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Intramolecular Mizoroki–Heck Reaction in the Regioselective Synthesis of 4-Alkylidene-tetrahydroquinolines

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The Mizoroki–Heck reaction of *N*-alkenyl-substituted 2-haloanilines is an effective protocol for the synthesis of substituted 4-alkylidene-tetrahydroquinoline derivatives, avoiding isomerization and oxidation. When non-substituted alkenes are used, the regioselectivity of the reaction can be directed towards the formation of an exocyclic or endocyclic double bond by choosing an adequate catalytic system. When the double bond is substituted by an amide moiety, the exocyclic double bond of *E* geometry is obtained selectively. Thus, this protocol efficiently synthesizes a series of 2-substituted tetrahydroquinolines with an *exo* α,β-unsaturated amide moiety at the C-4 position.

Introduction

Quinoline derivatives are an important class of compounds in the pharmaceutical and agrochemical industries, as well as building blocks for the total synthesis of natural products.[1] For example, several 2-aryl-tetrahydroquinolines and their aromatic counterparts have shown antifungal and anticancer activity,[2] whereas 1,2-dihydro derivatives as ethoxyquin are known by their antioxidant effects.[3] 4-Alkylidene-tetrahydroquinoline derivatives have attracted much attention as in vivo potent antagonists of the glycine binding site associated with the *N*-methyl-D-aspartic acid receptor, a target for innovative drugs to treat chronic neuropathic pain. The presence of an *exo* α,β-unsaturated amide moiety at the C-4 position of these compounds was found to play a pivotal role in their bioactivities.[4] In addition, many naturally occurring alkaloids[5] contain the tetrahydroquinoline or quinoline unit with the exocyclic double bond (Figure 1).[6]

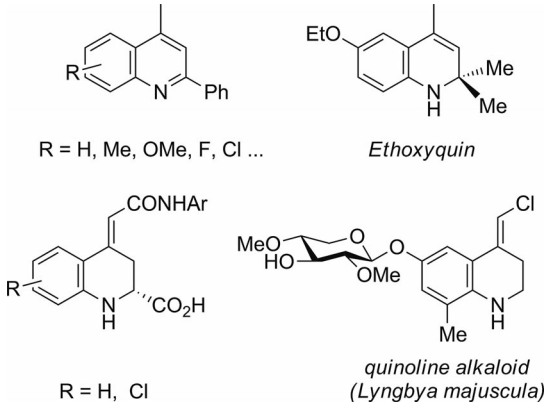

Figure 1. Selected bioactive quinoline derivatives.

Classical methods for quinoline synthesis often do not allow adequate diversity and substitution on the quinoline ring system.[7] Therefore, considerable efforts have been dedicated to developing new methods for the preparation of these pharmacophores: from acid promoted cycloaddition reactions to ruthenium or palladium-catalyzed methodologies.[8] Within that last category, we have reported that intermolecular palladium-catalyzed arylation followed by Grignard addition to imines, and ring-closing metathesis provides an efficient approach to 2-phenyl-substituted quinoline, benzazocine, and benzazepine derivatives.[9] 2,4-Substituted tetrahydroquinolines can be obtained through intramolecular carbolithiation of *N*-alkenyl-substituted 2-iodoanilines, even enantioselectively.[10]

However, the high reactivity associated with organolithium intermediates narrows the functional group tolerance for this procedure. Thus, although a variety of synthetic methods for preparing quinoline derivatives are available, it is still highly desirable to develop efficient procedures to obtain useful polyfunctionalized quinolines. In this context, palladium-catalyzed coupling reactions[11] and, in particular, the intramolecular Mizoroki–Heck reaction[12] is of special relevance. These reactions have found wide application in synthesis for preparing complex organic structures,[13] even asymmetrically,[14] and are also applied in the chemical and pharmaceutical industries.[15]

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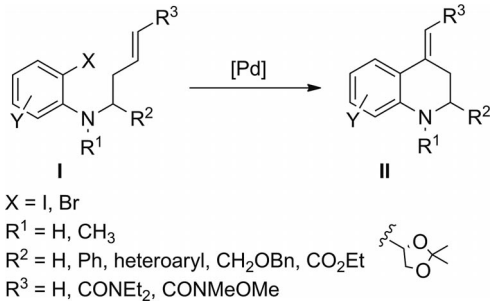
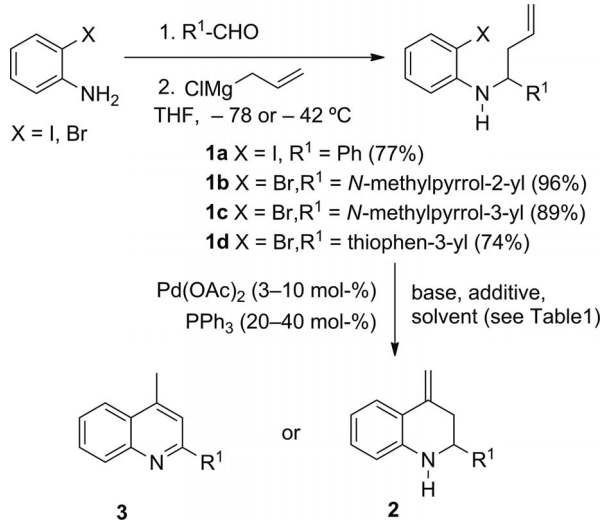
With these precedents, we envisioned that the Mizoroki–Heck reaction of *N*-alkenyl-substituted 2-haloanilines could lead to an effective protocol for the synthesis of substituted 4-alkylidene-tetrahydroquinoline derivatives **II**. Thus, we prepared a series of butenylanilines **I**, with different substitution patterns in the alkene and α to the nitrogen atom (Scheme 1), that would lead to tetrahydroquinolines **II**. This kind of approach has been studied before, but over-oxidation reactions or formation of regioisomeric mixtures have been observed. Pd-catalyzed cyclization of **I** (Y, R^1, R^2, R^3 = H) was previously reported by Larock[16] and 4-methylquinoline was obtained through 6-*exo* cyclization followed by double bond migration and oxidation. Starting from the same substrate, in the presence of Pd/N-heterocyclic carbene catalyst, Caddick[17] observed the formation of a mixture of isomers through 6-*exo* or 7-*endo* cyclization and double bond migration. Thus, the main issue would be to obtain a regioselective procedure, avoiding over-oxidation and double-bond isomerization reactions that may occur in this type of reaction. Here we present a full account of our investigations.



Scheme 1. Mizoroki–Heck approach to 4-alkylidene-substituted quinolines.

Results and Discussion

It has been shown that the presence of a heterocyclic ring substituent (R^2) is one of the main structural requirements for the biological activity of homoallylamines with general structure **I** and their quinoline or tetrahydroquinoline derivatives (**II**).[18] For this reason we started our study preparing a series of secondary butenylanilines **1a**–**d**, which carry a phenyl or heteroaryl group α to the nitrogen atom, in high overall yields, by condensation of *o*-iodo or *o*-bromoaniline and the corresponding aldehyde, followed by addition of allylmagnesium chloride (Scheme 2).[19] When **1a** was treated under phosphane-free Jeffery conditions,[20] (Table 1, Entry 1), 4-methyl-2-phenylquinoline **3a** was obtained in moderate yield after 6-*exo* cyclization, isomerization and oxidation, as has been described for *o*-iodobutenylaniline under analogous conditions.[16] Various reaction conditions were tested to avoid this isomerization and oxidation. A change in the solvent to acetonitrile (Table 1, Entry 2) gave a sluggish reaction, obtaining also **3a** as the main product, in moderate yield. However, in the presence of PPh_3, 4-methylene-trahydroquinoline **2a** was obtained (Table 1, Entry 3).



Scheme 2. Synthetic route to compounds **2** and **3**.

Table 1. Synthesis of 2-aryl-substituted 4-methylene-quinolines **2a**–**d**.

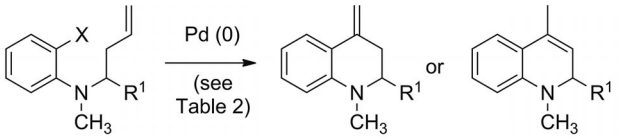
	Substrate	Base, additive	Solvent	**2** or **3** [%]
1	**1a**[a]	Na_2CO_3, Bu_4NBr	DMF	**3a**, 50
2	**1a**[a]	Na_2CO_3, Bu_4NBr	CH_3CN	**3a**, 33
3	**1a**[b]	Na_2CO_3, Bu_4NCl	CH_3CN	**2a**, 54
4	**1b**[a]	Na_2CO_3, Bu_4NCl	DMF	[d]
5	**1b**[b]	Na_2CO_3, Bu_4NCl	CH_3CN	**2b**, 71
6	**1b**[c]	Bu_4NOAc	DMSO	**2b**, 49
7	**1c**[b]	Na_2CO_3, Bu_4NCl	CH_3CN	[e]
8	**1c**[c]	Bu_4NOAc	DMSO	**2c**, 55
9	**1d**[b]	Na_2CO_3, Bu_4NCl	CH_3CN	**2d**, 18 **3d**, 30
10	**1d**[c]	Bu_4NOAc	DMSO	**2d**, 14

[a] 3 mol-% $Pd(OAc)_2$, no PPh_3 was added. [b] 3 mol-% $Pd(OAc)_2$, 20 mol-% PPh_3. [c] 10 mol-% $Pd(OAc)_2$, 40 mol-% PPh_3. [d] Starting material was recovered. [e] Mixture of products **2c** and **3c** were detected by NMR spectroscopy.

These conditions were applied to α-heteroaryl-substituted amines **1b**–**d**. Although **1b** gave expected product **2b** in good yield (Table 1, Entry 5), oxidation could not be avoided with **1c** and **1d**, leading to low isolated yields of tetrahydroquinoline **2d**, or a mixture of products in the case of **1c** (Table 1, Entries 7 and 9). However, the use of Bu_4NOAc and dimethyl sulfoxide (DMSO) with a larger amount of phosphane, improved the results with **1c** (Table 1, Entry 8). These conditions would favor a cationic pathway for the alkene insertion, and have been shown to favor the direct arylation reaction of the pyrrole nucleus.[21] However, no arylation products of the pyrrole or the thiophene ring were observed with **1b**–**d**.

We next focused our attention on the reaction of tertiary anilines. For this purpose, we chose butenyl anilines **4a**–**d**, that incorporate different functionality on the α position to nitrogen (Scheme 3). By using a similar approach, amines **4a**, **4c**, and **4d** were prepared by condensation with the corresponding aldehyde, followed by allylation of the imine,

and subsequent methylation. Amine **4b** was obtained by sequential alkylation reactions.[19]



4a X = I, R^1 = Ph
4b X = I, R^1 = H
4c X = I, R^1 = CH_2OBn
4d X = Br, R^1 = CO_2Et

5a R^1 = Ph
5b R^1 = H
5c R^1 = CH_2OBn
5d R^1 = CO_2Et

6a R^1 = Ph
6b R^1 = H
6c R^1 = CH_2OBn
6d R^1 = CO_2Et

Scheme 3. Synthesis of tetrahydroquinolines **5** and 1,2-dihydroquinolines **6**.

Under Pd^0 conditions, the substitution on the nitrogen atom on amines **4a**–**d** would avoid the formation of aromatic quinolines, but the regioselectivity of the formation of the double bond would still be an issue (Scheme 3). Thus, 1,2-dihydroquinolines **6**, with a more stable endocyclic double bond, could be formed by isomerization of the exocyclic double bond of tetrahydroquinolines **5** by reinsertion of the hydropalladium species formed after β-elimination, followed by a second elimination. Optimization of the reaction conditions led to the selective formation of each regioisomer, as shown in Table 2.

When butenylanilines **4a**–**d** were treated with $Pd(OAc)_2$ in the presence of a base and tetrabutylammonium halide, under various conditions, the reaction was non selective, obtaining mixtures of 4-methylenetetrahydroquinolines **5** together with isomerized **6** (Table 2, Entries 1, 6, 10 and 14). Phosphane-free conditions led to sluggish reactions, and a mixture of isomers (Table 2, Entries 2, 11 and 15). However, isomerization could be avoided by the addition of silver salts.[22] In the presence of silver carbonate, tetrahydroquinolines **5a**–**d** were formed regioselectively in good yields (Table 2, Entries 3, 7, 12 and 16). We also found that quinolines **5a** and **5b** could be selectively obtained without the use of silver additives, by using $Pd(dba)_2/Ph_3P$ in the presence of tetrabutylammonium acetate and allyltrimethylsilane, with lower catalyst loading (3 mol-%; Table 2, Entries 4 and 8). The presence of allylsilane is relevant because the reaction does not proceed without this additive. In fact, the presence of dibenzylideneacetone has been shown to decrease the rate of oxidative addition of aryl iodides when $Pd(dba)_2/PPh_3$ systems are employed.[23] Although the formation of palladium complexes with allysilanes is known,[24] the use of allyltrimethylsilane as an additive in Mizoroki–Heck reactions has not been described to the best of our knowledge, and its role has not been studied in detail. Dihydroquinolines **6a**–**d** were selectively obtained in good yields by using $Pd(PPh_3)_4/Et_3N$ as catalytic system (Table 2, Entries 5, 9, 13 and 17), though the reaction requires high catalyst loadings to reach reasonable yields. Thus, the Mizoroki–Heck reaction allowed the selective synthesis of quinolines with exocyclic or endocyclic double bonds, and it is compatible functional groups on C-2, like an ester (**5c** and **6c**) or a protected alcohol (**5d** and **6d**).

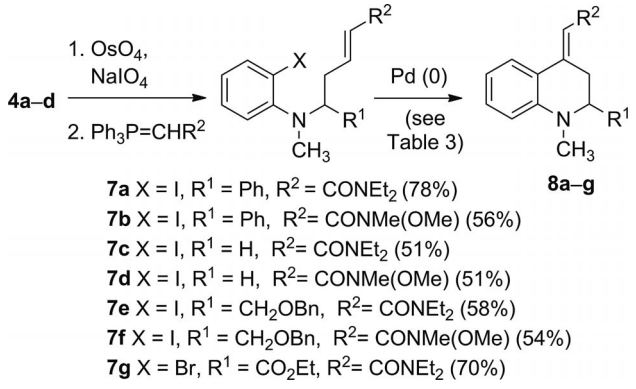
To access tetrahydroquinolines with an *exo* α,β-unsaturated amide moiety at the C-4 position, a series of tertiary butenylanilines with *trans*-substituted double bonds were prepared. Thus, **7a**–**g** were obtained in good yields diastereoselectivity from **4a**–**d** through oxidative cleavage of the double bond followed by a Wittig reaction in a one-pot procedure,[4b,19] as shown in Scheme 4.

When optimized reaction conditions [Method A: $Pd(OAc)_2/PPh_3$, $AgCO_3$, DMF, 90 °C] were applied to **7a** and **7b** the corresponding 2-phenyl-substituted quinolines **8a**,**b** were obtained regioselectivity in good yield (Table 3, Entries 1 and 2). No formation of the *endo* double bond was detected, and the tetrahydroquinolines were obtained as single *E* isomers. The geometry of the double bond, which was confirmed by NOESY experiments, is consistent with a *syn* β-hydride elimination. These conditions were extended to the synthesis of **8c**–**g**, with consistently good yields (Table 3, Entries 3–7). The same regioisomers were obtained when $Pd(PPh_3)_4/Et_3N$ was used as catalytic system

Table 2. Mizoroki–Heck reactions of **4a**–**d**.

	Substrate	Pd	PPh_3 [mol-%]	Base, additive	Solvent	Temperature	**5** [%]	**6** [%]
1	**4a**	$Pd(OAc)_2$[a]	20	Na_2CO_3, Bu_4NBr	DMF	90 °C	46	4
2	**4a**	$Pd(OAc)_2$[a]	–	Na_2CO_3, Bu_4NBr	DMF	90 °C	35	4
3	**4a**	$Pd(OAc)_2$[b]	30	Ag_2CO_3	DMF	90 °C	78	–
4	**4a**	$Pd(dba)_2$[a]	14	Bu_4NOAc, allylTMS	DMF	50 °C	75	–
5	**4a**	$Pd(PPh_3)_4$[c]	–	Et_3N	toluene	reflux	–	76
6	**4b**	$Pd(OAc)_2$[b]	30	$NaHCO_3$, Bu_4NCl	DMF	90 °C	[d]	
7	**4b**	$Pd(OAc)_2$[b]	30	Ag_2CO_3	DMF	90 °C	69	–
8	**4b**	$Pd(dba)_2$[a]	14	Bu_4NOAc, allylTMS	DMF	50 °C	71	
9	**4b**	$Pd(PPh_3)_4$[c]	–	Et_3N	toluene	reflux	–	55[e]
10	**4c**	$Pd(OAc)_2$[b]	30	$NaHCO_3$, Bu_4NCl	CH_3CN	reflux	22	51
11	**4c**	$Pd(OAc)_2$[b]	–	$NaHCO_3$, Bu_4NCl	CH_3CN	reflux	17	52
12	**4c**	$Pd(OAc)_2$[b]	30	Ag_2CO_3	DMF	90 °C	78	–
13	**4c**	$Pd(PPh_3)_4$[c]	–	Et_3N	toluene	reflux	–	69
14	**4d**	$Pd(OAc)_2$[b]	30	$NaHCO_3$, Bu_4NCl	CH_3CN	reflux	45	15
15	**4d**	$Pd(OAc)_2$[b]	–	$NaHCO_3$, Bu_4NCl	CH_3CN	reflux	52	10
16	**4d**	$Pd(OAc)_2$[b]	30	Ag_2CO_3	DMF	90 °C	53	–
17	**4d**	$Pd(PPh_3)_4$[c]	–	Et_3N	toluene	reflux	–	60

[a] 3 mol-% of precatalyst was used. [b] 10 mol-% $Pd(OAc)_2$. [c] 30 mol-% $Pd(PPh_3)_4$. [d] Mixture of products. [e] Reduced tetrahydroquinoline was obtained.



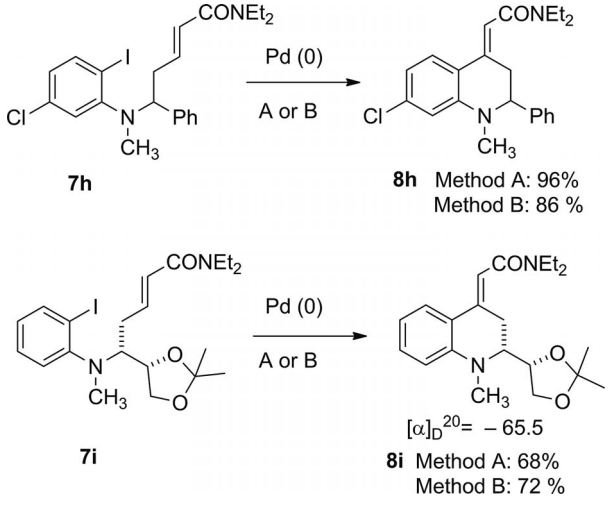
Scheme 4. Synthesis of 4-alkylidene-substituted quinolines **8a**–**g**.

Table 3. Synthesis of 4-alkylidene-substituted quinolines **8a**–**g**.

	Substrate	Method[a]	Product	Yield [%]
1	**7a**	A	**8a**	79
2	**7b**	A	**8b**	72
3	**7c**	A	**8c**	67
4	**7d**	A	**8d**	67
5	**7e**	A	**8e**	57
6	**7f**	A	**8f**	73
7	**7g**	A	**8g**	61
8	**7a**	B	**8a**	85
9	**7b**	B	**8b**	77
10	**7c**	B	**8c**	76
11	**7d**	B	**8d**	67
12	**7e**	B	**8e**	61
13	**7f**	B	**8f**	81
14	**7g**	B	**8g**	67
15	**7a**	C	**8a**	74
16	**7b**	C	**8b**	60
17	**7c**	C	**8c**	61
18	**7d**	C	**8d**	60
19	**7e**	C	**8e**	40
20	**7f**	C	**8f**	68
21	**7g**	C	**8g**	82

[a] Method A: $Pd(OAc)_2$ (10 mol-%), PPh_3 (30 mol-%), $AgCO_3$ (1.5 equiv.), dimethylformamide (DMF), 100 °C, 6 h; Method B: $Pd(PPh_3)_4$ (30 mol-%), Et_3N (2.2 equiv.), toluene, reflux, 6 h; Method C: $Pd(OAc)_2$ (15 mol-%), $NaHCO_3$ (2.2 equiv.), Bu_4NCl (1.3 equiv.) CH_3CN, reflux, 6 h.

(Table 3, Entries 8–14, Method B), probably owing to the stabilization of the *exo* double bond by the amide group that precludes isomerization. These conditions gave higher yields of the quinolines but, once again, required high catalyst loadings to reach completion in reasonable reaction times. Finally, the Mizoroki–Heck reaction could also be performed under phosphane-free conditions (Table 3, Entries 15–21, Method C) obtaining *E*-quinolines, though in generally lower yields, with the exception of **8g** (Table 3, Entry 21). As can be seen in Table 3, the use of diethyl amides or Weinreb amides led to comparable yields of corresponding tetrahydroquinolines **8**. Some biologically active quinolines bear chlorine atoms, mainly in the C-5 and/or C-7 position.[2,4] To access this type of 4-alkylidene-quinolines, butenylaniline **7h** was prepared starting from 5-chloro-2-iodoaniline,[19] and was submitted to Mizoroki–Heck conditions previously tested (Scheme 5). Tetrahydroquinoline **8h** was obtained in excellent yields, as a single *E* isomer, with no isomerization of the double bond. Finally, this procedure could be successfully applied to the synthesis of enantiomerically pure tetrahydroquinoline **8i**. Enantiomerically pure butenylaniline **7i** was prepared following the same synthetic strategy, staring from *o*-iodoaniline and (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde.[19] Treatment of **7i** with both catalytic systems afforded tetrahydroquinoline **8i** as a single isomer, with no loss of optical purity. The synthesis of enantiopure tetrahydroquinolines with an *exo* α,β-unsaturated amide moiety at the C-4 position had been reported by Di Fabio, in an approach that used an (*R*)-(+)-*tert*-butyl lactate as chiral auxiliary.[4b] The regioselectivity could also be controlled by the catalytic system, and the best results for the formation of the exocyclic double bond were obtained when the Heck reaction was carried out with $Pd(PPh_3)_4/Et_3N$ in toluene. Thus, the results obtained in this work are in agreement with these previous results, and expand the scope of this reaction for the synthesis of heterocycles.



Scheme 5. Synthesis of (*E*)-alkylidene-quinolines **8**.

Conclusions

An intramolecular Heck reaction provides mild and regioselective access to 2-substituted 4-alkylidene-tetrahydroquinoline derivatives, similar to other methods described in the literature.[25] In all cases a 6-*exo*-*trig* process occurs obtaining quinoline derivatives in good yields. When non-substituted alkenes are used, the regioselectivity of the reaction can be directed towards the formation of an exocyclic or endocyclic double bond by choosing a suitable catalytic system. When the double bond is substituted by an amide moiety, intramolecular cyclization is favored, obtaining selectively the exocyclic double bond of *E* geometry. The formation of this isomer does not depend on the precatalyst used.[26] Optimal conditions have been found for the efficient preparation of a variety of 2-substituted tetrahydroquinolines with an *exo* α,β-unsaturated amide moiety

at the C-4 position, showing high functional group tolerance. This procedure can also be applied to chiral substrates, thus achieving a synthesis of enantiopure quinolines with the configuration of known glycine antagonists.

Experimental Section

General Methods: Melting points were determined in unsealed capillary tubes. IR spectra were recorded as films over NaCl pellets, on KBr pellets or with an ATR. NMR spectra were recorded at 20–25 °C, at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C or at 500 MHz for ^{1}H and 125.7 MHz for ^{13}C in $CDCl_3$ solutions. Assignments of individual ^{13}C and ^{1}H resonances are supported by DEPT experiments and 2D correlation experiments (COSY, HSQCed or HMBC). Selective NOE or NOESY experiments were performed when necessary. Mass spectra were recorded with electron impact (EI) at 70 eV, under chemical ionization (CI) at 230 eV or with electrospray ionization (ESI). HRMS data was recorded with a TOF detector. TLC was carried out with 0.2 mm thick silica gel plates. Visualization was accomplished by UV light. Flash column chromatography[27] was performed on silica gel (230–400 mesh) or on alumina (70–230 mesh). All solvents used in reactions were anhydrous and purified according to standard procedures.[28] All air- or moisture-sensitive reactions were performed under argon; the glassware was dried (130 °C) and purged with argon.

Synthesis of 2-Aryl-4-methylenequinolines 2. General Procedure: $Pd(OAc)_2$ (3 mol-%) and PPh_3 (20 mol-%) were added to a mixture of butenylamine **1** (1 mmol), Na_2CO_3 (2.5 mmol) and nBu$_4$NCl (1.5 mmol) in dry CH_3CN. The mixture was heat to reflux until TLC showed complete reaction. The reaction mixture was then diluted with AcOEt (50 mL) and filtered through a Celite pad. The resulting filtrate was washed with saturated NH_4Cl (3× 30 mL) and brine (3× 30 mL), dried with Na_2SO_4, filtered and concentrated. The crude oil was purified by flash column chromatography (silica gel, hexane/AcOEt) to give corresponding tetrahydroquinolines **2**.

4-Methylene-2-phenyl-1,2,3,4-tetrahydroquinoline (2a): (Table 1, Entry 3) According to the general procedure, amine **1a** (111 mg, 0.318 mmol) was treated with $Pd(OAc)_2$ (2 mg, 0.009 mmol) and PPh_3 (17 mg, 0.064 mmol), Na_2CO_3 (90 mg, 0.80 mmol) and nBu$_4$NCl (124 mg, 0.47 mmol) in CH_3CN (10 mL). The reaction mixture was heated to reflux for 12 h. After work-up, flash column chromatography (silica gel, 2% hexane/AcOEt) afforded **2a** (38 mg, 54%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.74–2.78 (m, 2 H, H^3), 4.16 (s, 1 H, NH), 4.43–4.49 (m, 1 H, H^2), 4.81 (s, 1 H, =CH$_a$), 5.46 (s, 1 H, =CH$_b$), 6.58 (d, J = 8.0 Hz, 1 H, H^8), 6.72 (t, J = 8.0 Hz, 1 H, H^6), 7.10 (t, J = 8.0 Hz, 1 H, H^7), 7.31–7.53 (m, 5 H, Ph), 7.56 (d, J = 8.0 Hz, 1 H, H^5) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 40.8 (C^3), 57.2 (C^2), 106.7 (C=*C*H$_2$), 115.0 (C^8), 117.8 (C^6), 119.8 (C^{4a}), 124.7, 126.6, 127.6, 128.7, 129.2 (C^5, C^7, C–H$_{arom}$), 139.6 (C^{8a}), 143.4 (C–C$_{arom}$), 144.6 (C^4) ppm. MS (70 eV, EI): *m*/*z* (%) = 221 (2) [M$^+$], 219 (100), 218 (37), 204 (57), 109 (6), 77 (5).

2-(1-Methyl-1*H*-pyrrol-2-yl)-4-methylene-1,2,3,4-tetrahydroquinoline (2b): (Table 1, Entry 5) According to the general procedure, amine **1b** (158 mg, 0.52 mmol) was treated with $Pd(OAc)_2$ (4 mg, 0.016 mmol) and PPh_3 (26 mg, 0.11 mmol), Na_2CO_3 (137 mg, 1.30 mmol) and nBu$_4$NCl (173 mg, 0.62 mmol) in CH_3CN (20 mL). The reaction mixture was heated to reflux for 18 h. After work-up, flash column chromatography (silica gel, 10% hexane/AcOEt) afforded **2b** (83 mg, 71%) as an oil. IR (ATR): $\tilde{\nu}$ = 3375 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.68–2.96 (m, 2 H, H^3), 3.69 (s, 3 H, CH_3), 4.07 (s, 1 H, NH), 4.54 (dd, J = 11.2, 3.3 Hz, 1 H, H^2), 4.86 (s, 1 H, =CH$_a$), 5.50 (s, 1 H, =CH$_b$), 6.08–6.16 (m, 1 H, H$^{4'}$), 6.16–6.24 (m, 1 H, H$^{3'}$), 6.52–6.65 (m, 2 H, H^8, H$^{5'}$), 6.73 (t, J = 7.5 Hz, 1 H, H^6), 7.09 (t, J = 7.5 Hz, 1 H, H^7), 7.56 (d, J = 7.5 Hz, 1 H, H^5) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 34.1 (CH_3), 38.8 (C^3), 49.8 (C^2), 106.4 (C$^{3'}$), 106.8 (C=*C*H$_2$), 107.1 (C$^{4'}$), 115.3 (C^8), 118.0 (C^6), 120.0 (C^{4a}), 122.7 (C$^{5'}$), 124.7 (C^5), 129.1 (C^7), 133.5 (C$^{2'}$), 139.7 (C^{8a}), 144.3 (C^4) ppm. MS (70 eV, EI): *m*/*z* (%) = 224 (100) [M$^+$], 223 (87), 222 (39), 221 (85), 209 (32), 208 (11), 207 (15), 194 (11), 180 (10), 143 (99). 142 (25), 115 (39), 81 (45), 77 (10), 65 (6). HRMS (ESI$^+$): calcd. for $C_{15}H_{17}N_2$ [MH$^+$] 225.1392; found 225.1392.

4-Methylene-2-(thiophen-3-yl)-1,2,3,4-tetrahydroquinoline (2d): (Table 1, Entry 9) According to the general procedure, amine **1d** (385 mg, 1.25 mmol) was treated with $Pd(OAc)_2$ (9 mg, 0.037 mmol) and PPh_3 (66 mg, 0.25 mmol), Na_2CO_3 (332 mg, 3.13 mmol) and nBu$_4$NCl (417 mg, 1.8 mmol) in CH_3CN (20 mL). The reaction mixture was heated to reflux for 12 h. After work-up, flash column chromatography (silica gel, 1% hexane/AcOEt) afforded **2d** (50 mg, 18%) as an oil. IR (ATR): $\tilde{\nu}$ = 3385 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.76–2.83 (m, 2 H, H^3), 4.22 (s, 1 H, NH), 4.51–4.67 (m, 1 H, H^2), 4.84 (s, 1 H, =CH$_a$), 5.48 (s, 1 H, =CH$_b$), 6.58 (d, J = 7.5 Hz, 1 H, H^8), 6.73 (t, J = 7.5 Hz, 1 H, H^6), 7.09 (t, J = 7.5 Hz, 1 H, H^7), 7.14 (dd, J = 5.0, 1.0 Hz, 1 H, H$^{4'}$), 7.24–7.26 (m, 1 H, H$^{2'}$), 7.33 (dd, J = 5.0, 3.0 Hz, 1 H, H$^{5'}$), 7.57 (d, J = 7.5 Hz, 1 H, H^5) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 40.1 (C^3), 52.8 (C^2), 106.9 (C=*C*H$_2$), 115.1 (C^8), 118.0 (C^6), 120.1 (C^{4a}), 121.1 (C$^{2'}$), 124.7 (C^5), 126.1, 126.5 (C$_{4'}$, C$^{5'}$), 129.1 (C^7), 139.3 (C$^{3'}$), 144.2 (C^{8a}), 144.7 (C^4) ppm. MS (230 eV, CI): *m*/*z* (%) = 228 (100) [MH$^+$], 227 (72), 226 (30), 225 (7), 212 (6), 144 (12). HRMS (CI): calcd. for $C_{14}H_{14}NS$ [MH$^+$] 228.0847; found 228.0839.

4-Methyl-2-(thiophen-3-yl)quinoline (3d):[29] (Table 1, Entry 9; 85 mg, 30%). IR (ATR): $\tilde{\nu}$ = 1600 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.74 (s, 3 H, CH_3), 7.44 (dd, J = 5.1, 3.0 Hz, 1 H, H$^{4'}$), 7.52 (t, J = 7.5 Hz, 1 H, H^7), 7.62 (s, 1 H, H^3), 7.70 (t, J = 7.5 Hz, 1 H, H^6), 7.87 (dd, J = 5.1, 1.1 Hz, 1 H, H$^{5'}$), 7.97 (d, J = 7.5 Hz, 1 H, H^8), 8.03 (dd, J = 3.0, 1.1 Hz, 1 H, H$^{2'}$), 8.12 (d, J = 7.5 Hz, 1 H, H^5) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 18.9 (CH_3), 119.7 (C^3), 123.6 (C^8), 124.4 (C$^{2'}$), 125.8 (C^7), 126.2 (C$^{4'}$), 126.8 (C$^{5'}$), 127.2 (C^{4a}), 129.3 (C^6), 130.0 (C^5), 142.7 (C$^{3'}$), 144.7 (C^4), 148.1 (C^{8a}), 153.0 (C^2) ppm. MS (70 eV, EI): *m*/*z* (%) = 226.1 (19) [M$^+$ + 1], 225.1 (100) [M$^+$], 224.1 (40), 210 (11), 199 (5), 181.1 (6), 180.1 (6), 168.1 (3), 115 (5), 77 (1), 65 (1).

4-Methylene-2-(1-methyl-1*H*-pyrrol-3-yl)-1,2,3,4-tetrahydroquinoline (2c): (Table 1, Entry 8) $Pd(OAc)_2$ (11 mg, 0.049 mmol) and PPh_3 (52 mg, 0.20 mmol) were added to a mixture of amine **1c** (151 mg, 0.49 mmol) and nBu$_4$NOAc (231 mg, 0.74 mmol) in dry DMSO (10 mL), and the mixture was heated at 60 °C for 24 h. The reaction mixture was washed with saturated NH_4Cl (2× 30 mL) and brine (2× 30 mL), dried with Na_2SO_4, filtered and concentrated. The crude oil was purified by flash column chromatography (silica gel, 10% hexane/AcOEt) to afford **2c** (60 mg, 55%) as an oil. IR (ATR): $\tilde{\nu}$ = 3385 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.69–2.92 (m, 2 H, H^3), 3.66 (s, 3 H, CH_3), 4.13 (s, 1 H, NH), 4.43 (dd, J = 8.9, 5.3 Hz, 1 H, H^2), 4.85 (s, 1 H, =CH$_a$), 5.49 (s, 1 H, =CH$_b$), 6.20 (s, 1 H, H$^{4'}$), 6.52–6.67 (m, 3 H, H$_8$, H$_{2'}$, H$^{5'}$), 6.68–6.78 (m, 1 H, H^6), 7.04–7.15 (m, 1 H, H^7), 7.57 (d, J = 7.8 Hz, 1 H, H^5) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 36.1 (CH_3), 40.6 (C^3), 50.6 (C^2), 106.1 (C$^{4'}$), 106.5 (C=*C*H$_2$), 115.0 (C^8), 117.5 (C^6), 118.9, 121.9 (C$_{2'}$, C$^{5'}$), 120.0 (C$^{3'}$), 124.6 (C^5), 126.7 (C^{4a}), 129.0

(C^7), 140.3 (C^{8a}), 144.8 (C^4) ppm. MS (70 eV, EI): *m/z* (%) = 224 (100) [M^+], 223 (77), 209 (51), 208 (8), 207 (10), 194 (11), 180 (10), 143 (25), 115 (17), 81 (28), 77 (7), 65 (4). HRMS (ESI^+): calcd. for $C_{15}H_{17}N_2$ [MH^+] 225.1392; found 225.1392.

4-Methyl-2-phenylquinoline (3a):[30] (Table 1, Entry 1). $Pd(OAc)_2$ (8 mg, 0.036 mmol) was added to a mixture of butenylamine **1a** (432 mg, 1.2 mmol), Na_2CO_3 (341 mg, 3.2 mmol) and nBu$_4$NBr (498 mg, 1.5 mmol) in dry DMF (20 mL). The mixture was heated at 60 °C for 18 h. The reaction mixture was then diluted with of AcOEt (20 mL) and filtered through a Celite pad. The resulting filtrate was washed with saturated NH_4Cl (3× 20 mL) and brine (3× 20 mL), dried with Na_2SO_4 filtered and concentrated. The crude oil was purified by flash column chromatography (silica gel, 5% hexane/AcOEt) to give quinoline **3a** (130 mg, 50%) whose data are coincidental with those reported.[30] IR (NaCl): $\tilde{\nu}$ = 1600 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.75 (s, 3 H, CH_3), 7.47–7.58 (m, 4 H, H^3, $H^{3'}$, $H^{4'}$, $H^{5'}$), 7.70–7.76 (m, 2 H, $H^{2'}$, $H^{6'}$), 7.99 (d, J = 8.3 Hz, 1 H, H^8), 8.15–8.22 (m, 3 H, H^6, H^7, H^5) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 18.9 (CH_3), 119.7 (C^3), 123.5 (C^8), 125.9 (C^7), 127.1 (C^{4a}), 127.4, 128.7, 129.1, 129.2 (C^6, C–H_{arom}), 130.1 (C^5), 139.7 (C_{arom}–C), 144.7 (C^4), 148.0 (C^{8a}), 156.9 (C^2) ppm. MS (70 eV, EI): *m/z* (%) = 220 (18) [M^+ + 1], 219 (100) [M^+], 218 (35), 204 (63), 109 (13), 102 (14), 95 (11), 77 (8).

Synthesis of 4-Methylenequinolines 5. General Procedure A: Ag_2CO_3 (1.5 mmol), PPh_3 (30 mol-%) and $Pd(OAc)_2$ (10 mol-%), were added to a solution of amine **4** (1 mmol) in dry DMF (30 mL). The mixture was stirred at 90 °C until TLC showed complete reaction. The reaction mixture was then diluted with Et_2O (20 mL), and filtered through a Celite pad. The resulting filtrate was washed with brine (3× 30 mL), dried with Na_2SO_4, filtered and concentrated. The crude oil was purified by flash column chromatography (silica gel, hexane/AcOEt) to give corresponding tetrahydroquinolines **5**.

1-Methyl-4-methylene-2-phenyl-1,2,3,4-tetrahydroquinoline (5a): (Table 2, Entry 3) According to general procedure A, amine **4a** (135 mg, 0.37 mmol) was treated with $Pd(OAc)_2$ (8.3 mg, 0.037 mmol) PPh_3 (28.8 mg, 0.11 mmol) and Ag_2CO_3 (153 mg, 0.55 mmol) in DMF (10 mL). The reaction mixture was stirred at 90 °C for 12 h. After work-up, flash column chromatography (silica gel, hexane) afforded **5a** (68 mg, 78%) as a white solid. M.p. (hexane) 64–66 °C. IR (KBr): $\tilde{\nu}$ = 890 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.62–2.73 (m, 1 H, H^3), 2.88 (s, 3 H, NCH_3), 2.97–3.04 (m, 1 H, H^3), 4.50 (t, J = 5.2 Hz, 1 H, H^2), 4.61 (s, 1 H, =CH_a), 5.32 (s, 1 H, =CH_b), 6.67–6.73 (m, 2 H, H^6, H^8), 7.12–7.49 (m, 7 H, H^5, H^7, Ph) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 38.0 (NCH_3), 39.4 (C^3), 64.1 (C^2), 107.7 (C=*C*H_2), 111.1 (C^8), 116.0 (C^6), 121.4 (C^{4a}), 124.6, 126.4, 127.0, 128.3, 129.6 (C^5, C^7, C–H_{arom}), 138.2 (C–C_{arom}), 142.9 (C^{8a}), 145.4 (C^4) ppm. MS (70 eV, EI): *m/z* (%) = 235 (41) [M^+], 234 (16), 159 (15), 158 (100), 143 (10), 115 (13), 91 (11), 77 (11). $C_{17}H_{17}N$ (235.33): calcd. C 86.77, H 7.28, N 5.95; found C 86.56, H 7.02, N 5.72.

1-Methyl-4-methylene-1,2,3,4-tetrahydroquinoline (5b): (Table 2, Entry 7) According to general procedure A, amine **4b** (120 mg, 0.43 mmol) was treated with $Pd(OAc)_2$ (10 mg, 0.043 mmol) and PPh_3 (33.8 mg, 0.129 mmol) and Ag_2CO_3 (178 mg, 0.64 mmol) in DMF (10 mL). The reaction mixture was stirred at 90 °C for 12 h. After work-up, flash column chromatography (silica gel, hexanes) afforded **5b** (47 mg, 69%) as an oil. IR (NaCl): $\tilde{\nu}$ = 1595 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.69 (t, J = 6.0 Hz, 2 H, H^3), 2.91 (s, 3 H, NCH_3), 3.26 (t, J = 6.0 Hz, 2 H, H^2), 4.77 (s, 1 H, =CH_a), 5.38 (s, 1 H, =CH_b), 6.64–6.69 (m, 2 H, H^6, H^8), 7.16 (td, J = 7.7, 1.3 Hz, 1 H, H^7), 7.51 (dd, J = 7.7, 1.3 Hz, 1 H, H^5) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 32.1 (C^3), 39.6 (NCH_3), 51.8 (C^2), 105.7 (C=*C*H_2), 112.1 (C^8), 116.7 (C^6), 121.4 (C^{4a}), 124.6 (C^5), 129.3 (C^7), 140.6 (C^{8a}), 146.3 (C^4) ppm. $C_{11}H_{13}N$ (159.23): calcd. C 82.97, H 8.23, N 8.80; found C 82.71, H 7.93, N 8.77.

2-Benzyloxymethyl-1-methyl-4-methylene-1,2,3,4-tetrahydroquinoline (5c): (Table 2, Entry 12) According to general procedure A, amine **4c** (180 mg, 0.45 mmol) was treated with $Pd(OAc)_2$ (10 mg, 0.04 mmol), PPh_3 (36 mg, 0.13 mmol) and Ag_2CO_3 (176 mg, 0.67 mmol) in DMF (20 mL). The reaction mixture was stirred at 90 °C for 5 h. After work-up, flash column chromatography (silica gel, 5% hexane/AcOEt) afforded **5c** (96 mg, 78%) as an oil. IR (NaCl): $\tilde{\nu}$ = 875 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.71 (dd, J = 13.8, 2.3 Hz, 1 H, H^3), 2.78–2.82 (m, 1 H, H^3), 3.07 (s, 3 H, NCH_3), 3.39–3.46 (m, 1 H, CH_2O), 3.54–3.60 (m, 1 H, CH_2O), 3.63–3.72 (m, 1 H, H^2), 4.52–4.54 (m, 2 H, $PhCH_2$), 4.85 (s, 1 H, =CH_a), 5.49 (s, 1 H, =CH_b), 6.60 (d, J = 7.5 Hz, 1 H, H^8), 6.70 (t, J = 7.5 Hz, 1 H, H^6), 7.20 (t, J = 7.5 Hz, 1 H, H^7), 7.33–7.43 (m, 5 H, Ph), 7.53 (d, J = 7.5 Hz, 1 H, H^5) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 32.6 (C^3), 38.7 (NCH_3), 58.8 (C^2), 69.7 (CH_2O), 73.4 (Ph*C*H_2), 107.8 (C=*C*H_2), 111.0 (C^8), 115.6 (C^6), 120.3 (C^{4a}), 124.5 (C^5), 127.4, 127.5, 128.3 (C–H_{arom}), 128.4 (C–C_{arom}), 129.5 (C^7), 138.2 (C^{8a}), 143.8 (C^4) ppm. MS (70 eV, EI): *m/z* (%) = 279 (3) [M^+], 158 (100), 143 (11), 115 (10), 91 (12), 83 (18). HRMS (EI): calcd. for $C_{19}H_{21}NO$ 279.1623; found 279.1631. $C_{19}H_{21}NO$ (279.38): calcd. C 81.68, H 7.58, N 5.01; found C 81.45, H 7.32, N 5.22.

Ethyl 1-Methyl-4-methylene-1,2,3,4-tetrahydroquinoline-2-carboxylate (5d): (Table 2, Entry 16) According to general procedure A, amine **4d** (156 mg, 0.50 mmol) was treated with $Pd(OAc)_2$ (11 mg, 0.05 mmol), PPh_3 (40 mg, 0.15 mmol) and Ag_2CO_3 (210 mg, 0.75 mmol) in DMF (15 mL). The reaction mixture was stirred at 90 °C for 5 h. After work-up, flash column chromatography (silica gel, 10% hexane/AcOEt) afforded **5d** (59 mg, 53%) as an oil. IR (NaCl): $\tilde{\nu}$ = 1735, 875 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 2.91 (d, J = 4.0 Hz, 2 H, H^3), 2.99 (s, 3 H, NCH_3), 4.02–4.18 (m, 3 H, H^2, CH_2CH_3), 4.78 (d, J = 1.1 Hz, 1 H, =CH_a), 5.38 (s, 1 H, =CH_b), 6.63–6.70 (m, 2 H, H^6, H^8), 7.18 (t, J = 7.6 Hz, 1 H, H^7), 7.44 (dd, J = 7.7, 1.5 Hz, 1 H, H^5) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.2 (CH_2CH_3), 34.1 (C^3), 39.1 (NCH_3), 60.8 (CH_2CH_3), 63.1 (C^2), 107.9 (C=*C*H_2), 111.5 (C^8), 116.8 (C^6), 120.8 (C^{4a}), 124.4 (C^5), 129.5 (C^7), 137.4 (C^{8a}), 144.4 (C^4), 172.0 (CO) ppm. MS (70 eV, EI): *m/z* (%) = 231(<1) [M^+] 158 (56), 97 (15), 85 (40), 71 (39), 57 (100). HRMS (EI): calcd. for $C_{14}H_{17}NO_2$ 231.1259; found 231.1258. $C_{14}H_{17}NO_2$ (231.29): calcd. C 72.70, H 7.41, N 6.06; found C 72.32, H 7.18, N 5.80.

Synthesis of 1,2-Dihydroquinolines 6. General Procedure B: $Pd(PPh_3)_4$ (30 mol-%) and Et_3N (2 mmol) were added to a solution of amine **4** (1 mmol) in dry toluene (30 mL). The mixture was heated to reflux for 5–12 h. The reaction mixture was then diluted with AcOEt (20 mL), and filtered through a Celite pad. The resulting filtrate was washed with brine (3× 30 mL), dried with Na_2SO_4, filtered and concentrated. The crude oil was purified by flash column chromatography (silica gel, hexane/AcOEt) to give corresponding 1,2-dihydroquinolines **6**.

1,4-Dimethyl-2-phenyl-1,2-dihydroquinoline (6a): (Table 2, Entry 5) According to general procedure B, amine **4a** (201 mg, 0.55 mmol) was treated with $Pd(PPh_3)_4$ (192 mg, 0.17 mmol) and Et_3N (0.15 mL, 1.10 mmol) in dry toluene (15 mL), and the mixture was heated to reflux for 12 h. After work-up, flash column chromatog-

raphy (silica gel, hexanes) afforded **6a** (98 mg, 76%) as an oil. IR (NaCl): $\tilde{\nu}$ = 815 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.01 (s, 3 H, CH_3), 2.70 (s, 3 H, NCH_3), 5.07 (d, J = 4.7 Hz, 1 H, H^2), 5.53 (d, J = 4.7 Hz, 1 H, H^3), 6.44 (d, J = 8.3 Hz, 1 H, H^8), 6.65 (t, J = 7.3 Hz, 1 H H^6), 7.09–7.28 (m, 7 H, H^5, H^7, Ph) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 18.7 (CH_3), 36.2 (NCH_3), 65.5 (C^2), 109.4 (C^8), 116.0 (C^3), 122.2 (C^4), 123.1, 123.6 (C^5, C^6), 126.3, 127.5, 128.6, 129.6 (C^7, C–H_{arom}), 142.8, 144.8 (C^{4a}, C^{8a}, C–C_{arom}) ppm. MS (70 eV, EI): m/z (%) = 235 (13) [M^+], 221 (13), 220 (29), 158 (100), 115 (11), 77 (13).

2-Benzyloxymethyl-1,4-dimethyl-1,2-dihydroquinoline (6c): (Table 2, Entry 13) According to general procedure B, amine **4c** (230 mg, 0.56 mmol) was treated with $Pd(PPh_3)_4$ (192 mg, 0.17 mmol) and Et_3N (0.16 mL, 1.13 mmol) in dry toluene (15 mL), and the mixture was heated to reflux for 5 h. After work-up, flash column chromatography (silica gel, hexanes) afforded **6c** (107 mg, 69%) as an oil. IR (NaCl): $\tilde{\nu}$ = 1655, 740 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.05 (s, 3 H, CH_3), 3.03 (s, 3 H, NCH_3), 3.37 (dd, J = 9.7, 4.3 Hz, 1 H, C*H*HO), 3.56 (dd, J = 9.7, 7.0 Hz, 1 H, CH*H*O), 4.12–4.22 (m, 1 H, H^2), 4.45 (s, 2 H, $PhCH_2$), 5.54 (d, J = 5.8 Hz, 1 H, H^3), 6.54 (d, J = 8.0 Hz, 1 H, H^8), 6.68 (t, J = 7.4 Hz, 1 H, H^6), 7.10–7.19 (m, 2 H, H^5, H^7), 7.27–7.37 (m, 5 H, Ph) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 18.8 (CH_3), 38.2 (NCH_3), 60.1 (C^2), 72.7 (CH_2O), 73.1 (Ph*C*H_2), 110.7 (C^8), 116.0 (C^6), 119.5 (C^3), 122.9 (C^4), 123.6 (C^5), 127.3, 127.4, 128.3, 128.8 (C^7, C–H_{arom}), 131.8 (C^{4a}), 138.3 (C–C_{arom}), 144.4 (C^{8a}) ppm. MS (70 eV, EI): m/z (%) = 279 (1) [M^+], 173 (17), 82 (100), 77 (29). $C_{19}H_{21}NO$ (279.38): calcd. C 81.68, H 7.58, N 5.01; found C 81.39, H 7.45, N 5.34.

Ethyl 1,4-Dimethyl-1,2-dihydroquinoline-2-carboxylate (6d): (Table 2, Entry 17) According to general procedure B, amine **4d** (131 mg, 0.42 mmol) was treated with $Pd(PPh_3)_4$ (150 mg, 0.13 mmol) and Et_3N (0.12 mL, 0.84 mmol) in dry toluene (15 mL), and the mixture was heated to reflux for 5 h. After work-up, flash column chromatography (silica gel, 5% hexane/AcOEt) afforded **6d** (58 mg, 60%) as an oil. IR (NaCl): $\tilde{\nu}$ = 1740 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.23 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 2.03 (s, 3 H, CH_3), 2.92 (s, 3 H, NCH_3), 4.12 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 4.61 (d, J = 5.9 Hz, 1 H, H^2), 5.60 (d, J = 5.9 Hz, 1 H, H^3), 6.57 (d, J = 8.0 Hz, 1 H, H^8), 6.68 (t, J = 7.5 Hz, 1 H, H^6), 7.10 (dd, J = 7.5, 1.4 Hz, 1 H, H^7), 7.16 (td, J = 7.5, 1.4 Hz, 1 H, H^5) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.1 (CH_2CH_3), 18.7 (CH_3), 37.3 (NCH_3), 60.7 (CH_2CH_3), 63.4 (C^2), 110.2 (C^8), 116.3, 116.8 (C^3, C^6), 122.1 (C^4), 123.8 (C^5), 129.3 (C^7), 132.8 (C^{4a}), 144.5 (C^{8a}), 170.9 (CO) ppm. MS (70 eV, EI): m/z (%) = 231 (3) [M^+], 158 (67), 97 (11), 85 (42), 83 (100), 71 (23), 57 (62). HRMS (EI): calcd. for $C_{14}H_{17}NO_2$ 231.1259; found 231.1253.

(*E*)-*N*,*N*-Diethyl-2-[1-methyl-2-phenyl-2,3-dihydroquinolin-4(1*H*)-ylidene]acetamide (8a): (Table 3, Entry 8) According to general procedure B, amine **7a** (148 mg, 0.32 mmol) was treated with $Pd(PPh_3)_4$ (112 mg, 0.09 mmol) and Et_3N (0.09 mL, 0.64 mmol) in dry toluene (15 mL), and the mixture was heated to reflux for 6 h. After work-up, flash column chromatography (silica gel, 40% hexane/AcOEt) afforded **8a** (86 mg, 85%) as an oil. IR (NaCl): $\tilde{\nu}$ = 1600 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.83 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 1.01 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 2.69–2.85 (m, 2 H, CH_2CH_3), 2.93 (s, 3 H, NCH_3), 3.03–3.14 (m, 2 H, H^3, CH*H*CH_3), 3.31 (dd, J = 14.0, 4.2 Hz, 1 H, H^3), 3.41–3.53 (m, 1 H, C*H*HCH_3), 4.58 (t, J = 4.2 Hz, 1 H, H^2), 6.22 (s, 1 H, =CH), 6.64–6.70 (m, 2 H, H^6, H^8), 7.00–7.07 (m, 2 H, Ph, H^7), 7.16–7.29 (m, 4 H, Ph), 7.35 (dd, J = 7.6, 1.3 Hz, 1 H, H^5) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 12.8, 13.8 (CH_2CH_3), 33.8 (C^3), 37.9 (NCH_3), 39.2, 41.6 (CH_2CH_3), 63.2 (C^2), 110.7 (C^8), 115.2 (C=*C*H), 115.7 (C^6), 121.0 (C^{4a}), 125.0 (C^5), 126.1, 126.9, 128.3, 130.6 (C^7, C–H_{arom}), 141.1 (C–C_{arom}), 142.1 (C^{8a}), 145.8 (C^4), 167.0 (CO) ppm. MS (70 eV, EI): m/z (%) = 334 (56) [M^+], 260 (60), 234 (45), 220 (47), 219 (35), 184 (100), 158 (20), 130 (13), 69 (49). HRMS (EI): calcd. for $C_{22}H_{26}N_2O$ 334.2045; found 334.2041. $C_{22}H_{26}N_2O$ (334.46): calcd. C 79.00, H 7.84, N 8.38; found C 78.81, H 7.83, N 8.13.

(*E*)-*N*-Methoxy-*N*-methyl-2-[1-methyl-2-phenyl-2,3-dihydroquinolin-4(1*H*)-ylidene]acetamide (8b): (Table 3, Entry 9) According to general procedure B, amine **7b** (134 mg, 0.30 mmol) was treated with $Pd(PPh_3)_4$ (112 mg, 0.09 mmol) and Et_3N (0.08 mL, 0.60 mmol) in dry toluene (10 mL), and the mixture was heated to reflux for 6 h. After work-up, flash column chromatography (silica gel, 30% hexane/AcOEt) afforded **8b** (72 mg, 77%) as an oil. IR (NaCl): $\tilde{\nu}$ = 1640 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.93 (s, 3 H, NCH_3), 3.10 (s, 3 H, NCH_3), 3.24–3.32 (m, 1 H, H^3), 3.30 (s, 3 H, OCH_3), 3.75 (dd, J = 14.7, 4.5 Hz, 1 H, H^3), 4.56 (t, J = 4.5 Hz, 1 H, H^2), 6.58 (s, 1 H, =CH), 6.65–6.72 (m, 2 H, H^6, H^8), 7.09–7.32 (m, 6 H, H^7, Ph), 7.43 (dd, J = 7.8, 1.4 Hz, 1 H, H^5) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 32.2 (NCH_3), 33.1 (C^3), 38.0 (NCH_3), 61.2 (OCH_3), 63.3 (C^2), 110.3 (C=*C*H), 111.2 (C^8), 115.9 (C^6), 121.0 (C^{4a}), 125.3 (C^5), 126.4, 126.9, 128.3 (C–H_{arom}), 131.3 (C^7), 142.0 (C–C_{arom}), 146.3, 146.5 (C^4, C^{8a}), 167.5 (CO) ppm. MS (70 eV, EI): m/z (%) = 322 (6) [M^+], 292 (26), 281 (15), 262 (68), 234 (28), 215 (11), 184 (81), 126 (10), 84 (62), 72 (93), 69 (31), 59 (100), 55 (60). HRMS (EI): calcd. for $C_{20}H_{22}N_2O_2$ 322.1681; found 322.1693. $C_{20}H_{22}N_2O_2$ (322.41): calcd. C 74.51, H 6.88, N 8.69; found C 74.26, H 6.77, N 8.38.

(*E*)-*N*,*N*-Diethyl-2-[1-methyl-2,3-dihydroquinolin-4(1*H*)-ylidene]-acetamide (8c): (Table 3, Entry 3) According to general procedure A, amine **7c** (90 mg, 0.23 mmol) was treated with $Pd(OAc)_2$ (8 mg, 0.023 mmol) PPh_3 (20 mg, 0.07 mmol) and Ag_2CO_3 (100 mg, 0.35 mmol) in DMF (10 mL). The reaction mixture was stirred at 90 °C for 5 h. After work-up, flash column chromatography (silica gel, 20% hexane/AcOEt) afforded **8c** (40 mg, 67%) as an oil. IR (NaCl): $\tilde{\nu}$ = 1625 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.16–1.21 (m, 6 H, 2 × CH_2CH_3), 2.91 (s, 3 H, NCH_3), 3.05–3.12 (m, 2 H, H^3), 3.21–3.27 (m, 2 H, H^2), 3.38–3.50 (m, 4 H, 2 × CH_2CH_3), 6.39 (s, 1 H, =CH), 6.64–6.68 (m, 2 H, H^6, H^8), 7.20 (td, J = 7.4, 1.4 Hz, 1 H, H^7), 7.45 (dd, J = 7.4, 1.4 Hz, 1 H, H^5) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 13.3, 14.5 (2 × NCH_2CH_3), 27.2 (C^3), 39.4 (NCH_3), 39.9, 42.6 (2 × NCH_2CH_3), 51.0 (C^2), 111.7 (C=*C*H), 112.3 (C^8), 116.7 (C^6), 121.0 (C^{4a}), 124.7 (C^5), 130.4 (C^7), 144.2 (C^{8a}), 147.5 (C^4), 167.4 (CO) ppm. MS (70 eV, EI): m/z (%) = 258 (52) [M^+], 184 (56), 158 (100), 143 (21). HRMS (EI): calcd. for $C_{16}H_{22}N_2O$ 258.1732; found 258.1738. $C_{16}H_{22}N_2O$ (258.36): calcd. C 74.38, H 8.58, N 10.84; found C 74.86, H 8.77, N 10.96.

(*E*)-*N*-Methoxy-*N*-methyl-2-[1-methyl-2,3-dihydroquinolin-4(1*H*)-ylidene]acetamide (8d): (Table 3, Entry 11) According to general procedure B, amine **7d** (95 mg, 0.25 mmol) was treated with $Pd(PPh_3)_4$ (89 mg, 0.08 mmol) and Et_3N (0.08 mL, 0.50 mmol) in dry toluene (10 mL), and the mixture was heated to reflux for 6 h. After work-up, flash column chromatography (silica gel, 40% hexane/AcOEt) afforded **8d** (40 mg, 67%) as an oil. IR (NaCl): $\tilde{\nu}$ = 1650 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.91 (s, 3 H, NCH_3), 3.21–3.23 (m, 2 H, H^3), 3.23 (s, 3 H, NCH_3), 3.37–3.39 (m, 2 H, H^2), 3.72 (s, 3 H, OCH_3), 6.64–6.72 (m, 3 H, C=CH, H^6, H^8), 7.22 (t, J = 7.1 Hz, 1 H, H^7), 7.55 (d, J = 7.9 Hz, 1 H, H^5) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 26.7 (C^3), 32.3 (NCH_3), 39.3 (NCH_3), 50.8 (C^2), 61.5 (OCH_3), 106.9 (C=*C*H), 112.4 (C^8), 116.6 (C^6), 121.0 (C^{4a}), 124.9 (C^5), 131.0 (C^7), 148.1 (C^{8a}), 149.4 (C^4), 168.1 (CO) ppm. MS (230 eV, CI): m/z (%) = 247 (34) [MH^+], 246

(21) [M+], 217 (82), 216 (81), 186 (100), 158 (30), 144 (17). HRMS (CI): calcd. for $C_{14}H_{19}N_2O_2$ 247.1447; found 247.1436.

(*E*)-2-[2-Benzyloxymethyl-1-methyl-2,3-dihydroquinolin-4(1*H*)-ylidene]-*N*,*N*-diethylacetamide (8e): (Table 3, Entry 12) According to general procedure B, amine **7e** (132 mg, 0.26 mmol) was treated with $Pd(PPh_3)_4$ (91 mg, 0.08 mmol) and Et_3N (0.08 mL, 0.52 mmol) in dry toluene (10 mL), and the mixture was heated to reflux for 6 h. After work-up, flash column chromatography (silica gel, 40% hexane/AcOEt) afforded **8e** (60 mg, 61%) as an oil. IR (NaCl): $\tilde{\nu}$ = 1630 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.16–1.21 (m, 6 H, 2× CH_2CH_3), 2.71 (dd, J = 14.6, 5.5 Hz, 1 H, H^3), 3.07 (s, 3 H, NCH_3), 3.35–3.50 (m, 5 H, C*H*HO, 2× CH_2CH_3), 3.55–3.60 (m, 2 H, H^3, CH*H*O), 3.67–3.72 (m, 1 H, H^2), 4.48 (d, J = 11.9 Hz, 2 H, CH_2Ph), 6.48 (s, 1 H, =CH), 6.59 (d, J = 8.0 Hz, 1 H, H^8), 6.60–6.70 (m, 1 H, H^6), 7.21–7.36 (m, 6 H, H^7, Ph), 7.44 (dd, J = 8.0, 1.3 Hz, 1 H, H^5) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 13.2, 14.4 (2× CH_2CH_3), 27.8 (C^3), 38.9 (NCH_3), 39.8, 42.6 (2× CH_2CH_3), 58.7 (C^2), 71.0 (CH_2O), 73.4 (CH_2Ph), 111.5 (C^8), 113.7 (C=CH), 115.4 (C^6), 119.7 (C^{4a}), 124.6 (C^5), 127.4, 127.5, 128.4, 130.7 (C^7, C–H_{arom}), 138.4 (C–C_{arom}), 142.1 (C^{8a}), 144.9 (C^4), 167.2 (CO) ppm. MS (70 eV, EI): m/z (%) = 257 (15) [M^+ – CH_2OBn], 184 (100), 91 (8). HRMS (EI): calcd. for $C_{24}H_{30}N_2O_2$ 378.2307; found 378.2328. $C_{24}H_{30}N_2O_2$ (378.51): calcd. C 76.16, H 7.99, N 7.40; found C 75.98, H 8.01, N 6.99.

(*E*)-2-[2-Benzyloxymethyl-1-methyl-2,3-dihydroquinolin-4(1*H*)-ylidene]-*N*-methoxy-*N*-methylacetamide (8f): (Table 3, Entry 13) According to general procedure B, amine **7f** (176 mg, 0.35 mmol) was treated with $Pd(PPh_3)_4$ (120 mg, 0.11 mmol) and Et_3N (0.10 mL, 0.71 mmol) in dry toluene (10 mL), and the mixture was heated to reflux for 6 h. After work-up, flash column chromatography (silica gel, 40% hexane/AcOEt) afforded **8f** (101 mg, 81%) as an oil. IR (NaCl): $\tilde{\nu}$ = 1640 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.70–2.77 (m, 1 H, H^3), 3.06 (s, 3 H, NCH_3), 3.24 (s, 3 H, NCH_3), 3.41–3.46 (m, 1 H, C*H*HO), 3.54–3.59 (m, 1 H, CH*H*O), 3.69 (broad s, 4 H, OCH_3, H^2), 4.11 (dd, J = 15.1, 2.3 Hz, 1 H, H^3), 4.44 (s, 2 H, CH_2Ph), 6.57–6.66 (m, 2 H, H^6, H^8), 6.76 (s, 1 H, =C*H*), 7.22–7.34 (m, 6 H, H^7, H_{arom}), 7.50 (dd, J = 7.8, 1.4 Hz, 1 H, H^5) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 27.2 (C^3), 32.4 (NCH_3), 38.9 (NCH_3), 58.6 (C^2), 61.5 (OCH_3), 70.8 (CH_2O), 73.3 (CH_2Ph), 109.1 (C=CH), 111.7 (C^8), 115.5 (C^6), 119.7 (C^{4a}), 124.9 (C^5), 127.2, 127.4, 128.3, 131.4 (C^7, C–H_{arom}), 138.3 (C–H_{arom}), 145.4 (C^{8a}), 147.2 (C^4), 168.1 (CO) ppm. MS (70 eV, EI): m/z (%) = 366 (9) [M^+], 306 (39), 245 (45), 215 (82), 184 (100), 157 (19), 144 (12), 136 (11), 122 (12), 91 (52), 72 (24), 59 (32), 55 (28). HRMS (EI): calcd. for $C_{22}H_{26}N_2O_3$ 366.1943; found 366.1936. $C_{22}H_{26}N_2O_3$ (366.46): calcd. C 72.11, H 7.15, N 7.64; found C 72.03, H 7.16, N 7.53.

Ethyl (*E*)-4-[2-(Diethylamino)-2-oxoethylidene]-1-methyl-1,2,3,4-tetrahydroquinoline-2-carboxylate (8g): (Table 3, Entry 21) $Pd(OAc)_2$ (16 mg, 0.07 mmol), $NaHCO_3$ (88 mg, 1.05 mmol) and n-Bu_4NCl (176 mg, 0.632 mmol) were added to a solution of butenylamine **7g** (197 mg, 0.48 mmol) and in dry CH_3CN (10 mL), and the mixture was heated to reflux for 6 h. The reaction mixture was then diluted with Et_2O (10 mL), and filtered through a Celite pad. The resulting filtrate was washed with saturated NH_4Cl (2× 10 mL) and brine (2× 10 mL), dried with Na_2SO_4, filtered and concentrated. The crude oil was purified by flash column chromatography (silica gel, 50% hexane/AcOEt) to afford **8g** (130 mg, 82%) as an oil. IR (NaCl): $\tilde{\nu}$ = 1735, 1680 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.17 (t, J = 7.1, Hz, 9 H, CH_2CH_3), 2.92 (dd, J = 15.1, 3.0 Hz, 1 H, H^3), 2.98 (s, 3 H, NCH_3), 3.26–3.54 (m, 4 H, CH_2CH_3), 3.85 (dd, J = 15.1, 3.0 Hz, 1 H, H^3), 4.03–4.11 (m, 3 H, H^2, CH_2CH_3), 6.41 (s, 1 H, =CH), 6.64–6.70 (m, 2 H, H^6, H^8), 7.22 (td, J = 7.7, 1.5 Hz, 1 H, H^7), 7.38 (dd, J = 7.8, 1.5 Hz, 1 H, H^5) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 13.2, 14.1, 14.3 (3× CH_3), 28.8 (C^3), 38.8 (NCH_3), 39.8, 42.5 (2× CH_2CH_3), 60.8 (OCH_2CH_3), 62.3 (C^2), 111.8 (C^6), 113.6 (C=CH), 116.8 (C^8), 120.3 (C^{4a}), 124.5 (C^5), 130.7 (C^7), 141.8 (C^{8a}), 145.4 (C^4), 166.6 (CO), 171.6 (CO) ppm. MS (70 eV, EI): m/z (%) = 330 (7) [M^+], 257 (42), 184 (92), 84 (100), 72 (12), 59 (15). HRMS (EI): calcd. for $C_{19}H_{26}N_2O_3$ 330.1943; found 330.1940.

(*E*)-2-[7-Chloro-1-methyl-2-phenyl-2,3-dihydroquinolin-4(1*H*)-ylidene]-*N*,*N*-diethylacetamide (8h): According to general procedure A, amine **7h** (120 mg, 0.24 mmol) was treated with $Pd(OAc)_2$ (8 mg, 0.024 mmol) PPh_3 (20 mg, 0.07 mmol) and Ag_2CO_3 (100 mg, 0.36 mmol) in DMF (10 mL). The reaction mixture was stirred at 90 °C for 5 h. After work-up, flash column chromatography (silica gel, hexane) afforded **8h** (85 mg, 96%) as an oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.81 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 0.99 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 2.65–2.82 (m, 2 H, CH_2CH_3), 2.92 (s, 3 H, NCH_3), 2.99–3.11 (m, 2 H, H^3, CH*H*CH_3), 3.32 (dd, J = 14.1, 3.7 Hz, 1 H, H^3), 3.38–3.54 (m, 1 H, C*H*HCH_3), 4.53–4.63 (m, 1 H, H^2), 6.19 (d, J = 1.3 Hz, 1 H, C=CH), 6.56–6.69 (m, 2 H, H^6, H^8), 6.95–7.05 (m, 2 H, Ph, H^5), 7.12–7.29 (m, 4 H, Ph) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 12.8, 13.7 (2× CH_2CH_3), 33.6 (C^3), 38.0 (NCH_3), 39.2, 41.6 (2× CH_2CH_3), 63.0 (C^2), 110.3 (C^8), 115.6 (C=CH), 115.7 (C^6), 119.4 (C^{4a}), 127.0 (C^5), 125.9, 128.5 (C–H_{arom}), 136.21 (C^7), 139.9 (C–C_{arom}), 141.5 (C^{8a}), 146.5 (C^4), 166.6 (CO) ppm. MS (230 eV, CI): m/z (%) = 371 (31) [MH^+ + 2], 369 (100) [MH^+], 333 (37), 296 (17). HRMS (CI): calcd. for $C_{22}H_{26}ClN_2O$ [MH^+] 369.1734; found 369.1736.

(–)-(*E*)-2-{(*R*)-2-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-1-methyl-2,3-dihydroquinolin-4(1*H*)-ylidene}-*N*,*N*-diethylacetamide (8i): According to general procedure A, amine **7i** (160 mg, 0.32 mmol) was treated with $Pd(OAc)_2$ (7 mg, 0.032 mmol) PPh_3 (23 mg, 0.09 mmol) and Ag_2CO_3 (132 mg, 0.48 mmol) in DMF (10 mL). The reaction mixture was stirred at 90 °C for 5 h. After work-up, flash column chromatography (silica gel, 20% hexane/AcOEt) afforded **8i** (80 mg, 68%) as an oil. $[\alpha]_D^{20}$ = –65.5 (c = 5, CH_2Cl_2). IR (NaCl): $\tilde{\nu}$ = 1630 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.00 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 1.17 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 1.30 (s, 3 H, CH_3), 1.41 (s, 3 H, CH_3), 2.62 (dd, J = 13.3, 2.2 Hz, 1 H, H^3), 2.73 (ddd, J = 13.3, 5.1, 2.2 Hz, 1 H, H^3), 3.03 (s, 3 H, NCH_3), 3.20–3.40 (m, 2 H, CH_2CH_3), 3.43–3.48 (m, 1 H, H^2), 3.54–3.66 (m, 2 H, CH_2CH_3), 3.77 (t, J = 7.5 Hz, 1 H, OC*H*H), 3.92 (dd, J = 13.1, 7.5 *Hz*, 1 H, OC*H*), 4.02 (dd, J = 7.5, 5.6 *Hz*, 1 H, OCH*H*), 5.69 (s, 1 H, =CH), 6.50–6.58 (m, 2 H, H^8, H^6), 7.12–7.18 (m, 1 H, H^7), 7.43 (dd, J = 7.8, 1.4 Hz, 1 H, H^5) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 12.4, 14.1 (CH_2CH_3), 25.7, 26.8 (CH_3), 33.0 (C^3), 39.0 (CH_2CH_3), 40.0 (NCH_3), 42.6 (CH_2CH_3), 62.0 (C^2), 67.6 (OCH), 76.7 (OCH_2), 108.5 (OOC), 111.2 (C^8), 115.9 (C^6), 118.6 (C^{4a}), 118.9 (C=CH), 127.8 (C^5), 130.3 (C^7), 134.0 (C^{8a}), 144.3 (C^4), 168.9 (CO) ppm. $C_{21}H_{30}N_2O_3$ (358.48): calcd. C 70.36, H 8.44, N 7.81; found C 70.27, H 8.37, N 7.61.

Supporting Information (see footnote on the first page of this article): Synthesis and characterization of precursors **1a**–**d**, **4a**–**d**, and **7a**–**i**. Copies of ^1H and ^{13}C NMR spectra of compounds described

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