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Regioselective Synthesis of C-3-Functionalized Quinolines via Hetero-Diels–Alder Cycloaddition of Azadienes with Terminal Alkynes

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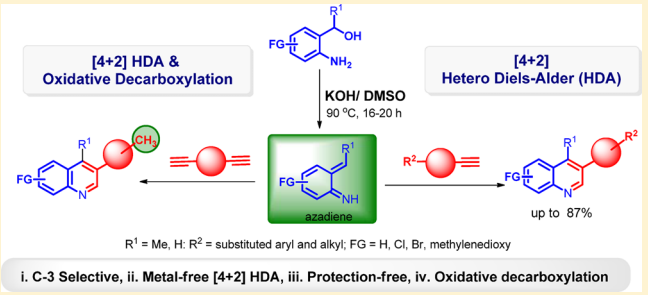
Supporting Information

ABSTRACT: A highly efficient metal and protection-free approach for the regioselective synthesis of C-3-functionalized quinolines from azadienes (in situ generated from 2-aminobenzyl alcohol) and terminal alkynes through [4 + 2] cycloaddition has been developed. An unprecedented reaction of 2-aminobenzyl alcohol with 1,3- and 1,4-diethynylbenzene provided the C-3 tolylquinolines via [4 + 2] HDA and oxidative decarboxylation. The $-NH_2$ group directed mechanistic approach was well supported by the control experiments and deuterium-labeling studies and by isolating the azadiene intermediate. The reactivity and selectivity of unprotected azadiene in metal-free base-assisted hetero-Diels-Alder reaction is exploited to quickly assemble an important class of C-3-functionalized quinolines, which are difficult to access.



INTRODUCTION

Quinolines are commonly occurring structural motifs found in numerous pharmaceuticals[1,2] and are extensively used in drug discovery (Figure 1).[3] The quinoline core structure can be synthesized by various traditional methods such as the Skraup reaction,[4] Friedlaender synthesis,[5] Combes quinoline synthesis,[6] Larock quinoline synthesis,[7] and other[8] quinoline syntheses. Alternatively, the groups of Wang,[9] Huang,[10] and Kwon[11] have demonstrated the transition-metal-catalyzed synthesis of C-3-functionalized quinolines from *ortho*-substituted anilines. Very recently, Balaraman and co-workers reported the Rh/dppm-catalyzed synthesis of C-3 quinoline via C–H activation (Scheme 1a).[12] The wide utility of these metal-catalyzed processes is inconsistent for the base-mediated regioselective intermolecular [4 + 2] cycloaddition to synthesize substituted quinolines.

The [4 + 2] cycloaddition reactions of azadiene[13] with an electron-rich carbon–carbon triple bond are a useful method for the synthesis of six-membered *N*-heterocyclic rings and have wide application in natural product synthesis;[14] however, the low reactivity of alkynes as dienophiles has limited their efficacy within the reaction. The metal-catalyzed regioselective intermolecular reactions of alkynes with azadiene is well reported;[15] however, base-promoted [4 + 2] annulation of terminal alkynes with in situ generated azadiene is still challenging.

In recent decades, the groups of Bergman,[16] Jun,[17] Cheng[18] and Wang[19] elaborated the regioselective transition-metal-catalyzed synthesis of pyridine via hetero-Diels–Alder reaction. In 2008, Arndt[20] et al. demonstrated the [4 + 2] cycloaddition chemistry for the synthesis of pyridines at a higher temperature. Later, Zimmer[21] and co-workers investigated the Lewis acid mediated cycloaddition process with both electron-neutral and electron-rich dienophiles (Scheme 1b). An attractive strategy for the synthesis of pyridines using azadiene motif was presented by Rovis group.[22] In contrast to the synthesis of pyridines, access of quinolines from azadienes remain elusive. In 2015, Ravikumar[22e] and co-workers have developed an efficient protocol which utilizes the DMSO for the oxidation of benzyl alcohol to benzaldehyde (Scheme 1c). The research activity of our group is mainly focused on the superbase-mediated[23] reactions and heterocyclic[24] synthesis. Very recently, we have explored the [4 + 2] cycloaddition chemistry of 2-aminobenzyl alcohol with internal alkynes;[24d] herein, we report an extended chemistry of C-3-functionalized quinolines via KOH–DMSO-mediated [4 + 2] cycloaddition of azadiene with terminal alkynes. We assumed that the direct synthesis of C-2-functionalized quinolines could occur via KOH–DMSO-promoted oxidation of 2-aminobenzyl alcohol into 2-aminobenzaldehyde followed by the reaction with an alkyne, though the designed pathway was unsuccessful (Scheme 1d, route A). We also visualized the regioselective synthesis of C-3-functionalized quinolines via KOH–DMSO-mediated [4 + 2] cycloaddition of azadiene (can be generated in situ from *o*-aminobenzyl alcohol) with alkyne (Scheme 1d, route B).

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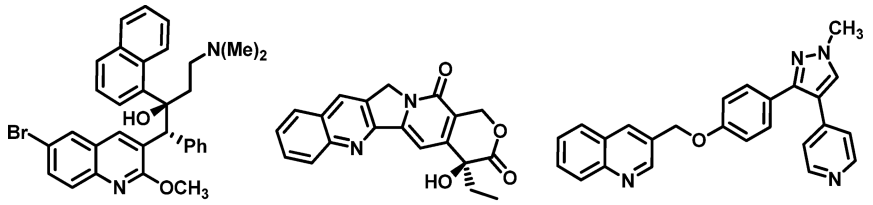
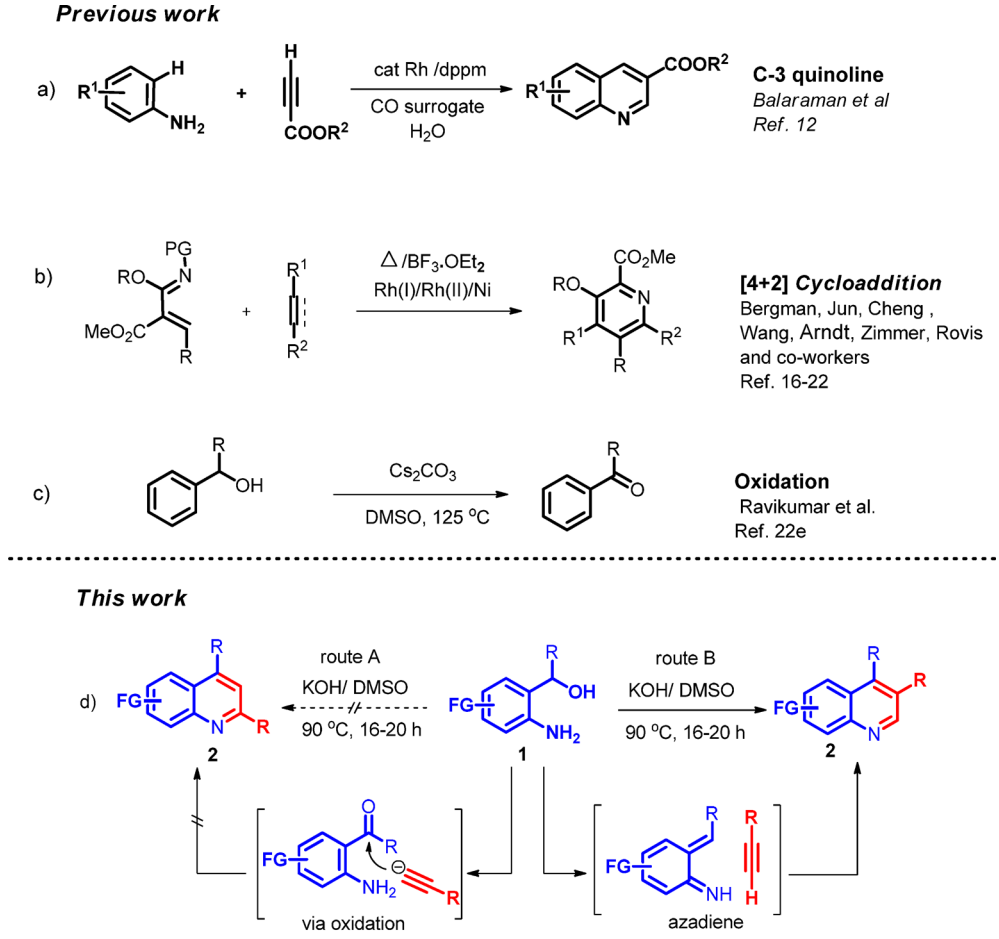


Figure 1. Biologically active quinoline skeleton.

Scheme 1. Previous Synthetic Approaches and Our Designed Approach for the Synthesis of Quinolines



RESULTS AND DISCUSSION

In preliminary experiments, a number of acids and bases were examined using 2-aminobenzyl alcohol **1a** and phenylacetylene **2a** as model substrates (Table 1). We carried out the reaction of **1a** with alkyne **2a** using HCl and BF_3·OEt at 80 °C for 24 h; the product **3a** was not obtained (entries 1 and 2). Using our hydroamination conditions,[23] the desired product **3a** was obtained in 65% yield at 120 °C (entry 3). Lowering the reaction temperature provided the product **3a** in 68% yield (entry 4). A further decrease in the reaction time and temperature provided the desired product **3a** in 70 and 80% yields, respectively, at 90 °C (entries 5 and 6). Other alkali bases provided the desired product **3a** in lower yield (entries 7−10) (for detailed optimization, see the Supporting Information).

With optimized conditions in hand, we examined the substrate scope of the developed chemistry by using a variety of alkynes (**2a−q**) (Table 2). The reaction of substrate **1a**, with phenylacetylene **2a**, provided the desired product **3a** in 80% yield (entry 1). The reaction proceeded well with alkynes **2b−g** bearing electron-donating groups such as *p*-Me, *m*-Me, *o*-Me, *p*-Et, *p*-^{n}Bu, and *p*-^{t}Bu on the phenyl ring and afforded the desired products **3b−g** in 81−84% yields (entries 2−7). Alkynes **2h,i** with strong electron-donating substituents such as −OMe and −OPh afforded the corresponding quinoline compounds **3h,i** in 87 and 85% yields, respectively (entries 8 and 9). When an electron-rich thienyl ring was used for the reaction, the desired product **3j** was obtained in 84% yield (entry 10). It was interesting to note that under the optimized reaction conditions electron-deficient heteroaromatic alkynes **2k** and bulky 9-

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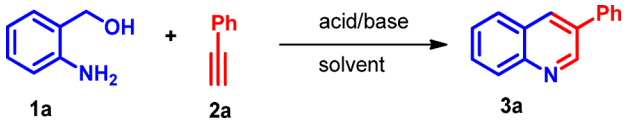
Table 1. Reaction Development[a]



entry	acid/base	solvent	time (h)	temp (°C)	yield[b] (%)
1	HCl	DMSO	24	80	NR
2	BF_3.OEt	DMSO	24	80	NR
3	KOH	DMSO	24	120	65
4	KOH	DMSO	24	100	68
5	KOH	DMSO	20	90	70
6	KOH	DMSO	16	90	80
7[25]	KtOBu	DMSO	16	90	75
8	NaOH	DMSO	16	90	65
9	CsOH	DMSO	16	90	63
10	K_3PO_4	DMSO	16	90	65

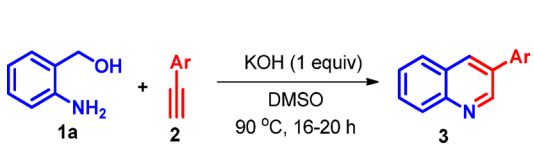
[a]Reactions were performed using 0.5 mmol of (2-aminophenyl)-methanol **1a**, phenylacetylene **2a** (0.4 mmol), and base/acid (1.0 equiv) in 2.0 mL of solvent. [b]Isolated yield. NR = no reaction.

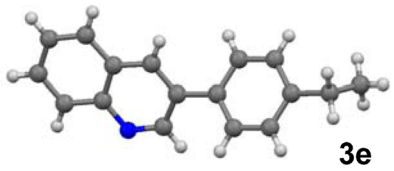
ethynylphenanthrene **2l** also provided the targeted products **3k** and **3l** in 74 and 76% yields, respectively (entries 11 and 12). We further extended the scope of the developed protocol with electron-withdrawing alkynes **2m−p**; the desired products **3m−p** were obtained in 68−73% yields with an excellent regioselectivity (entries 13−16). An inseparable complex mixture was obtained in the reaction of 2-aminobenzyl alcohol (**1a**) with 1-hexyne (**2q**) (entry 17). All of the above results infer that the regio- and chemoselectivity of the reaction depend on the electronic density distribution along the C−C triple bond.[26]

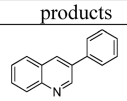
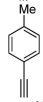
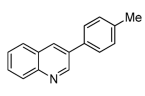
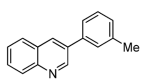
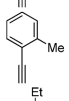
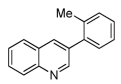
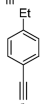
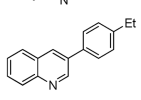
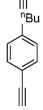
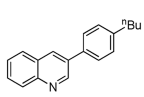
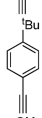
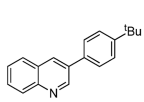
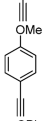
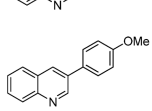
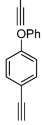
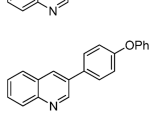
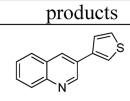
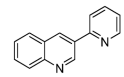
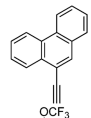
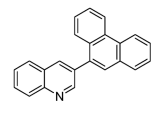
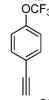
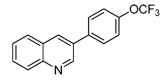
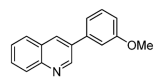
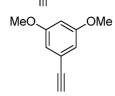
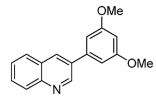
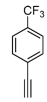
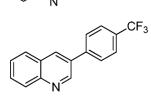
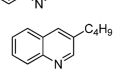
Next, we extended the substrate scope using varied of 2-aminobenzyl alcohols **1b−d** as another coupling partner (Table 3). The reaction of (2-amino-5-chlorophenyl)methanol **1b** with alkynes **2a**, **2e**, and **2k** provided the desired products **4a−c** in good yields (entries 1−3). The reaction accommodates the bromo-substituted aminobenzyl alcohol **1c** with alkynes **2a**, **2c**, and **2g** to give the desired products **4d−f** in 72−74% yields (entries 4−6). Further, reaction of (6-aminobenzo[*d*][1,3]-dioxol-5-yl)methanol **1d** with alkynes **2j−k,a,e,g** provided the regioselective C-3-functionalized quinolines **4g−k** in good yields (entries 7−11).

Encouraged by the above results, we next elaborate the substrate scope of the developed chemistry using dialkynes (Scheme 2). It is interesting to note that the reaction of 1,3- and 1,4-diethynylbenzenes **2q,r** with substrate **1a**, provided the

Table 2. Substrate Scope of the Alkynes[a]





entry	alcohol	alkyne		products		yields (%)[b]
1	 **1a**		**2a**		**3a**	80
2	**1a**		**2b**		**3b**	82
3	**1a**		**2c**		**3c**	81
4	**1a**		**2d**		**3d**	84
5	**1a**		**2e**		**3e**	82
6	**1a**		**2f**		**3f**	83
7	**1a**		**2g**		**3g**	80
8	**1a**		**2h**		**3h**	87
9	**1a**		**2i**		**3i**	85
10	**1a**		**2j**		**3j**	84
11	**1a**		**2k**		**3k**	74
12	**1a**		**2l**		**3l**	76
13	**1a**		**2m**		**3m**	73
14	**1a**		**2n**		**3n**	71
15	**1a**		**2o**		**3o**	68
16	**1a**		**2p**		**3p**	70
17	**1a**		**2q**		**3q**	-[c]

[a]Using optimized conditions (entry 6, Table 1). [b]Isolated yield. [c]Inseparable complex mixture. CCDC no. for **3e** is 1456743.

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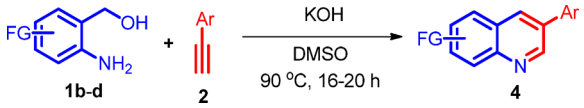
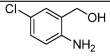
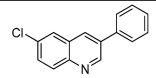
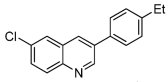
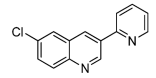
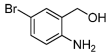
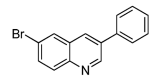
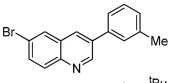
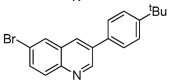
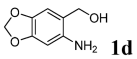
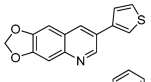
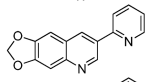
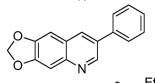
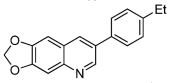
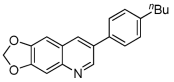
Table 3. Substrate Scope of the *o*-Aminobenzyl Alcohols[a]



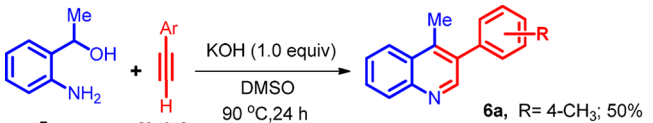
entry	alcohols	alkyne	products		yields (%)[b]
1	 **1b**	**2a**		**4a**	70[c]
2	**1b**	**2e**		**4b**	73[c]
3	**1b**	**2k**		**4c**	68[c]
4	 **1c**	**2a**		**4d**	72[c]
5	**1c**	**2c**		**4e**	74[c]
6	**1c**	**2g**		**4f**	72[c]
7	 **1d**	**2j**		**4g**	80
8	**1d**	**2k**		**4h**	78
9	**1d**	**2a**		**4i**	75
10	**1d**	**2e**		**4j**	77
11	**1d**	**2f**		**4k**	78

[a]Using optimized conditions (entry 6, Table 1). [b]Isolated yield. [c]20 h for **4a**–**f**

unexpected product **3b**,**c** in 52% and 49% yields, respectively, along with unidentified complex mixture.

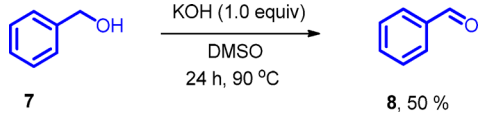
After attaining successful results with 2-aminobenzyl alcohol (primary alcoholic group), we next examined the scope of 1-(2-aminophenyl)ethan-1-ol **5** with terminal alkynes (Scheme 3). The reaction of substrate **5** with electron-releasing alkyne **2k** and electron-withdrawing alkyne **2p** was fruitful in affording the desired cycloaddition products **6a**,**b** in moderate yields.

Scheme 3. Scope of Secondary Alcohol



Inspired by the previous literature conditions,[22f,g] we performed the reaction of benzyl alcohol **7** with KOH/DMSO at 90 °C for 24 h; the methodology provided the oxidation of benzyl alcohol **7** to benzaldehyde **8** in 50% yield (Scheme 4).

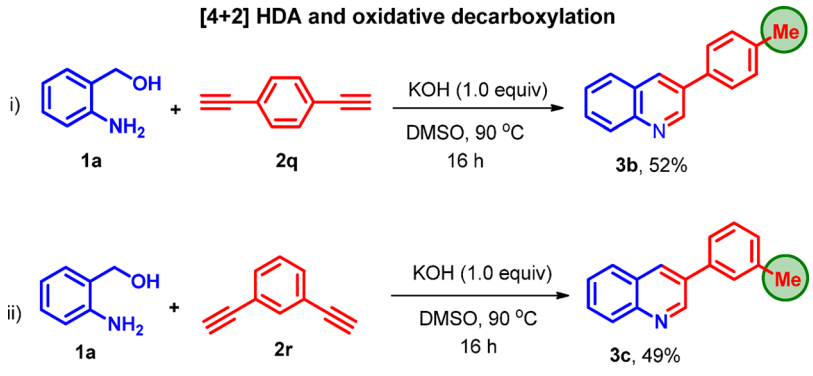
Scheme 4. KOH/DMSO-Promoted Oxidation



In order to support the proposed mechanistic pathway, various preliminary experiments were performed (Scheme 5). For the validation of the possible reaction pathway, we performed the reaction of 2-aminobenzaldehyde **9** with alkyne **2a** under optimized reaction conditions, but the quinoline **3a** was not observed (Scheme 5, (i)). We further examined the reaction of 1-(2-aminophenyl)ethanone **11** with **2a**, instead of quinoline **3a**, and 2-(4-methylquinolin-2-yl)aniline **12** (self-condensation product of **11**) was obtained in 90% yield (Scheme 5, (ii)). For the confirmation of the possible reaction intermediate, we performed a gram-scale reaction of 2-aminobenzyl alcohol **1a** with KOH–DMSO at 90 °C; the oxidation of benzyl alcohol was not observed; however, highly unstable azadiene **13** was obtained in 5% yield along with the inseparable complex mixture (Scheme 5, (iii)). The reaction of unstable azadiene **13** with alkyne **2a** under standard reaction conditions provided the quinoline **3a** in 12% yield. The above control experiments clearly suggest the formation of quinoline via azadiene intermediate **13** (Scheme 5, (iv)). Use of molecular sieves decreases the yield of the product **3a**, probably due to the low concentration of H^+ counterions (Scheme 5, (v)).

When we performed the reaction of benzyl alcohol **7** with **2a** in the presence of KOH–DMSO, the hydroxyalkoxylation product **14** was obtained in 55% yield, which suggests the crucial role of the $-NH_2$ group in the reaction (Scheme 5, (vi)).[23] A competition experiment between **1a** and **7** with

Scheme 2. Scope of Dialkynes



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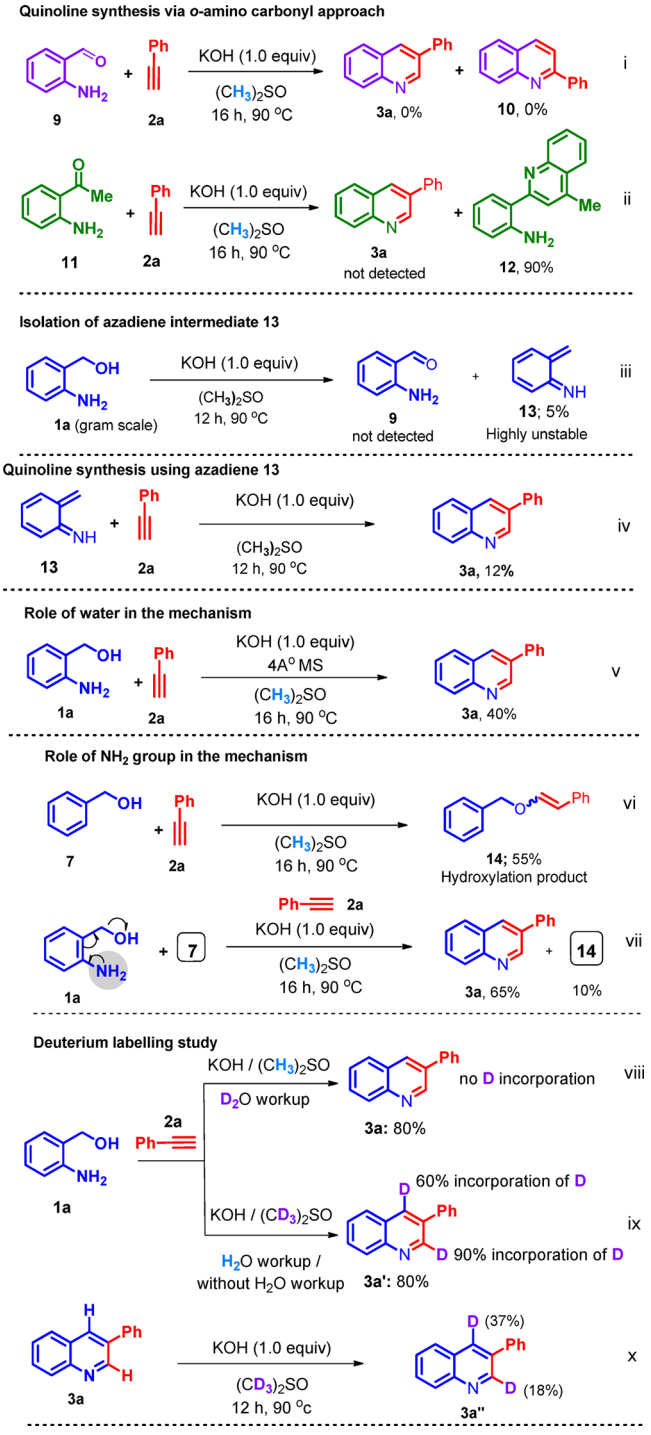
Scheme 5. Preliminary Mechanistic Studies



alkyne **2a** was performed. The product **3a** was found in 65% yield; however, hydroxylated product **14** was observed only in 10% yield. This experiment indicated that the presence of an *o*-NH_2 group directs the formation of intermediate **13** (Scheme 5, (vii) vs (vi)).

Deuterium-labeling experiments were conducted to investigate the detailed mechanism of the reaction (Scheme 5, (viii–x)). When alcohol **1a** and alkyne **2a** were subjected to the standardized reaction conditions followed by workup using D_2O, no exchange of proton was observed in product **3a** (Scheme 5, (viii)). Surprising results were obtained when we performed the reaction using DMSO-d_6 as a solvent; product **3a′** was obtained in 80% yield with 60% and 90% incorporation of deuterium at the C-2 and C-4 positions (Scheme 5, (ix)). Interestingly, when final product quinoline **3a** was subjected to KOH/DMSO-d_6 at 90 °C, product **3a″** was obtained with 18% and 37% incorporation of deuterium at the C-2 and C-4 positions, respectively (Scheme 5, (x)). The above isotopic labeling experiments infer that the reaction proceeds via H−D exchange within the reaction (Scheme 5, (ix) vs (x)).

On the basis of the evidence obtained from the control experiments and isotopic studies, a plausible mechanism is proposed in Scheme 6.[27] We have designed two possible pathways for the generation of azadiene intermediate **13**. The mechanism is initiated by the protonation of the 2-aminobenzyl alcohol **1** via KOH−DMSO suspension, which leads to the formation of imine type motif **Q**. The anion of the DMSO abstracts the proton and forms azadiene **13**[23] (route A, Scheme 6). Another route to achieve the key intermediate **13** is via an attack of −OH nucleophile onto the soft electrophilic sulfur of dimethyl sulfoxide to form an intermediate **X**. The intermediate **X** leads to the formation of azadiene **13** through the formation of intermediate **Y** (route B). The subsequent [4 + 2] cycloaddition (**R**) of azadiene **13** with alkyne **2**/**2′**[28] forms dihydroquinoline **S**. The H−D exchange of species **S** would generate species **T**, which upon auto-oxidation leads to the formation of quinoline (Scheme 6, (i)).

An unusual result obtained in Scheme 2 led us to investigate the mechanism of the reaction of 1,3- and 1,4-diethynylbenzene **2q**,**r** with substrate **1a** as described in Scheme 6, (ii). The mechanism proceeded via nucleophilic addition of in situ formed water onto quinoline **A** and generated the ion **B**, which formed aldehyde intermediate **D** through enol **C**. The auto-oxidation of intermediate **D** triggered the formation of carboxylate intermediate **E**, which subsequently led to the formation of product **3b** and **3c** via decarboxylation (Scheme 6, (ii)).

CONCLUSION

In summary, a novel base-promoted synthesis of C-3-functionalized quinolines from azadiene (generated in situ from *o*-aminobenzyl alcohol) and terminal alkynes have been developed via [4 + 2] HDA reaction with excellent chemo- and regioselectivity. Reaction of 2-aminobenzyl alcohol with 1,3- and 1,4-diethynylbenzene provided the unusual C-3 tolylquinolines via [4 + 2] HDA and successive oxidative decarboxylation. The developed chemistry also flourished with secondary 2-aminobenzyl alcohol with terminal alkynes. The results of the control experiments support the $-NH_2$ group directed mechanistic pathway via azadiene formation and not through aldehyde formation. We overcame the challenges of selectivity (chemo and regio) and constructed biologically important quinolines in a site-selective fashion.

EXPERIMENTAL SECTION

General Method. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$/DMSO-d_6. Chemical shifts for protons and carbons are reported in ppm from tetramethylsilane and are referenced to the carbon resonance of the solvent. Data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet), coupling constants in hertz, and integration. High-resolution mass spectra were recorded on electrospray mass spectrometer. Crystal structure analysis was accomplished on a single-needle X-ray diffractometer. TLC analysis was performed on commercially prepared 60 F_{254} silica gel plates and visualized by

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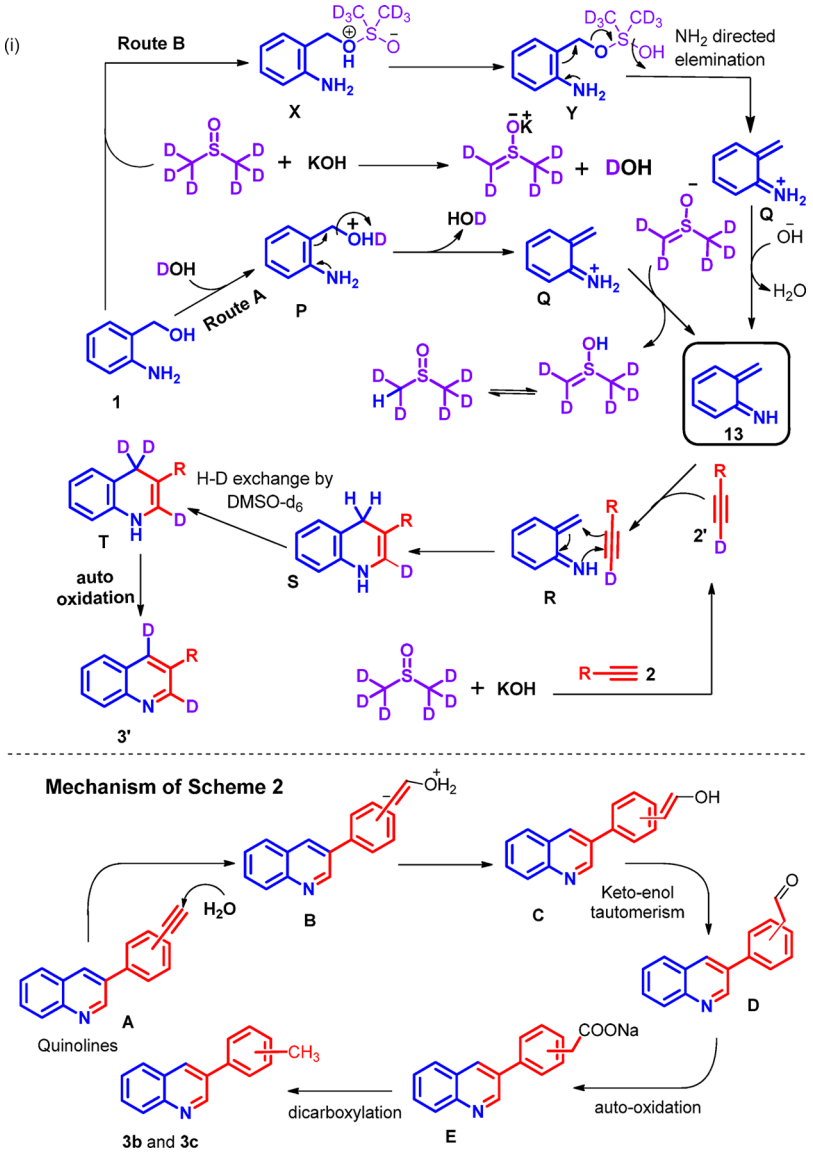
Scheme 6. Final Mechanistic Pathway



either UV irradiation or by staining with I_2. All purchased chemicals were used as received. All melting points are uncorrected.

2-Amino-5-bromobenzyl alcohol (**1c**) was prepared by the literature reported method.[29]

Synthesis of (6-Aminobenzo[d][1,3]dioxol-5-yl)methanol. **Step 1.** To a cooled (ice bath) solution of 6-nitrobenzo[*d*][1,3]dioxole-5-carbaldehyde (1.0 g, 10 mmol) in EtOH (15 mL) was added $NaBH_4$ (1.5 equiv), and the mixture stirred for 2 h at 0 °C. Careful evaporation of the solvent gave an orange semisolid, which was slowly treated with satd aq NH_4Cl (10 mL) solution. After evolution of H_2 gas ceased, the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with H_2O and brine, dried over Na_2SO_4, and filtered. Evaporation of the solvent gave (6-nitrobenzo-[*d*][1,3]dioxol-5-yl)methanol (0.9 g, 90%), which was used in the next step without further purification.

Step 2. (6-Nitrobenzo[*d*][1,3]dioxol-5-yl)methanol (0.9 g) was dissolved in EtOH (35 mL) and H_2O (5 mL). NH_4Cl (1.0 equiv) and Fe powder (6.0 equiv) were added, and the mixture was heated to reflux for 6 h. After being cooled at room temperature, the solution was decanted from the solids, diluted with CH_2Cl_2, and washed with satd aq $NaHCO_3$ (35 mL) solution. The aqueous phase was extracted extensively with CH_2Cl_2, and the combined organic phases were washed with brine solution, dried over Na_2SO_4, filtered, and evaporated to give (6-aminobenzo[*d*][1,3]dioxol-5-yl)methanol as an off-white solid.[30]

*(6-Aminobenzo[d][1,3]dioxol-5-yl)methanol (**1d**).* The product was obtained as a off-white solid: ^{1}H NMR (400 MHz, DMSO) δ 6.64 (s, 1H), 6.29 (s, 1H), 5.79 (s, 2H), 4.91 (t, J = 5.3 Hz, 1H), 4.64 (s, 2H), 4.27 (d, J = 5.3 Hz, 2H); ^{13}C NMR (100 MHz, DMSO) δ 146.4, 141.3, 137.9, 117.6, 108.2, 99.8, 96.9, 60.7; HRMS (ESI-TOF) $[M]^+$ calcd for $[C_8H_9NO_3]$ 167.0582, found 167.0582.

*1-(2-Aminophenyl)ethanol (**12**).*[31] A mixture of 2-aminoacetophenone (0.159 g, 1.1 mmol) and $NaBH_4$ (0.061g, 1.5 mmol) in EtOH (12 mL) was refluxed under argon for 2 h, affording after workup 1-(2-aminophenyl)ethanol as a white solid. The structure and purity of 1-(2-aminophenyl) ethanol were confirmed by comparison of their physical and spectral data (^{1}H NMR and ^{13}C NMR) with those reported in the literature.[7]

General Procedure for the Synthesis of Functionalized Quinolines 3a–p. In an oven-dried round-bottom flask, a solution of aminophenylmethanol **1** (0.5 mmol), internal alkyne **2** (0.4 mmol), and 1.0 equiv of crushed KOH in 2.0 mL of DMSO was added under inert atmosphere. The resulting reaction mixture was heated at 90 °C for 24–30 h. Progression of the reaction was monitored by TLC analysis; after complete consumption of the starting material, the reaction was cooled to room temperature. The reaction mixture was

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diluted with ethyl acetate (10 mL) and water (15 mL). The layers were separated, and the organic layer was washed with aqueous saturated brine solution and dried over Na_2SO_4. The organic layer was concentrated under reduced pressure. The crude material so obtained was purified by column chromatography on silica gel (100−200) (hexane/ethyl acetate; 90/10). The structure and purity of known starting materials were confirmed by comparison of their physical and spectral data (^{1}H NMR, ^{13}C NMR, and HRMS).

*3-Phenylquinoline (**3a**).* The product was obtained as a pale yellow oil (82.0 mg, 80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (d, J = 3.0 Hz, 1H), 8.55 (d, J = 2.3 Hz, 1H), 8.03−7.97 (m, 2H), 7.80 (d, J = 8.4 Hz, 2H), 7.72−7.68 (m, 1H), 7.57 (t, J = 6.9 Hz, 1H), 7.50−7.43 (m, 2H), 7.40−7.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.4, 146.8, 137.0, 132.8, 129.5, 129.2, 128.6, 128.4, 128.2, 127.7, 127.2, 127.0; HRMS (ESI-TOF) $[M + H]^+$ calcd for $[C_{15}H_{11}N]$ 206.0970, found 206.0963.

*3-(p-Tolyl)quinoline (**3b**).* The product was obtained as pale brown needles: mp 91−94 °C (89.7 mg, 82%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (d, J = 2.3 Hz, 1H), 8.26 (d, J = 2.3 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 6.9 Hz, 1H), 7.71−7.67 (m, 1H), 7.60 (d, J = 7.6 Hz, 2H), 7.57−7.53 (m, 1H), 7.32 (d, J = 7.6 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.9, 147.1, 138.0, 134.9, 133.7, 132.8, 129.8, 129.2, 129.1, 128.0, 127.9, 127.2, 126.9, 21.2; HRMS (ESI-TOF) $[M + H]^+$ calcd for $[C_{16}H_{13}N]$ 220.1126, found 220.1153.

*3-(m-Tolyl)quinoline (**3c**).* The product was obtained as a brown oil (88.6 mg, 81%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (d, J = 2.3 Hz, 1H), 8.28 (d, J = 2.3 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.73−7.69 (m, 1H), 7.57 (t, J = 6.9 Hz, 1H), 7.51 (d, J = 6.9 Hz, 2H), 7.41 (t, J = 7.6 Hz, 1H), 7.26−7.24 (m, 1H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 147.2, 138.8, 137.8, 133.9, 133.1, 129.3, 129.1, 129.0, 128.8, 128.1, 128.0, 127.9, 126.9, 124.5, 21.5; HRMS (ESI-TOF) $[M + H]^+$ calcd for $[C_{16}H_{13}N]$ 220.1126, found 220.1148.

*3-(o-Tolyl)quinoline (**3d**).* The product was obtained as a brown oil (91.9 mg, 84%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, J = 2.3 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 8.01 (d, J = 1.52 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.68−7.64 (m, 1H), 7.52−7.48 (m, 1H), 7.26−7.24 (m, 4H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 146.9, 138.0, 135.8, 135.3, 134.7, 130.6, 130.1, 129.3, 129.2, 128.1, 127.8, 127.7, 126.9, 126.1, 20.4; HRMS (ESI-TOF) $[M + H]^+$ calcd for $[C_{16}H_{13}N]$ 220.1126, found 220.1149.

*3-(4-Ethylphenyl)quinoline (**3e**).* The product was obtained as brown needles: mp 83−86 °C (95.5 mg, 82%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (d, J = 2.3 Hz, 1H), 8.15 (s, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.60−7.56 (m, 1H), 7.52 (d, J = 6.9 Hz, 2H), 7.44 (t, J = 6.9 Hz, 1H), 7.24 (d, J = 7.6 Hz, 2H), 2.61 (q, J = 7.6 Hz, 2H), 1.19 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 146.5, 144.3, 135.9, 133.2, 129.2, 128.8, 128.6, 128.3, 127.8, 127.5, 126.9, 126.3, 28.4, 15.6; HRMS (ESI-TOF) $[M + H]^+$ calcd for $[C_{17}H_{15}N]$ 234.1282, found 234.1299.

*3-(4-Butylphenyl)quinoline (**3f**).* The product was obtained as a brown oil (108.3 mg, 83%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (d, J = 2.3 Hz, 1H), 8.32 (d, J = 2.3 Hz, 1H), 8.21 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.78−7.74 (m, 1H), 7.68 (d, J = 8.4 Hz, 2H), 7.61 (t, J = 8.4 Hz, 1H), 7.39 (d, J = 7.6 Hz, 2H), 2.77−2.69 (m, 2H), 1.76−1.69 (m, 2H), 1.52−1.43 (m, 2H), 1.05−1.02 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 147.1, 142.9, 135.0, 133.6, 132.7, 129.14, 129.07, 129.0, 127.9, 127.8, 127.1, 126.8, 35.2, 33.5, 22.3, 13.9; HRMS (ESI-TOF) $[M + H]^+$ calcd for $[C_{19}H_{19}N]$ 262.1595, found 262.1599.

*3-(4-tert-Butylphenyl)quinoline (**3g**).* The product was obtained as an orange semisolid (104.4 mg, 80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (d, J = 3.0 Hz, 1H), 8.28 (d, J = 1.5 Hz, 1H), 8.14 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.73−7.66 (m, 3H), 7.58−7.54 (m, 3H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ151.2, 149.9, 147.1, 134.9, 133.6, 132.8, 129.2, 129.1, 128.0, 127.9, 127.0, 126.9, 126.1, 34.6, 31.3; HRMS (ESI-TOF) $[M + H]^+$ calcd for $[C_{19}H_{19}N]$ 262.1595, found 262.1612.

*3-(4-Methoxyphenyl)quinoline (**3h**).* The product was obtained as pale yellow needles: mp 99−102 °C; (102.2 mg, 87%), ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (d, J = 1.16 Hz, 1H), 7.97 (s, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 7.6 Hz, 1H), 7.67−7.64 (m, 3H), 7.56 (t, J = 7.6 Hz, 1H), 6.76 (d, J = 8.4 Hz, 2H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 157.8, 149.8, 136.0, 132.4, 129.2, 129.1, 129.0, 128.8, 127.8, 126.9, 126.2, 114.6, 55.4; HRMS (ESI-TOF) $[M + H]^+$ calcd for $[C_{16}H_{13}NO]$ 236.1075, found 236.1095.

*3-(4-Phenoxyphenyl)quinoline (**3i**).* The product was obtained as yellow needles: mp 86−88 °C, (126.2 mg, 85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (d, J = 2.3 Hz, 1H), 8.22 (d, J = 2.3 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 6.9 Hz, 1H), 7.70−7.66 (m, 1H), 7.65−7.61 (m, 2H), 7.53 (t, J = 8.4 Hz, 1H), 7.38−7.35 (m, 2H), 7.15−7.11 (m, 3H), 7.08−7.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 156.6, 149.6, 147.0, 133.0, 132.7, 132.5, 129.8, 129.2, 129.0, 128.6, 127.9, 127.8, 126.9, 123.6, 119.1; HRMS (ESI-TOF) $[M + H]^+$ calcd for $[C_{21}H_{15}NO]$ 298.1232, found 298.1251.

*3-(Thiophene-3-yl)quinoline (**3j**).* The product was obtained as brown needles: mp 80−83 °C (88.6 mg, 84%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (d, J = 2.3 Hz, 1H), 8.27−8.26 (m, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.71−7.64 (m, 2H), 7.57−7.51 (m, 2H), 7.49−7.47 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.4, 147.1, 138.8, 132.0, 129.2, 128.7, 128.0, 127.8, 127.0, 126.0, 121.6; HRMS (ESI-TOF) $[M + H]^+$ calcd for $[C_{13}H_9NS]$ 212.0534, found 212.0553.

*3-(Pyridin-2-yl)quinoline (**3k**).* The product was obtained as a dark brown oil (76.2 mg, 74%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (d, J = 3.0 Hz, 1H), 8.76 (d, J = 2.2 Hz, 2H), 8.15 (d, J = 8.4 Hz, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.88−7.80 (m, 2H), 7.74 (t, J = 6.8 Hz, 1H), 7.60−7.53 (m, 1H), 7.31 (t, J = 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 150.1, 149.1, 137.1, 133.9, 130.0, 129.2, 129.0, 128.5, 127.0, 122.8, 120.8; HRMS (ESI-TOF) $[M + H]^+$ calcd for $[C_{14}H_{10}N_2]$ 207.0922, found 207.0919.

*3-(Phenanthren-9-yl)quinoline (**3l**).* The product was obtained as a brown oil (115.9 mg, 76%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 (br s, 1H), 8.79 (d, J = 8.4 Hz, 1H), 8.73 (d, J = 8.4 Hz, 1H), 8.29−8.27 (m, 2H), 7.91−7.86 (m, 3H), 7.81−7.76 (m, 2H), 7.69 (t, J = 6.9 Hz, 2H), 7.65−7.59 (m, 2H), 7.57−7.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 147.2, 136.2, 134.8, 133.7, 131.2, 130.7, 130.6, 130.1, 129.5, 129.2, 128.7, 127.8, 127.77, 127.0, 126.98, 126.8, 126.7, 126.2, 123.0, 122.5; HRMS (ESI-TOF) $[M + H]^+$ calcd for $[C_{23}H_{15}N]$ 306.1282, found 306.1305.

*3-(4-(Trifluoromethoxy)phenyl)quinoline (**3m**).* The product was obtained as a brown semisolid (105.4 mg, 73%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (d, J = 1.5 Hz, 1H), 8.18 (s, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.66−7.61 (m, 3H), 7.50 (t, J = 6.8 Hz, 1H), 7.28 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 149.2, 147.4, 136.6, 133.4, 132.4, 129.7, 129.2, 128.8, 128.0, 127.8, 127.2, 121.6; HRMS (ESI-TOF) $[M + H]^+$ calcd for $[C_{16}H_{10}F_3NO]$ 290.0792, found 290.0796.

*3-(3-Methoxyphenyl)quinoline (**3n**).* The product was obtained as a yellow oil (83.4 mg, 71%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (d, J = 7.3 Hz, 1H), 8.28 (d, J = 1.5 Hz, 1H), 8.15 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.74−7.70 (m, 1H), 7.57 (t, J = 8.4 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.30−7.24 (m, 2H), 6.98 (dd, J = 8.4 and 2.3 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 149.8, 147.3, 139.2, 133.6, 133.2, 130.1, 129.3, 129.1, 127.9, 127.86, 126.9, 119.7, 113.3, 113.1, 55.3; HRMS (ESI-TOF) $[M + H]^+$ calcd for $[C_{16}H_{13}NO]$ 236.1075, found 236.1096.

*3-(3,5-Dimethoxyphenyl)quinoline (**3o**).* The product was obtained as an orange oil (90.1 mg, 68%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (d, J = 2.2 Hz, 1H), 8.28 (s, 1H), 8.14 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.72 (t, J = 7.6 Hz, 1H), 7.58 (t, J = 7.2 Hz, 1H), 6.84−6.83 (m, 2H), 6.55−6.54 (m, 1H), 3.88 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 149.8, 140.6, 133.3, 129.4, 129.1, 129.0, 128.0, 127.0, 126.8, 118.0, 114.4, 105.7, 99.8, 55.1; HRMS (ESI-TOF) $[M + H]^+$ calcd for $[C_{17}H_{15}NO_2]$ 266.1181, found 266.1180.

*3-(4-(Trifluoromethyl)phenyl)quinoline (**3p**).* The product was obtained as yellow needles: mp 131−133 °C. (95.5 mg, 70%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (d, J = 2.3 Hz, 1H), 8.22 (d, J = 2.3 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.71−7.64 (m, 3H), 7.50 (t, J = 8.4 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.33−7.29

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(m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 140.5, 133.8, 130.0, 129.16, 129.12, 128.1, 127.7, 127.3, 127.1, 126.9 (q, J = 2.9 Hz, 1C); HRMS (ESI-TOF) $[M + H]^+$ calcd for $[C_{16}H_{10}F_3N]$ 274.0843, found 274.0842.

*6-Chloro-3-phenylquinoline (**4a**).* The product was obtained as yellow needles: mp 93−95 °C (83.6 mg, 70%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (d, J = 2.3 Hz, 1H), 8.20 (d, J = 2.3 Hz, 1H), 8.07 (d, J = 9.2 Hz, 1H), 7.86 (d, J = 1.5 Hz, 1H), 7.71−7.69 (m, 2H), 7.66−7.61 (m,1H), 7.55−7.52 (m 2H), 7.47−7.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 145.6, 137.4, 134.7, 132.7, 132.2, 130.8, 130.3, 129.2, 128.6, 128.4, 127.4, 126.6; HRMS (ESI-TOF) $[M + H]^+$ calcd for $[C_{15}H_{10}ClN]$ 240.0580, found 240.0577.

*6-Chloro-3-(4-ethylphenyl)quinoline (**4b**).* The product was obtained as a yellow oil (97.4 mg, 73%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (d, J = 1.9 Hz, 1H), 8.18 (d, J = 1.5 Hz, 1H), 8.06 (d, J = 9.2 Hz, 1H), 7.85 (d, J = 2.3 Hz, 1H), 7.64−7.61 (m, 3H), 7.36 (d, J = 8.4 Hz, 2H), 2.74 (q, J = 7.6 Hz, 2H), 1.30 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 145.5, 144.8, 134.6, 132.6, 131.8, 130.8, 130.1, 128.8, 128.7, 127.3, 126.5, 28.6, 15.5; HRMS (ESI-TOF) $[M + H]^+$ calcd for $[C_{17}H_{14}ClN]$ 268.0893, found 268.0890.

*6-Chloro-3-(pyridin-2-yl)quinoline (**4c**).* The product was obtained as a brown oil (81.6 mg, 68%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (d, J = 1.5 Hz, 1H), 8.77 (d, J = 1.9 Hz, 2H), 8.15 (d, J = 8.4 Hz, 1H), 7.94−7.81 (m, 3H), 7.74 (t, J = 7.6 Hz, 1H), 7.58 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 150.1, 149.1, 148.0, 137.1, 134.0, 131.8, 130.0, 129.0, 128.5, 127.8, 127.0, 122.8, 120.8; HRMS (ESI-TOF) $[M + H]^+$ calcd for $[C_{14}H_9ClN_2]$ 241.0533, found 241.0523.

*6-Bromo-3-phenylquinoline (**4d**).* The product was obtained as a yellow oil (102.2 mg, 72%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (d, J = 1.5 Hz, 1H), 8.30 (d, J = 1.9 Hz, 1H), 8.14 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 7.6 Hz, 1H), 7.74−7.68 (m, 3H), 7.60−7.56 (m, 1H), 7.55−7.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 141.8, 137.8, 133.3, 130.5, 129.4, 129.1, 128.5, 128.1, 128.0, 127.4, 127.0, 126.3; HRMS (ESI-TOF) $[M + H]^+$ calcd for $[C_{15}H_{10}BrN]$ 284.0075, found 284.0068.

*6-Bromo-3-(m-tolyl)quinoline (**4e**).* The product was obtained as a yellow oil (110.2 mg, 74%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (d, J = 1.5 Hz, 1H), 8.30 (d, J = 1.5 Hz, 1H), 8.14 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 7.6 Hz, 1H), 7.72 (t, J = 6.8 Hz, 1H), 7.52−7.51 (m, 3H), 7.42 (t, J = 7.6 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 138.9, 137.8, 133.2, 129.3, 129.13, 129.07, 128.8, 128.1, 128.0, 127.0, 124.5, 21.6; HRMS (ESI-TOF) $[M + H]^+$ calcd for $[C_{16}H_{12}BrN]$ 298.0231, found 298.0223.

*6-Bromo-3-(4-tert-butylphenyl)quinoline (**4f**).* The product was obtained as a yellow oil (122.4 mg, 72%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (d, J = 2.3 Hz, 1H), 8.30 (d, J = 1.5 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.74−7.66 (m, 3H), 7.60−7.55 (m, 3H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 150.1, 135.0, 133.7, 133.1, 129.4, 129.3, 128.1, 127.2, 127.0, 126.3, 53.6, 31.4; HRMS (ESI-TOF) $[M + H]^+$ calcd for $[C_{19}H_{18}BrN]$ 340.0701, found 340.0699.

*7-(Thiophene-3-yl)-[1,3]dioxolo[4,5-g]quinoline (**4g**).* The product was obtained as a dark brown oil (102 mg, 80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (d, J = 2.3 Hz, 1H), 8.03 (d, J = 1.5 Hz, 1H), 7.50 (t, J = 2.3 Hz, 1H), 7.39 (s, 2H), 7.33 (s, 1H), 7.00 (s, 1H), 6.03 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 148.3, 146.6, 145.1, 138.9, 131.5, 127.4, 126.9, 126.0, 125.2, 121.0, 105.4, 102.7, 101.8; HRMS (ESI-TOF) $[M + H]^+$ calcd for $[C_{14}H_9NO_2S]$ 256.0432, found 256.0429.

*7-(Pyridin-2-yl)[1,3]dioxolo[4,5-g]quinoline (**4h**).* The product was obtained as brown needles: mp 90−92 °C (97.5 mg, 78%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 3.8 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 7.09−7.07 (m, 1H), 6.52 (s, 2H), 6.06 (s, 2H), 5.81 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 149.4, 146.4, 140.2, 136.1, 135.3, 121.4, 121.1, 112.2, 108.7, 100.3, 96.9; HRMS (ESI-TOF) $[M + H]^+$ calcd for $[C_{15}H_{10}N_2O_2]$ 251.0820, found 251.0814.

*7-Phenyl-[1,3]dioxolo[4,5-g]quinoline (**4i**).* The product was obtained as dark brown needles: mp 67−70 °C (93.3 mg, 75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (d, J = 2.3 Hz, 1H), 8.12 (d, J = 2.2 Hz, 1H), 7.67 (d, J = 7.6 Hz, 2H), 7.50 (t, J = 6.8 Hz, 2H), 7.43−7.39 (m, 2H), 7.10 (s, 1H), 6.12 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 148.2, 147.2, 145.4, 137.9, 132.5, 132.4, 129.1, 127.8, 127.2, 125.1, 105.4, 102.9, 101.8; HRMS (ESI-TOF) $[M + H]^+$ calcd for $[C_{16}H_{11}NO_2]$ 250.0868, found 250.0872.

*7-(4-Ethylphenyl)[1,3]dioxolo[4,5-g]quinoline (**4j**).* The product was obtained as a yellow solid (106.6 mg, 77%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, J = 2.3 Hz, 1H), 8.02 (d, J = 1.5 Hz, 1H), 7.53 (d, J = 7.6 Hz, 2H), 7.33 (s, 1H), 7.26 (d, J = 7.6 Hz, 2H), 7.03 (s, 1H), 6.04 (s, 2H), 2.66 (q, J = 7.6 Hz, 2H), 1.22 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 147.4, 145.4, 144.1, 135.3, 132.4, 132.1, 128.6, 127.9, 127.1, 125.2, 105.6, 104.6, 102.8, 28.6, 15.6; HRMS (ESI-TOF) $[M + H]^+$ calcd for $[C_{18}H_{15}NO_2]$ 278.1181, found 278.1154.

*7-(4-Butylphenyl)[1,3]dioxolo[4,5-g]quinoline (**4k**).* The product was obtained as a brown semisolid (118.9 mg, 78%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.02 (s, 1H), 7.50 (d, J = 8.4 Hz, 2H), 7.33 (s, 1H), 7.23 (d, J = 7.6 Hz, 2H), 7.01 (s, 1H), 6.03 (d, J = 1.1 Hz, 2H), 2.62−2.58 (m, 2H), 1.61−1.53 (m, 2H), 1.36−1.29 (m, 2H), 0.91−0.86 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 148.2, 147.2, 145.2, 142.8, 135.2, 132.4, 132.2, 129.2, 127.0, 125.2, 105.4, 102.8, 101.8, 35.3, 33.6, 29.7, 22.4, 14.0; HRMS (ESI-TOF) $[M + H]^+$ calcd for $[C_{20}H_{19}NO_2]$ 306.1494, found 306.1495.

*4-Methyl-3-(p-tolyl)quinoline (**6a**).* The product was obtained as a yellow oil (58.2 mg, 50%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.10 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 7.6 Hz, 1H), 7.69−7.65 (m, 1H), 7.58−7.54 (m, 1H), 7.28−7.24 (m, 4H), 2.60 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 146.8, 140.5, 137.3, 135.6, 134.3, 129.8, 129.77, 129.1, 128.7, 127.9, 126.6, 124.1, 21.2, 15.6; HRMS (ESI-TOF) $[M + H]^+$ calcd for $[C_{17}H_{15}N]$ 234.1283, found 234.1276.

*4-Methyl-3-(4-(trifluoromethyl)phenyl)quinoline (**6b**).* The product was obtained as a yellow oil (64.5 mg, 45%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.14 (d, J = 8.4 Hz, 1H), 8.09 (d, J = 7.6 Hz, 1H), 7.76−7.72 (m, 3H), 7.65−7.61 (m, 1H), 7.51 (d, J = 8.4 Hz, 2H), 2.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 147.1, 142.3, 141.0, 133.1, 130.3, 130.0, 129.4, 127.1, 125.4 (q, J = 3.8 Hz, 1C), 124.2, 15.6; HRMS (ESI-TOF) $[M + H]^+$ calcd for $[C_{17}H_{12}F_3N]$ 288.1000, found 288.0970.

Mechanistic Control Experiments. Benzaldehyde (**8**) was reported in ref 22f.

*2-(4-Methylquinolin-2-yl)aniline (**12**).* The product was obtained as yellow needles: mp 75−77 °C (105.3 mg, 90%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 8.4 Hz, 1H), 7.96 (d, J = 8.3 Hz, 1H), 7.73−7.67 (m, 3H), 7.55−7.51 (m, 1H), 7.25−7.21 (m, 1H),6.87−6.81 (m, 2H), 6.22 (br s, 2H), 2.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 147.3, 146.5, 144.5, 130.0, 129.6, 129.2, 129.1, 126.3, 125.7, 123.4, 121.5, 120.9, 117.2, 117.1, 18.9; HRMS (ESI-TOF) $[M + H]^+$ calcd for $[C_{16}H_{14}N_2]$ 235.1235, found 235.1245.

*6-Methylenecyclohexa-2,4-dienimine (**13**).* The product was obtained as yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15−7.11 (m, 1H), 7.03 (d, J = 7.6 Hz, 1H), 6.72−6.66 (m, 2H), 4.50 (s, 2H), 3.76 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 130.4, 129.4, 121.7, 118.0, 115.8, 70.2; HRMS (ESI-TOF) $[M + H]^+$ calcd for $[C_7H_7N]$ 106.0657, found 106.0665.

*(2-(Benzyloxy)vinyl)benzene (**14**).* The product was reported ref 23d.

*2,4-D-3-Phenylquinoline (**3a′**).* The product was obtained as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 0.1H), 8.25 (s, 0.4H), 8.13 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 7.6 Hz, 1H), 7.70−7.66 (m, 3H), 7.55 (d, J = 7.6 Hz, 1H), 7.51−7.47 (m, 2H), 7.41 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7 (d, J = 10.5 Hz, 1C), 149.3 (d, J = 26.8 Hz, 1C), 147.1, 137.6 (d, J = 2.9 Hz, 1C), 133.5(d, J = 9.6 Hz, 1C), 133.1 (d, J = 12.5, Hz, 1C), 129.3, 129.1, 129.0, 127.9, 127.8, 127.3, 126.9, 126.8 (d, J = 7.6 Hz, 1C); HRMS (ESI-TOF) $[M + H]^+$ calcd for $[C_{15}H_9D_2N]$ 208.1095, found 208.1068.

*Deuterated 3-Phenylquinoline (**3a″**).* The product was obtained as dark orange needles: mp 119−121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (d, J = 1.5 Hz, 0.8 H), 8.62 (s, 0.63 H), 8.06−8.03 (m, 2H), 7.86

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(d, J = 7.6 Hz, 2H), 7.75 (t, J = 7.6 Hz, 1H), 7.63 (t, J = 6.8 Hz, 1H), 7.54 (t, J = 7.6 Hz, 2H), 7.46−7.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 146.8, 137.1, 132.9, 132.8, 129.5, 129.2, 128.7, 128.42, 128.38, 128.2, 127.7, 127.6, 127.2, 127.0; HRMS (ESI-TOF) $[M + H]^+$ calcd for $[C_{15}H_9D_2N]$ 208.1095, found 208.1068.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01186.

^{1}H NMR ^{13}C NMR and HRMS spectra (PDF)

X-ray crystallographic data for compound **3e** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Musiol, R.; Magdziarz, T.; Kurczyk, A. In *Science against Microbial Pathogens: Communicating Current Research and Technological Advances*; Mendez-Villas, A., Ed.; Formatex: Badajoz, 2011; Vol. *1*, p 72. (b) Afzal, O.; Kumar, S.; Haider, M. R.; Ali, M. R.; Kumar, R.; Jaggi, M.; Bawa, S. *Eur. J. Med. Chem.* **2015**, *97*, 871. (c) Matteelli, A.; Carvalho, A. C. C.; Dooley, K. E.; Kritski, A. *Future Microbiol.* **2010**, *5*, 849.

(2) (a) Achan, J.; Talisuna, A. O.; Erhart, A.; Yeka, A.; Tibenderana, J. K.; Baliraine, F. N.; Rosenthal, P. J.; D'Alessandro, U. *Malar. J.* **2011**, *10*, 144. (b) Michael, J. P. *Nat. Prod. Rep.* **2001**, *18*, 543. (c) Tatsuta, K.; Tamura, T. J. *J. Antibiot.* **2000**, *53*, 418.

(3) (a) Balasubramanian, M.; Keay, J. G. *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Ed.; Pergamon: New York, 1996; Vol. *5*, p 245. (b) Drahl, C. Rethinking Schizophrenia. *Chem. Eng. News* **2008**, *86*, 38. (c) Thayer, A. *Chem. Eng. News* **2007**, *85*, 21.

(4) (a) Theoclitou, M. − E.; Robinson, L. A. *Tetrahedron Lett.* **2002**, *43*, 3907. (b) Yamashkin, S. A.; Oreshkina, E. A. *Chem. Heterocycl. Compd.* **2006**, *42*, 701.

(5) (a) Wu, J.; Xia, H.-G.; Gao, K. *Org. Biomol. Chem.* **2006**, *4*, 126. (b) Martínez, R.; Ramón, D. J.; Yus, M. *J. Org. Chem.* **2008**, *73*, 9778. (c) Dormer, P. G.; Eng, K. K.; Farr, R. N.; Humphrey, G. H.; McWilliams, J. C.; Reider, P. J.; Sager, J. W.; Volante, R. P. *J. Org. Chem.* **2003**, *68*, 467.

(6) (a) Sloop, J. C. *J. Phys. Org. Chem.* **2009**, *22*, 110. (b) Bergstrom, F. W. *Chem. Rev.* **1944**, *35*, 77.

(7) (a) Stone, M. T. *Org. Lett.* **2011**, *13*, 2326. (b) Larock, R. C.; Kuo, M.-Y. *Tetrahedron Lett.* **1991**, *32*, 569. (c) Zhang, X.; Yao, T.; Campo, M. A.; Larock, R. C. *Tetrahedron* **2010**, *66*, 1177. (d) Larock, R. C.; Babu, S. *Tetrahedron Lett.* **1987**, *28*, 5291.

(8) (a) Jia, X.; Peng, F.; Qing, C.; Huo, C.; Wang, X. *Org. Lett.* **2012**, *14*, 4030. (b) Sakai, N.; Tamura, K.; Shimamura, K.; Ikeda, R.; Konakahara, T. *Org. Lett.* **2012**, *14*, 836. (c) Liu, X.-Y.; Ding, P.; Huang, J.-S.; Che, C.-M. *Org. Lett.* **2007**, *9*, 2645. (d) Toh, K. K.; Sanjaya, S.; Sahnoun, S.; Chong, S. Y.; Chiba, S. *Org. Lett.* **2012**, *14*, 2290. (e) Zhao, P.; Yan, X.; Yin, H.; Xi, C. *Org. Lett.* **2014**, *16*, 1120. (f) Liu, J.; Liu, F.; Zhu, Y.; Ma, X.; Jia, X. *Org. Lett.* **2015**, *17*, 1409. (g) Kong, L.; Zhou, Y.; Huang, H.; Yang, Y.; Liu, Y.; Li, Y. *J. Org. Chem.* **2015**, *80*, 1275. (h) Senadi, G. C.; Hu, W.-P.; Garkhedkar, A. M.; Boominathan, S. S. K.; Wang, J. − J. *Chem. Commun.* **2015**, *51*, 13795. (i) Bharate, J. B.; Vishwakarma, R. A.; Bharate, S. B. *RSC Adv.* **2015**, *5*, 42020 and references cited therein.

(9) Zhang, Y.; Wang, M.; Li, P.; Wang, L. *Org. Lett.* **2012**, *14*, 2206.

(10) Yan, R.; Liu, X.; Pan, C.; Zhou, X.; Li, X.; Kang, X.; Huang, G. *Org. Lett.* **2013**, *15*, 4876.

(11) (a) Khong, S.; Kwon, O. *J. Org. Chem.* **2012**, *77*, 8257. (b) O'Del, D. K.; Nicholas, K. M. *J. Org. Chem.* **2003**, *68*, 6427.

(12) Midya, S. P.; Sahoo, M. K.; Landge, V.; Rajamohanan, P. R.; Balaraman, E. *Nat. Commun.* **2015**, *6*, 8591.

(13) (a) Behforouz, M.; Ahmadian, M. *Tetrahedron* **2000**, *56*, 5259. (b) Wojciechowski, K. *Eur. J. Org. Chem.* **2001**, *2001*, 3587.

(14) (a) Oppolzer, W. Intermolecular Diels−Alder Reactions. In *Comprehensive Organic Chemistry*; Paquette, L. A., Ed.; Pergamon: New York, 1991; Vol. *5*, pp 315. (b) Weinreb, S. M. Heterodienophile Addition to Dienes. In *Comprehensive Organic Synthesis*; Paquette, L. A., Ed.; Pergamon: New York, 1991; Vol. *5*, pp 401. (c) Boger, D. L. Heterodiene Additions. In *Comprehensive Organic Synthesis*; Paquette, L. A., Ed.; Pergamon: New York, 1991; Vol. *5*, p 451.

(15) (a) Too, P. C.; Noji, T.; Lim, Y. J.; Li, X.; Chiba, S. *Synlett* **2011**, *2011*, 2789. (b) Yoshida, Y.; Kurahashi, T.; Matsubara, S. *Chem. Lett.* **2012**, *41*, 1498.

(16) (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 3645. (b) Martin, R. M.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2012**, *77*, 2501. (c) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814 and other azadiene references cited therein.

(17) (a) Lee, H.; Sim, Y.-K.; Park, J.-W.; Jun, C.-H. *Chem. - Eur. J.* **2014**, *20*, 323. (b) Sim, Y.-K.; Lee, H.; Park, J.-W.; Kim, D.-S.; Jun, C.-H. *Chem. Commun.* **2012**, *48*, 11787.

(18) (a) Parthasarathy, K.; Cheng, C.-H. *Synthesis* **2009**, *2009*, 1400. (b) Parthasarathy, K.; Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2008**, *10*, 325.

(19) Wu, J.; Xu, W.; Yu, Z. − X.; Wang, J. *J. Am. Chem. Soc.* **2015**, *137*, 9489.

(20) (a) Lu, J.-Y.; Arndt, H.-D. *J. Org. Chem.* **2007**, *72*, 4205. (b) Lu, J.-Y.; Keith, J. A.; Shen, W.-Z.; Schürmann, M.; Preut, H.; Jacob, T.; Arndt, H.-D. *J. Am. Chem. Soc.* **2008**, *130*, 13219.

(21) Linder, L.; Gerhard, M.; Schefzig, L.; Andrä, M.; Bentz, C.; Reissig, H.-U.; Zimmer, R. *Eur. J. Org. Chem.* **2011**, *2011*, 6070.

(22) (a) Neely, J. M.; Rovis, T. *Org. Chem. Front.* **2014**, *1*, 1010. (b) Hyster, T. K.; Rovis, T. *Chem. Commun.* **2011**, *47*, 11846. (c) Neely, J. M.; Rovis, T. *J. Am. Chem. Soc.* **2014**, *136*, 2735. (d) Neely, J. M.; Rovis, T. *J. Am. Chem. Soc.* **2013**, *135*, 66. (e) Chebolu, R.; Bahuguna, A.; Sharma, R.; Mishra, V. K.; Ravikumar, P. C. *Chem. Commun.* **2015**, *51*, 15438. (f) Traynelis, V. J.; Hergenrother, W. L. *J. Am. Chem. Soc.* **1964**, *86*, 298. (g) Epstein, W. W.; Sweat, F. W. *Chem. Rev.* **1967**, *67*, 247.

(23) (a) Verma, A. K.; Patel, M.; Joshi, M.; Likhar, P. R.; Tiwari, R. K.; Parang, K. *J. Org. Chem.* **2014**, *79*, 172. (b) Patel, M.; Saunthawal, R. K.; Verma, A. K. *Tetrahedron Lett.* **2014**, *55*, 1310. (c) Patel, M.; Saunthwal, R. K.; Dhaked, D. K.; Bharatam, P. V.; Verma, A. K. *Asian J. Org. Chem.* **2015**, *4*, 894. (d) Patel, M.; Saunthwal, R. K.; Dhaked, D. K.; Bharatam, P. V.; Verma, A. K. *Asian J. Org. Chem.* **2016**, *5*, 213.

(24) (a) Saunthwal, R. K.; Patel, M.; Danodia, A. K.; Verma, A. K. *Org. Biomol. Chem.* **2015**, *13*, 1521. (b) Saunthwal, R. K.; Patel, M.; Tiwari, R. K.; Parang, K.; Verma, A. K. *Green Chem.* **2015**, *17*, 1434. (c) Saunthwal, R. K.; Patel, M.; Kumar, S.; Danodia, A. K.; Verma, A. K. *Chem. - Eur. J.* **2015**, *21*, 18601. (d) Saunthwal, R. K.; Patel, M.; Verma, A. K. *Org. Lett.* **2016**, *18*, 2200.

(25) Rehan, M.; Hazra, G.; Ghorai, P. *Org. Lett.* **2015**, *17*, 1668.

(26) (a) Maity, B.; Gooßen, L. J.; Koley, D. *Chem. Sci.* **2015**, *6*, 2532. (b) Rubin, M.; Trofimov, A.; Gevorgyan, V. *J. Am. Chem. Soc.* **2005**, *127*, 10243. (c) Verma, A. K.; Joshi, M.; Singh, V. P. *Org. Lett.* **2011**, *13*, 1630.

(27) (a) Zhan, G.; Shi, M. − L.; He, Q.; Du, W.; Chen, Y.-C. *Org. Lett.* **2015**, *17*, 4750. (b) Lai, Z.; Wang, Z.; Sun, J. *Org. Lett.* **2015**, *17*, 6058.

DOI: 10.1021/acs.joc.6b01186
J. Org. Chem. 2016, 81, 6563−6572

(28) Dvorko, M. Y.; Schmidt, E. Y.; Glotova, T. E.; Shabalin, D. A.; Ushakov, I. A.; Kobychev, V. B.; Petrushenko, K. B.; Mikhaleva, A. I.; Trofimov, B. A. *Tetrahedron* **2012**, *68*, 1963.
(29) (a) Sabbatini, P.; Wellendorph, P.; Hog, S.; Pedersen, M. H. F.; Bräuner-Osborne, H.; Martiny, L.; Frølund, B.; Clausen, R. P. *J. Med. Chem.* **2010**, *53*, 6506. (b) Snider, B. B.; Ahn, Y.; O'Hare, S. M. *Org. Lett.* **2001**, *3*, 4217.
(30) Selig, P.; Raven, W. *Org. Lett.* **2014**, *16*, 5192.
(31) (a) Dzierzbicka, K.; Trzonkowski, P.; Sewerynek, P. L.; Mysliwski, A. *J. Med. Chem.* **2003**, *46*, 978. (b) Martínez-Viturro, C. M.; Domínguez, D. *Tetrahedron Lett.* **2007**, *48*, 1023.

DOI: 10.1021/acs.joc.6b01186
J. Org. Chem. 2016, 81, 6563−6572