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Regioselective Synthesis of 1,2-Dihydroquinolines by a Solvent-Free $MgBr_2$-Catalyzed Multicomponent Reaction

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Supporting Information

ABSTRACT: A highly efficient and regioselective synthesis of 1,2-dihydroquinolines via a multicomponent reaction between an aniline and two ketones is described. This reaction was catalyzed by magnesium bromide and carried out under solvent-free conditions. When the reaction was performed by using 3-substituted anilines and nonsymmetrically substituted ketones, principally a single product was found among the four expected regioisomers. A variety of anilines and ketones, including cyclic ketones, were evaluated providing a series of 1,2-dihydroquinolines with diverse substitution patterns. A study of the mechanism is discussed. There is evidence of the in situ formation of the imine as a result of the reaction between the aniline and one of the ketones, before annulation to the heterocyclic ring.

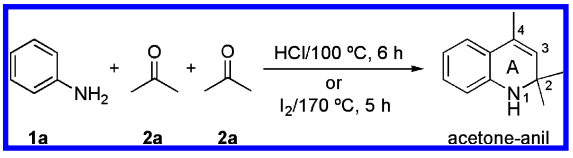
INTRODUCTION

1,2-Dihydroquinolines (1,2-DHQ) represent a privileged heterocyclic scaffold to build pharmacologically and biologically active molecules, as well as compounds for industrial uses. Examples are antibacterial,[1] antitrypanosomal,[2] antioxidant[3] and antidiabetic agents,[4] antijuvenile hormone insecticides,[5] and natural products.[6] Furthermore, 1,2-DHQ are antioxidants used as preservatives in animal nutriments and in vegetable and animal oils,[7] as rubber antioxidants,[8] as linkers for solid-phase organic synthesis,[9] and as the core in ferromagnetic compounds.[10] Despite their biological and industrial importance, only in the few past decades has 1,2-DHQ received considerable attention as synthetic targets. In the 1880s, they were prepared as intermediates in the quinoline synthesis carried out by Skraup, Riehm, and Doebner, and von Miller.[11] This multicomponent reaction (MCR)[12] was performed by Reddelien,[13] Craig,[14] and Vaughan[15] years later for the synthesis of acetone−anil by using aniline (**1a**) and acetone (**2a**), catalyzed by hydrochloric acid or iodine (Scheme 1).

The latter methodology was recently employed with more versatile reaction conditions, which led to greater yield[16] and suggested a mechanistic pathway.[17] Analogous MCR catalyzed by transition metals used terminal acetylenes instead of ketones.[18] Recently, an Au/Ag-catalyzed cyclization of *o*-(hydroxyallyl)anilines under mild conditions was reported.[19] Other methodologies include transition-metal catalysts,[20] zeolite,[21] Lewis[16,22] and Brønsted[23] acids, a cascade Michael/aldol reaction,[24] and an Ir-catalyzed allylic amination/ring-closing metathesis reaction,[25] which were mainly designed on the basis of heterocyclic moiety formation, starting from the respective functionalized anilines. However, most of these methods have severe limitations, such as the difficulty in properly introducing the A-ring substituents and the generation of undesirable byproducts, or compounds with low regioselectivity. Additionally, many use expensive catalysts, complex multistep pathways, harmful solvents, or harsh reaction conditions.

Owing to the relevance of 1,2-DHQ, and within the context of our ongoing studies oriented toward the design of new approaches for the preparation of pharmacologically key heterocyclic frameworks,[26] we herein disclose an efficient, versatile and regioselective method for the synthesis of these heterocycles, via a solvent-free $MgBr_2$-catalyzed MCR process. Due to the controversial nature of the mechanism for their formation,[17] the mechanistic pathway was also explored in an attempt to establish the possible species involved in such cascade reaction.

Scheme 1. Synthesis of Acetone−Anil by Reaction of Aniline (1a) and Acetone (2a)



RESULTS AND DISCUSSION

With a new and more efficient catalyst for the synthesis of 1,2-DHQ **3**, the reaction was carried out on the basis of the MCR method depicted in Scheme 1, and with the use of solvent-free conditions. Preliminary results showed that compound **3b** could be obtained, albeit in low to modest yields (Table 1,

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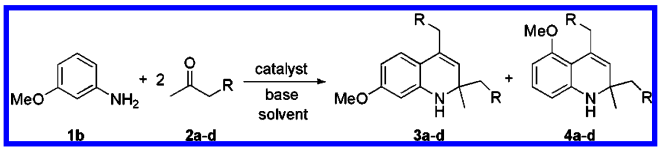
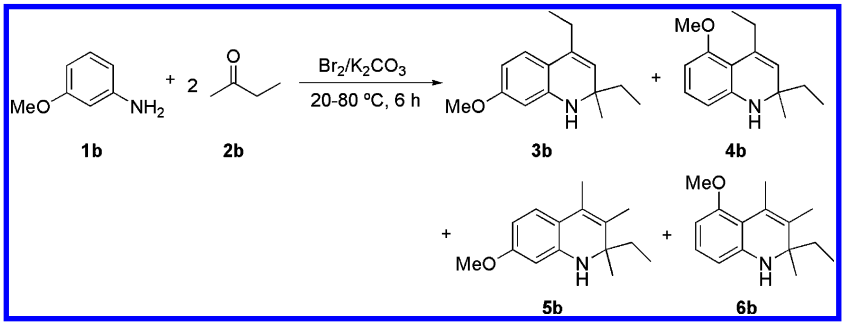
Table 1. Yields of 1,2-DHQ 3a–d/4a, Obtained by Reaction of 3-Methoxyaniline (1b) and Ketones 2a–d[a]



entry	2 (R)	cat.[b]	base	solvent[c]	T (°C)	time (h)	products[d] (%)
1	**2b** (Me)	Br_2	K_2CO_3		20	6	**3b** (6)
2	**2b** (Me)	Br_2	K_2CO_3		40	6	**3b** (19)
3	**2b** (Me)	Br_2	K_2CO_3		80	6	**3b** (58)
4	**2b** (Me)	NBS	K_2CO_3		60	6	[e]
5	**2b** (Me)	HBr	K_2CO_3		60	6	[e]
6	**2b** (Me)	*n*-Bu_4NBr	K_2CO_3		60	6	**3b** (25)
7	**2b** (Me)	$CuBr_2$	Li_2CO_3		60	12	**3b** (<3)
8	**2b** (Me)	KBr	Li_2CO_3		60	12	**3b** (8)
9	**2b** (Me)	LiBr	Li_2CO_3		60	12	**3b** (5)
10	**2b** (Me)	I_2	Li_2CO_3		60	12	**3b** (13)
11	**2b** (Me)	BBr_3	K_2CO_3		60	6	**3b** (50)
12	**2b** (Me)	$PyHBr_3$	K_2CO_3		70	6	**3b** (62)
13	**2b** (Me)	$PyHBr_3$	Li_2CO_3		45	12	**3b** (75)
14	**2b** (Me)	$PyHBr_3$	Li_2CO_3		60	12	**3b** (85)
15	**2b** (Me)	$MgBr_2$	Li_2CO_3		20	12	**3b** (13)
16	**2b** (Me)	$MgBr_2$	Li_2CO_3		60	12	**3b** (93)
17	**2b** (Me)	$MgCO_3$	Li_2CO_3		60	12	[e]
18	**2b** (Me)	$PyHBr_3$	Li_2CO_3	MeCN	60	12	**3b** (10)
19	**2b** (Me)	$MgBr_2$	Li_2CO_3	THF	60	12	**3b** (19)
20	**2b** (Me)	$MgBr_2$	Li_2CO_3	$(CH_2)_2Cl_2$	60	12	**3b** (8)
21	**2a** (H)	$PyHBr_3$	Li_2CO_3[f]		60	1	**3a**/**4a** (98:2) (77)
22	**2a** (H)	$MgBr_2$[g]	Li_2CO_3[g]		60	1	**3a**/**4a** (98:2) (89)
23	**2b** (Me)	$MgBr_2$	Li_2CO_3[g]		60	1	**3b** (98)
24	**2c** (Et)	$MgBr_2$	Li_2CO_3[g]		60	1	**3c** (80)
25	**2d** (Pr)	$MgBr_2$	Li_2CO_3[g]		60	1	**3d** (62)

[a]Reaction conditions: **1b** (1.0 molar equiv), **2** (5.0 molar equiv), catalyst (0.5–1.0 molar equiv), and M_2CO_3 (0.5–2.0 molar equiv). [b]All the catalysts in 1.0 molar equiv, except $PyHBr_3$ (0.5 molar equiv). [c]3.0 mL. [d]After column chromatography. [e]No reaction. [f]2.0 molar equiv. [g]0.5 molar equiv.

Scheme 2. Possible Regioisomeric Products from the Reaction of 1b with 2b



entries 1–3), by using bromine along with potassium carbonate at 20–80 °C for 6 h. Interestingly, among the four possible isomeric products, **3b**–**6b**, only **3b** was detected in the crude mixture (Scheme 2).

Whereas the desired product was yielded with bromine (Table 1, entries 4 and 5), which has both bromonium and bromide species, this was not the case with agents that provide only one of these species, such as *N*-bromosuccinimide (NBS) or hydrobromic acid. Other bromide salt catalysts or even iodine provided **3b** in low yields (Table 1, entries 6–10). However, when the reaction was carried out in the presence of BBr_3 and $PyHBr_3$, reagents that can generate both kinds of species,[27] derivative **3b** was obtained in higher yields (Table 1, entries 11 and 12). The yields from the latter catalyst were improved by using Li_2CO_3 as the base, decreasing the temperature, and increasing the reaction time (Table 1, entries 13 and 14).

Unlike with copper, potassium, or lithium bromides, magnesium bromide proved to be highly efficient and regioselective (Table 1, entries 7–9 and 16). The latter and other magnesium salts have been used as Lewis acid promoters in diverse procedures, where both the magnesium and bromide ions play an important role in transformations.[28] It seems that both ions are also important in the present case, since with magnesium carbonate the reaction did not occur (Table 1, entry 17). Moreover, the highest efficacy was obtained under

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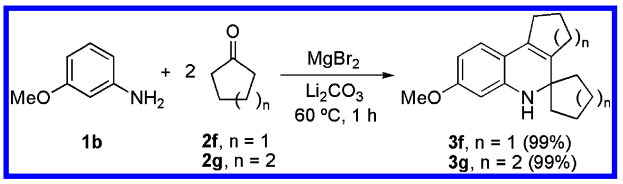
solvent-free conditions (Table 1, entries 16 and 18–20). Although the regioselectivity is similar between $MgBr_2$ and $PyHBr_3$, the efficiency of the former catalyst was an advantage, as shown by the reaction between aniline **1b** and acetone (**2a**) (Table 1, entries 21 and 22). It was necessary to use twice the amount of Li_2CO_3 for the $PyHBr_3$–catalyzed process, as otherwise the reaction was too slow and the mixture of products was obtained in only 40% yield after 1 h of reaction. Contrarily, with the use of $MgBr_2$ gave a total conversion of the starting material and a higher isolated yield of **3a**/**4a**. The amount of $PyHBr_3$ cannot be increased to improve the conversion because the product decomposes.

Upon applying the optimal reaction conditions, the series of 1,2-DHQ **3b–d** was prepared by condensing the corresponding alkyl methyl ketones **2b–d** with aniline **1b** (Table 1, entries 23–25). It is noteworthy that the bigger the substituent in the ketone, the lower the yield. Actually, the reaction of diethyl ketone (**2e**) with **1b** leads to a very low yield (6%) of product **3e**, which can be attributed to the low reactivity of the hindered ketone.[22b]

Consequently, we investigated the behavior of cyclic ketones **2f,g** under the same reaction conditions. In contrast to **2e**, the procedure with **2f,g** was highly efficient, leading to the desired products **3f,g** in quantitative yields (Scheme 3). The yield was

Scheme 3. Highly Efficient Synthesis of Polycyclic 1,2-DHQ 3f,g

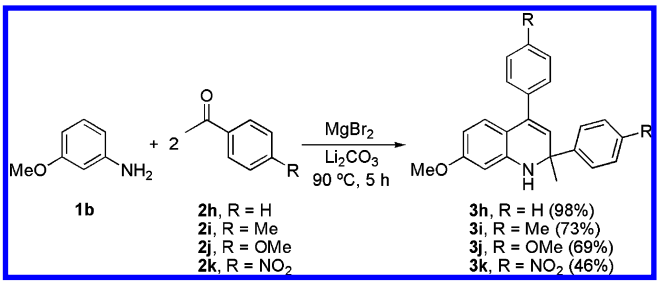


low (45%) when using $PyHBr_3$ as the catalyst in the reaction with **2g** to give **3g**. These results are in contrast with a recent report for an analogous iodine-catalyzed reaction,[17] in which the main products were the 1,2-dihydroquinolines substituted not only by the expected 2-spirocycloalkyl 4-cycloalkenyl-fused 1,2-dihydroquinoline core, similar to products **3f,g** (Scheme 3), but also by derivatives bearing cycloalkenyl groups at the C-6 and/or C-8 position of the heterocycle. This polyalkenylation was not observed in our reactions in spite of the relatively large amount of cycloalkanones **2f,g** employed (5 molar equiv) to upgrade the conversion into **3f,g**. The greater quantity of **2f–g** was necessary in order to compensate for the formation of dimers or oligomers of these cyclic ketones under the reaction conditions.

Therefore, the highly efficient reactions obtained with cyclic ketones **2f–g**, in comparison with the poor yield observed with diethyl ketone (**2e**), indicates that the process is indeed sterically dependent on the substituents in the ketone.

With the aim of evaluating the versatility of this methodology and of standardizing a method of synthesis for a broad series of 1,2-DHQ **3**, we performed an $MgBr_2$-catalyzed condensation with acetophenones **2h–k** using similar conditions. The series of heterocycles **3h–k** were obtained in low to moderate yields (10–50%) as stable solids. To enhance the yields, reactions were carried out with different temperatures and periods of time, finding that compounds **3h–k** could be isolated in better yields and in high regioselectivity at 90 °C and for 5 h (Scheme 4). It is worth mentioning that the presence of electron-

Scheme 4. Synthesis of 2,4-Diaryl-1,2-DHQ 3h–k



withdrawing groups in the benzene ring of the acetophenone (i.e., **2k**) led to a less efficient conversion, which suggests that the reaction mechanism is sensitive to the electron-demand in the carbonyl group of the ketone (vide infra).

Considering that the electronic effect of the substituent is involved in the reactivity of the ketone, methyl pyruvate (**2l**) was submitted to the same conditions as those used for alkyl ketones, limiting the reaction time to 1 h in order to compare their reactivity and conversion rate (Scheme 5).[29] Whereas $PyHBr_3$ was unable to promote the reaction, $MgBr_2$ catalyzed the conversion into a mixture of regioisomers **3l**/**4l** (79:21) in modest yields. It was found that this reaction is very fast, and after 1 h of heating the starting material was consumed, though with the presence of side products. Indeed, ketone **2l** is a much more reactive substrate probably due to the presence of the vicinal electron-withdrawing methoxycarbonyl group.[22b] Since the latter group can also be activated by the catalyst, a synergic activation effect is promoted.

The course and rate conversion of the reaction seems to be dictated not only by the electron demand or the hindrance of substituents in the ketone but also by the electron demand of the aniline substituents. Taking this into account, the reactivity of aniline **1b** should depend on the electron-donating effect of the methoxy group at the *meta* position of the amino group. To test this hypothesis, we evaluated the reactivity of a series of *meta*-substituted anilines **1c,d**, whose substituents have a lesser electron-donating effect than the methoxy group (Table 2). Thus, *m*-chloroaniline (**1c**) reacted with **2b** under the same conditions to cleanly give 1,2-dihydroquinoline **3m** with high regioselectivity, albeit in moderate yield, and recovery of the starting material (Table 2, entry 1). In the case of *m*-toluidine (**1d**), when using a reaction time of 1 h the conversion was less than that observed for **1b**, as evidenced by the fact that **3n** was isolated in low yield, though with excellent regioselectivity (Table 2, entry 2). It took 7 h of reaction to consume all the starting material, furnishing an almost quantitative yield of **3n** (Table 2, entry 3). When the ketone was changed to **2f**, a similar behavior was observed for 1 and 7 h of heating at 60 °C (Table 2, entries 4 and 5). With the latter period of time, **3o** was obtained in a quantitative yield. Acetophenones reacted in an analogous way, affording 1,2-dihydroquinoline **3p** in excellent yield with a temperature of 90 °C and longer reaction times (Table 2, entries 6 and 7).

Interestingly, and in contrast with **1b**, aniline **1e** regioselectively reacted with methyl pyruvate (**2l**) to form the single isomer of the tricyclic 1,2-DHQ **3q** in almost quantitative yield (Scheme 6). Although **1e** should not be as reactive as **1b**, the conversion efficiency of the former aniline into **3q** suggests the efficacy of the catalyst when the ketone is activated with the ester group.[22b] This activation of the ketone seems to be relevant, considering that with dialkyl ketones, such as **2a** and

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Scheme 5. Formation of Regioisomers 3l/4l by Condensation of 1b with Methyl Pyruvate (2l)

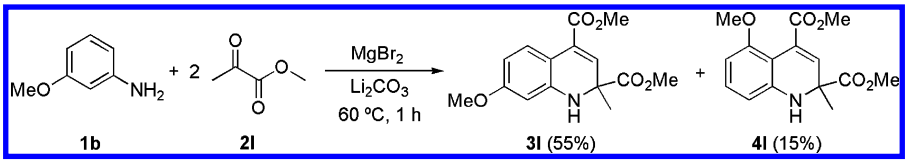
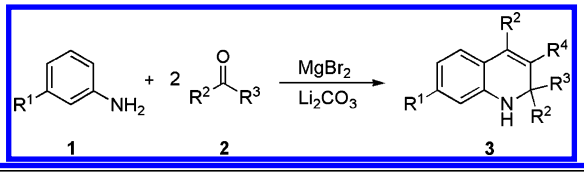
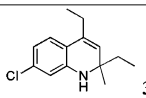
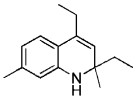
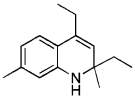
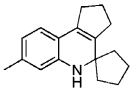
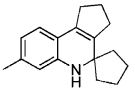
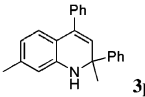
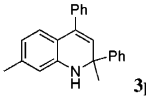


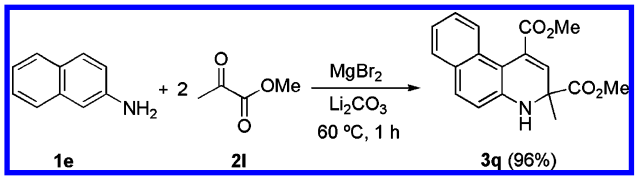
Table 2. Yields of 1,2-DHQ 3m–p, Obtained by Reaction of *Meta*-Substituted Anilines 1c,d and Ketones 2b,f,h[a]



Entry	**1** (R^1)	**2** (R^2, R^3)	T (°C)	t (h)	**3** (%)[b]
1	**1c** (3-Cl)	**2b** (Et, Me)	60	6	 **3m** (45)
2	**1d** (3-Me)	**2b** (Et, Me)	60	1	 **3n** (39)
3	**1d** (3-Me)	**2b** (Et, Me)	60	7	 **3n** (98)
4	**1d** (3-Me)	**2f** (-$(CH_2)_4$-)	60	1	 **3o** (26)
5	**1d** (3-Me)	**2f** (-$(CH_2)_4$-)	60	7	 **3o** (99)
6	**1d** (3-Me)	**2h** (C_6H_5, Me)	90	5	 **3p** (17)
7	**1d** (3-Me)	**2h** (C_6H_5, Me)	90	19	 **3p** (98)

[a]Reaction conditions: **1** (1.0 molar equiv), **2** (5.0 molar equiv), $MgBr_2$ (1.0 molar equiv), and Li_2CO_3 (0.5 molar equiv). [b]After column chromatography.

Scheme 6. Synthesis of Tricyclic 1,2-DHQ 3q



2b, the reaction with **1e** did not furnish the expected 1,2-DHQ, but instead complex mixtures of products after heating at 90 °C for a longer reaction time than that employed with **2l**.

We investigated the reactivity of anilines substituted by electron-donating and electron-withdrawing groups in the *para* position to the amino group. Thus, the reaction of **1f** with ketone **2l** under milder reaction conditions resulted in the desired 1,2-DHQ **3r** in high yield (Table 3, entry 1). Low reactive anilines, such as **1g-i**, were assessed with ketones **2b** and **2l**. These reactions furnished the corresponding 1,2-DHQ **3s-v** in low to high yields (Table 3, entries 2–6). As expected, anilines **1h,i** bearing electron-withdrawing groups also reacted with **2b** or **2l**, albeit more slowly, with recovery of the starting material in some cases (Table 3, entries 5 and 6). Unexpectedly, the reaction between aniline **1i** or 3-nitroaniline (**1j**) with ketone **2l** resulted in a complex mixture of products. These results support the idea that the reaction process depends on the electron demand of both anilines and ketones. That is, the reaction is favored with electron-donating substituted anilines and electron-withdrawing substituted ketones.

o-Anisidine (**1k**) was also evaluated with ketones **2b** and **2l**. The former ketone reacted under harder conditions (90 °C, 15 h) than the latter (60 °C, 1 h) to give 1,2-dihydroquinolines **3w,x**, respectively, in modest to high yields (Scheme 7). These results could be explained by a steric effect of the *ortho*-substituent in the arylamine, which possibly prevents full conjugation of the amino group with the phenyl ring.[30] Consequently, this effect could diminish the efficiency of the reaction with **2b**, but is not significant enough to affect the cyclization reaction with ketone **2l**.

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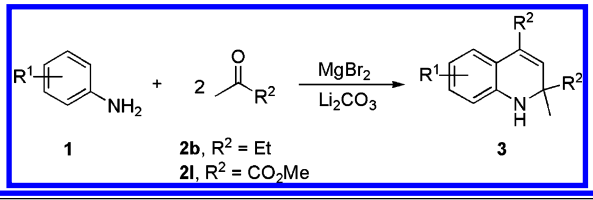
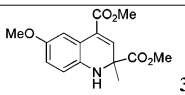
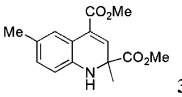
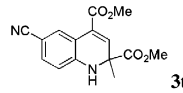
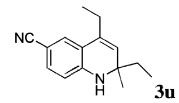
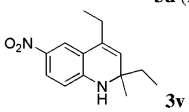
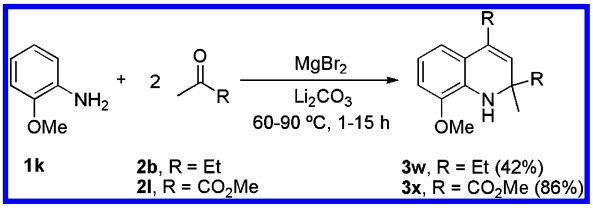
Table 3. Yields of 1,2-DHQ 3r–v, Obtained by Reaction of Substituted Anilines 1f–i and Ketones 2b and 2l[a]



Entry	1 (R^1)	2 (R^2)	T (°C)	t (h)	3 (%)[b]
1	**1f** (4-OMe)	**2l** (CO_2Me)	60	1	 **3r** (82)
2	**1g** (4-Me)	**2l** (CO_2Me)	60	1	 **3s** (78)
3	**1h** (4-CN)	**2l** (CO_2Me)	90	3	 **3t** (94)
4	**1h** (4-CN)	**2b** (Et)	90	15	 **3u** (26)[c]
5	**1i** (4-NO_2)	**2b** (Et)	90	15	 **3v** (31)[c]

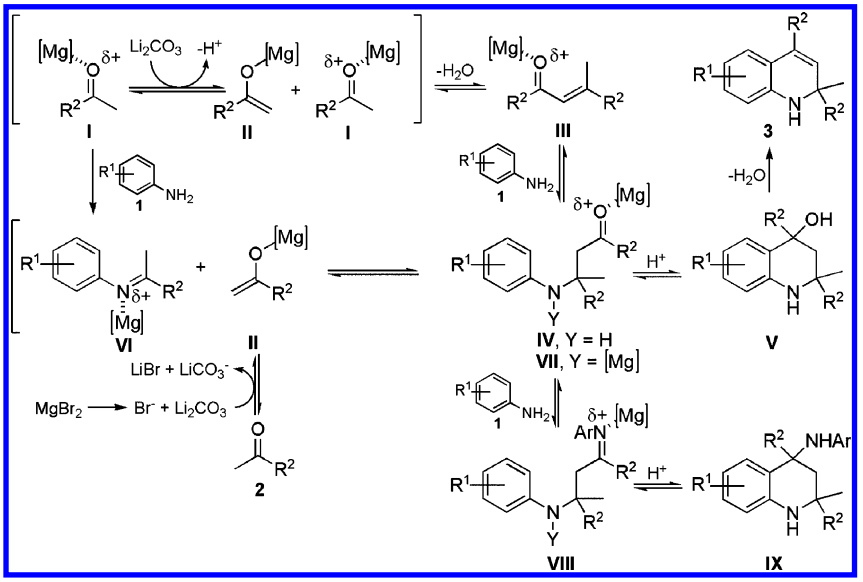
[a]Reaction conditions: **1** (1.0 molar equiv), **2** (5.0 molar equiv), $MgBr_2$ (1.0 molar equiv), and Li_2CO_3 (0.5 molar equiv). [b]After column chromatography. [c]Starting aniline is recovered.

Scheme 7. Reaction of Hindered Aniline 1k with 2b and 2l To Yield 1,2-DHQ 3w and 3x



Compound **3x** crystallized and its structure was established by X-ray diffraction crystallography (see the Supporting Information). The crystal structure shows a half-chair conformation for the dihydroheterocyclic ring, where the C-2 methoxycarbonyl group adopts an axial conformation, and consequently the methyl group assumes the equatorial conformation. Interestingly, the C-4 methoxycarbonyl group is not completely coplanar to the C-3/C-4 double bond of the heterocycle (torsion angle C(3)–C(4)–C(16)–O(17) = −149.52(15)°).

Scheme 8. Proposed Reaction Mechanisms for the Synthesis 1,2-DHQ 3, Starting from anilines 1 and Ketones 2



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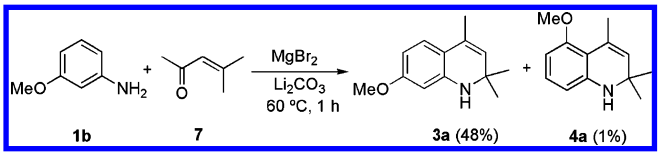
Two proposed mechanisms for the formation of 1,2-dihydroquinolines are useful to consider[17,22b,23,31,32] in regard to our conditions and catalysts. Mechanism (1): The previous formation of enone **III**, as the Mg^{2+}-catalyzed self-condensation product of ketone **2** species **I** and **II**, is followed by the conjugate addition of the aniline **1** to yield the β-anilino ketone intermediate **IV**.[31,32a] This in turn undergoes consecutive cyclization and dehydration reactions,[22c] again catalyzed by the Mg^{2+} species, to give precursor **V** and the final product **3**[32a] (Scheme 8). Mechanism (2): The previous formation of imine species **VI**, as the product of the Mg^{2+}−catalyzed reaction between species **I** and aniline **1**, is followed by the addition of enolate **II** of ketone **2** to yield the β-anilino ketone intermediate **VII**,[32a] which in turns is converted into the observed 1,2-dihydroquinoline **3** via precursor **V**[23] (Scheme 8). Of course, both mechanisms can also involve the formation of the corresponding imine and 4-amino species **VIII** and **IX**, respectively, as possible precursors of **3**.[32a]

The solvent-free conditions of this methodology avoid unfavorable coordinating interactions between the Mg^{2+} ions and the solvent, maintaining the wanted coordinating interactions with the oxygen of the ketone carbonyl group that enhance the electrostatic catalytic effect.[33] This would explain the inefficiency of the assays when a solvent is used (Table 1, entries 18−20). Furthermore, the stronger coordinating ability of Mg^{2+} or $BrMg^{+}$ ([Mg]) ions compared to Li^{+} ions prevents a competitive effect between both species for the catalytic sites.[33] The large number of these sites accounts for the amount of catalyst required in the process. It is likely that the bromide ion assists the generation of the base species, such as $LiCO_3^{-}$, in the middle of the solvent-free reaction. We monitored several reactions attempting to detect or isolate some intermediates under typical reaction conditions. However, we were unable to isolate any of these intermediates or to detect them by ^1H NMR analysis. Therefore, in order to test the feasibility of these two mechanisms, some of the plausible stable intermediates were independently prepared or purchased and submitted to the same reaction conditions.

To test the first mechanism, mesityl oxide (**7**) (Mg-free complex of **III**) was treated with *m*-anisidine (**1b**) for 1 h, providing a mixture of 1,2-dihydroquinolines **3a**/**4a** (98:2). This was purified to give 48% and 1% yields, respectively, along with recovery of the starting material (Scheme 9). Although the

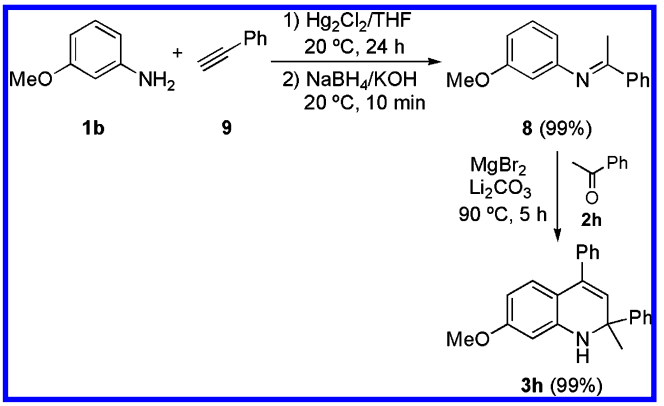
Scheme 9. Reaction of Aniline 1b with Mesityl Oxide (7)



regioselectivity was identical to that obtained with **1b** and acetone (**2a**) as starting materials (Table 1, entry 22), the conversion rate was less, evidenced by the fact that only half of the aniline was consumed in the former reaction.

To test the second mechanism, we examined the in situ generation of the imine Mg complex **VI** as by performing the Hg(I)-catalyzed reaction of aniline **1b** with phenylacetylene (**9**), followed by treatment with sodium borohydride, giving imine **8** in good yield (Scheme 10).[34] In contrast with the process depicted in Scheme 9, that of **8** with ketone **2h** turned out to efficiently produce the desired 1,2-dihydroquinoline **3h**

Scheme 10. Formation of Imine 8 and Its Conversion into 1,2-Dihydroquinoline 3h



in quantitative yield. This result provides evidence that imine is the most probable intermediate in the formation of the heterocycles, which is in agreement with other reports.[22b,23,32,35] Although the formation of the imine can be favored by the presence of electron-withdrawing groups in the benzene ring of the acetophenone (i.e., **2k**), the enhanced stability of the conjugate base species **II** of the latter compound may lead to a decrease in its reactivity and performance in the condensation process toward the heterocycle. This could be the reason for the modest yield of **3k** (Scheme 4). On the other hand, it is expected that the formation of the imine should not be favored by the presence of electron-withdrawing groups in the aniline, due to a decrease in nucleophilicity. This idea is in accordance with the observed depletion of reactivity when anilines **1h,i** reacted with ketones **2b** and **2l** (Table 3).

However, the reaction mechanism may be much more complex than either of those illustrated in Scheme 8, since diverse intermediate species can be associated with the mechanistic steps,[36] mainly depending on the starting materials and reaction conditions.[32a] For instance, recent mechanistic studies were conducted to rationalize the formation of spiro-1,2-dihydroquinoline analogues of **3f,g**,[17] proposing that an isolated *o*-alkenylimino intermediate is involved at the final annulation step toward the observed products. This finding is supported by the fact that the acid- or iodine-catalyzed reactions of *o*-alkenylanilines with cyclic ketones yielded 2-spiro-1,2-dihydroquinoline derivatives.[32c,d,37] However, in our transformations this kind of intermediate was not detected or isolated, nor were alkenyl-substituted 1,2-dihydroquinoline products[17] α,β-unsaturated ketones[32a] or 4-amino tetrahydroquinolines.[38]

It is noteworthy that most of the reported quinoline and 1,2-dihydroquinoline syntheses have been carried out in the presence of solvents, such as benzene, toluene or acetonitrile, which may stabilize some of the proposed intermediates and therefore lead not only to the expected quinoline products but also to a variety of side-products. In contrast, under our solvent-free conditions only anilines and ketones are interacting, of course with the assistance of the catalyst, to give the 1,2-DHQ with high regioselectivity and efficiency, even if some deactivated anilines are used. Consequently, compared to methods involving a condensing phase, it seems that our approach follows a simpler pathway, probably limiting side pathways by the strong magnesium ion coordination. Nevertheless, the first proposal involving the enone **7** cannot be

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completely ruled out as a competitive mechanism in view of the complexity of the quinoline formation.[32a]

The high regioselectivity observed in the cyclization step, affording 1,2-dihydroquinoline **3** as the major and **4** as the minor regioisomer, could be rationalized on the basis of two factors,[36,39] the electronic effects of the substituents in the aniline ring and the steric hindrance generated by both the aniline and ketone.[40] The electrophilic aromatic substitution, which is presumably involved in the 1,2-dihydroquinoline heterocyclic ring formation, is usually kinetically controlled during the reaction step leading to the arenium ion intermediate (Wheland σ-complex).[41] Although the *ortho*−*para*-directing groups in anilines such as **1b** reinforce each other to orient the position of the incoming group, the stability of the arenium ion in a *para*-quinoid canonical structure with respect to the methoxy group (attack at the C-6 position) is greater than that in the *ortho*-quinoid structure (attack at the C-2 position).[30] Therefore, the fact that **3** is obtained as the major regioisomer in detriment to **4** is expected.[39,42]

Furthermore, an explanation for this preference is offered on the basis of hard and soft interaction arguments.[43] Since the *ortho* position (C-2) is harder than the *para* position (C-6) in a benzene ring monosubstituted by an electron-donating group, then the softer electrophiles give more *para* substitution (C-6). Considering that in the proposed mechanisms (Scheme 8) the soft metal complex species **VII** or **VIII** (rather than harder small positive-charged species) are formed as precursors in the cyclization step, it is likely that the process takes place rather at the C-6 position (*ortho*−*para* orientation), which would favor regioisomer **3**, rather than at the hardered C-2 position (*ortho*−*ortho* orientation), which would favor regioisomer **4**. Molecular orbital calculations agree with this prediction indicating that the attack preferentially occurs at the *para* position in anisole, among other electron-donating groups, which has the highest π-electron density and the lowest energy of the π-molecular orbital of the σ-complex.[43,44] Among other theoretical constructs,[45] density-functional theory (DFT)-based reactivity criteria and descriptors have been used to clarify this question,[46] predicting the preferential *para* approach of the electrophile as a result of a stronger tendency to electron-transfer (nucleophilicity) from the aromatic ring.[47]

It is well-known that steric effects tend to reduce the proportion of the *ortho* products.[30,40a,41] Therefore, if the bulky metal-complexed species **VII** or **VIII** are the reactive species during the cyclization step, it is reasonable that the preference for closing the ring takes place at the C-6 position rather than at the most hindered C-2 position (in between both substituents).[30,48]

CONCLUSION

In summary, we have developed a highly efficient, versatile, and regioselective solvent-free methodology to prepare 1,2-DHQ **3** through a magnesium bromide-catalyzed condensation of the MCR, with 1 equiv of the aniline and 2 equiv of the ketone. The scope of the method includes a variety of symmetrical and nonsymmetrical alkyl ketones, cyclic ketones, acetophenones, and diverse substituted anilines. Interestingly, the latter substrates were reactive enough to activate the cyclization process, even when having either weak electron-donating or electron-withdrawing substituents or being attached in an inadequate position at the benzene ring. Among the evaluated brominated catalysts, magnesium bromide proved to be the most efficient, leading to the desired products in moderate to high yields. The synthesis was designed under a solvent-free procedure[49] and with a nontoxic and inexpensive catalyst. All these advantageous properties of the current approach are attractive in comparison with many of the already known methods, the latter of which are modestly selective,[16,17] use complex or scope-limited functionalized starting materials,[23a,24,25,37] require expensive or highly toxic catalysts,[16,19,20a,22a−c] and/or involve severe and mostly solvent-dependent reaction conditions.[21,22d] However, our method suffers from low reaction conversion for strongly inactivated anilines and some acyclic hindered ketones. The mechanistic study provides evidence that the most likely pathway includes the formation of an imine derivative, **8**, as the key intermediate, which undergoes condensation by the second equivalent of the ketone, followed by the cyclization process to yield the heterocyclic ring. The reaction between anilines and two different carbonylic starting materials to obtain quinolines and more complex 1,2-DHQ is currently under study, and the results will be reported in due course.

EXPERIMENTAL SECTION[50]

General Procedure for the $MgBr_2$-Catalyzed Synthesis of 2,2,4-Trialkyl-1,2-dihydroquinolines 3a−g/4a, 3l−o/4l, 3q−s, and 3x (Method A). In a 25-mL round-bottomed flask, a mixture of aniline **1b−g** or **1k** (1.0 molar equiv), ketone, **2a−g** or **2l** (5.0 molar equiv), Li_2CO_3 (0.5 molar equiv), and anhydrous $MgBr_2$ (1.0 molar equiv) was vigorously stirred at 60 °C for 1−7 h. A 10% aqueous solution of NH_4Cl (5 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried (Na_2SO_4) and the solvent removed under vacuum. The residue was purified by column chromatography over silica gel (15 g/g of crude, hexane) to give either the corresponding 1,2-dihydroquinoline **3a−g**, **3m−o**, **3q−s**, or **3x** or the isomeric mixture of 1,2-dihydroquinolines **3a**/**4a** or **3l**/**4l**.

General Procedure for the $PyHBr_3$-Catalyzed Synthesis of 2,2,4-Trialkyl-1,2-dihydroquinolines 3a−c/4a and 3g (Method B). In a 25-mL round-bottomed flask, a mixture of aniline **1b** (1.0 molar equiv), ketone, **2a−c** or **2g** (5.0 molar equiv), Li_2CO_3 (2.0 molar equiv), and $Py{\cdot}HBr_3$ (0.5 molar equiv) was vigorously stirred at 60 °C for 12 h. A 10% aqueous solution of NH_4Cl (5 mL) was added, and the mixture was stirred for 10 min, and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried (Na_2SO_4) and the solvent removed under vacuum. The residue was purified by column chromatography over silica gel (15 g/g of crude, hexane) to give either the corresponding 1,2-dihydroquinoline **3b**,**c** or **3g** or the isomeric mixture of 1,2-dihydroquinolines **3a**/**4a**.

General Procedure for the $MgBr_2$-Catalyzed Synthesis of 2-Alkyl-2,4-diaryl-1,2-dihydroquinolines 3h−k, 3p, 3t−v, and 3w (Method C). In a 25-mL round-bottomed flask, a mixture of aniline **1b**, **1d**, **1h−i**, or **1k** (1.0 molar equiv), acetophenone, **2b**, **2h−k**, or **2l** (5.0 molar equiv), Li_2CO_3 (0.5 molar equiv), and $MgBr_2$ (1.0 molar equiv) was vigorously stirred at 90 °C for 5−19 h. A 10% aqueous solution of NH_4Cl (5 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried (Na_2SO_4) and the solvent removed under vacuum. The residue was purified by column chromatography over silica gel (15 g/g of crude, hexane/EtOAc, 99:1) to give the corresponding 1,2-dihydroquinoline **3h−k**, **3p**, **3t−v**, or **3w**.

*7-Methoxy-2,2,4-trimethyl-1,2-dihydroquinoline (**3a**) and 5-Methoxy-2,2,4-trimethyl-1,2-dihydroquinoline (**4a**). Method A.* A mixture of **1b** (0.100 g, 0.813 mmol), **2a** (0.235 g, 4.06 mmol), Li_2CO_3 (0.030 g, 0.41 mmol), and $MgBr_2$ (0.150 g, 0.815 mmol) was heated to 60 °C for 1 h, affording a mixture of **3a**/**4a** (98:2) which was purified over silica gel (15 g/g of crude, hexane) to give 0.143 g (87%) of **3a** as a white powder, and 0.003 g (2%) of **4a** as a pale yellow powder. **Method B.** A mixture of **1b** (0.150 g, 1.22 mmol), **2a** (0.348 g, 6.00 mmol), Li_2CO_3 (0.180 g, 2.43 mmol), and $Py{\cdot}HBr_3$ (0.195 g, 0.61 mmol) afforded a mixture of **3a**/**4a** (98:2) which was purified over

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silica gel (15 g/g of crude, hexane) to give 0.188 g (76%) of **3a** as a white powder and 0.003 g (1%) of **4a** as a pale yellow powder. **Method D.** A mixture of **1b** (0.100 g, 0.813 mmol), **7** (0.400 g, 4.07 mmol), Li_2CO_3 (0.030 g, 0.41 mmol), and $MgBr_2$ (0.150 g, 0.815 mmol) was vigorously stirred at 60 °C for 1 h. A 10% aqueous solution of NH_4Cl (5 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried (Na_2SO_4) and the solvent removed under vacuum. The residue was purified by column chromatography over silica gel (15 g/g of crude, hexane) to afford a mixture of **3a**/**4a** (97:3) which was purified over silica gel (15 g/g of crude, hexane) to give 0.079 g (48%) of **3a** as a white powder and 0.0017 g (1%) of **4a** as a pale yellow powder. Data for **3a**: R_f 0.72 (hexane/EtOAc, 7:3); mp 61−62 °C (lit.[51] mp 67−69 °C); IR (KBr) 3386, 2966, 1651, 1612, 1577, 1511, 1483, 1452, 1381, 1336, 1276, 1259, 1208, 1162, 1026, 1000, 832, 811 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 6H, 2Me-C2), 1.95 (d, J = 1.5 Hz, 3H, Me-C4), 3.73 (br, 1H, N*H*), 3.74 (s, 3H, CH_3O), 5.18 (q, J = 1.5 Hz, 1H, H-3), 6.01 (d, J = 2.7 Hz, 1H, H-8), 6.19 (dd, J = 8.4, 2.7 Hz, 1H, H-6), 6.96 (d, J = 8.4 Hz, 1H, H-5); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 18.6 (*C*H_3-C4), 31.0 (2 *C*H_3-C2), 51.9 (C-2), 55.0 (*C*H_3O), 98.5 (C-8), 102.2 (C-6), 115.3 (C-4a), 124.6 (C-5), 125.9 (C-3), 128.1 (C-4), 144.6 (C-8a), 160.1 (C-7); MS (70 eV) m/z 203 (M^+, 8), 188 (100), 186 (2), 173 (6), 159 (2), 145 (24); HRMS (EI) m/z [M^+] calcd for $C_{13}H_{17}NO$ 203.1310, found 203.1313. Data of **4a**: R_f 0.75 (hexane/EtOAc, 7:3); mp 81−82 °C. IR (film) 2961, 1640, 1597, 1493, 1464, 1268, 1230, 1162, 1106, 777, 728 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (s, 6H, 2Me-C2), 2.16 (d, J = 1.5 Hz, 3H, Me-C4), 3.70 (br, 1H, N*H*), 3.75 (s, 3H, OCH_3), 5.22 (q, J = 1.5 Hz, 1H, H-3), 6.15 (dd, J = 8.1, 1.1 Hz, 1H, H-6 or H-8), 6.23 (dd, J = 8.1, 1.1 Hz, 1H, H-8 or H-6), 6.92 (t, J = 8.1 Hz, 1H, H-7); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 23.0 (*C*H_3-C4), 29.6 (2 *C*H_3-C2), 50.7 (C-2), 55.2 (*C*H_3O), 101.3 (C-6 or C-8), 107.5 (C-8 or C-6), 111.1 (C-4a), 128.4 (C-7), 128.9 (C-3), 129.3 (C-4), 145.5 (C-8a), 157.6 (C-5); MS (70 eV) m/z 203 (M^+, 5), 188 (100), 173 (50), 157 (2), 145 (21), 130 (5), 115 (4); HRMS (EI) m/z [M^+] calcd for $C_{13}H_{17}NO$ 203.1310, found 203.1309.

*2,4-Diethyl-7-methoxy-2-methyl-1,2-dihydroquinoline (**3b**). Method A.* A mixture of **1b** (0.100 g, 0.813 mmol), **2b** (0.292 g, 4.06 mmol), Li_2CO_3 (0.030 g, 0.41 mmol), and $MgBr_2$ (0.150 g, 0.815 mmol) was heated to 60 °C for 1 h to give 0.184 g (98%) of **3b** as a white powder. **Method B.** A mixture of **1b** (0.200 g, 1.62 mmol), **2b** (0.585 g, 8.12 mmol), Li_2CO_3 (0.060 g, 0.82 mmol), and Py·HBr_3 (0.259 g, 0.81 mmol) gave 0.32 g (85%) of **3b** as a white powder: R_f 0.81 (hexane/EtOAc, 7:3); mp 59−60 °C; IR (film) 3376, 2963, 1649, 1612, 1577, 1514, 1479, 1462, 1373, 1327, 1298, 1270, 1219, 1207, 1166, 1038, 826, 796 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 7.5 Hz, 3H, CH_3CH$_2$-C2), 1.15 (t, J = 7.5 Hz, 3H, CH_3CH$_2$-C4), 1.21 (s, 3H, CH_3-C2), 1.42−1.56 (m, 2H, CH$_3$CH_2-C2), 2.35 (qd, J = 7.5, 1.2 Hz, 2H, CH$_3$CH_2-C4), 3.62 (br s, 1H, N*H*), 3.74 (s, 3H, CH_3O), 5.07 (t, J = 1.2 Hz, 1H, H-3), 6.00 (d, J = 2.4 Hz, 1H, H-8), 6.15 (dd, J = 8.4, 2.4 Hz, 1H, H-6), 6.99 (d, J = 8.4 Hz, 1H, H-5); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 8.5 (CH$_3$CH$_2$-C2), 12.9 (CH$_3$CH$_2$-C4), 24.6 (CH$_3$CH$_2$-C4), 29.5 (CH$_3$-C2), 36.5 (CH$_3$CH$_2$-C2), 54.7 (C-2), 55.0 (CH$_3$O), 98.3 (C-8), 101.7 (C-6), 114.3 (C-4a), 122.6 (C-5), 124.2 (C-3), 134.4 (C-4), 145.3 (C-8a), 160.0 (C-7); MS (70 eV) m/z 231 (M^+, 1), 216 (15), 202 (100), 187 (9), 158 (8); HRMS (EI) m/z [M^+] calcd for $C_{15}H_{21}NO$ 231.1623, found 231.1624.

*7-Methoxy-2-methyl-2,4-di-n-propyl-1,2-dihydroquinoline (**3c**). Method A.* A mixture of **1b** (0.051 g, 0.415 mmol), **2c** (0.190 g, 2.21 mmol), Li_2CO_3 (0.015 g, 0.20 mmol) and $MgBr_2$ (0.075 g, 0.41 mmol) was heated to 60 °C for 1 h to give 0.086 g (80%) of **3c** as a pale brown oil. **Method B.** A mixture of **1b** (0.05 g, 0.4 mmol), **2c** (0.172 g, 2.00 mmol), Li_2CO_3 (0.06 g, 0.8 mmol), and Py·HBr_3 (0.064 g, 0.2 mmol) gave 0.034 g (33%) of **3c** as a pale brown oil: R_f 0.78 (hexane/EtOAc, 7:3); IR (film) 3377, 2956, 2930, 2869, 1648, 1612, 1577, 1514, 1464, 1327, 1297, 1277, 1264, 1211, 1166, 1039, 820, 789 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86−0.91 (m, 3H, CH_3CH$_2$CH$_2$-C2), 0.95 (t, J = 7.2 Hz, 3H, CH_3CH$_2$CH$_2$-C4), 1.21 (s, 3H, CH_3-C2), 1.35−1.49 (m, 4H, CH$_3$CH_2CH$_2$-C2), 1.56 (sext, J = 7.2 Hz, 2H, CH$_3$CH$_2$CH$_2$-C4), 2.20−2.39 (m, 2H, CH$_3$CH$_2$CH_2-C4), 3.61 (br s, 1H, N*H*), 3.73 (s, 3H, CH_3O), 5.07 (br s, 1H, H-3), 5.98 (d, J = 2.6 Hz, 1H, H-8), 6.14 (dd, J = 8.3, 2.6 Hz, 1H, H-6), 6.97 (d, J = 8.3 Hz, 1H, H-5); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.0 (CH$_3$CH$_2$CH$_2$-C4), 14.5 (CH$_3$CH$_2$CH$_2$-C2), 17.5 (CH$_3$CH$_2$CH$_2$-C2), 21.4 (CH$_3$CH$_2$CH$_2$-C4), 30.1 (CH$_3$-C2), 34.1 (CH$_3$CH$_2$CH$_2$-C4), 46.7 (CH$_3$CH$_2$CH$_2$-C2), 54.6 (C-2), 55.0 (CH$_3$O), 98.2 (C-8), 101.6 (C-6), 114.1 (C-4a), 124.2 (C-3), 124.3 (C-5), 132.4 (C-4), 145.3 (C-8a), 159.9 (C-7); MS (70 eV) m/z 259 (M^+, 4), 244 (11), 228 (23), 215 (100), 200 (7), 187 (29). HRMS (EI) m/z [M^+] calcd for $C_{17}H_{25}NO$: 259.1936; found: 259.1930.

*2,4-Dibutyl-7-methoxy-2-methyl-1,2-dihydroquinoline (**3d**).*[18c] *Method A.* A mixture of **1b** (0.050 g, 0.41 mmol), **2d** (0.205 g, 2.05 mmol), Li_2CO_3 (0.015 g, 0.20 mmol) and $MgBr_2$ (0.075 g, 0.41 mmol) was heated to 60 °C for 1 h to give 0.073 g (62%) of **3d** as a pale yellow oil. R_f 0.76 (hexane/EtOAc, 7:3). IR (film) 3379, 2956, 2930, 2859, 1647, 1613, 1578, 1514, 1465, 1328, 1297, 1273, 1210, 1166, 1046, 825 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 7.5 Hz, 3H, CH_3CH$_2$CH$_2$CH$_2$-C2), 0.93 (t, J = 7.2 Hz, 3H, CH_3CH$_2$CH$_2$CH$_2$-C4), 1.21 (s, 3H, CH_3-C2), 1.24−1.57 (m, 10H, 5CH_2), 2.27−2.39 (m, 2H, CH$_3$CH$_2$CH$_2$CH_2-C4), 3.62 (br s, 1H, N*H*), 3.74 (s, 3H, CH_3O), 5.08 (s, 1H, H-3), 5.98 (d, J = 2.4 Hz, 1H, H-8), 6.15 (dd, J = 8.4, 2.4 Hz, 1H, H-6), 6.97 (d, J = 8.4 Hz, 1H, H-5); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.0 (CH$_3$), 14.1 (CH$_3$), 22.6 (CH$_3$CH$_2$CH$_2$CH$_2$-C4), 23.1 (CH$_3$CH$_2$CH$_2$CH$_2$-C2), 26.4 (CH$_3$CH$_2$CH$_2$CH$_2$-C2), 30.0 (CH$_3$-C2), 30.6 (CH$_3$CH$_2$CH$_2$CH$_2$-C4), 31.8 (CH$_3$CH$_2$CH$_2$CH$_2$-C4), 43.9 (CH$_3$CH$_2$CH$_2$CH$_2$-C2), 54.5 (C-2), 55.0 (CH$_3$O), 98.3 (C-8), 101.7 (C-6), 114.2 (C-4a), 124.1 (C-3), 124.3 (C-5), 132.6 (C-4), 145.3 (C-8a), 159.9 (C-7); MS (70 eV) m/z 287 (M^+, 5), 272 (8), 231 (17), 230 (100), 200 (5), 187 (21), 144 (6). HRMS (EI) m/z [M^+] calcd for $C_{19}H_{29}NO$: 287.2249; found: 287.2255.

*2,2,4-Triethyl-7-methoxy-3-methyl-1,2-dihydroquinoline (**3e**). Method A.* A mixture of **1b** (0.050 g, 0.41 mmol), **2e** (0.180 g, 2.09 mmol), Li_2CO_3 (0.015 g, 0.20 mmol) and $MgBr_2$ (0.075 g, 0.41 mmol) was heated to 60 °C for 1 h to give 0.007 g (6%) of **3e** as a pale yellow oil. R_f 0.80 (hexane/EtOAc, 7:3). IR (film) 2964, 2929, 1614, 1462, 1416, 1271, 1218, 1164, 1033, 852, 823 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, J = 7.2 Hz, 6H, 2CH_3CH$_2$-C2), 1.08 (t, J = 7.5 Hz, 3H, CH_3CH$_2$-C4), 1.11−1.24 (m, 2H, CH$_3$CH_2-C2), 1.68 (br s, 3H, CH_3-C3), 1.72−1.85 (m, 2H, CH$_3$CH_2-C2), 2.42 (q, J = 7.5 Hz, 2H, CH$_3$CH_2-C4), 3.26 (br s, 1H, N*H*), 3.73 (s, 3H, CH_3O), 5.90 (d, J = 2.5 Hz, 1H, H-8), 6.06 (dd, J = 8.5, 2.5 Hz, 1H, H-6), 6.92 (d, J = 8.5 Hz, 1H, H-5); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 8.6 (2CH$_3$CH$_2$-C2), 13.1 (CH$_3$CH$_2$-C4), 13.2 (CH$_3$-C3), 20.8 (CH$_3$CH$_2$-C4), 34.7 (2CH$_3$CH$_2$-C2), 55.0 (CH$_3$O), 62.0 (C-2), 96.7 (C-8), 100.5 (C-6), 113.6 (C-4a), 123.7 (C-5), 124.2 (C-3), 132.4 (C-4), 145.8 (C-8a), 159.4 (C-7); MS (70 eV) m/z 259 (M^+, 1), 230 (5), 229 (45), 228 (100), 212 (5), 200 (11), 184 (7). HRMS (EI) m/z [M^+-C_2H_5] calcd for $C_{15}H_{20}NO$: 230.1545; found: 230.1550.

*7-Methoxy-1,2,3,5-tetrahydrospiro[cyclopenta[c]quinoline-4,1′-cyclopentane] (**3f**). Method A.* A mixture of **1b** (0.050 g, 0.41 mmol), **2f** (0.172 g, 2.05 mmol), Li_2CO_3 (0.015 g, 0.20 mmol) and $MgBr_2$ (0.075 g, 0.41 mmol) was heated to 60 °C for 1 h, and after purification by column chromatography over pretreated silica gel gave 0.103 g (99%) of **3f** as a white solid. R_f 0.75 (hexane/EtOAc, 7:3); mp 107−108 °C [Lit.[52] 113−116 °C]. IR (film) 3370, 2948, 2838, 1658, 1610, 1516, 1487, 1370, 1335, 1317, 1296, 1268, 1198, 1164, 1072, 1044, 842, 767 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.63−1.81 (m, 6H, H-2′, 2H-3′, 2H-4′, H-5′), 1.82−1.92 (m, 2H, H-2′, H-5′), 1.93−2.05 (m, 2H, H-2), 2.44−2.52 (m, 2H, H-1), 2.57−2.66 (m, 2H, H-3), 3.74 (s, 3H, CH_3O), 3.95 (br s, 1H, N*H*), 6.02 (d, J = 2.3 Hz, 1H, H-6), 6.16 (dd, J = 8.3, 2.3 Hz, 1H, H-8), 6.78 (d, J = 8.3 Hz, 1H, H-9); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 22.2 (C-2), 23.8 (C-3′, C-4′), 31.1 (C-3), 31.9 (C-1), 39.7 (C-2′, C-5′), 55.0 (CH$_3$O), 65.0 (C-4), 98.1 (C-6), 101.9 (C-8), 114.1 (C-9a), 123.9 (C-9), 131.6 (C-9b), 135.7 (C-3a), 143.8 (C-5a), 159.5 (C-7); MS (70 eV) m/z 255 (M^+, 24), 254 (10), 227 (22), 212 (22), 213 (47), 183 (15), 135 (12). HRMS (EI) m/z [M^+] calcd for $C_{17}H_{21}NO$: 255.1623; found: 255.1622.

*3′-Methoxy-7′,8′,9′,10′-tetrahydro-5′H-spiro[cyclohexane-1,6′-phenanthridine] (**3g**). Method A.* A mixture of **1b** (0.050 g, 0.41 mmol), **2g** (0.201 g, 2.05 mmol), Li_2CO_3 (0.015 g, 0.20 mmol) and

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$MgBr_2$ (0.075 g, 0.41 mmol) was heated to 60 °C for 1 h, and after purification by column chromatography over pretreated silica gel gave 0.115 g (99%) of **3g** as a white solid. **Method B**: A mixture of **1b** (0.050 g, 0.41 mmol), **2g** (0.201 g, 2.05 mmol), Li_2CO_3 (0.060 g, 0.82 mmol) and Py.HBr_3 (0.064 g, 0.2 mmol) gave 0.052 g (45%) of **3g** as a white powder. R_f 0.75 (hexane/EtOAc, 7:3); mp 97−98 °C [Lit.[53] 95−97 °C]. IR (KBr) 3383, 2925, 2848, 2832, 1640, 1612, 1582, 1518, 1479, 1461, 1320, 1302, 1256, 1207, 1164, 1045, 843 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26−1.80 (m, 14H, H-2, H-3, H4, H-5, H-6, H-8′, H-9′), 1.98−2.06 (m, 2H, H-10′), 2.22−2.33 (m, 2H, H-7′), 3.69 (s, 3H, CH_3O), 4.32 (br s, 1H, N*H*), 6.07 (d, J = 2.5 Hz, 1H, H-8), 6.17 (dd, J = 8.5, 2.5 Hz, 1H, H-6), 6.90 (d, J = 8.5 Hz, 1H, H-5); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.0 (C-3, C-5), 22.4 (C-8′), 23.1 (C-9′), 24.6 (C-10′), 25.2 (C-4), 25.3 (C-7′), 32.4 (C-2, C-6), 54.6 (C-6′), 54.9 (CH_3O), 99.3 (C-4′), 102.8 (C-2′), 117.9 (C-10b′), 123.0 (C-1′), 124.8 (C-10a′), 133.0 (C-6a′), 143.3 (C-4a′), 159.1 (C-3′); MS (70 eV) m/z 283 (M^+, 25), 241 (20), 240 (100), 227 (30), 226 (24), 212 (18), 197 (8). HRMS (EI) m/z [M^+] calcd for $C_{19}H_{25}NO$: 283.1936; found: 283.1936. Anal. Calcd for $C_{19}H_{25}NO$: C, 80.52; H, 8.89; N, 4.94. Found: C, 80.65; H, 8.97; N, 4.96.

*7-Methoxy-2-methyl-2,4-diphenyl-1,2-dihydroquinoline (**3h**).*[18c] *Method C.* A mixture of **1b** (0.050 g, 0.41 mmol), **2h** (0.24 g, 2.0 mmol), Li_2CO_3 (0.015 g, 0.20 mmol) and $MgBr_2$ (0.075 g, 0.41 mmol) was heated to 90 °C for 5 h to give 0.13 g (98%) of **3h** as a white powder. **Method E**: In a 10 mL round-bottomed flask, a mixture of imine **8** (0.1210 g, 0.536 mmol), **2h** (0.257 g, 2.14 mmol), Li_2CO_3 (0.0190 g, 0.268 molar equiv) and $MgBr_2$ (0.098g, 0.536 mmol) was vigorously stirred at 90 °C under N_2 atmosphere for 5 h. A 10% aqueous solution of NH_4Cl (5 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried (Na_2SO_4) and the solvent removed under vacuum. The residue was purified by column chromatography over silica gel (2.5 g/g of crude, hexane/EtOAc, 99:1) to give 0.173 (99%) of **3h** as a white powder. R_f 0.71 (hexane/EtOAc, 7:3); mp 114−115 °C [Lit.[54] 108−110 °C]. IR (KBr) 3370, 2961, 2930, 1607, 1575, 1512, 1463, 1443, 1350, 1276, 1223, 1204, 1174, 1125, 1030, 826, 771, 761, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.75 (s, 3H, CH_3-C2), 3.74 (s, 3H, CH_3O), 4.22 (br s, 1H, N*H*), 5.50 (s, 1H, H-3), 6.09−6.15 (m, 2H, H-6, H-8), 6.82 (d, J = 9.0 Hz, 1H, H-5), 7.22 (tt, J = 7.4, 1.2 Hz, 1H, H-4′), 7.29−7.36 (m, 7H, H-3′, H-2″, H-3″, H-4″), 7.52−7.56 (m, 2H, H-2′); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 30.1 (CH_3-C2), 55.1 (CH_3O), 57.1 (C-2), 98.7 (C-8), 102.5 (C-6), 114.0 (C-4a), 125.3 (C-2′), 126.6 (C-4′), 126.7 (C-3), 127.2 (C-5), 127.3 (C-4″), 128.1 (PhH), 128.4 (PhH), 128.9 (PhH), 135.3 (C-4), 139.6 (C-1″), 144.5 (C-8a), 148.8 (C-1′), 160.5 (C-7); MS (70 eV) m/z 327 (M^+, 4), 312 (100), 269 (17), 250 (25), 207 (11), 77 (4). HRMS (EI) m/z [M^+] calcd for $C_{23}H_{21}NO$: 327.1623; found: 327.1624.

*7-Methoxy-2-methyl-2,4-di-p-tolyl-1,2-dihydroquinoline (**3i**).*[18c] *Method C.* A mixture of **1b** (0.050 g, 0.41 mmol), **2i** (0.27 g, 2.0 mmol), Li_2CO_3 (0.015 g, 0.20 mmol) and $MgBr_2$ (0.075 g, 0.41 mmol) was heated to 90 °C for 5 h to give 0.105 g (73%) of **3i** as a pale yellow oil. R_f 0.70 (hexane/EtOAc, 7:3). IR (film) 3376, 2920, 1612, 1509, 1464, 1294, 1276, 1221, 1167, 1114, 1039, 814 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.65 (s, 3H, CH_3-C2), 2.23 (s, 3H, CH_3Ph), 2.29 (s, 3H, CH_3Ph), 3.66 (s, 3H, CH_3O), 4.11 (br s, 1H, N*H*), 5.40 (s, 1H, H-3), 6.01−6.06 (m, 2H, H-6, H-8), 6.73−6.78 (m, 1H, H-5), 7.02−7.08 (m, 2H, H-3′), 7.06−7.12 (m, 2H, H-3″), 7.12−7.20 (m, 2H, H-2″), 7.31−7.37 (m, 2H, H-2′); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 20.9 (CH_3Ph-C2), 21.2 (CH_3Ph-C4), 30.2 (CH_3-C2), 55.1 (CH_3O), 56.8 (C-2), 98.6 (C-8), 102.4 (C-6), 114.1 (C-4a), 125.2 (C-2′), 126.5 (C-3), 127.2 (C-5), 128.8 (C-2″, C-3″), 129.0 (C-3′), 135.0 (C-4), 136.3 (C-4′), 136.7 (C-4″), 136.9 (C-1″), 144.6 (C-8a), 146.0 (C-1′), 160.4 (C-7). MS (70 eV) m/z 355 (M^+, 4), 340 (100), 297 (16), 264 (24), 221 (15). HRMS (EI) m/z [M^+] calcd for $C_{25}H_{25}NO$: 355.1936; found: 355.1943.

*7-Methoxy-2-methyl-2,4-bis(4-methoxyphenyl)-1,2-dihydroquinoline (**3j**). Method C.* A mixture of **1b** (0.050 g, 0.41 mmol), **2j** (0.300 g, 2.05 mmol), Li_2CO_3 (0.015 g, 0.20 mmol) and $MgBr_2$ (0.075 g, 0.41 mmol) was heated to 90 °C for 5 h to give 0.108 g (69%) of **3j** as a pale yellow oil. R_f 0.73 (hexane/EtOAc, 7:3). IR (film) 3372, 2959, 2931, 1610, 1509, 1463, 1291, 1246, 1176, 1034, 828 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.73 (s, 3H, CH_3-C2), 3.75 (s, 3H, CH_3O), 3.79 (s, 3H, CH_3O), 3.83 (s, 3H, CH_3O), 5.44 (s, 1H, H-3), 6.11 (d, J = 2.1 Hz, 1H, H-8), 6.12 (dd, J = 8.3, 2.1 Hz, 1H, H-6), 6.84 (d, J = 8.4 Hz, 1H, H-5), 6.82−6.88 (m, 2H, H-3′), 6.88−6.96 (m, 2H, H-3″), 7.22−7.31 (m, 2H, H-2′), 7.44−7.51 (m, 2H, H-2″); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 30.0 (CH_3-C2), 55.08 (CH_3O), 55.22 (CH_3O), 55.25 (CH_3O), 56.6 (C-2), 98.6 (C-8), 102.4 (C-6), 113.5 (C-3′ or C-3″), 113.6 (C-3″ or C-3′), 114.2 (C-4a), 126.4 (C-3), 126.5 (C-2′), 127.2 (C-5), 130.0 (C-2″), 132.0 (C-1″), 134.5 (C-4), 141.2 (C-1′), 144.5 (C-8a), 158.3 (C-4′), 158.9 (C-4″), 160.4 (C-7); MS (70 eV) m/z 387 (M^+, 7), 330 (16), 263 (90), 262 (100), 236 (31), 219 (36), 204 (20), 177 (17). HRMS (EI) m/z [M^+] calcd for $C_{25}H_{25}NO_3$: 387.1834; found: 387.1835.

*7-Methoxy-2-methyl-2,4-bis(4-nitrophenyl)-1,2-dihydroquinoline (**3k**). Method C.* A mixture of **1b** (0.050 g, 0.41 mmol), **2k** (0.33 g, 2.0 mmol), Li_2CO_3 (0.015 g, 0.20 mmol) and $MgBr_2$ (0.075 g, 0.41 mmol) was heated to 90 °C for 5 h to give 0.078 g (46%) of **3k** as a pale red oil. *Rf* 0.66 (hexane/EtOAc, 7:3). IR (film) 3381, 2925, 1613, 1596, 1516, 1465, 1346, 1289, 1275, 1223, 1169, 1108, 1037, 852, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.82 (s, 3H, CH_3-C2), 3.79 (s, 3H, CH_3O), 4.38 (br s, 1H, N*H*), 5.57 (s, 1H, H-3), 6.19 (dd, J = 8.6, 2.4 Hz, 1H, H-6), 6.24 (d, J = 2.4 Hz, 1H, H-8), 6.70 (d, J = 8.6 Hz, 1H, H-5), 7.46−7.52 (m, 2H, H-2″), 7.67−7.73 (m, 2H, H-2′), 8.16−8.20 (m, 2H, H-3′), 8.20−8.26 (m, 2H, H-3″); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 30.3 (CH_3-C2), 55.5 (CH_3O), 57.5 (C-2), 99.5 (C-8), 103.9 (C-6), 113.1 (C-4a), 123.8 (C-3′), 124.1 (C-3″), 126.3 (C-2′), 126.4 (C-3), 127.5 (C-5), 130.0 (C-2″), 135.53 (C-4a), 144.4 (C-8a), 146.3 (C-1″), 147.1 (C-4′), 147.6 (C-4″), 155.7 (C-1′), 161.5 (C-7); MS (70 eV) m/z 417 (M^+, 2), 371 (100), 356 (18), 340 (28), 284 (46), 270 (32), 241 (66), 152 (25). HRMS (EI) m/z [M^+-CH_3] calcd for $C_{22}H_{16}N_3O_5$: 402.1090; found: 402.1095.

*Dimethyl 7-Methoxy-2-methyl-1,2-dihydroquinoline-2,4-dicarboxylate (**3l**). Dimethyl 5-Methoxy-2-methyl-1,2-dihydroquinoline-2,4-dicarboxylate (**4l**). Method A.* A mixture of **1b** (0.050 g, 0.41 mmol), **2l** (0.23 g, 2.25 mmol), Li_2CO_3 (0.015 g, 0.20 mmol) and $MgBr_2$ (0.075 g, 0.41 mmol) was heated to 60 °C for 1 h to give 0.065 g (55%) of **3l** as a yellow solid and 0.017 g (15%) of **4l** as a white solid. Data of **3l**: R_f 0.55 (hexane/EtOAc, 7:3); mp 106−107 °C. IR (film) 3369, 2953, 1723, 1614, 1517, 1438, 1272, 1232, 1198, 1170, 1146, 1117, 1022, 838, 800 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.55 (s, 3H, CH_3-C2″), 3.74 (s, 3H, CO_2CH_3-1), 3.77 (s, 3H, CH_3O-7″), 3.85 (s, 3H, CO_2CH_3-1′), 4.52 (br s, 1H, N*H*), 6.18 (d, J = 2.6 Hz, 1H, H-8″), 6.30 (dd, J = 8.8, 2.6 Hz, 1H, H-6″), 6.54 (br s, 1H, H-3″), 7.73 (d, J = 8.8 Hz, 1H, H-5″); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 27.5 (CH_3-C2″), 52.0 (CO_2CH_3-1′), 52.8 (CO_2CH_3-1), 55.1 (CH_3O-7″), 58.6 (C-2″), 99.4 (C-8″), 104.5 (C-6″), 109.9 (C-4a″), 118.0 (C-8a″), 127.9 (C-5″), 130.0 (C-3″), 144.1 (C-4″), 160.9 (C-7″), 166.3 (CO_2CH_3-1′), 174.6 (CO_2CH_3-1); MS (70 eV) m/z 291 (M^+, 1), 276 (1), 246 (5), 232 (100), 189 (5), 173 (10), 130 (5). HRMS (EI) m/z [M^+] calcd for $C_{15}H_{17}NO_5$: 291.1107; found: 291.1106. Data of **4l**: R_f 0.48 (hexane/EtOAc, 7:3); mp 144−145 °C. IR (KBr) 3368, 2947, 1725, 1636, 1602, 1502, 1469, 1435, 1358, 1324, 1274, 1246, 1198, 1173, 1127, 1089, 1026, 967, 758, 737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.52 (s, 3H, CH_3-C2″), 3.73 (s, 3H, CO_2CH_3-1), 3.75 (s, 3H, CH_3O-5″), 3.80 (s, 3H, CO_2CH_3-1′), 4.57 (br s, 1H, N*H*), 6.04 (d, J = 1.8 Hz, 1H, H-3″), 6.27 (d, J = 8.1 Hz, 1H, H-6″), 6.33 (dd, J = 8.1, 0.9 Hz, 1H, H-8″), 7.05 (t, J = 8.1 Hz, 1H, H-7″); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 26.7 (CH_3-C2″), 52.0 (CO_2CH_3-1′), 52.7 (CO_2CH_3-1), 55.8 (CH_3O-5″), 57.8 (C-2″), 101.7 (C-6″), 104.7 (C-4a″), 107.8 (C-8″), 126.3 (C-3″), 129.1 (C-4″), 130.4 (C-7″), 144.1 (C-8a″), 155.7 (C-5″), 169.6 (CO_2CH_3-1′), 174.6 (CO_2CH_3-1); MS (70 eV) m/z 291 (M^+, 1), 276 (2), 260 (3), 232 (100), 204 (2), 186 (3), 172 (7), 159 (12), 143 (4), 131 (4). HRMS (EI) m/z [M^+-OMe] calcd for $C_{14}H_{14}NO_4$: 260.0923; found: 260.0916.

*7-Chloro-2,4-diethyl-2-methyl-1,2-dihydroquinoline (**3m**).*[55] *Method A.* A mixture of **1c** (0.050 g, 0.39 mmol), **2b** (0.140 g, 1.95 mmol), Li_2CO_3 (0.015 g, 0.20 mmol) and $MgBr_2$ (0.072 g, 0.39 mmol) was heated to 60 °C for 6 h to give 0.041 g (45%) of **3m** as a pale yellow oil. R_f 0.95 (hexane/EtOAc, 7:3). IR (film) 3391, 2965,

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2924, 1650, 1597, 1569, 1493, 1478, 1454, 1376, 1305, 1161, 1091, 880, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 7.4, 3H, CH_3CH_2-C2), 1.13 (t, J = 7.2 Hz, 3H, CH_3CH_2-C4), 1.22 (s, 3H, CH_3-C2), 1.41−1.56 (m, 2H, CH_3CH_2-C2), 2.34 (qd, J = 7.2, 1.1 Hz, 2H, CH_3CH_2-C4), 3.63 (br s, 1H, N*H*), 5.17 (s, 1H, H-3), 6.39 (d, J = 2.0 Hz, 1H, H-8), 6.51 (dd, J = 8.2, 2.0 Hz, 1H, H-6), 6.95 (d, J = 8.2 Hz, 1H, H-5); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 8.5 (CH_3CH_2-C2), 12.7 (CH_3CH_2-C4), 24.5 (CH_3CH_2-C4), 29.7 (CH_3-C2), 36.7 (CH_3CH_2-C2), 54.9 (C-2), 112.1 (C-8), 116.3 (C-6), 119.0 (C-4a), 124.2 (C-5), 125.0 (C-3), 133.3 (C-4), 134.1 (C-7), 145.0 (C-8a); MS (70 eV) m/z 236 (M^+, 1), 207 (38), 205 (100), 190 (25), 170 (13), 154 (22), 140 (12), 127 (17). HRMS (EI) m/z [M^+] calcd for $C_{14}H_{18}ClN$: 235.1128; found: 235.1139.

*2,4-Diethyl-2,7-dimethyl-1,2-dihydroquinoline (**3n**). Method A.* A mixture of **1d** (0.15 g, 1.4 mmol), **2b** (0.504 g, 7.00 mmol), Li_2CO_3 (0.052 g, 0.70 mmol) and $MgBr_2$ (0.258 g, 1.40 mmol) was heated to 60 °C for 7 h to give 0.295 g (98%) of **3n** as a pale yellow oil. R_f 0.80 (hexane/EtOAc, 7:3). IR (film) 3377, 2964, 2918, 1648, 1614, 1475, 1452, 1374, 1321, 841, 802 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, J = 7.5 Hz, 3H, CH_3CH_2-C2), 1.15 (t, J = 7.5 Hz, 3H, CH_3CH_2-C4), 1.21 (s, 3H, CH_3-C2), 1.38−1.60 (m, 2H, CH_3CH_2-C2), 2.21 (s, 3H, CH_3-C7), 2.30−2.41 (m, 2H, CH_3CH_2-C4), 3.53 (br s, 1H, N*H*), 5.14 (s, 1H, H-3), 6.26 (d, J = 0.9 Hz, 1H, H-8), 6.41 (dd, J = 7.8, 0.9 Hz, 1H, H-6), 6.97 (d, J = 7.8 Hz, 1H, H-5); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.5 (CH_3CH_2-C2), 12.9 (CH_3CH_2-C4), 21.3 (CH_3-C7), 24.6 (CH_3CH_2-C4), 29.4 (CH_3-C2), 36.4 (CH_3CH_2-C2), 54.5 (C-2), 113.4 (C-8), 117.5 (C-6), 118.0 (C-4a), 123.1 (C-5), 124.1 (C-3), 134.7 (C-4), 138.1 (C-7), 143.8 (C-8a); MS (70 eV) m/z 215 (M^+, 4), 200 (14), 186 (100), 171 (27), 154 (10), 144 (6), 128 (7). HRMS (EI) m/z [M^+] calcd for $C_{15}H_{21}N$: 215.1674; found: 215.1677.

*7-Methyl-1,2,3,5-tetrahydrospiro[cyclopenta[c]quinoline-4,1′-cyclopentane] (**3o**). Method A.* A mixture of **1d** (0.100 g, 0.93 mmol), **2f** (0.391 g, 4.65 mmol), Li_2CO_3 (0.034 g, 0.46 mmol) and $MgBr_2$ (0.171 g, 0.93 mmol) was heated to 60 °C for 7 h to give 0.221 g (99%) of **3o** as a white solid. R_f 0.80 (hexane/EtOAc, 7:3); mp 102−103 °C.[52] IR (film) 3391, 2951, 2864, 1658, 1610, 1595, 1509, 1458, 1366, 1168, 884, 808 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60−1.80 (m, 6H, H-2′, 2H-3′, 2H-4′, H-5′), 1.80−1.92 (m, 2H, H-2′, H-5′), 1.94−2.06 (m, 2H, H-2), 2.20 (s, 3H, CH_3-7), 2.44−2.54 (m, 2H, H-1), 2.59−2.68 (m, 2H, H-3), 3.85 (br, 1H, N*H*) 6.27 (d, J = 0.6 Hz, 1H, H-6), 6.42 (dd, J = 7.2, 0.6 Hz, 1H, H-8), 6.76 (d, J = 7.2 Hz, 1H, H-9); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.4 (CH_3-7), 22.3 (C-2), 23.8 (C-3′, C4′), 31.1 (C-3), 32.0 (C-1), 39.6 (C-2′, C-5′), 65.0 (C-4), 112.8 (C-6), 117.9 (C-8), 123.1 (C-9), 132.0 (C-9b), 137.3 (C-7), 137.5 (C-3a), 142.5 (C-5a); MS (70 eV) m/z 239 (M^+, 2), 224 (10), 210 (22), 181 (18), 167 (8). HRMS (EI) m/z [M^+] calcd for $C_{17}H_{21}N$: 239.1674; found: 239.1672.

*2,7-Dimethyl-2,4-diphenyl-1,2-dihydroquinoline (**3p**).[18c,54] Method C.* A mixture of **1d** (0.100 g, 0.93 mmol), **2h** (0.561 g, 4.67 mmol), Li_2CO_3 (0.034 g, 0.47 mmol) and $MgBr_2$ (0.171 g, 0.93 mmol) was heated to 90 °C for 19 h to give 0.285 g (98%) of **3p** as a yellow oil. R_f 0.78 (hexane/EtOAc, 7:3). IR (film) 3378, 3025, 2968, 2921, 1615, 1490, 1467, 1443, 1320, 1181, 1028, 805, 763, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.75 (s, 3H, CH_3-C2), 2.22 (s, 3H, CH_3-C7), 4.12 (br s, 1H, N*H*), 5.50 (s, 1H, H-3), 6.36−6.37 (m, 2H, H-6, H-8), 6.78 (d, J = 8.0 Hz, 1H, H-5), 7.22 (tt, J = 8.0 Hz, 1H, H-4′), 7.28−7.38 (m, 7H, H-3′, H-2″, H-3″, H-4″), 7.54−7.56 (m, 2H, H-2′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4 (CH_3-C7), 30.1 (CH_3-C2), 57.1 (C-2), 113.7 (C-8), 117.7 (C-4a), 118.1 (C-6), 125.4 (C-2′), 126.0 (C-5), 126.7 (PhH), 127.3 (PhH), 128.1 (C-3), 128.1 (PhH), 128.4 (PhH), 128.9 (PhH), 135.6 (C-4), 139.0 (C-7), 139.6 (C-1″), 143.1 (C-8a), 148.9 (C-1′); MS (70 eV) m/z 296 (M^+-15, 54), 280 (8), 234 (100), 218 (23), 204 (16), 189 (8), 77 (44). HRMS (EI) m/z [M^+] calcd for $C_{23}H_{21}N$: 311.1674; found: 311.1675.

*Dimethyl 3-Methyl-3,4-dihydrobenzo[f]quinoline-1,3-dicarboxylate (**3q**). Method A.* A mixture of **1e** (0.100 g, 0.70 mmol), **2l** (0.356 g, 3.50 mmol), Li_2CO_3 (0.026 g, 0.35 mmol) and $MgBr_2$ (0.129 g, 0.70 mmol) was heated to 60 °C for 1 h to give 0.208 g (96%) of **3q** as a yellow solid. R_f 0.32 (hexane/EtOAc, 7:3); mp 179−180 °C. IR (film) 3365, 1720, 1625, 1519, 1446, 1386, 1243, 1195, 1173, 1120, 816, 748 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.56 (s, 3H, CH_3-C3), 3.72 (s, 3H, CO_2CH_3-C3), 3.79 (s, 3H, CO_2CH_3-C1), 4.86 (br s, 1H, N*H*), 6.43 (s, 1H, H-2), 6.97 (d, J = 8.3 Hz, 1H, H-5), 7.23 (td, J = 8.3, 1.0 Hz, 1H, H-8), 7.34 (td, J = 8.3, 1.0 Hz, 1H, H-9), 7.38 (br d, J = 8.3 Hz, 1H, H-10), 7.63 (d, J = 8.3 Hz, 1H, H-6), 7.67 (d, J = 8.3 Hz, 1H, H-7); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.4 (CH_3-C3), 52.2 (CO_2CH_3-C3), 52.8 (CO_2CH_3-C1), 57.8 (C-3), 110.5 (C-10b), 117.0 (C-5), 122.5 (C-8), 123.2 (C-10), 126.2 (C-9), 128.6 (C-6a), 128.7 (C-7), 129.6 (C-2), 130.0 (C-10a), 130.4 (C-1), 131.0 (C-6), 142.1 (C-4a), 169.6 (CO_2CH_3-C1), 174.5 (CO_2CH_3-C3); MS (70 eV) m/z 311 (M^+, 3), 269 (5), 253 (21), 252 (100), 236 (4), 192 (12), 91 (13), 86 (13). HRMS (EI) m/z [M^+] calcd for $C_{18}H_{17}NO_4$: 311.1158; found: 311.1151.

*Dimethyl 6-Methoxy-2-methyl-1,2-dihydroquinoline-2,4-dicarboxylate (**3r**).[22b,d,23] Method A.* A mixture of **1f** (0.100 g, 0.81 mmol), **2l** (0.414 g, 4.06 mmol), Li_2CO_3 (0.03 g, 0.4 mmol) and $MgBr_2$ (0.149 g, 0.81 mmol) was heated to 60 °C for 1 h gave 0.194 g (82%) of **3r** as a yellow oil. R_f 0.56 (hexane/EtOAc, 7:3). IR (film) 3368, 2916, 1723, 1626, 1498, 1436, 1220, 1154, 1115, 1035, 814, 737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.55 (s, 3H, CH_3-C2), 3.72 (s, 3H, CO_2CH_3-C2), 3.75 (s, 3H, CH_3O), 3.86 (s, 3H, CO_2CH_3-4), 4.41 (br s, 1H, N*H*), 6.69 (d, J = 8.7 Hz, 1H, H-8), 6.72 (dd, J = 8.7, 3.0 Hz, 1H, H-7), 6.75 (s, 1H, H-3), 7.50 (d, J = 3.0 Hz, 1H, H-5); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 26.8 (CH_3-C2), 52.0 (CO_2CH_3-C4), 52.7 (CO_2CH_3-C2), 55.6 (CH_3O), 58.5 (C-2), 111.4 (C-5), 115.1 (C-8), 116.1 (C-7), 117.3 (C-4a), 127.8 (C-4), 134.2 (C-3), 136.6 (C-8a), 152.5 (C-6), 165.3 (CO_2CH_3-4), 174.6 (CO_2CH_3-2); MS (70 eV) m/z 291 (M^+, 1), 283 (1), 217 (16), 216 (100), 215 (52), 188 (16), 184 (22), 157 (32), 156 (65), 155 (23), 129 (17). HRMS (EI) m/z [M^+-MeOH] calcd for $C_{14}H_{14}NO_4$: 260.0923; found: 260.0923.

*Dimethyl 2,6-Dimethyl-1,2-dihydroquinoline-2,4-dicarboxylate (**3s**).[22b] Method A.* A mixture of **1g** (0.100 g, 0.93 mmol), **2l** (0.476 g, 4.67 mmol), Li_2CO_3 (0.034 g, 0.46 mmol) and $MgBr_2$ (0.171 g, 0.93 mmol) was heated to 60 °C for 1 h to give 0.20 g (78%) of **3s** as a yellow oil. R_f 0.57 (hexane/EtOAc, 7:3). IR (film) 3370, 2952, 1724, 1627, 1499, 1437, 1272, 1221, 1154, 1116, 1035, 814, 780, 737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.54 (s, 3H, CH_3-C2), 2.23 (s, 3H, CH_3-C6), 3.73 (s, 3H, CO_2CH_3-C2), 3.86 (s, 3H, CO_2CH_3-4), 4.41 (br s, 1H, N*H*), 6.55 (d, J = 8.0 Hz, 1H, H-8), 6.65 (d, J = 2.0 Hz, 1H, H-3), 6.90 (dd, J = 8.0, 2.0 Hz, 1H, H-7), 7.60 (br s, 1H, H-5); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.8 (CH_3-C6), 27.2 (CH_3-C2), 52.0 (CO_2CH_3-C4), 52.7 (CO_2CH_3-C2), 58.5 (C-2), 114.2 (C-8), 116.5 (C-4a), 126.8 (C-5), 127.9 (C-6), 128.3 (C-4), 130.3 (C-7), 132.9 (C-3), 140.2 (C-8a), 166.2 (CO_2CH_3-C4), 174.6 (CO_2CH_3-C2); MS (70 eV) m/z 275 (M^+, 2), 216 (60), 215 (80), 184 (37), 156 (100), 155 (36), 129 (26), 115 (14). HRMS (EI) m/z [M^+] calcd for $C_{15}H_{17}NO_4$: 275.1158; found: 275.1159.

*Dimethyl 6-Cyano-2-methyl-1,2-dihydroquinoline-2,4-dicarboxylate (**3t**).[22d] Method C.* A mixture of **1h** (0.300 g, 2.54 mmol), **2l** (1.301 g, 12.75 mmol), Li_2CO_3 (0.094 g, 1.27 mmol) and $MgBr_2$ (0.467 g, 2.54 mmol) was heated to 90 °C for 5 h to give 0.69 g (94%) of **3t** as a greenish solid. R_f 0.42 (hexane/EtOAc, 7:3); mp 139−140 °C. IR (film) 3357, 2954, 2217, 1720, 1629, 1602, 1498, 1438, 1282, 1217, 1149, 1116, 1032, 823, 779, 736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60 (s, 3H, CH_3-C2), 3.79 (s, 3H, CO_2CH_3-C2), 3.89 (s, 3H, CO_2CH_3-C4), 4.93 (br s, 1H, N*H*), 6.60 (d, J = 8.3 Hz, 1H, H-8), 6.77 (d, J = 2.1 Hz, 1H, H-3), 7.32 (dd, J = 8.3, 1.7 Hz, 1H, H-7), 8.20 (d, J = 1.7 Hz, 1H, H-5); ^{13}C NMR (75.4 MHz, $CDCl_3$) $\delta\delta$ 28.3 (CH_3-C2), 52.4 (CO_2CH_3-C4), 53.2 (CO_2CH_3-C2), 58.9 (C-2), 100.7 (C-6), 114.1 (C-8), 115.6 (C-4a), 119.9 (CN), 126.4 (C-4), 131.1 (C-5), 133.5 (C-7), 133.6 (C-3), 145.8 (C-8a), 165.2 (CO_2CH_3-C4), 173.3 (CO_2CH_3-C2); MS (70 eV) m/z 286 (M^+, 1), 228 (16), 227 (100), 213 (14), 199 (19), 185 (9), 168 (16). HRMS (EI) m/z [M^+] calcd for $C_{15}H_{14}N_2O_4$ 286.0954, found 286.0966.

*2,6-Diethyl-2-methyl-1,2-dihydroquinoline-6-carbonitrile (**3u**). Method C.* A mixture of **1h** (0.300 g, 2.54 mmol), **2b** (0.918 g, 12.75 mmol), Li_2CO_3 (0.094 g, 1.27 mmol), and $MgBr_2$ (0.467 g, 2.54 mmol) was heated to 90 °C for 15 h to give 0.15 g (26%) of **3u** as a yellow solid: R_f 0.67 (hexane/EtOAc, 7:3); mp 105−106 °C. IR (film) 3342, 2965, 2210, 1652, 1599, 1503, 1450, 1333, 1309, 1185, 891, 816

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cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, J = 7.5 Hz, 3H, CH_3CH_2-C2), 1.16 (t, J = 7.5 Hz, 3H, CH_3CH_2-C4), 1.28 (s, 3H, CH_3-C2), 1.42−1.60 (m, 2H, CH_3CH_2-C2), 2.35 (qd, J = 7.5, 1.2 Hz, 2H, CH_3CH_2-C4), 4.05 (br s, 1H, N*H*), 5.21 (br s, 1H, H-3), 6.35 (d, J = 8.4 Hz, 1H, H-8), 7.19 (dd, J = 8.4, 2.1 Hz, 1H, H-7), 7.27 (d, J = 2.1 Hz, 1H, H-5); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 8.5 (CH_3CH_2-C2), 12.5 (CH_3CH_2-C4), 24.2 (CH_3CH_2-C4), 30.8 (CH_3-C2), 37.5 (CH_3CH_2-C2), 55.7 (C-2), 97.7 (C-6), 112.1 (C-8), 119.8 (C-4a), 121.0 (CN), 125.5 (C-3), 127.2 (C-5), 132.6 (C-7), 133.5 (C-4), 147.5 (C-8a); MS (70 eV) m/z 226 (M^+, 1), 211 (12), 198 (15), 197 (100), 196 (9), 183 (6), 182 (26), 181 (6). HRMS (EI) m/z [M^+] calcd for $C_{15}H_{18}N_2$ 226.1470, found 226.1480.

*2,6-Diethyl-2-methyl-6-nitro-1,2-dihydroquinoline (**3v**). Method C.* A mixture of **1i** (0.300 g, 2.16 mmol), **2b** (0.778 g, 10.80 mmol), Li_2CO_3 (0.081 g, 1.08 mmol), and $MgBr_2$ (0.397 g, 2.16 mmol) was heated to 90 °C for 15 h to give 0.165 g (31%) of **3v** as redish crystals: R_f 0.65 (hexane/EtOAc, 7:3); mp 150−151 °C. IR (film) 3324, 2966, 1656, 1602, 1582, 1533, 1505, 1460, 1368, 1283, 1251, 1154, 1108, 821, 748, 734, 651 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, J = 7.5 Hz, 3H, CH_3CH_2-C2), 1.19 (t, J = 7.5 Hz, 3H, CH_3CH_2-C4), 1.32 (s, 3H, CH_3-C2), 1.48−1.61 (m, 2H, CH_3CH_2-C2), 2.42 (m, 2H, CH_3CH_2-C4), 4.53 (br s, 1H, N*H*), 5.25 (br s, 1H, H-3), 6.34 (d, J = 9.0 Hz, 1H, H-8), 7.89 (dd, J = 9.0, 2.5 Hz, 1H, H-7), 6.96 (d, J = 2.5 Hz, 1H, H-5); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.5 (CH_3CH_2-C2), 12.4 (CH_3CH_2-C4), 24.3 (CH_3CH_2-C4), 31.1 (CH_3-C2), 37.6 (CH_3CH_2-C2), 56.3 (C-2), 111.1 (C-8), 118.6 (C-4a), 119.8 (C-5), 125.4 (C-3), 125.7 (C-7), 133.6 (C-4), 137.4 (C-6), 149.9 (C-8a); MS (70 eV) m/z 246 (M^+, 1), 231 (9), 218 (14), 217 (100), 185 (24), 172 (14), 171 (78), 170 (15), 159 (8); HRMS (EI) m/z [M^+] calcd for $C_{14}H_{18}N_2O_2$ 246.1368, found 246.1360.

*2,6-Diethyl-8-methoxy-2-methyl-1,2-dihydroquinoline (**3w**). Method C.* A mixture of **1k** (0.300 g, 2.44 mmol), **2b** (0.88 g, 12.2 mmol), Li_2CO_3 (0.090 g, 1.22 mmol), and $MgBr_2$ (0.449 g, 2.44 mmol) was heated to 90 °C for 15 h to give 0.24 g (42%) of **3w** as a greenish oil: R_f 0.81 (hexane/EtOAc, 7:3); IR (film) 3406, 2964, 2933, 1646, 1608, 1578, 1488, 1460, 1375, 1256, 1217, 1044, 993, 968, 915, 843, 777, 728, 635 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, J = 7.5 Hz, 3H, CH_3CH_2-C2), 1.15 (t, J = 7.5 Hz, 3H, CH_3CH_2-C4), 1.23 (s, 3H, CH_3-C2), 1.45−1.57 (m, 2H, CH_3CH_2-C2), 2.35−2.45 (m, 2H, CH_3CH_2-C4), 3.82 (s, 3H, CH_3O), 4.16 (br s, 1H, N*H*), 5.19 (br s, 1H, H-3), 6.53 (t, J = 8.0 Hz, 1H, H-6), 6.64 (d, J = 8.0 Hz, 1H, H-7), 6.77 (d, J = 8.0 Hz, 1H, H-5); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.5 (CH_3CH_2-C2), 13.0 (CH_3CH_2-C4), 24.9 (CH_3CH_2-C4), 29.5 (CH_3-C2), 36.4 (CH_3CH_2-C2), 54.1 (C-2), 55.6 (CH_3O), 109.4 (C-7), 115.0 (C-6), 115.9 (C-5), 120.5 (C-4a), 125.0 (C-3), 133.7 (C-8a), 134.9 (C-4), 145.4 (C-8); MS (70 eV) m/z 231 (M^+, 8), 216 (10), 203 (15), 202 (100), 185 (8), 187 (44), 186 (9), 172 (6); HRMS (EI) m/z [M^+] calcd for $C_{15}H_{21}NO$ 231.1623, found 231.1615.

*Dimethyl 8-Methoxy-2-methyl-1,2-dihydroquinoline-2,4-dicarboxylate (**3x**). Method A.* A mixture of **1k** (0.300 g, 2.44 mmol), **2l** (1.24 g, 12.2 mmol), Li_2CO_3 (0.090 g, 1.22 mmol), and $MgBr_2$ (0.440 g, 2.39 mmol) was heated to 60 °C for 1 h to give 0.61 g (86%) of **3x** as a greenish solid: R_f 0.54 (hexane/EtOAc, 7:3); mp 99−100 °C; IR (KBr) 3372, 3080, 2953, 1726, 1630, 1580, 1452, 1378, 1238, 1121, 1082, 1030, 959, 841, 737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.58 (s, 3H, CH_3-C2), 3.74 (s, 3H, CO_2CH_3-C2), 3.85 (s, 3H, CO_2CH_3-4), 3.87 (s, 3H, CH_3O), 5.12 (br s, 1H, N*H*), 6.67 (d, J = 2.1 Hz, 1H, H-3), 6.67 (t, J = 8.1 Hz, 1H, H-6), 6.74 (dd, J = 8.1, 1.5 Hz, 1H, H-7), 7.43 (br dd, J = 8.1, 0.9 Hz, 1H, H-5); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 27.5 (CH_3-C2), 52.0 (CO_2CH_3-C4), 52.7 (CO_2CH_3-C2), 55.7 (CH_3O), 58.3 (C-2), 110.5 (C-7), 116.2 (C-4a), 117.2 (C-6), 118.6 (C-5), 128.2 (C-4), 132.6 (C-8a), 132.7 (C-3), 145.9 (C-8), 166.2 (CO_2CH_3-C4), 174.5 (CO_2CH_3-C2); MS (70 eV) m/z 291 (M^+, 1), 276 (2), 246 (5), 232 (100), 217 (32), 159 (17), 131 (4), 103 (3); HRMS (EI) m/z [M^+] calcd for $C_{15}H_{17}NO_5$ 291.1107, found 291.1121.

*(E)-3-Methoxy-N-(1-phenylethylidene)aniline (**8**).* In a 25-mL round-bottomed flask, a mixture of **1b** (0.388 g, 3.15 mmol), phenylacetylene (**9**) (0.082 g, 0.80 mmol), and mercury(I) chloride (0.035 g, 0.074 mmol) was vigorously stirred at 20 °C for 24 h. A 3 M aqueous solution of KOH (10 mL) and $NaBH_4$ (0.0076 g, 0.20 mmol) was added, and the mixture was stirred at 20 °C for 10 min and then filtered followed by the extraction of the aqueous layer with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed under vacuum. The excess of **1b** was removed by distillation with a Kugelrohr apparatus, giving a pure residue of **8** (0.179 g, 99%) as a pale yellow oil: R_f 0.75 (hexane/EtOAc, 7:3); IR (film) 1634, 1595, 1579, 1483, 1447, 1287, 1261, 1147, 1043, 912, 851, 764, 693 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.27 (s, 3H, $CH_3C{=}N$), 3.83 (s, 3H, CH_3O), 6.38−6.46 (m, 2H, H-2, H-4), 6.68 (dd, J = 8.1, 2.4 Hz, 1H, H-6), 7.29 (t, J = 8.1 Hz, 1H, H-5), 7.42−7.54 (m, 3H, H-3′, H-4′), 7.96−8.05 (m, 2H, H-2′); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 17.3 ($CH_3C{=}N$), 55.1 (CH_3O), 104.9 (C-2), 108.7 (C-6), 111.6 (C-4), 127.1 (C-2′), 128.3 (C-3′), 129.7 (C-4′), 130.4 (C-5), 139.2 (C-1′), 153.0 (C-1), 160.2 (C-3), 165.5 (*C*=N); MS (70 eV) m/z 225 (M^+, 43), 210 (100), 195 (11), 180 (10), 167 (12), 148 (18), 103 (21), 92 (22), 77 (50); HRMS (EI) m/z [M^+] calcd for $C_{15}H_{15}NO$ 225.1154, found 225.1139.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of the ^1H NMR, ^{13}C NMR, and MS spectra of all compounds. Crystallographic information for **3x**, including X-ray diffraction data, atomic coordinates, thermal parameters, torsion angles, and complete bond distances and angles. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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