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A Novel, Highly Efficient, One-Pot Synthesis of 1,4-Dihydroquinoline Derivatives in the Presence of a $Pd(OAc)_2$/DABCO Catalytic System

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The $Pd(OAc)_2$/DABCO catalytic system was first found to be highly efficient for C–N cross-coupling reactions. With the aid of this transformation, a variety of new 1,4-dihydroquinoline derivatives were synthesized from *o*-halobenzaldehydes and various β-enaminones in good to excellent yields.

Introduction

The quinoline ring system occurs in various natural products, especially in alkaloids. The quinoline skeleton is widely used for the design of many important compounds with pharmacological properties including antimalarial,[1] anti-inflammatory,[2] and antibacterial activities.[3] Accordingly, many methods for the assembly of the quinoline ring system have been developed. The most well-recognized ones should be those proposed by Skraup,[4] Doebner–Miller,[4] Friedlander,[5] and Combes,[6] and all of these processes may involve an initial intermolecular reaction of an aniline with a carbonyl-containing compound or its precursor. The most notable limitations in these procedures include the need to employ strongly acidic conditions and sometimes the use of refractory substrates such as *o*-aminobenzaldehydes.

The recent past has witnessed many successful methods for the synthesis of quinolines mediated by transition metals.[7] The palladium-catalyzed C–C cross-coupling reaction, due to its efficiency and wide substrate scope, is one of the most useful approaches for the construction of quinoline derivatives. Some well-investigated examples include the Heck,[8] Sonogashira,[9] Suzuki,[10] and Ullmann reactions.[11] Although palladium-catalyzed C–N bond formation reactions have been pioneered and extensively investigated by Buchwald[12] and Hartwig,[13] very few studies on the synthesis of the quinoline ring have been reported.[14]

In addition, as for the cyclization process in quinoline formation, interaction between two donor–acceptor bifunctionalities has been the most explored way (Mode A, Figure 1).[15] Rare examples were exhibited by the reaction of bidonor with biacceptor (Mode B, Figure 1), which is reasonably accessible. We have been interested in the synthesis of heterocyclic compounds for years.[16] Recently, we found that β-enaminone, as a popular candidate for a bidonor, had been extensively applied to the construction of N-containing heterocycles,[17] and *o*-halobenzaldehyde, as a commercially available biacceptor, provided an active site (C–X bond) for C–N bond formation by Buchwald–Hartwig methodology; furthermore, another part of the acceptor, the formyl group, can be attacked by the electron-rich β-C atom in β-enaminones to fulfill the demand of cyclization through the Baylis–Hillman reaction.[18] Meanwhile, it was interesting to find that, in comparison to commonly used PPh_3, DABCO (triethylenediamine) is a cheap and stable ligand, and it was confirmed to be the best choice in the reaction. Herein, we report these results.

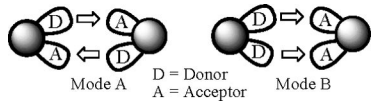

Figure 1. Known and explored modes for the synthesis of the quinoline core.

Results and Discussion

Initial attempts focused on exploring the feasibility of the proposed process. It is well known that an extra ligand plays an important role in Pd-mediated C–N cross-coupling reactions. Phosphane ligands are generally used to activate and stabilize the palladium species, and excellent results have been reported for the Buchwald–Hartwig reaction.[12,13,19] However, phosphane ligands are air sensitive and poison-

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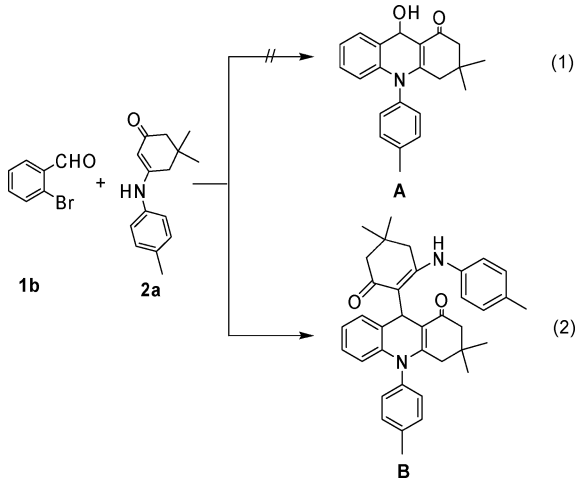
ous, which significantly limit their applications. Therefore, the development of phosphane-free palladium catalysts for C–N cross-coupling reactions comes to be the focus of attention. $Pd(OAc)_2$/DABCO, as a stable, inexpensive, and highly efficient catalytic system, has been widely used in C–C cross-coupling reactions such as Suzuki–Miyaura,[20] Stille,[21] Sonogashira,[22] Hiyama,[23] and Heck reactions.[24] However, to our best knowledge, the application of the $Pd(OAc)_2$/DABCO catalytic system in C–N cross-coupling reactions has never been reported. Thus, a preliminary attempt was carried out by using *o*-bromobenzaldehyde and 5,5-dimethyl-3-(*p*-tolylylamino)cyclohex-2-enone as substrates in the presence of $Pd(OAc)_2$ (5 mol-%), DABCO (10 mol-%), and K_2CO_3 (3 equiv.) in refluxing toluene. As expected, the cyclization was successfully accomplished, but to our surprise, instead of the formation of expected target product **A**, a more complex quinoline derivative **B** was obtained [Scheme 1, Equation (2)].



Scheme 1. Synthesis of 1,4-dihydroquinoline derivative **B**.

The definite structure of the final product was confirmed by X-ray analysis (Figure 2).[25] Thus, the reaction was then repeated with the use of *o*-bromobenzaldehyde (1 equiv.) and 5,5-dimethyl-3-(*p*-tolylylamino)cyclohex-2-enone (2 equiv.) in the presence of $Pd(OAc)_2$/DABCO, and after workup, a high yield of **B** was achieved.

Subsequently, sets of experiments were performed to optimize the reaction conditions. Several other commonly used palladium catalytic systems were tested for the coupling reactions, and the results are shown in Table 1. Among the various catalytic systems used, the $Pd(OAc)_2$/DABCO system proved superior and generated the desired product in 81% yield (Table 1, Entry 1). Other combinatory palladium catalytic systems only gave the product in lower yields (52–64%; Table 1, Entries 2 and 3).

Furthermore, a brief study of the influence of base on the reaction was carried out as well. As shown in Table 2, according to their increasing basicities, K_2CO_3 and Cs_2CO_3 led to sharply ascending efficiencies in the synthesis of the target product (Table 2, Entries 1 and 2), whereas, the use of other inorganic and organic bases (such as K_3PO_4, Na_2CO_3, NaOAc, NaOH, KOH, and Et_3N) gave the desired products in poor yields (Table 2, Entries 3–8). Cs_2CO_3 was found to be the most appropriate base. Then, the effect of solvent was also evaluated: CH_3CN, CH_3NO_2, and dioxane were not suitable solvents for the reaction (Table 2, Entries 10–12). To our surprise, commonly used solvents for coupling reactions, such as THF, NMP, and DMSO, gave disappointing results (Table 2, Entries 9, 13, and 14). Otherwise toluene performed as the most-suitable solvent (Table 2, Entry 2).

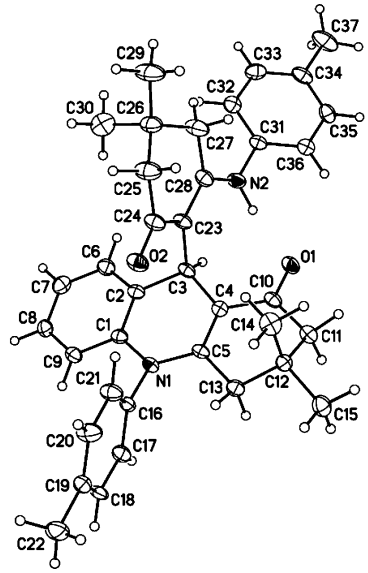


Figure 2. The crystal structure for **B**.

Table 1. Influence of the catalysts for the reaction of **1b** with **2a**.[a]

Entry	Catalyst	Yield[b] [%]
1	$Pd(OAc)_2$/DABCO	81
2	$PdCl_2$/DABCO	52
3	$Pd_2(dba)_3$/DABCO	64

[a] Reaction conditions: **1b** (0.25 mmol), **2a** (0.5 mmol), palladium catalyst (0.0125 mmol), DABCO (0.025 mmol), K_2CO_3 (3 equiv.), toluene (3.0 mL), 110 °C, 12 h. [b] Isolated yield.

Table 2. Optimization of conditions for the reaction of **1b** with **2a**.[a]

Entry	Base	Solvent	Yield[b] [%]
1	K_2CO_3	toluene	81
2	Cs_2CO_3	toluene	92
3	K_3PO_4	toluene	60
4	Na_2CO_3	toluene	21
5	NaOAc	toluene	40
6	NaOH	toluene	11
7	KOH	toluene	34
8	NEt_3	toluene	27
9	Cs_2CO_3	THF	21
10	Cs_2CO_3	CH_3CN	trace
11	Cs_2CO_3	CH_3NO_2	trace
12	Cs_2CO_3	dioxane	trace
13	Cs_2CO_3	NMP	32
14	Cs_2CO_3	DMSO	26

[a] Reaction conditions: **1b** (0.25 mmol), **2a** (0.5 mmol), $Pd(OAc)_2$ (0.0125 mmol), DABCO (0.025 mmol), base (3 equiv.), solvent (3.0 mL), 110 °C, 12 h. [b] Isolated yield.

Further optimization of the reaction conditions by using other commonly used ligands such as 8-hydroxyquinoline (L1), L-proline (L2), hexamethylenetetramine (L3), PPh_3 (L4), 2,9-dimethyl-1,10-phenanthroline (L6), DBU (1,8-diazabicyclo[5.4.0]undec-7-ene, L7), and 1,10-phenanthroline (L8) compared with DABCO (L5) was also examined under the same conditions. As shown in Figure 3, the catalytic activity strongly depended on the choice of ligands, and dramatic changes in yields were observed. Fortunately, DABCO was the best ligand among those tested. Besides, without the use of DABCO, the reaction proceeded sluggishly to give the product in much lower yield (Figure 3, L9), which also implied that the addition of ligand was critically necessary. Furthermore, the $Pd(OAc)_2$/DABCO complex has also been proved by Li.[26]

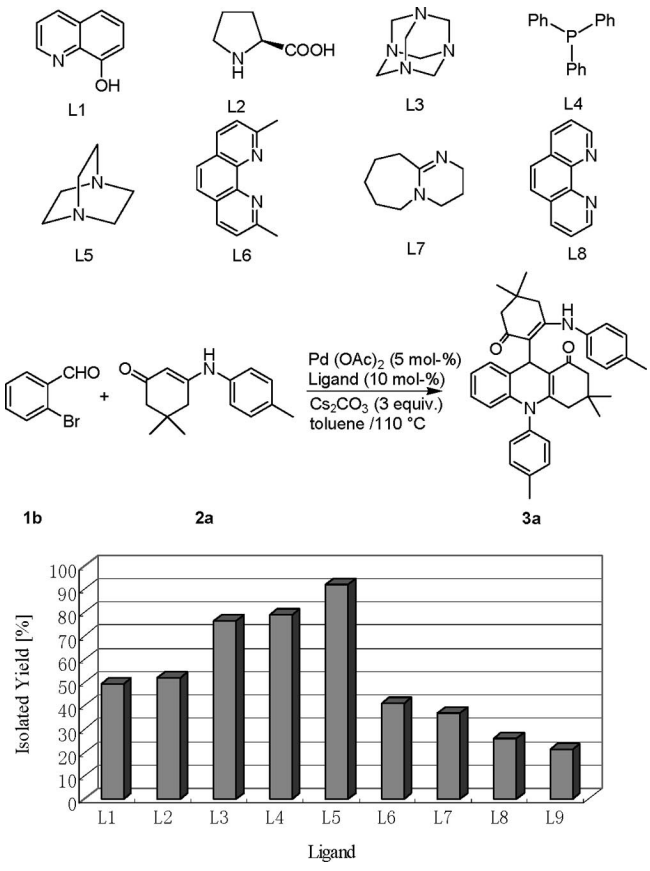
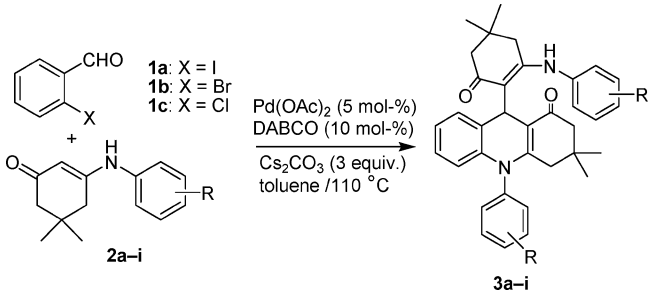


Figure 3. Various ligands investigated in the reaction.

With the optimized conditions in hand, we continued to examine the substrate scope of the reaction by using a wide variety of β-enaminones and *o*-halobenzaldehyde. As shown in Table 3, the representative examples illustrate the generality of this reaction. Various electron-donating groups on the β-enaminones such as 4-Me and 4-OMe were well tolerated by the catalytic system and gave the desired products in excellent yields (Table 3, Entries 1 and 2). In addition, the use of 5,5-methyl-3-(phenylamino)cyclohex-2-enone could also afford a satisfactory yield of the desired product (Table 3, Entry 5).

Table 3. Scope for palladium-catalyzed synthesis of 1,4-dihydroquinoline derivatives.[a]



Entry	Substrate		Product	Time [h]	Yield[b] [%]
	X	R			
1	**1a**	4-CH_3 (**2a**)	**3a**	12	98
2	**1a**	4-OCH_3 (**2b**)	**3b**	12	97
3	**1a**	3-CH_3 (**2c**)	**3c**	24	71
4	**1a**	2-CH_3 (**2d**)	**3d**	24	75
5	**1a**	H (**2e**)	**3e**	12	95
6	**1a**	4-Cl (**2f**)	**3f**	12	81
7	**1a**	3-Cl (**2g**)	**3g**	24	75
8	**1a**	4-Br (**2h**)	**3h**	24	78
9	**1a**	4-I (**2i**)	**3i**	24	76
10	**1b**	**2a**	**3a**	12	92
11	**1b**	**2b**	**3b**	12	88
12	**1b**	**2c**	**3c**	24	61
13	**1b**	**2d**	**3d**	24	65
14	**1b**	**2e**	**3e**	12	81
15	**1b**	**2f**	**3f**	12	76
16	**1b**	**2g**	**3g**	24	66
17	**1b**	**2h**	**3h**	24	70
18	**1b**	**2i**	**3i**	24	72
19	**1c**	**2a**	**3a**	16	81
20	**1c**	**2b**	**3b**	16	85
21	**1c**	**2c**	**3c**	30	65
22	**1c**	**2d**	**3d**	30	61
23	**1c**	**2e**	**3e**	24	74
24	**1c**	**2f**	**3f**	12	70
25	**1c**	**2g**	**3g**	30	60
26	**1c**	**2h**	**3h**	24	73
27	**1c**	**2i**	**3i**	24	71

[a] Reaction conditions: **1** (0.25 mmol), **2** (0.5 mmol), $Pd(OAc)_2$ (0.0125 mmol), DABCO (0.025 mmol), Cs_2CO_3 (0.75 mmol), toluene (3.0 mL). [b] Isolated yield.

To our delight, although electron-withdrawing groups on the β-enaminones usually inhibited the efficiency of the reactions to a certain extent,[27] various electron-withdrawing groups on the β-enaminones such as 4-I, 4-Br, and 4-Cl also afforded the desired products in good yields after 24 h (Table 3, Entries 6, 8, and 9). In order to study the steric influence for the approach, we tested several β-enaminones with substituent groups in different positions. Noteworthy, the reactions of enaminones including substituents in the 2,3-positions are usually very sensitive,[27] yet our catalytic system was very efficient for 2,3-substituted β-enaminones, which reacted to furnish the corresponding products in 71, 75, and 75% yield, respectively (Table 3, Entries 3, 4, and 7). Unfortunately, this catalytic system was ineffective for 2-chloro-substituted β-enaminone and the corresponding

product was obtained only in 45% yield. We supposed it was the result of strong steric and electron-withdrawing influences. Encouraged by these results, the catalyst was then utilized for the reactions of 2-bromo- or 2-chlorobenzaldehyde with β-enaminones (Table 3, Entries 10–27). Satisfactory yields were also obtained after longer reaction times. The influence of steric and electronic effects was similar to the reactions performed with the use of 2-iodobenzaldehyde as substrate. Furthermore, in the $Pd(OAc)_2$/DABCO catalytic system, some other enaminones containing alkylamine

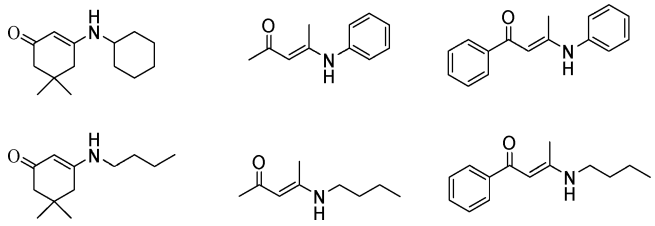
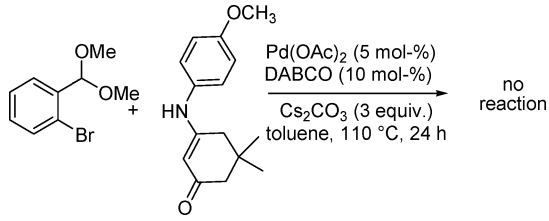
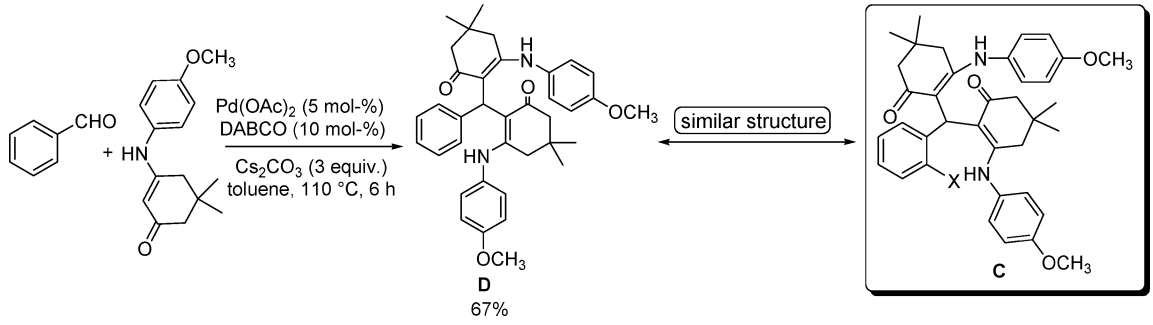


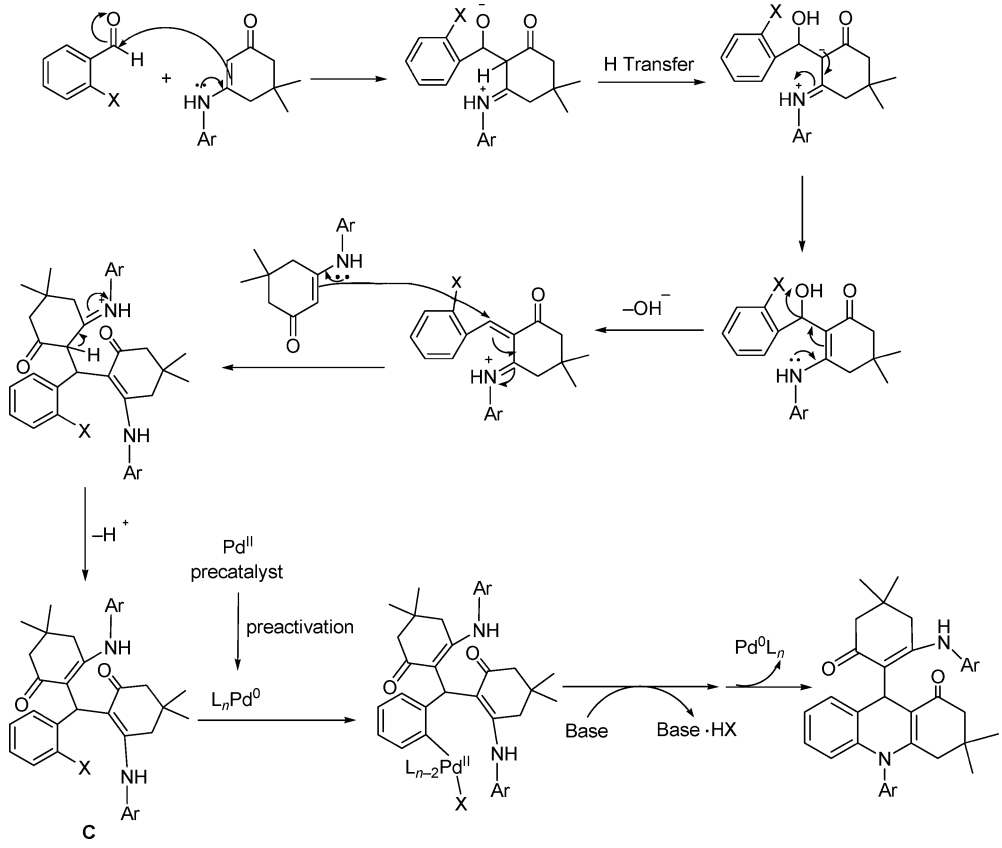
Figure 4. Various enaminones investigated in the reaction.



Scheme 2.



Scheme 3.



Scheme 4. Possible mechanism for the formation of 1,4-dihydroquinoline derivatives.

or acyclic β-enone fragments were chosen as the substrates. As shown in Figure 4, unfortunately no reaction occurred even with the use of the most active 2-iodobenzaldehyde as substrate.

Finally, we turned our attention to the mechanism of the reaction. According to the literature,[28] a common mechanistic hypothesis involved first an intermolecular cross-coupling reaction followed by an intramolecular cyclization. To explore this possibility, we initially attempted the reaction with the appropriately protected aldehyde aryl bromide as substrate, under the $Pd(OAc)_2$/DABCO catalytic conditions, but the intermolecular reaction did not occur (Scheme 2). This result clearly indicates that the synthetic route may involve an intramolecular Buchwald–Hartwig reaction. Next, without the palladium catalyst, a blank test was done to attain expected intermediate **C** from *o*-bromobenzaldehyde and 3-(4-methoxyphenylamino)-5,5-dimethylcyclohex-2-enone; unfortunately, intermediate **C** was not trapped. In order to confirm our assumption, a further test was done with a similar substrate, benzaldehyde, which could not participate in a C–N cross-coupling reaction (Scheme 3). As expected, structure **D**, similar to possible intermediate **C**, was afforded under the $Pd(OAc)_2$/DABCO catalytic conditions.

On the basis of these observations, it is reasonable to generate product **B** instead of **A** in our initial reaction (Scheme 1). Therefore, a possible reaction mechanism for the formation of 1,4-dihydroquinoline derivatives from *o*-halobenzaldehyde and a wide range of β-enaminones was proposed (Scheme 4). Firstly, expected intermediate **C** was generated through a Baylis–Hillman-type reaction and nucleophilic substitution of another β-enaminone. Then the final product was afforded from an intramolecular Buchwald–Hartwig reaction of expected intermediate **C**.

Conclusions

In summary, we have developed a novel and efficient method for the synthesis of various 1,4-dihydroquinoline derivatives from *o*-halobenzaldehyde and a wide range of *β*-enaminones. Noteworthy, the $Pd(OAc)_2$/DABCO catalytic system was employed in the C–N crossing coupling reaction for the first time and showed outstanding performance. Further study on the synthesis of some other heterocyclic compounds with the use of the present approach is currently in progress.

Experimental Section

General Experimental Methods: All reactions were carried out in air. All *o*-halobenzaldehydes, $Pd(OAc)_2$, and DABCO were purchased from Aldrich or Alfa. β-Enaminones were prepared according to known methods.[17] Analytical thin-layer chromatography was performed using glass plates precoated with 200–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Melting points were recorded with an electrothermal digital melting point apparatus and are uncorrected. IR spectra were recorded with a Varian FT-1000 spectrophotometer using KBr optics. NMR spectra were recorded in $CDCl_3$ with a Varian Inova-400 NMR spectrometer (400 MHz for ^1H and 100 MHz for ^{13}C) with TMS as an internal reference. High resolution mass spectra were obtained by using a Micromass GCT-TOF instrument. X-ray diffraction data were recorded with a Rigaku Mercury CCD area detector with graphite monochromated Mo-K_α radiation.

General Procedure for the Synthesis of Quinoline Derivatives 3: A mixture of **1a** (0.25 mmol), **2** (0.5 mmol), $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol), DABCO (2.9 mg, 0.025 mmol), Cs_2CO_3 (144.7 mg, 0.75 mmol), and toluene (3.0 mL) was stirred at 110 °C for the desired time until complete consumption of the starting material as monitored by TLC. The mixture was then poured into water and extracted with ethyl acetate. The organic phase was dried with anhydrous $MgSO_4$ and filtered, and the solvents were evaporated under vacuum. The residue was purified by flash column chromatography (ethyl acetate/petroleum ether, 1:6) to afford product **3**.

9-[2-(*p*-Tolylamino)-4,4-dimethyl-6-oxocyclohex-1-enyl]-3,4-dihydro-3,3-dimethyl-10-*p*-tolylacridin-1(2*H*,9*H*,10*H*)-one (3a): Yield: 133 mg (98%). Yellow solid. M.p. 246–248 °C. IR (KBr): $\tilde{\nu}$ = 3147, 3029, 2954, 2871, 1634, 1589, 1512, 1458, 1389, 810, 756 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (d, J = 5.7 Hz, 6 H, 2 CH_3), 0.99 (d, J = 8.4 Hz, 6 H, 2 CH_3), 1.98–2.32 (m, 7 H), 2.36 (s, 3 H, CH_3), 2.46 (s, 3 H, CH_3), 2.80 (d, J = 16.6 Hz, 1 H), 5.11 (s, 1 H, CH), 6.10–6.14 (m, 1 H, ArH), 6.84–7.19 (m, 8 H, ArH), 7.32 (d, J = 7.8 Hz, 1 H, ArH), 7.38 (d, J = 8.0 Hz, 1 H, ArH), 7.77 (d, J = 7.3 Hz, 1 H, ArH), 10.15 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.8, 195.5, 156.5, 156.4, 141.1, 138.8, 138.6, 138.5, 137.9, 137.8, 133.0, 131.8, 130.7, 130.2, 130.1, 129.9, 128.8, 127.7, 126.3, 123.2, 122.8, 120.6, 115.8, 107.5, 52.1, 50.1, 42.6, 40.7, 33.0, 32.5, 32.2, 30.1, 28.5, 27.9, 26.8, 21.6, 21.1 ppm. HRMS: calcd. for $C_{37}H_{40}N_2O_2$ $[M]^+$ 544.3090; found 544.3078.

9-[2-(4-Methoxyphenylamino)-4,4-dimethyl-6-oxocyclohex-1-enyl]-3,4-dihydro-10-(4-methoxyphenyl)-3,3-dimethylacridin-1(2*H*,9*H*,10*H*)-one (3b): Yield: 139 mg (97%). Yellow solid. M.p. 218–220 °C. IR (KBr): $\tilde{\nu}$ = 3218, 3063, 2955, 2871, 1613, 1589, 1512, 1458, 1389, 833, 756 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (d, J = 8.1 Hz, 6 H, 2 CH_3), 0.98 (s, 6 H, 2 CH_3), 2.00–2.31 (m, 7 H), 2.69 (d, J = 16.5 Hz, 1 H), 3.84 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 5.10 (s, 1 H, CH), 6.14–6.17 (m, 1 H, ArH), 6.85–6.87 (m, 2 H, ArH), 6.92 (d, J = 8.6 Hz, 2 H, ArH), 6.99–7.17 (m, 6 H, ArH), 7.82 (d, J = 8.5 Hz, 1 H, ArH), 10.01 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.9, 195.3, 159.8, 157.3, 156.6, 156.4, 141.5, 134.2, 133.3, 132.2, 131.5, 128.9, 127.9, 126.5, 125.1, 123.3, 119.8, 116.2, 115.9, 114.9, 114.8,107.7, 55.9, 52.0, 50.2, 42.8, 40.8, 32.9, 32.5, 32.4, 30.4, 30.2, 28.6, 28.4, 27.0 ppm. HRMS: calcd. for $C_{37}H_{40}N_2O_4$ $[M]^+$ 576.2988; found 576.3008.

9-[2-(*m*-Tolylamino)-4,4-dimethyl-6-oxocyclohex-1-enyl]-3,4-dihydro-3,3-dimethyl-10-*m*-tolylacridin-1(2*H*,9*H*,10*H*)-one (3c): Yield: 97 mg (71%). Yellow solid. M.p. 242–244 °C. IR (KBr): $\tilde{\nu}$ = 3129, 3063, 3013, 2954, 2867, 1636, 1584, 1558, 1495, 1457, 1394, 889, 750, 727 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.90 (d, J = 6.4 Hz, 6 H, 2 CH_3), 1.00 (d, J = 12.3 Hz, 6 H, 2 CH_3), 2.00–2.33 (m, 7 H), 2.39 (s, 3 H, CH_3), 2.46 (s, 3 H, CH_3), 2.86 (d, J = 15.2 Hz, 1 H), 5.12 (s, 1 H, CH), 6.08–6.13 (m, 1 H, ArH), 6.85–6.87 (m, 2 H, ArH), 6.92 (d, J = 7.6 Hz, 1 H, ArH), 6.98–7.24 (m, 5 H, ArH), 7.27–7.31 (m, 1 H, ArH), 7.40–7.50 (m, 1 H, ArH), 7.68–7.72 (m, 1 H, ArH), 10.21 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.9, 195.8, 156.2, 155.9, 141.5, 141.1, 140.4, 140.3, 139.6, 139.4, 131.1, 129.8, 129.4, 129.1, 128.8, 127.6,

127.4, 126.3, 124.0, 123.3, 121.2, 119.5, 115.8, 107.3, 52.1, 50.1, 42.6, 40.8, 33.2, 32.6, 32.3, 32.2, 30.2, 28.6, 27.8, 26.9, 21.7 ppm. HRMS: calcd. for $C_{37}H_{40}N_2O_2$ $[M]^+$ 544.3090; found 544.3099.

9-[2-(*o*-Tolylamino)-4,4-dimethyl-6-oxocyclohex-1-enyl]-3,4-dihydro-3,3-dimethyl-10-*o*-tolylacridin-1(2*H*,9*H*,10*H*)-one (3d): Yield: 102 mg (75%). Yellow solid. M.p. 236–238 °C. IR (KBr): $\tilde{\nu}$ = 3142, 3014, 2957, 2867, 1640, 1592, 1559, 1486, 1393, 750, 709 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.91 (d, J = 10.1 Hz, 6 H, 2 CH_3), 0.98 (d, J = 3.0 Hz, 6 H, 2 CH_3), 2.03–2.12 (m, 4 H), 2.19 (s, 3 H, CH_3), 2.26 (s, 3 H, CH_3), 2.53–2.62 (m, 4 H), 5.20 (s, 1 H, CH), 5.99–6.01 (m, 1 H, ArH), 6.86–6.88 (m, 2 H, ArH), 7.01–7.10 (m, 1 H, ArH), 7.13 (d, J = 7.1 Hz, 2 H, ArH), 7.23 (d, J = 7.3 Hz, 1 H, ArH), 7.28 (d, J = 7.3 Hz, 1 H, ArH), 7.34–7.43 (m, 3 H, ArH), 7.85–7.87 (m, 1 H, ArH), 9.63 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.8, 190.8, 152.5, 150.7, 135.0, 134.9, 134.7, 132.9, 128.0, 127.2, 126.4, 125.5, 124.4, 124.2, 124.1, 122.9, 122.0, 121.9, 120.1, 119.9, 118.4, 116.5, 110.2, 103.8, 47.1, 45.5, 36.7, 36.2, 27.9, 27.8, 27.5, 27.3, 24.7, 24.4, 23.1, 22.6, 14.0 ppm. HRMS: calcd. for $C_{37}H_{40}N_2O_2$ $[M]^+$ 544.3090; found 544.3089.

3,4-Dihydro-3,3-dimethyl-9-[4,4-dimethyl-6-oxo-2-(phenylamino)-cyclo-hex-1-enyl]-10-phenylacridin-1(2*H*,9*H*,10*H*)-one (3e): Yield: 123 mg (95%). Yellow solid. M.p. 152–154 °C. IR (KBr): $\tilde{\nu}$ = 3148, 3033, 2955, 2871, 1736, 1589, 1559, 1489, 1458, 1389, 748, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (s, 6 H, 2 CH_3), 0.98 (s, 3 H, CH_3), 1.02 (s, 3 H, CH_3), 1.96–2.33 (m, 7 H), 2.85 (d, J = 16.4 Hz, 1 H), 5.14 (s, 1 H, CH), 6.09–6.11 (m, 1 H, ArH), 6.85–7.00 (m, 3 H, ArH), 7.10 (t, J = 7.0 Hz, 1 H, ArH), 7.20–7.62 (m, 8 H, ArH), 7.93 (d, J = 7.3 Hz, 1 H, ArH), 10.26 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.1, 195.9, 156.1, 155.9, 141.1, 140.7, 131.4, 131.2, 130.6, 129.7, 129.5, 129.1, 129.0, 127.7, 126.5, 123.5, 123.3, 122.6, 121.3, 115.9, 107.6, 60.8, 52.3, 50.2, 42.8, 40.9, 33.3, 32.8, 32.4, 28.7, 28.0, 26.8 ppm. HRMS: calcd. for $C_{35}H_{36}N_2O_2$ $[M]^+$ 516.2777; found 516.2752.

9-[2-(4-Chlorophenylamino)-4,4-dimethyl-6-oxocyclohex-1-enyl]-10-(4-chlorophenyl)-3,4-dihydro-3,3-dimethylacridin-1(2*H*,9*H*,10*H*)-one (3f): Yield: 118 mg (81%). Yellow solid. M.p. 234–236 °C. IR (KBr): $\tilde{\nu}$ = 3156, 3040, 2955, 2871, 1620, 1589, 1559, 1489, 1389, 825, 756 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (s, 6 H, 2 CH_3), 1.00 (d, J = 5.4 Hz, 6 H, 2 CH_3), 1.94–2.33 (m, 7 H), 2.78 (d, J = 16.3 Hz, 1 H), 5.09 (s, 1 H, CH), 6.09–6.12 (m, 1 H, ArH), 6.87–7.24 (m, 6 H, ArH), 7.33 (d, J = 8.5 Hz, 2 H, ArH), 7.52–7.58 (m, 2 H, ArH), 7.90 (d, J = 6.4 Hz, 1 H, ArH), 10.27 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.3, 195.9, 155.8, 155.7, 140.9, 140.0, 139.2, 135.1, 132.7, 132.1, 131.8, 130.1, 129.6, 129.1, 128.5, 127.6, 126.7, 123.7, 121.5, 115.9, 107.9, 52.3, 50.2, 42.9, 41.0, 40.9, 33.5, 32.7, 32.4, 30.5, 28.9, 27.9 ppm. HRMS: calcd. for $C_{35}H_{34}Cl_2N_2O_2$ $[M]^+$ 584.1997; found 584.1967.

9-[2-(3-Chlorophenylamino)-4,4-dimethyl-6-oxocyclohex-1-enyl]-10-(3-chlorophenyl)-3,4-dihydro-3,3-dimethylacridin-1(2*H*,9*H*,10*H*)-one (3g): Yield: 110 mg (75%). Yellow solid. M.p. 202–204 °C. IR (KBr): $\tilde{\nu}$ = 3156, 3063, 2955, 2871, 1628, 1582, 1489, 1389, 887, 748, 725 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (s, 6 H, 2 CH_3), 1.02 (d, J = 8.3 Hz, 6 H, 2 CH_3), 1.94–2.34 (m, 7 H), 2.84 (d, J = 16.4 Hz, 1 H), 5.08 (s, 1 H, CH), 6.01 (s, 1 H, ArH), 6.89–7.07 (m, 5 H, ArH), 7.19–7.98 (m, 6 H, ArH), 10.33 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.3, 196.1, 155.5, 142.8, 141.9, 140.9, 136.9, 135.2, 132.5, 131.4, 130.9, 130.7, 130.6, 129.7, 129.6, 129.1, 127.4, 126.8, 123.8, 123.1, 122.0, 120.3, 115.8, 107.9, 52.4, 50.2, 49.0, 42.9, 41.0, 33.6, 32.8, 32.5, 29.1, 27.8, 27.0 ppm. HRMS: calcd. for $C_{35}H_{34}Cl_2N_2O_2$ $[M]^+$ 584.1997; found 584.1968.

9-[2-(4-Bromophenylamino)-4,4-dimethyl-6-oxocyclohex-1-enyl]-10-(4-bromophenyl)-3,4-dihydro-3,3-dimethylacridin-1(2*H*,9*H*,10*H*)-one(3h): Yield: 131 mg (78%). Yellow solid. M.p. 241–243 °C. IR (KBr): $\tilde{\nu}$ = 3156, 3056, 2955, 2871, 1613, 1589, 1566, 1489, 1389, 825, 756 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (s, 6 H, 2 CH_3), 1.00 (d, J = 5.2 Hz, 6 H, 2 CH_3), 1.94–2.33 (m, 7 H), 2.79 (d, J = 16.3 Hz, 1 H), 5.08 (s, 1 H, CH), 6.09–6.11 (m, 1 H, ArH), 6.87–6.98 (m, 3 H, ArH), 7.07 (d, J = 8.4 Hz, 2 H, ArH), 7.17 (d, J = 6.6 Hz, 1 H, ArH), 7.47 (d, J = 8.5 Hz, 2 H, ArH), 7.71–7.85 (m, 3 H, ArH), 10.27 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.1, 195.8, 155.5, 140.8, 140.5, 140.3, 139.6, 133.6, 132.9, 132.4, 129.2, 128.9, 127.4, 126.9, 126.5, 124.0, 123.8, 123.5, 123.0, 121.5, 115.8, 115.7, 111.7, 107.7, 60.6, 52.1, 49.9, 42.7, 41.8, 40.7, 36.6, 33.3, 32.2, 30.2, 27.6 ppm. HRMS: calcd. for $C_{35}H_{34}Br_2N_2O_2$ $[M]^+$ 674.0967; found 674.0970.

9-[2-(4-Iodophenylamino)-4,4-dimethyl-6-oxocyclohex-1-enyl]-3,4-dihydro-10-(4-iodophenyl)-3,3-dimethylacridin-1(2*H*,9*H*,10*H*)-one (3i): Yield: 146 mg (76%). Yellow solid. M.p. 264–266 °C. IR (KBr): $\tilde{\nu}$ = 3143, 3058, 2953, 2864, 1609, 1583, 1566, 1483, 1389, 824, 750 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.87 (s, 6 H, 2 CH_3), 1.00 (d, J = 4.8 Hz, 6 H, 2 CH_3), 1.94–2.32 (m, 7 H), 2.80 (d, J = 16.7 Hz, 1 H), 5.07 (s, 1 H, CH), 6.09–6.11 (m, 1 H, ArH), 6.87–6.89 (m, 2 H, ArH), 6.95 (d, J = 7.6 Hz, 4 H, ArH), 7.02–7.04 (m, 1 H, ArH), 7.75 (d, J = 7.7 Hz, 2 H, ArH), 7.89–7.93 (m, 2 H, ArH), 10.29 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.1, 195.9, 155.4, 155.2, 143.5, 141.1, 140.8, 140.7, 140.3, 138.9, 138.3, 133.1, 132.5, 128.9, 128.5, 127.7, 127.5, 127.3, 126.5, 124.0, 123.6, 121.7, 115.8, 107.7, 52.2, 50.0, 42.8, 41.9, 40.8, 40.3, 33.4, 32.2, 30.2, 28.9, 26.6 ppm. HRMS: calcd. for $C_{35}H_{34}I_2N_2O_2$ $[M]^+$ 768.0710; found 768.0721.

9-[2-(2-Chlorophenylamino)-4,4-dimethyl-6-oxocyclohex-1-enyl]-10-(2-chlorophenyl)-3,4-dihydro-3,3-dimethylacridin-1(2*H*,9*H*,10*H*)-one (3j): Yield: 66 mg (45%). Yellow solid. M.p. 212–214 °C. IR (KBr): $\tilde{\nu}$ = 3133, 3071, 2955, 2871, 1582, 1481, 1389, 756 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.91 (s, 6 H, 2 CH_3), 1.00 (s, 6 H, 2 CH_3), 1.97–2.34 (m, 7 H), 2.60 (d, J = 16.8 Hz, 1 H), 5.24 (s, 1 H, CH), 5.99–6.01 (m, 1 H, ArH), 6.88–7.13 (m, 4 H, ArH), 7.47–7.62 (m, 6 H, ArH), 8.05 (d, J = 8.0 Hz, 1 H, ArH), 9.87 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.4, 196.2, 155.6, 155.3, 142.8, 141.9, 140.9, 137.0, 135.2, 132.5, 131.4, 131.0, 130.8, 130.6, 129.7, 129.2, 127.4, 126.8, 123.8, 123.1, 122.0, 120.3, 115.9, 107.9, 52.4, 50.2, 42.9, 41.0, 33.6, 32.8, 32.4, 30.4, 29.0, 27.6, 26.8 ppm. HRMS: calcd. for $C_{35}H_{34}Cl_2N_2O_2$ $[M]^+$ 584.1997; found 584.1974.

2,2′-(Phenylmethylene)bis[3-(4-methoxyphenylamino)-5,5-dimethylcyclohex-2-enone] (D): Yield: 97 mg (67%). White solid. IR (KBr): $\tilde{\nu}$ = 3438, 2954, 2928, 2836, 1737, 1617, 1569, 1510, 1408, 832 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.09 (s, 12 H, 4 CH_3), 2.05–2.44 (m, 8 H), 3.79 (s, 6 H, 2 OCH_3), 6.03 (s, 1 H, CH), 6.83–7.22 (m, 13 H, ArH), 10.53 (d, J = 9.7 Hz, 2 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.4, 157.7, 141.0, 132.4, 127.8, 127.4, 126.9, 125.0, 114.5, 55.7, 41.5, 34.8, 32.4, 28.6 ppm. HRMS: calcd. for $C_{37}H_{42}N_2O_4$ $[M]^+$ 578.3145; found 578.3147.

Supporting Information (see footnote on the first page of this article): Copies of the ^1H NMR, ^{13}C NMR, and mass spectra; crystal data and structure refinement details for **B**.

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[25] CCDC-670335 (for **3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Structural parameters for **3a**: data collection: Rigaku Mercury CCD area detector; crystal size: $0.72 \times 0.40 \times 0.20$ mm^3. $C_{37}H_{40}N_2O_2$, M_r = 544.71, Triclinic, space group $P\bar{1}$, a = 11.9357(11) Å, b = 15.1588(13) Å, c = 18.9987(14) Å, α = 111.618(9) °, β = 100.972(12) °, γ = 98.956(14)°, V = 3039.7(4) Å^3, Z = 4, $D_{calcd.}$ = 1.190 mg cm^{-3}, $R[I > 2\sigma(I)]$ = 0.1032, w$R[I > 2\sigma(I)]$ = 0.2455.

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