2	R_3	Product **4**	Reaction time (min)		Yield (%)[a]
					Time 1[b]	Time 2[c]	
1	4-OMe	3-NO_2	H	**4a**	40	75	81
2	4-Me	3-NO_2	H	**4b**	50	75	78
3	4-OMe	4-Cl	H	**4c**	40	75	83
4	4-Me	3-NO_2	4-F	**4d**	50	60	83
5	4-OMe	3-NO_2	4-F	**4e**	40	60	92
6	4-OMe	4-NO_2	4-F	**4f**	45	60	86
7	4-Me	3-NO_2	4-Me	**4g**	45	80	78
8	4-Me	4-Cl	4-Me	**4h**	50	80	85
9	4-OMe	4-Cl	4-Me	**4i**	50	80	86
10	4-OMe	3-NO_2	4-Me	**4j**	40	80	84
11	4-Cl	4-NO_2	4-Me	**4k**	55	80	71
12	4-Me	4-NO_2	4-Me	**4l**	45	80	77
13	4-OMe	4-Cl	4-OMe	**4m**	50	90	75
14	4-Me	3-NO_2	4-OMe	**4n**	45	90	78
15	4-Me	4-Cl	4-OMe	**4o**	50	90	77
16	4-Cl	4-NO_2	4-OMe	**4p**	55	90	70
17	3-Me	4-NO_2	4-OMe	**4q**	50	90	75

[a] Reactions were carried out with aniline **1** (1.0 mmol) and benzaldehyde **2** (1.0 mmol), and afterward added phenylacetylene **3** (1.25 mmol) and $FeCl_3$ (2.0 mmol) under ball milling (vibration frequency: 30 Hz) at room temperature.
[b] Optimized time for complete conversion of aniline **1** or benzaldehyde **2** by TLC analysis.
[c] Optimized time for complete conversion of *in situ* generated imine by TLC analysis.
[d] Isolated yield combined from two parallel runs by washing the resulting reaction mixture with water and recrystallization from EtOH/H_2O.

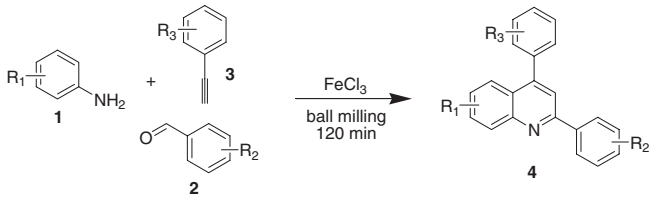


Scheme 1. Proposed mechanism.

attack to the triple bond of propargylamine **B**. Furthermore, all the desired products **4a–q** were obtained through a very simple work-up, just involving washing the resulting reaction mixture with water and recrystallization from EtOH–H_2O.

Inspired by widely reported multicomponent strategy toward the synthesis of quinolines, we further explored the three-component reaction of anilines **1**, benzaldehydes **2,** and phenylacetylene **3** mediated by $FeCl_3$ under ball milling for the synthesis of 2,4-diphenylquinolines **4**. Gratifyingly and as expected, the desired products **4a–q** could also be obtained as efficiently as that from above stepwise work. The crude

Table 3. Three-component synthesis of 2,4-diphenyl-quinolines **4** from anilines **1**, benzaldehydes **2**, and phenylacetylene **3** mediated by $FeCl_3$ under ball milling[a]



Entry	R_1	R_2	R_3	Product **4**	Yield (%)[b]
1	4-OMe	3-NO_2	H	**4a**	84
2	4-Me	3-NO_2	H	**4b**	79
3	4-OMe	4-Cl	H	**4c**	86
4	4-Me	3-NO_2	4-F	**4d**	85
5	4-OMe	3-NO_2	4-F	**4e**	95
6	4-OMe	4-NO_2	4-F	**4f**	90
7	4-Me	3-NO_2	4-Me	**4g**	82
8	4-Me	4-Cl	4-Me	**4h**	87
9	4-OMe	4-Cl	4-Me	**4i**	90
10	4-OMe	3-NO_2	4-Me	**4j**	87
11	4-Cl	4-NO_2	4-Me	**4k**	75
12	4-Me	4-NO_2	4-Me	**4l**	82
13	4-OMe	4-Cl	4-OMe	**4m**	78
14	4-Me	3-NO_2	4-OMe	**4n**	82
15	4-Me	4-Cl	4-OMe	**4o**	80
16	4-Cl	4-NO_2	4-OMe	**4p**	74
17	3-Me	4-NO_2	4-OMe	**4q**	79

[a] Reactions were carried out with aniline **1** (1.0 mmol) and benzaldehyde **2** (1.0 mmol), and afterward added phenylacetylene **3** (1.25 mmol) and $FeCl_3$ (2.0 mmol) under ball milling (vibration frequency: 30 Hz) at room temperature for 120 min.
[b] Yield combined from two parallel runs by washing the resulting reaction mixture with 3% HCl and water.

products were collected just by washing the reaction mixture with dilute hydrochloric acid and water without further recrystallization, with the purity of most products being >95%; thus the yields are somewhat higher than the stepwise results (Table 3).

EXPERIMENTAL

General

NMR spectra were recorded on a Bruker AV300 or AV500 NMR spectrometer in $CDCl_3$. TMS was used as the internal standard. Chemical shifts (δ) and J values are reported in ppm and Hz, respectively. All melting points were determined on a XT-4 binocular microscope (Beijing Tech Instrument Co., China) and are not corrected. Analytical TLC and column chromatography were performed on silica gel GF254, and silica gel H60, respectively. GC-MS was conducted on a GC-MS-QP 2010 instrument (Rtx-17, 30 m × 25 mm ID, film thickness 0.25 μm df) with column flow rate of 2 mL/min and heating rate of 10°C/min rising from 70°C to 250°C. A mixer mill (MM 400; Retsch GmbH, Germany) was used for ball milling. Phenylacetylenes, all liquid benzaldehydes, and anilines were further purified using standard methods before use. All solid benzaldehydes and anilines were purchased from Acros or Aldrich Chemical Co., and used without further purification. All solvents were obtained from SCRC (Sinopharm Chemical Reagent Co., Ltd) in AR grade and used without further purification.

Typical procedure

Aniline **1** (1.0 mmol) and benzaldehyde **2** (1.0 mmol), together with a stainless ball of 7.0 mm in diameter, were introduced into a stainless jar (25 mL). The same mixture was also introduced into a second similar jar. The two reaction vessels were sealed

with screw caps, fixed on the vibration arms of the ball milling apparatus, and were vibrated vigorously at a rate of 1800 rounds per minute (30 Hz) at room temperature for the designated time (Time 1). After the vessels were opened, phenylacetylene **3** (1.25 mmol) and $FeCl_3$ (2.0 mmol) were added into the *in situ* generated imine, and the sealed vessels were continued to vibrate for the designated time (Time 2). The combined reaction mixtures were immersed in 30 mL water under ultrasonic irradiation. After Büchner filtration and washing with water several times until the filtrate became colorless, the solid was collected and recrystallized from $EtOH/H_2O$ (v/v = 5/1) to afford 2,4-diphenylquinoline **4**.

6-Methoxy-2-(3-nitro-phenyl)-4-phenyl-quinoline (4a)

Yellow solid; yield: 81%; m.p. 129–131°C; ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm) 9.03 (s, 1H, ArH), 8.56 (d, J = 7.5 Hz, 1H, ArH), 8.29 (d, J = 8.0 Hz, 1H, ArH), 8.16 (d, J = 9.0 Hz, 1H, ArH), 7.81 (s, 1H, ArH), 7.69 (t, J = 7.5 Hz, 1H, ArH), 7.54–7.59 (m, 5H, ArH), 7.44 (d, J = 9.0 Hz, 1H, ArH), 7.21 (s, 1H, ArH), 3.82 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 158.3, 151.4, 148.8, 148.3, 144.8, 141.2, 138.3, 132.9, 131.7, 129.7, 129.3, 128.8, 128.7, 127.1, 123.5, 122.4, 122.0, 118.9, 103.6, 55.5; HRMS (ESI) *m/z* calcd for $C_{22}H_{17}N_2O_3$ $(M + H)^+$: 357.1239, found: 357.1233.

6-Methyl-2-(3-nitro-phenyl)-4-phenyl-quinoline (4b)

Slightly yellow solid; yield: 78%; m.p. 146–149°C; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 9.06 (s, 1H, ArH), 8.59 (d, J = 7.5 Hz, 1H, ArH), 8.32 (d, J = 7.8 Hz, 1H, ArH), 8.19 (d, J = 7.7 Hz, 1H, ArH), 7.83 (s, 1H, ArH), 7.58–7.74(m, 8H, ArH), 2.51 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 153.0, 149.2, 148.8, 147.4, 141.3, 138.2, 137.2, 133.2, 132.3, 130.0, 129.7, 129.5 (2C), 128.7 (2C), 128.6, 126.1, 124.5, 123.7, 122.3, 118.7, 21.9; HRMS (ESI) *m/z* calcd for $C_{22}H_{17}N_2O_2$ $(M + H)^+$: 341.1290, found: 341.1296.

2-(4-Chloro-phenyl)-6-methoxy-4-phenyl-quinoline (4c)

Pale solid; yield: 83%; m.p. 118–121°C; ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.07–8.08 (m, 3H, ArH), 7.69 (s, 1H, ArH), 7.42–7.52 (m, 6H, ArH), 7.36 (d, J = 9.0 Hz, 1H, ArH), 7.22 (s, 1H, ArH), 7.14 (s, 1H, ArH), 3.76 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 158.0, 153.1, 147.9, 144.9, 138.6, 138.1, 135.1, 131.6, 129.4, 128.9, 128.8, 128.5, 128.5, 126.8, 122.0, 119.1, 103.7, 55.4; HRMS (ESI) *m/z* calcd for $C_{22}H_{17}ClNO$ $(M + H)^+$: 346.0999, found: 346.0992.

4-(4-Fluoro-phenyl)-6-methyl-2-(3-nitro-phenyl)-quinoline (4d)

Gray solid; yield: 83%; m.p. 169–171°C; ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm) 9.00 (s, 1H, ArH), 8.54 (d, J = 7.5 Hz, 1H, ArH), 8.27 (d, J = 8.5 Hz, 1H, ArH), 8.15 (d, J = 6.5 Hz, 1H, ArH), 7.75 (s, 1H, ArH), 7.66 (t, J = 8.0 Hz, 1H, ArH), 7.58–7.60 (m, 2H, ArH), 7.49–7.52 (m, 2H, ArH), 7.22–7.26 (m, 2H, ArH), 2.47 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 164.0, 162.0, 153.0, 148.8, 148.1, 147.3, 141.2, 137.4, 134.1, 133.2, 132.4, 131.3, 130.0, 129.7, 126.1, 124.2, 123.8, 122.3, 118.7, 116.0, 115.7, 21.9; HRMS (ESI) *m/z* calcd for $C_{22}H_{16}FN_2O_2$ $(M + H)^+$: 359.1196, found: 359.1187.

4-(4-Fluoro-phenyl)-6-methoxy-2-(3-nitro-phenyl)-quinoline (4e)

Brown solid; yield: 92%; m.p. 193–196°C; ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.97 (s, 1H, ArH), 8.53 (d, J = 7.5 Hz, 1H, ArH), 8.26 (d, J = 8.0 Hz, 1H, ArH), 8.19 (d, J = 8.0 Hz, 1H, ArH), 7.75 (s, 1H, ArH), 7.66 (t, J = 8.0 Hz, 1H, ArH), 7.51–7.54 (m, 2H, ArH), 7.40–7.42 (m, 1H, ArH), 7.22–7.16 (m, 2H, ArH), 7.10 (d, J = 2.5 Hz, 1H, ArH), 3.79 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 164.0, 162.0, 158.5, 151.6, 148.8, 147.4, 144.9, 141.2, 134.2, 133.0, 131.8, 131.1, 129.8, 127.2, 123.6, 122.6, 122.1, 119.0, 116.0, 115.9, 103.4, 55.5; HRMS (ESI) *m/z* calcd for $C_{22}H_{16}FN_2O_3$ $(M + H)^+$: 375.1145, found: 375.1151.

4-(4-Fluoro-phenyl)-6-methoxy-2-(4-nitro-phenyl)-quinoline (4f)

Brown solid; yield: 86%; m.p. 180–181°C; ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm) 8.28–8.33 (m, 4H, ArH), 7.75 (s, 1H, ArH), 7.51–7.53 (m, 2H, ArH), 7.42–7.45 (m, 1H, ArH), 7.11–7.26 (m, 3H, ArH), 7.10 (s, 1H, ArH), 3.79 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 164.0, 162.0, 158.7, 151.6, 148.1, 147.3, 145.4, 144.9, 134.2, 134.2, 131.9, 131.1, 131.0, 128.0, 127.3, 124.0, 122.7, 119.5, 116.1, 115.9, 103.4, 55.6; HRMS (ESI) *m/z* calcd for $C_{22}H_{16}FN_2O_3$ $(M + H)^+$: 375.1145, found: 375.1155.

6-Methyl-2-(3-nitro-phenyl)-4-*p*-tolyl-quinoline (4g)

Slightly yellow solid; yield: 78%; m.p. 177–179°C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 9.06 (s, 1H, ArH), 8.57 (d, J = 8.0 Hz, 1H, ArH), 8.31 (d, J = 8.0 Hz, 1H, ArH), 8.16 (d, J = 9.0 Hz, 1H, ArH), 7.81 (s, 1H, ArH), 7.68–7.72 (m, 2H, ArH), 7.62 (d, J = 9.0 Hz, 1H, ArH), 7.48 (d, J = 8.0 Hz, 2H, ArH), 7.40 (d, J = 8.0 Hz, 2H, ArH), 2.52 (s, 3H, CH_3), 2.51 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 152.8, 149.2, 148.7, 147.3, 141.3, 138.6, 137.1, 135.2, 133.1, 132.2, 129.9, 129.7, 129.4 (overlapped), 126.1, 124.6, 123.6, 122.2, 118.6, 21.9, 21.4; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{19}N_2O_2$ $(M + H)^+$: 355.1447, found: 355.1440.

2-(4-Chloro-phenyl)-6-methyl-4-*p*-tolyl-quinoline (4h)

Pale solid; yield: 85%; m.p. 154–155°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.10–8.14 (m, 3H, ArH), 7.72 (s, 1H, ArH), 7.68 (s, 1H, ArH), 7.58–7.59 (m, 1H, ArH), 7.44–7.50 (m, 4H, ArH), 7.26–7.36 (m, 2H, ArH), 2.50 (s, 3H, CH_3), 2.48 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 154.6, 148.7, 147.4, 138.3, 138.2, 136.4, 135.6, 135.3, 131.9, 129.9, 129.5, 129.4, 129.0, 128.7, 125.9, 124.6, 118.9, 21.9, 21.4; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{19}ClN$ $(M + H)^+$: 344.1206, found: 344.1217.

2-(4-Chloro-phenyl)-6-methoxy-4-*p*-tolyl-quinoline (4i)

Pale solid; yield: 86%; m.p. 132–134°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.09–8.15 (m, 3H, ArH), 7.71 (s, 1H, ArH), 7.35–7.49 (m, 6H, ArH), 7.21–7.26 (m, 2H, ArH), 3.81 (s, 3H, OCH_3), 2.48 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 158.3, 153.6, 148.4, 145.3, 138.7, 138.6, 136.1, 135.5, 132.0, 129.9, 129.6, 129.3, 128.9, 127.3, 122.4, 119.6, 104.1, 55.9, 21.7; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{19}ClNO$ $(M + H)^+$: 360.1155, found: 360.1164.

6-Methoxy-2-(3-nitro-phenyl)-4-*p*-tolyl-quinoline (4j)

Brown solid; yield: 84%; m.p. 176–177°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 9.03 (s, 1H, ArH), 8.55 (d, J = 7.8 Hz, 1H, ArH), 8.27–8.30 (m, 1H, ArH), 8.15 (d, J = 9.2 Hz, 1H, ArH), 7.80 (s, 1H, ArH), 7.68 (t, J = 8.0 Hz, 1H, ArH), 7.37–7.50 (m, 5H, ArH), 7.24–7.26 (m, 1H, ArH), 3.83 (s, 3H, OCH_3), 2.50 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 158.7, 151.9, 149.2, 148.8, 145.2, 141.8, 139.0, 135.7, 133.4, 132.1, 130.1, 129.9, 129.6, 127.6, 123.8, 122.8, 122.4, 119.3, 104.0, 55.9, 21.8; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{19}N_2O_3$ $(M + H)^+$: 371.1396, found: 371.1387.

6-Chloro-2-(4-nitro-phenyl)-4-*p*-tolyl-quinoline (4k)

Slightly yellow solid; yield: 71%; m.p. 188–189°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.37 (s, 4H, ArH), 8.19 (d, J = 9.0 Hz, 1H, ArH), 7.93 (s, 1H, ArH), 7.86 (s, 1H, ArH), 7.69–7.72 (m, 1H, ArH), 7.38–7.46 (m, 4H, ArH), 2.50 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 154.6, 149.6, 148.8, 147.6, 145.4, 139.5, 134.7, 133.6, 132.3, 131.3, 130.1, 129.7, 128.7, 127.4, 125.1, 124.4, 120.1, 21.8; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{16}ClN_2O_2$ $(M + H)^+$: 375.0900, found: 375.0911.

6-Methyl-2-(4-nitro-phenyl)-4-*p*-tolyl-quinoline (4l)

Slightly yellow solid; yield: 77%; m.p. 180–182°C;^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.36 (s, 4H, ArH), 8.14 (d, J = 8.4 Hz, 1H, ArH), 7.79 (s, 1H, ArH), 7.71 (s, 1H, ArH), 7.61 (d, J = 8.7 Hz, 1H, ArH), 7.46 (d, J = 7.8 Hz, 2H, ArH), 7.38 (d, J = 7.8 Hz, 2H, ArH), 2.50 (s, 6H, CH_3, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 153.4, 149.5, 148.5, 147.8, 145.9, 139.0, 137.8, 135.6, 132.7, 130.5, 129.8 (overlapped), 128.4, 126.6, 125.0, 124.3, 119.4, 22.3, 21.8; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{19}N_2O_2$ $(M + H)^+$: 355.1447, found: 355.1441.

2-(4-Chloro-phenyl)-6-methoxy-4-(4-methoxy-phenyl)-quinoline (4m)

Brown solid; yield: 75%; m.p. 144–146°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.10–8.14 (m, 3H, ArH), 7.71 (s, 1H, ArH), 7.46–7.53 (m, 4H, ArH), 7.38–7.42 (m, 1H, ArH), 7.22–7.26 (m, 1H, ArH), 7.08–7.10 (m, 2H, ArH), 3.92 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 160.2, 158.3, 153.6, 148.1, 145.3, 138.6, 135.4, 131.9, 131.2, 131.0, 129.3, 128.9, 127.3, 122.4, 119.5, 114.6, 104.1, 55.9, 55.8; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{19}ClNO_2$ $(M + H)^+$: 376.1104, found: 376.1108.

4-(4-Methoxy-phenyl)-6-methyl-2-(3-nitro-phenyl)-quinoline (4n)

Yellow solid; yield: 78%; m.p. 156–157°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 9.04 (s, 1H, ArH), 8.57 (d, J = 7.8 Hz, 1H, ArH), 8.30 (d, J = 8.0 Hz, 1H, ArH), 8.16 (d, J = 8.6 Hz, 1H, ArH), 7.80 (s, 1H, ArH), 7.67–7.72 (m, 2H, ArH), 7.61 (d, J = 8.6 Hz,

1H, ArH), 7.52 (d, J = 8.5 Hz, 2H, ArH), 7.11 (d, J = 8.5 Hz, 2H, ArH), 3.94 (s, 3H, OCH_3), 2.51 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 160.4, 153.3, 149.2, 149.1, 147.8, 141.7, 137.4, 133.5, 132.5, 131.2 (2C), 130.8, 130.3, 130.0, 126.6, 124.9, 124.0, 122.6, 119.0, 114.6 (2C), 55.8, 22.3; HRMS (ESI) *m/z* calcd for $C_{23}H_{19}N_2O_3$ $(M + H)^+$: 371.1396, found: 371.1387.

2-(4-Chloro-phenyl)-4-(4-methoxy-phenyl)-6-methyl-quinoline (4o)

Slightly yellow solid; yield: 77%; m.p. 136–139°C; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.09–8.14 (m, 3H, ArH), 7.71 (s, 1H, ArH), 7.69 (s, 1H, ArH), 7.56 (d, J = 8.7 Hz, 1H, ArH), 7.46–7.50 (m, 4H, ArH), 7.09 (d, J = 8.4 Hz, 2H, ArH), 3.92 (s, 3H, OCH_3), 2.48 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 160.3, 154.9, 148.8, 147.8, 138.6, 136.8, 135.7, 132.3, 131.2, 131.1, 130.2, 129.3, 129.1, 126.4, 124.9, 119.2, 114.5, 55.8, 22.3; HRMS (ESI) *m/z* calcd for $C_{23}H_{19}ClNO$ $(M + H)^+$: 360.1155, found: 360.1162.

6-Chloro-4-(4-methoxy-phenyl)-2-(4-nitro-phenyl)-quinoline (4p)

Slightly yellow solid; yield: 70%; m.p. 216–217°C; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.37 (s, 4H, ArH), 8.19 (d, J = 9.0 Hz, 1H, ArH), 7.94 (s, 1H, ArH), 7.85 (s, 1H, ArH), 7.69–7.72 (m, 1H, ArH), 7.49 (d, J = 8.7 Hz, 2H, ArH), 7.11 (d, J = 8.7 Hz, 2H, ArH), 3.93 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 160.7, 154.7, 149.3, 148.9, 147.7, 145.5, 133.6, 132.3, 131.3, 131.1, 129.9, 128.7, 127.5, 125.1, 124.5, 120.1, 114.9, 55.9; HRMS (ESI) *m/z* calcd for $C_{22}H_{16}ClN_2O_3$ $(M + H)^+$: 391.0849, found: 391.0842.

4-(4-Methoxy-phenyl)-7-methyl-2-(4-nitro-phenyl)-quinoline (4q)

Slightly yellow solid; yield: 75%; m.p. 166–167°C; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.36 (s, 4H, ArH), 8.03 (s, 1H, ArH), 7.87 (d, J = 8.7 Hz, 1H, ArH), 7.76 (s, 1H, ArH), 7.50 (d, J = 8.4 Hz, 1H, ArH), 7.37 (d, J = 8.7 Hz, 2H, ArH), 7.09 (d, J = 8.4 Hz, 2H, ArH), 3.92 (s, 3H, OCH_3), 2.59 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 160.4, 154.3, 149.6, 149.5, 148.5, 146.0, 140.7, 131.2, 130.7, 129.9, 129.7, 128.5, 125.9, 124.7, 124.3, 118.6, 114.6, 55.8, 22.1; HRMS (ESI) *m/z* calcd for $C_{23}H_{19}N_2O_3$ $(M + H)^+$: 371.1396, found: 371.1385.

CONCLUSION

In summary, we have developed a straightforward and efficient method for the synthesis of 2,4-diphenylquinolines by employing a time-saving ball milling technique at room temperature. Through the solvent-free and one-pot cyclization–aromatization of anilines, benzaldehydes, and phenylacetylenes promoted by easily available and environmentally friendly $FeCl_3$, a series of quinoline derivatives with broad molecular diversity were rapidly obtained in good to excellent yields. This protocol has the advantages of short reaction time, use of no organic solvent, low cost, employment of cheap, easily available, and nontoxic catalyst, and simple work-up procedure. These merits make it a new and green alternative to the synthesis of substituted quinolines over existing methods.

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Supporting information

Additional supporting information is available in the online version of this article.

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