DOI: 10.1002/ejoc.200600674

Aporphine Alkaloid Synthesis and Diversification via Direct Arylation

Marc Lafrance,[a] Nicole Blaquiere,[a] and Keith Fagnou*[a]

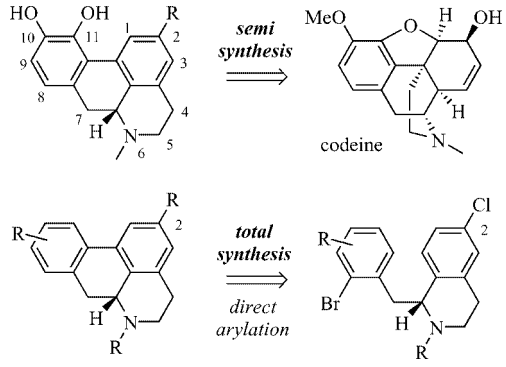
Keywords: Aporphine alkaloids / Natural products / Palladium / Direct arylation / Homogeneous catalysis

Palladium-catalyzed direct arylation of aryl chlorides, bromides and iodides has been applied to the preparation of new aporphine analogues including C2-substituted aporphines by reaction with benzodioxole, pyridine *N*-oxide and pyrazine *N*-oxide. Successful application of direct arylation in these diversification reactions highlights its utility not only in convergent, but also in divergent synthesis. We also describe enantioselective syntheses of (*R*)-nornuciferine and (*R*)-nuciferine employing a catalytic asymmetric transfer hydrogenation in high yield and excellent enantiomeric excess.

Introduction

The aporphine alkaloids are a diverse family of isoquinoline alkaloids with more than 300 members.[1] They share a characteristic tetracyclic motif with different levels of oxidation on both aromatic rings (Scheme 1). A range of interesting biological activities has been documented, including serotonergic,[2] antiplatelet,[3] anticancer,[4] antimalarial[5] and vasorelaxing activity.[6] These properties have prompted intensive structure–activity relationship (SAR) studies over the past three decades.[7] A recent 2005 study of the effect of carbon substituents at C2 on binding to the dopamine D_2 receptor supported the notion that this receptor contains a lipophilic cavity in the vicinity of the 2-position.[8] In most aporphine SAR studies, the preparation of the C2 analogues is performed via semi-synthesis commencing with codeine (or morphine) as the starting material (Scheme 1).[7] While this grants access to the aporphine core, it also limits the range of substrates that can be examined. Thus, the development of novel total synthesis routes remains an important goal.[9]

We recently reported the use of direct arylation methodology[10,11] in aporphine alkaloid synthesis[12] employing recently developed conditions for the intramolecular direct arylation of unactivated arenes.[13] Herein, we describe improved conditions for the formation of the aporphine aryl–aryl bond and several new examples of A-ring analogues including reactions of challenging aryl chlorides which occur in very high yield. We also describe the utilization of this approach in the synthesis of C2-substituted compounds via selective arylation of an aryl bromide **1** in the presence of a C2 aryl chloride. Retention of the aryl chloride after direct arylation allows facile introduction of a wide range of different substituents. In this respect, we also describe the use of recently reported direct arylation reactions with benzodioxole and aromatic *N*-oxides in the preparation of aporphine analogues. The successful inclusion of direct arylation in these derivatization reactions highlights the utility of these processes not only in convergent synthesis (formation of the key biaryl bond in the formation of the aporphine core) but also in divergent synthesis which is typical of most potential medicinal chemistry applications. Finally, we also describe the enantioselective syntheses of both natural (*R*)-nornuciferine and (*R*)-nuciferine employing a catalytic asymmetric transfer hydrogenation to form the stereocenter in high yield and excellent enantiomeric excess.



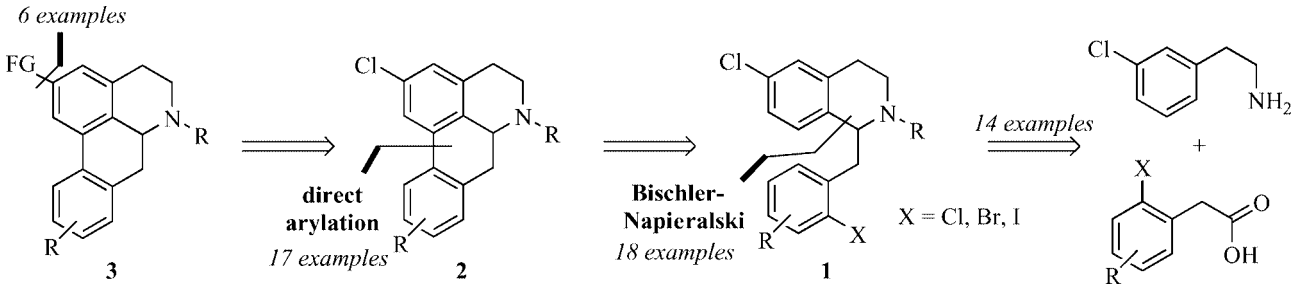
Scheme 1. Semi-synthetic and synthetic routes to C2 aporphine analogues.

Results and Discussion

The retrosynthesis is outlined in Scheme 2. Commencing with phenethylamine and arylacetic acid derivatives, amide bond formation and subsequent Bischler–Napieralski cycli-

[a] Center for Catalysis Research and Innovation, University of Ottawa,
Department of Chemistry, 10 Marie Curie, Ottawa, Ontario, Canada K1N 6N5, Canada
Fax: +1-613-562-5170
E-mail: keith.fagnou@ uottawa.ca

Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

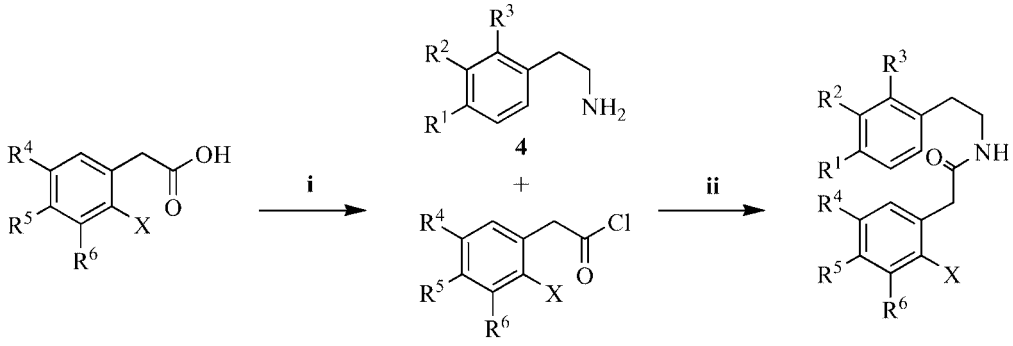


Scheme 2. Direct arylation as a convergent and divergent strategy for aporphine synthesis.

zation would give rise to the key intermediates **1**. At this point, direct arylation would be employed to form the key carbon–carbon biaryl linkage to give the aporphine core **2**. When a C2 chloride is present, further elaboration of the A-ring to give C2-substituted aporphines **3** could then be achieved by different palladium-catalyzed transformations, including recently developed direct arylation reactions.

A total of 14 different amides **6a**–**n** were prepared by initial conversion of the carboxylic acids to the acyl chloride **5** by reaction with oxalyl chloride followed by treatment with the desired 2-phenyl ethylamine **4**. These reactions occur in good yield, typically 72–99% yield (Table 1). With the necessary amides in hand, reaction conditions for the Bischler–Napieralski cyclization were investigated. The optimal conditions for the different amides **6a**–**n** were found to be substrate dependent. Treatment of the electron-rich substrates **6a**–**f**, bearing two electron-donating groups on the aromatic ring, with phosphorus oxychloride in refluxing

Table 1. Amide synthesis.[a]

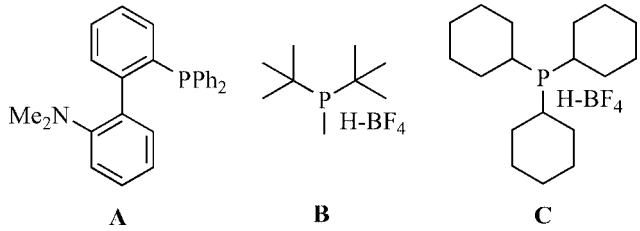


Entry	R^1	R^2	R^3	R^4	R^5	R^6	X	Amide	Yield [%][b]
1	OMe	OMe	H	H	H	H	Br	**6a**	99%
2	OMe	OMe	H	OMe	H	H	Br	**6b**	99%
3	OMe	OMe	H	F	H	H	Br	**6c**	72%
4	OMe	OMe	H	-O-CH_2-O-		H	Br	**6d**	99%
5	H	H	H	H	-CH=CH-CH=CH-		Br	**6e**	76%
6	-O-CH_2-O-		H	H	H	H	Br	**6f**	91%
7	OMe	H	H	H	H	H	Br	**6g**	91%
8	H	OMe	H	H	H	H	Br	**6h**	80%
9	H	H	H	H	H	H	Br	**6i**	99%
10	H	H	H	H	H	H	I	**6j**	93%
11	H	H	H	H	H	H	Cl	**6k**	98%
12	H	-CH=CH-CH=CH-		H	H	H	Br	**6l**	79%
13	H	Me	H	H	H	H	Br	**6m**	82%
14	Cl	H	H	H	H	H	Br	**6n**	79%

[a] Reagents and conditions: (i) $(COCl)_2$, CH_2Cl_2, 25 °C, 1 h; (ii) **4**, Et_3N, CH_2Cl_2 then **5**, 25 °C, 12 h. [b] Isolated yield.

dichloromethane gave the corresponding Bischler–Napieralski products in good yield (Entries 1 to 9). Amides **6g**–**h**, which possess one electron-donating group on the aromatic ring could be cyclized under similar conditions but required more elevated temperatures such as refluxing toluene and acetonitrile, respectively (Entries 10, 11). Unactivated amides **6i**–**n** did not react under either of these conditions. The difficulty of reacting unactivated arenes by Bischler–Napieralski cyclization has been previously reported.[9a,14] Fortunately, we found that more forcing conditions, such as treatment with polyphosphoric acid at 150 °C for 4 to 48 h, gave the desired isoquinoline products in moderate to good yields (Entries 12 to 18). Longer reaction time (48 h) was required for **6n**. The dihydroisoquinoline compounds proved to be unstable, and were therefore reduced immediately using $NaBH_4$ in methanol to give the tetrahydroisoquinolines **8a**–**n** in 54–98% yields over two chemical steps. The amines were then protected as *tert*-butyl carbamates (Boc), methyl carbamates, acetates (Ac) as well as a *para*-toluenesulfonamides (Ts) in 54–88% yields (Table 2).

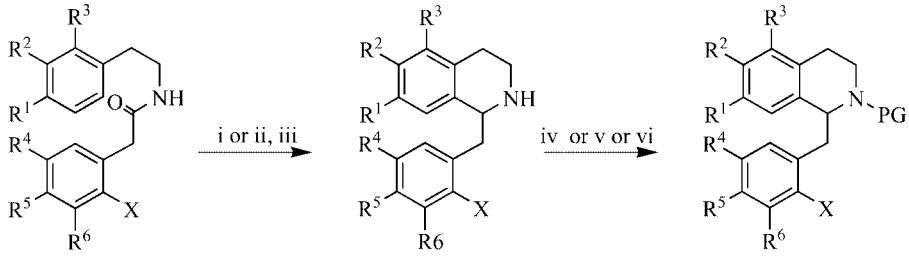
With 18 Bischler–Napieralski substrates **9** in hand, we turned to the key direct arylation carbon–carbon bond-forming step. In our initial report, we described the use of 2-(diphenylphosphanyl)-2′-(dimethylamino)biphenyl **A** for



A **B** **C**

Scheme 3. Ligands employed for direct arylation.

Table 2. Isoquinoline synthesis.[a]

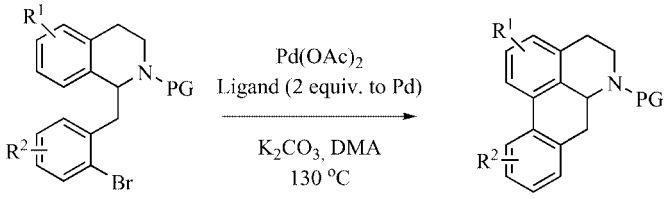


6a–n **8a–n** **9a–n**

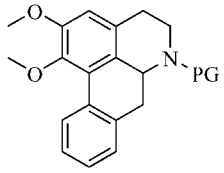
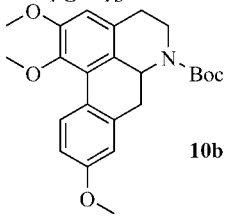
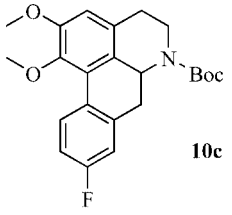
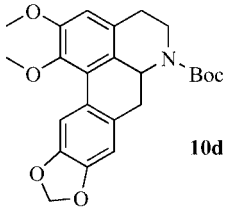
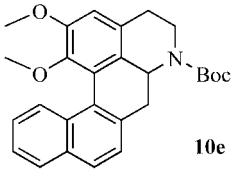
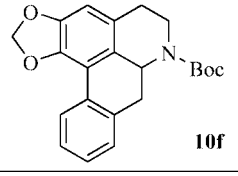
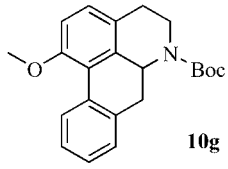
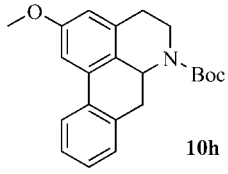
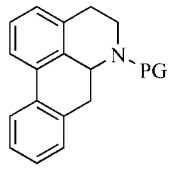
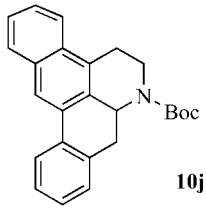
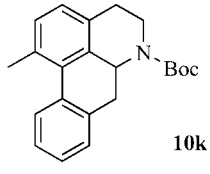
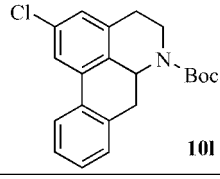
Entry	R^1	R^2	R^3	R^4	R^5	R^6	X	Method	Product	Yield [%][b] **8a–s**	PG	Product	Yield [%][c] **9a–s**
1	OMe	OMe	H	H	H	H	Br	A	**8a**	99%	Boc	**9aa**	80%
2											CO_2Me	**9ab**	84%
3											Ac	**9ac**	78%
4											Ts	**9ad**	54%
5	OMe	OMe	H	OMe	H	H	Br	A	**8b**	68%	Boc	**9b**	77%
6	OMe	OMe	H	F	H	H	Br	A	**8c**	75%	Boc	**9c**	65%
7	OMe	OMe	H	-O-CH_2-O-		H	Br	A	**8d**	90%	Boc	**9d**	71%
8	OMe	OMe	H	H	-CH=CH-CH=CH-		Br	A	**8e**	79%	Boc	**9e**	87%
9	-O-CH_2-O-		H	H	H	H	Br	A	**8f**	54%	Boc	**9f**	70%
10	OMe	H		H	H	H	Br	A[d]	**8g**	88%	Boc	**9g**	86%
11	H	OMe	H	H	H	H	Br	A[e]	**8h**	73%	Boc	**9h**	57%
12	H	H	H	H	H	H	Br	B	**8i**	89%	Boc	**9ia**	88%
13											Ac	**9ib**	81%
14	H	H	H	H	H	H	I	B	**8j**	83%	Boc	**9j**	82%
15	H	H	H	H	H	H	Cl	B	**8k**	77%	Boc	**9k**	75%
16	H	-CH=CH-CH=CH-		H	H	H	Br	B	**8l**	68%	Boc	**9l**	67%
17	H	Me	H	H	H	H	Br	B	**8m**	85%	Boc	**9m**	82%
18	H	Cl	H	H	H	H	Br	B[f]	**8n**	98%	Boc	**9n**	69%

[a] Reagents and conditions: (i) Method A: $POCl_3$, CH_2Cl_2, reflux, 12 h; (ii) Method B: Polyphosphoric acid, 150 °C, 12 h; (iii) $NaBH_4$, MeOH, 25 °C, 3 h; (iv) $(ROC)_2O$, DMAP (cat.), iPr$_2$EtN, CH_2Cl_2; (v) pyridine, TsCl, CH_2Cl_2; (vi) Acetic anhydride, DMAP (cat.), iPr$_2$EtN, CH_2Cl_2. [b] Isolated yield over 2 chemical steps. [c] Isolated yield. [d] Reaction performed in refluxing toluene. [e] Reaction performed in acetonitrile. [f] Reaction was heated for 48 h. PG = protecting group.

Table 3. Formation of the aporphine core by direct arylation.[a]



9a–n **10a–l**

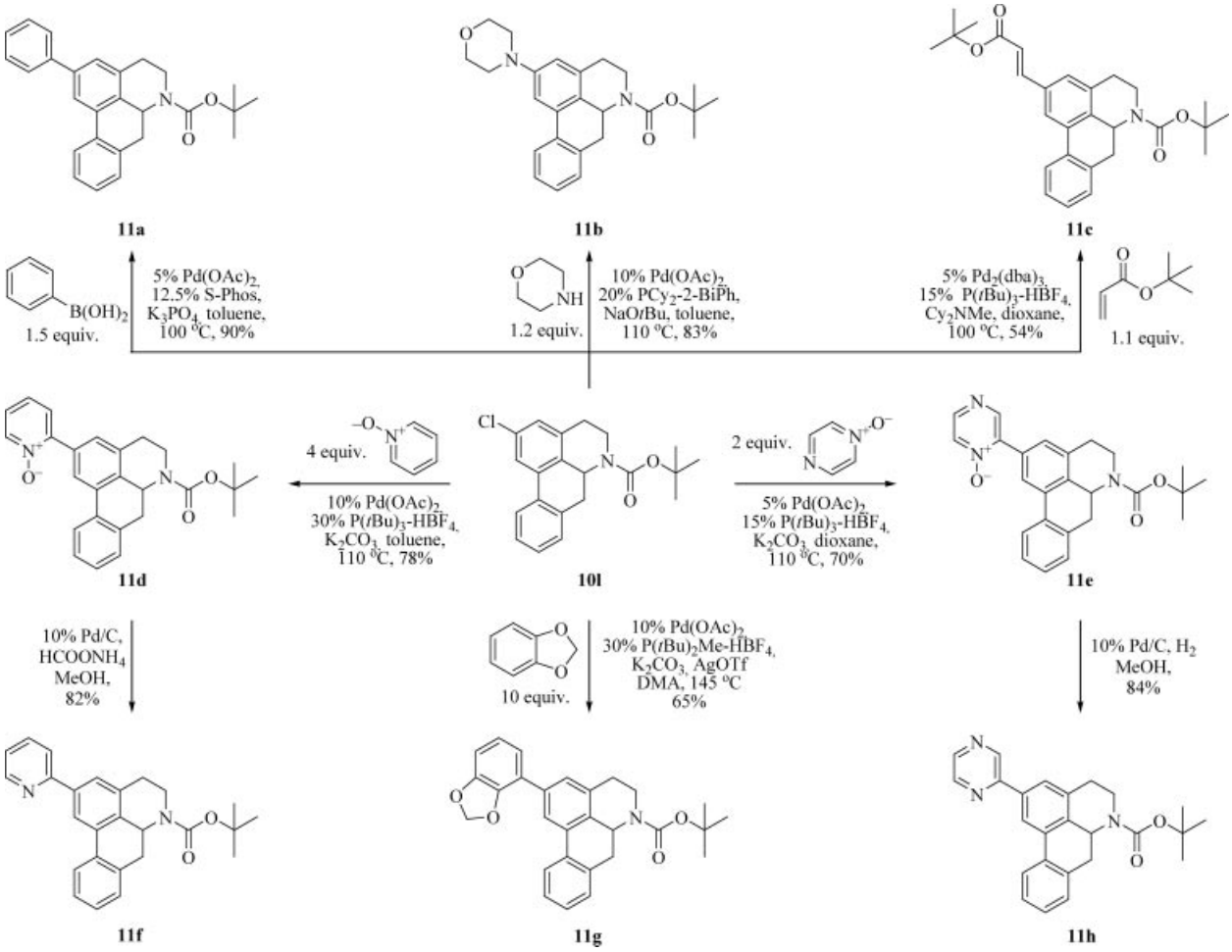
Entry	Product	Ligand	mol% Pd	Yield[b]
				
1	PG = Boc	A	5	87
2	PG = Boc	A	1	80
3	PG = Boc	B	1	88
4	PG = Boc **10aa**	C	1	79
5	PG = CO_2Me **10ab**	A	5	58
6	PG = Ac **10ac**	A	5	99
7	PG = Ts **10ad**	A	5	99
8	 **10b**	B	5	99
9	 **10c**	A	5	99
10	 **10d**	A	5	99
11	 **10e**	A	5	86
12	 **10f**	B	5	99
13	 **10g**	A	5	99
14	 **10h**	A	5	99
				
15	PG = Boc **10ia**	A	5	88
16	PG = Ac **10ib**	A	5	81
17[c]	PG = Boc	B	5	98
18[d]	PG = Boc	B	5	78
19	 **10j**	B	5	92
20	 **10k**	A	5	99
21	 **10l**	A	5	86

[a] Reaction conditions: isoquinoline **9a**–**n**, $Pd(OAc)_2$, ligand (2 equiv. to Pd), K_2CO_3 (2 equiv.), DMA (0.2 M). [b] Isolated yield. [c] Using aryl chloride as a substrate. [d] Using aryl iodide as a substrate and 0.5 equiv. of Ag_2CO_3 was added as an additive. PG = protecting group.

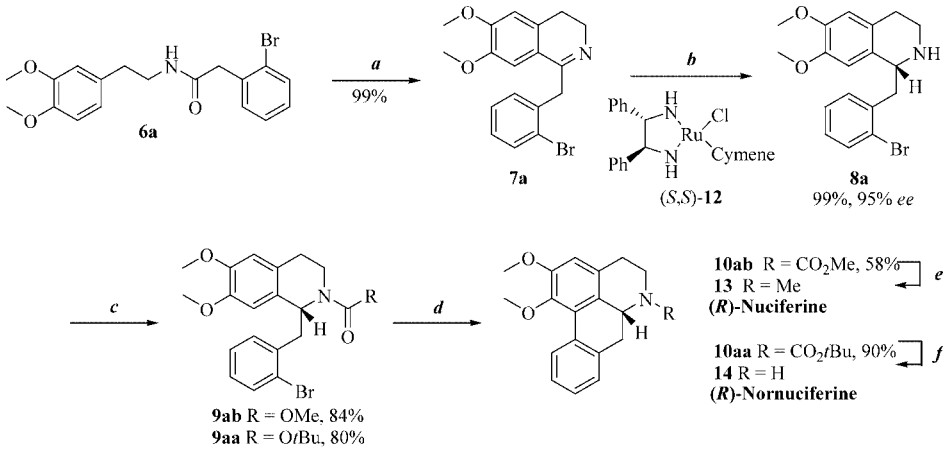
the synthesis of the aporphine core (Scheme 3). In subsequent studies, we discovered that this particular catalyst system was unable to achieve completion when employing less than 3 mol-% catalyst loading with aryl bromides (Entry 2) and failed to induce arylation using aryl chlorides. These limitations prompted us to search for a more reactive catalyst which led to the finding that treatment of **9aa** with 1 mol-% $Pd(OAc)_2$, 2 mol-% di-*tert*-butyl(methyl)phosphane (added as the air-stable HBF_4 salt[15]), 2 equiv. of K_2CO_3 in DMA (0.2 M) at 130 °C gave the aporphine **10aa** in 88% yield (Entry 3). Under both our initial and new conditions, no dehalogenated by-product is observed, being a common side reaction associated to these processes. During the assessment of substrate scope, 5 mol-% catalyst loading was typically employed for convenience of scale.

The different *N*-protecting groups were found to be variably compatible with the reaction conditions. The *N*-toluenesulfonyl **9ad** and *N*-acetyl isoquinolines **9ac** and **9ib** all reacted to give the aporphines in high yield (Entries 6, 7 and 16). Conversely, use of the slightly more labile *N*-Boc and *N*-methylcarbamate isoquinolines **9aa**, **9ab** resulted yields of typically greater than 80% and 58% respectively (Entries 1 to 5). Because of the regularly high yields and the greater ease of deprotecting the *N*-Boc group subsequent to direct arylation, it was employed as the standard nitrogen protecting group in scope studies. In addition to arylbromides, chlorides and iodides are also compatible (Entries 17 and 18). In accord with our previous studies, the use of silver carbonate as an additive was required for the reaction using an aryl iodide (Entry 18).[13] Deactivated aryl bromides can be used without any negative impact (Entries 8 and 10) as can electron deficient aryl bromides (Entry 9). Sterically hindered bromides can also be employed to generate a tetra-substituted aporphine in 86% yield (Entry 11). The ring-A can be an electron rich (Entries 12–14) or unactivated arene (Entries 19 and 20) to give the aporphine in excellent yield. Direct arylation of an isoquinoline having both chloride and bromide functionalities was also achieved in 86% yield using 2-(diphenylphosphanyl)-2′-(dimethylamino)biphenyl as the ligand (Entry 21). This ligand does not interact with the aryl chloride functionality under the reaction conditions leaving it intact for subsequent elaboration (Table 3).

Inspired by the SAR studies that pointed to the importance of C2 substituents,[7] aryl chloride **10l** was derivatized by different cross-coupling reactions (Scheme 4). Introduction of a phenyl substituent by Suzuki–Miyaura coupling gave **11a** in 90% yield.[16] Buchwald–Hartwig amination



Scheme 4. Formation of C2 aporphine analogues through various cross-coupling reactions.



Scheme 5. *a*) Reaction conditions: (a) $POCl_3$, DCM, reflux; b) (*S*,*S*)-**12** (5 mol-%), HCO_2H/NEt_3, DMF, room temp., 60 min, 99% over 2 steps, 95% *ee*; c) $(ROC)_2O$, DMAP (cat.), iPr_2EtN, yield indicated; d) $Pd(OAc)_2$ (5 mol-%), 2-(diphenylphosphanyl)-2′-(dimethylamino)-biphenyl (10 mol-%), KOAc (2.0 equiv.), DMA, 130 °C, 4 h, yield indicated; (e) LAH, THF, 0 °C to room temp., 24 h, 88%; (f) trifluoroacetic acid (13 equiv.), DCM, room temp., 1 h, 53%.

was also achieved with morpholine to give the analogue **11b** in 83% yield.[17] A vinyl group could also be installed using conditions developed by Fu for aryl chlorides to give **11c** in 54% yield.[18] In addition to the established cross-coupling process, we also evaluated the use of direct arylation as a means of enabling divergent synthesis. For example, direct arylation of pyridine and pyrazine *N*-oxides at C2 was achieved using conditions developed in our laboratories[19] followed by subsequent reduction of the *N*-oxides to give **11f** and **11 h** in 64% and 59% over the 2 steps. Direct intermolecular arylation of benzodioxole[13a] can also be achieved to give rise to **11g** in 65% yield. These results begin to validate the role of direct arylation for the preparation of analogues in medicinal chemistry.

The direct arylation methodology was also employed in enantioselective syntheses of (*R*)-nornuciferine and (*R*)-nuciferine alkaloids. We were gratified to find that Bischler–Napieralski cyclization of the amide **6a** and catalytic asymmetric transfer hydrogenation of the newly generated imine **7a** using Noyori's ruthenium-based catalyst provides **8a** in 99% yield and 95% *ee*.[20] Immediate protection as the methyl and *tert*-butyl carbamates to give **9ab** and **9aa** was achieved by treatment with the corresponding carbamate anhydrides and direct arylation using standard conditions gave **10ab** in 58% and **10aa** in 90% yields. Reduction of the methyl carbamate of **10ab** with lithium aluminum hydride gave the natural product (*R*)-nuciferine in 42% overall yield and 95%ee. Finally, deprotection of the *tert*-butyl carbamate group of **10aa** under acidic conditions gave (*R*)-nornuciferine in 37% overall yield and 95% *ee*. The low yield of 53% for the last step is due to the instability of the aporphine core to strongly acidic conditions resulting in some decomposition (Scheme 5).[9b,21]

In conclusion, a wide range of aporphine compounds, including C2 analogues, can be efficiently prepared by making use of direct arylation for both the key carbon–carbon biaryl bond forming and C2 diversification steps. These reactions can be performed with aryl chlorides, bromides and iodides with 1 to 5 mol-% catalyst. These syntheses highlight the utility of the direct arylation methodology both in target oriented synthesis as well as a tool for the introduction of diversity in medicinal compounds. We have also achieved an enantioselective synthesis of the (*R*)-nornuciferine in 37% overall yield and (*R*)-nuciferine in 42% yield.

Experimental Section

General Remarks: Unless otherwise stated, all experiments were carried out under nitrogen, in oven-dried glassware with magnetic stirring. ^1H and ^{13}C NMR were recorded in $CDCl_3$ or $(CD_3)_2SO$ solutions with a Bruker AVANCE 300 spectrometer or INOVA 500. Chemical shifts are referenced to residual chloroform (δ = 7.27 ppm for ^1H and δ = 77.0 ppm for ^{13}C) or TMS (δ = 0 ppm for ^1H and ^{13}C). High-resolution mass spectra were obtained with a Kratos Concept IIH. Infrared analysis was performed with a Bruker EQUINOX 55. HPLC Grade THF, Et_2O, benzene, toluene and CH_2Cl_2 are dried and purified with MBraun SP Series solvent purification system. Triethylamine was freshly distilled from NaOH before every use. Dimethylacetamide degassed with Argon prior to every use. Phosphonium salts were synthesized according to literature procedures[15] or purchased from Strem, stored in a dessicator and used without further purification. Palladium sources were stored in a dessicator and were weighed out to air unless otherwise specified. Compounds **5b**,[22] **6a**,[12] **6i**,[12] **8a**,[12] **8i**,[12] **9aa**,[12] **9ac**,[12] **9ad**,[12] **9ia**,[12] **9ib**,[12] **10aa**,[12] **10ac**,[12] **10ad**,[12] **10ia**,[12] **10ib**,[12] were prepared according to literature procedures and exhibited identical spectroscopic data to that reported, all other reagents and solvents were used as is from commercial sources.

General Procedure for the Synthesis of Amides 6a–6n: The acid (1 equiv.) and oxalyl chloride in dry dichloromethane (0.25 M) were stirred at room temperature in a flask attached to a bubbler. To this solution is added one drop of dimethylformamide and the solution is stirred for 1 h (or until no gas is formed). The solution is then concentrated and the resulting acid chloride is employed without further purification. The amine (1 equiv.) and triethylamine (1.1 equiv.) were dissolved in dry dichloromethane (0.25 M). To this mixture was added the freshly prepared acid chloride dropwise (1.05 equiv.) at 0 °C. The reaction was stirred at room temperature

overnight. The reaction was then quenched with brine then extracted with dichloromethane followed by evaporation under reduced pressure and the crude reaction mixture was purified by column chromatography on silica gel eluting with Et_2O/hexane mixtures.

2-(2-Bromo-5-methoxyphenyl)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-acetamide (6b): The amide was prepared following the general procedure (99%), m.p. 134.7–137.1 °C ($CHCl_3$). IR: $\tilde{\nu}_{max}$ = 3302, 1635, 1517, 1236, 1141, 1026 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 2.71 (t, J = 6.9 Hz, 2 H), 3.47 (q, J = 6.9 Hz, 2 H), 3.62 (s, 2 H), 3.77 (s, 3 H), 3.84 (s, 3 H), 3.85 (s, 3 H), 5.51 (br, 1 H), 6.57–6.64 (m, 2 H), 6.69–6.73 (m, 2 H), 6.82 (d, J = 3.0 Hz, 1 H), 7.42 (d, J = 8.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 34.9, 40.7, 44.2, 55.40, 55.7, 55.8, 111.1, 111.6, 115.0, 115.1, 116.8, 120.5, 131.0, 133.5, 135.5, 147.5, 148.9, 159.1, 169.2 ppm. HRMS calcd. for $C_{19}H_{22}BrNO_4$ (M^+) 407.0732; found: 407.0731.

2-(2-Bromo-5-fluorophenyl)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]acetamide (6c): The amide was prepared following the general procedure (72%), m.p. 149.7–151.3 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 3292, 1636, 1552, 1517, 1235, 1142, 1029. ^1H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 2.73 (t, J = 6.9 Hz, 2 H), 3.49 (q, J = 6.8 Hz, 2 H), 3.62 (s, 2 H), 3.84 (s, 3 H), 3.86 (s, 3 H), 5.50 (br, 1 H), 6.62 (dd, J = 8.0, 1.9 Hz, 1 H), 6.64 (d, J = 1.9 Hz, 1 H), 6.75 (d, J = 8.0 Hz, 1 H), 6.89 (ddd, $J_{4,F}$ = 8.0, $J_{3,4}$ = 8.0, $J_{4,6}$ = 3.0 Hz, 1 H, H-4), 7.04 (dd, $J_{6,F}$ = 8.9, $J_{4,6}$ = 3.0 Hz, 1 H, H-6), 7.49 (dd, $J_{3,F}$ = 8.8, $J_{3,4}$ = 5.3 Hz, 1 H, H-3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 34.9, 40.7, 43.9, 55.8, 55.8, 111.13, 111.6, 116.2 (J_F = 22.4 Hz), 118.5 (J_F = 23.0 Hz), 118.9 (J_F = 3.3 Hz), 120.5, 130.8, 134.1 (J_F = 8.1 Hz), 136.6 (J_F = 7.8 Hz), 147.6, 148.9, 163.5 (J_F = 247.9 Hz), 168.6 ppm. HRMS calcd. for $C_{18}H_{19}BrFNO_3$ (M^+) 395.0532; found: 395.0521.

2-(5-Bromobenzo[1,3]dioxol-6-yl)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-acetamide (6d): The amide was prepared following the general procedure (99%), m.p. 166.3–167.9 °C ($CHCl_3$); ($CHCl_3$). $\tilde{\nu}_{max}$ = 3281, 1641, 1517, 1480, 1233, 1027. ^1H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 2.71 (t, J = 6.9 Hz, 2 H), 3.47 (q, J = 6.8 Hz, 2 H), 3.56 (s, 2 H), 3.84 (s, 3 H), 3.85 (s, 3 H), 5.51 (br, 1 H), 5.98 (s, 2 H), 6.61–6.64 (m, 2 H), 6.73–6.76 (m, 2 H), 7.0 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 34.9, 40.6, 43.7, 55.7, 55.8, 101.9, 110.8, 111.1, 111.6, 112.7, 115.2, 120.5, 127.4, 130.9, 147.5, 147.6, 147.7, 148.9, 169.5 ppm. HRMS calcd. for $C_{19}H_{20}BrNO_5$ (M^+) 421.0525; found: 421.0521.

2-(1-Bromo-2-naphthyl)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]acetamide (6e): The amide was prepared following the general procedure (76%), m.p. 164.9–166.2 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 3293, 1648, 1517, 1262, 1237, 1028. ^1H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 2.73 (t, J = 6.8 Hz, 2 H), 3.47 (q, J = 6.7 Hz, 2 H), 3.68 (s, 2 H), 5.45 (br, 1 H), 6.94–6.97 (m, 2 H), 7.08 (s, 1 H), 7.13–7.18 (m, 2 H), 7.26–7.29 (m, 1 H), 7.57 (d, J = 7.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 34.9, 40.6, 45.2, 55.7, 55.7, 110.8, 111.4, 120.4, 125.0, 126.6, 127.38, 127.8, 128.1, 128.2, 128.2, 130.8, 132.4, 132.9, 133.6, 147.4, 148.8, 169.3 ppm. HRMS calcd. for $C_{22}H_{22}BrNO_3$ (M^+) 427.0783; found: 427.0758.

***N*-[2-Benzo[1,3]dioxol-5-yl-ethyl]-2-(2-bromophenyl)acetamide (6f):** The amide was prepared following the general procedure (91%), m.p. 129.1–131.8 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 3290, 2874, 1636, 1547, 1489, 1246, 1028. ^1H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 2.65 (t, J = 6.8 Hz, 2 H), 3.42 (q, J = 6.7 Hz, 2 H), 3.66 (s, 2 H), 5.54 (br, 1 H), 5.90 (s, 2 H), 6.48 (dd, J = 7.9, 1.7 Hz, 1 H), 6.56 (d, J = 1.7 Hz, 1 H),, J = 7.9, 1 H Hz 6.65 (d), 7.10–7.18 (m, 1 H), 7.27–7.28 (2 h, m), 7.56 (d, J = 7.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 35.6, 41.3, 44.4, 101.3, 108.7, 109.5, 122.0, 125.4, 128.4, 129.5, 132.1, 132.8, 133.5, 135.2, 146.5, 148.1, 169.9 ppm. HRMS calcd. for $C_{17}H_{16}BrNO_3$ (M^+) 361.0314; found: 361.0305.

2-(2-Bromophenyl)-*N*-[2-(3-methoxyphenyl)ethyl]acetamide (6g): The amide was prepared following the general procedure (91%), m.p. 86.9–88.0 °C ($CHCl_3$). IR (nujol): $\tilde{\nu}_{max}$ = 3286, 1641, 1544, 1459, 1155 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 2.71 (t, J = 6.8 Hz, 2 H), 3.48 (q, J = 6.6 Hz, 2 H), 3.66 (s, 2 H), 3.77 (s, 3 H), 5.51 (br, 1 H), 6.64–6.74 (m, 3 H), 7.11–7.17 (m, 2 H), 7.27 (d, J = 3.9 Hz, 2 H), 7.55 (d, J = 7.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 35.17, 40.47, 43.24, 54.70, 111.37, 114.04, 120.66, 124.65, 127.41, 128.49, 129.16, 131.20, 132.49, 134.75, 140.09, 159.30, 169.40 ppm. HRMS calcd. for $C_{17}H_{18}BrNO_2$ (M^+) 347.0521; found: 347.0516.

2-(2-Bromophenyl)-*N*-[2-(4-methoxyphenyl)ethyl]acetamide (6h): The amide was prepared following the general procedure (80%), m.p. 109.9–110.7 °C ($CHCl_3$). IR (nujol): $\tilde{\nu}_{max}$ = 3297, 1644, 1461, 1238, 1029 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 2.68 (t, J = 6.9 Hz, 2 H), 3.44 (q, J = 6.7 Hz, 2 H), 3.66 (s, 2 H), 3.77 (s, 3 H), 5.50 (br, 1 H), 6.77 (d, J = 8.6 Hz, 2 H), 6.98 (d, J = 8.5 Hz, 2 H), 7.12–7.17 (m, 1 H), 7.27 (d, J = 4.5 Hz, 2 H), 7.56 (d, J = 7.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 34.51, 40.91, 44.00, 55.22, 113.94, 124.96, 127.94, 129.03, 129.60, 130.58, 131.67, 133.06, 134.78, 158.11, 169.42 ppm. HRMS calcd. for $C_{17}H_{18}BrNO_2$ (M^+) 347.0521; found: 347.0529.

2-(2-Iodophenyl)-*N*-[2-phenylethyl]acetamide[9i] (6j): The amide was prepared following the general procedure (93%), m.p. 122.7–123.9 °C ($CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 3287, 3084, 1636, 1552, 1015 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 2.76 (t, J = 6.9 Hz, 2 H), 3.48 (q, J = 6.8 Hz, 2 H), 3.67 (s, 2 H), 5.45 (br, 1 H), 6.94–6.99 (m, 1 H), 7.05–7.08 (m, 2 H), 7.15–7.33 (m, 5 H), 7.36–7.39 (dd, J = 1.1, 7.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 35.4, 40.7, 48.5, 101.2, 126.4, 128.5, 128.6, 128.8, 129.0, 130.8, 138.2, 138.5, 139.7, 169.3 ppm. HRMS calcd. for $C_{16}H_{16}INO$ (M^+) 365.0277; found: 365.0266.

2-(2-Chlorophenyl)-*N*-[2-phenylethyl]acetamide[23] (6k): The amide was prepared following the general procedure (98%), m.p. 105–106 °C ($CHCl_3$).IR (KBr): $\tilde{\nu}_{max}$ = 3283, 3086, 1644, 1557, 1352 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 2.74 (t, J = 6.9 Hz, 2 H), 3.48 (q, J = 6.8 Hz, 2 H), 3.64 (s, 2 H), 5.51 (br, 1 H), 7.04–7.08 (m, 2 H), 7.18–7.29 (m, 6 H), 7.36–7.39 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 35.4, 40.7, 41.4, 126.0, 127.3, 128.5, 128.6, 128.8, 129.7, 131.6, 132.9, 134.3, 138.6, 169.4 ppm. HRMS calcd. for $C_{16}H_{16}ClNO$ (M^+) 273.0920; found: 273.0930.

2-(2-Bromophenyl)-*N*-[2-(naphth-1-yl)ethyl]acetamide (6l): The amide was prepared following the general procedure (79%), m.p. 119.7–122.5 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 3295, 3064, 1646, 1545, 1026. ^1H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 3.23 (t, J = 6.9 Hz, 2 H), 3.60 (q, J = 6.8 Hz, 2 H), 3.67 (s, 2 H), 5.49 (br, 1 H), 7.10–7.17 (m, 2 H), 7.21–7.24 (m, 2 H), 7.28–7.33 (m, 1 H), 7.43–7.56 (m, 3 H), 7.71 (d, J = 8.2 Hz, 1 H), 7.82–7.85 (m, 1 H) 8.05 (d, J = 7.7 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 32.5, 40.2, 44.0, 123.5, 124.9, 125.4, 125.6, 126.1, 126.7, 127.2, 127.9, 128.7, 129.0, 131.6, 131.7, 133.0, 133.8, 134.6, 134.6, 169.6 ppm. HRMS calcd. for $C_{20}H_{18}BrNO$ (M^+) 367.0572; found: 367.0571.

2-(2-Bromophenyl)-*N*-[2-(4-methylphenyl)ethyl]acetamide (6m): The amide was prepared following the general procedure (82%), m.p. 148.7–150.8 °C ($CHCl_3$). IR (nujol): $\tilde{\nu}_{max}$ = 3272, 3077, 1643, 1556,

1146, 1377, 1024 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 2.31 (s, 3 H), 2.71 (t, J = 6.9 Hz, 2 H), 3.46 (q, J = 6.6 Hz, 2 H), 3.67 (s, 2 H), 5.41 (br, 1 H), 6.96 (d, J = 7.9 Hz, 2 H), 7.04 (d, J = 7.8 Hz, 2 H), 7.12–7.18 (m, 1 H), 7.28 (d, J = 4.2 Hz, 2 H), 7.57 (d, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 21.01, 35.02, 40.84, 44.09, 124.99, 127.95, 128.55, 129.03, 129.25, 131.69, 133.09, 134.79, 135.49, 135.90, 169.38 ppm. HRMS calcd. for $C_{17}H_{18}BrNO$ (M^+) 331.0572; found: 331.0550.

2-(2-Bromophenyl)-*N*-[2-(3-chlorophenyl)ethyl]acetamide (6n): The amide was prepared following the general procedure (79%), m.p. 107.5–109.7 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 3290, 3065, 1641, 1547, 1472, 1027. ^1H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 2.73 (t, J = 6.8 Hz, 2 H), 3.47 (q, J = 6.7 Hz, 2 H), 3.68 (s, 2 H), 5.45 (br, 1 H), 6.94–6.97 (m, 2 H), 7.08 (s, 1 H), 7.13–7.18 (m, 2 H), 7.26–7.29 (m, 1 H), 7.57 (d, J = 7.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 35.1, 40.5, 44.0, 124.9, 126.6, 126.8, 128.0, 128.8, 129.2, 129.8, 131.6, 133.1, 134.2, 134.6, 140.7, 169.4 ppm. HRMS calcd. for $C_{16}H_{15}ClBrNO$ (M^+) 351.0026; found: 351.0007.

General Procedure for the Synthesis of Amine 8a–8n

Method A: To a solution of the amide (1.0 equiv.) in DCM (0.2 M) in a round-bottomed flask equipped with a magnetic stirrer and a condenser was added phosphorus oxychloride (4.0 equiv.) and the resulting mixture was refluxed overnight. The reaction was then cooled to 0 °C and the solution was neutralized with a saturated solution of Na_2CO_3. The resulting mixture was extracted with Et_2O to afford the crude dihydroisoquinoline. These compounds were found to be unstable and decompose on standing or exposure to silica gel. They were therefore reacted without further purification immediately. To a solution of the crude dihydroisoquinoline (1.0 equiv.) in MeOH (0.2 M) at 0 °C, was added slowly sodium borohydride (1.3 equiv.). The resulting mixture was stirred for 3 h at 23 °C. The reaction mixture was then cooled to 0 °C and a brine solution was added and then extracted with DCM. The amine was then purified by column chromatography on TEA neutralized silica gel using EtOAc/hexane as eluent.

Method B: To a solution of the amide (1.0 equiv.) in a round-bottomed flask equipped with a magnetic stirrer was added polyphosphoric acid (25 equiv.) and the resulting mixture was heated to 150 °C overnight. The reaction was then cooled to 0 °C, and the solution was neutralized with a saturated solution of Na_2CO_3. The resulting mixture was extracted with Et_2O to afford the crude dihydroisoquinoline. These compounds were found to be unstable and decompose on standing or exposure to silica gel. They were therefore reacted without further purification immediately. To a solution of the crude dihydroisoquinoline (1.0 equiv.) in MeOH (0.2 M) at 0 °C, was added slowly sodium borohydride (1.3 equiv.). The resulting mixture was stirred for 3 h at 23 °C. The reaction mixture was then cooled to 0 °C and a brine solution was added and then extracted with DCM. The amine was then purified by column chromatography on TEA neutralized silica gel using EtOAc/hexane as eluent.

1-(2-Bromo-5-methoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (8b): The amine was prepared following the general procedure (method B). (68%): $\tilde{\nu}_{max}$ = 3340, 2935, 1595, 1517, 1466, 1246, 1112, 1017. ^1H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 1.88 (br, 1 H), 2.74–2.75 (m, 2 H), 2.88–2.99 (m, 2 H), 3.12–3.25 (m, 1 H), 3.31 (dd, J = 13.6, 3.4 Hz, 1 H), 3.75 (s, 3 H), 3.82 (s, 3 H), 3.84 (s, 3 H), 4.23 (dd, J = 9.6, 2.8 Hz, 1 H), 6.59 (s, 1 H), 6.67 (dd, J = 8.7, 2.8 Hz, 1 H), 6.74 (s, 1 H), 6.82 (d, J = 2.8 Hz, 1 H), 7.45 (d, J = 8.7 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 29.1, 39.8, 43.1, 54.7, 55.3, 55.7, 55.7, 109.4, 111.5, 113.5, 115.1, 117.5, 126.9, 130.1, 133.3, 139.5, 146.9, 147.3, 158.6 ppm. HRMS calcd. for $C_{19}H_{20}NO_3$ ($M^+ - H_2Br$) 310.1443; found: 310.1433.

1-(2-Bromo-5-fluorobenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (8c): The amine was prepared following the general procedure (method B). (75%): $\tilde{\nu}_{max}$ = 3334, 2941, 1607, 1579, 1519, 1462, 1258, 1227, 1112, 1030. ^1H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 1.66 (br, 1 H), 2.68–2.73 (m, 2 H), 2.89–2.97 (m, 2 H), 3.19–3.30 (m, 2 H), 3.81 (s, 3 H), 3.83 (s, 3 H), 4.21 (d, J = 7.6 Hz, 1 H), 6.58 (s, 1 H), 6.72 (s, 1 H), 6.82 (dd, J = 6.9, 5.7 Hz, 1 H), 7.02 (d, J = 7.5 Hz, 1 H), 7.49 (dd, J = 7.5, 5.7 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 28.8, 39.3, 42.6, 54.2, 55.2, 55.3, 109.0, 111.2, 114.8 (J_F = 22.2 Hz), 118.2 (J_F = 19.4 Hz), 118.4, 126.7, 129.7, 133.4 (J_F = 7.8 Hz), 140.6 (J_F = 7.6 Hz), 146.6, 147.0, 161.1 (J_F = 247.0 Hz) ppm. HRMS calcd. for $C_{18}H_{17}FNO_2$ ($M^+ - H_2Br$) 298.1243; found: 298.1232.

1-[(5-Bromobenzo[*d*][1,3]dioxol-6-yl)methyl]-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (8d): The amine was prepared following the general procedure (method B). (90%): $\tilde{\nu}_{max}$ = 3334, 2925, 1610, 1515, 1476, 1261, 1112, 1038. ^1H NMR (TMS, 293 K, 300 MHz, $CDCl_3$): δ = 1.90 (br, 1 H), 2.72–2.76 (m, 2 H), 2.84–3.01 (m, 2 H), 3.19–3.27 (m, 2 H), 3.84 (s, 3 H), 3.85 (s, 3 H), 4.19 (dd, J = 9.9, 3.1 Hz, 1 H), 5.94 (s, 2 H), 6.59 (s, 1 H), 6.74 (s, 1 H), 6.77 (s, 1 H), 7.03 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 29.1, 39.8, 42.6, 54.9, 55.6, 55.7, 101.5, 109.3, 111.1, 111.4, 112.6, 114.6, 126.9, 130.2, 131.5, 146.8, 146.9, 147.0, 147.3 ppm. HRMS calcd. for $C_{19}H_{18}NO_4$ ($M^+ - H_2Br$) 324.1236; found: 324.1229.

1-[(1-Bromonaphthalen-2-yl)methyl]-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (8e): The amine was prepared following the general procedure (method B). (79%): $\tilde{\nu}_{max}$ = 3332, 2933, 1611, 1523, 1476, 1261, 1223, 1111, 1031. ^1H NMR (TMS, 293 K, 300 MHz, $CDCl_3$): δ = 1.73 (br, 1 H), 2.70–2.74 (m, 2 H), 2.91–2.99 (m, 1 H), 3.17–3.30 (m, 2 H), 3.58 (dd, J = 13.5, 3.9 Hz, 1 H), 3.76 (s, 3 H), 3.84 (s, 3 H), 4.36 (dd, J = 9.7, 3.8 Hz, 1 H), 6.58 (s, 1 H), 6.73 (s, 1 H), 7.36 (d, J = 8.3 Hz, 1 H), 7.46 (dd, J = 7.9, 7.9 Hz, 1 H), 7.53–7.58 (m, 1 H), 7.72 (d, J = 8.3 Hz, 1 H), 7.77 (d, J = 8.0 Hz, 1 H), 8.32 (d, J = 8.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 29.2, 39.9, 44.0, 55.2, 55.6, 55.6, 109.4, 111.4, 124.3, 125.9, 126.9, 127.0, 127.2, 127.8, 129.0, 129.0, 130.3, 132.3, 133.2, 136.9, 146.8, 147.2 ppm. HRMS calcd. for $C_{22}H_{20}NO_2$ ($M^+ - H_2Br$) 330.1494; found: 314.0945.

5-(2-Bromobenzyl)-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline (8f): The amine was prepared following the general procedure (method B). (54%): $\tilde{\nu}_{max}$ = 3461, 2901, 1503, 1483, 1247, 1040. ^1H (300 MHz, $CDCl_3$, 293 K, TMS): δ = 1.76 (br, 1 H), 2.73 (t, J = 5.7 Hz, 2 H), 2.89–2.97 (m, 2 H), 3.17–3.26 (m, 1 H), 3.33 (dd, J = 13.7, 3.1 Hz, 1 H), 4.22 (dd, J = 10.4, 2.6 Hz, 1 H), 5.90 (s, 2 H), 6.57 (s, 1 H), 6.83 (s, 1 H), 7.08–7.16 (m, 1 H), 7.25–7.28 (m, 2 H), 7.59 (d, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 29.9, 39.8, 42.9, 55.1, 100.6, 106.5, 108.7, 124.8, 127.3, 128.1, 128.2, 131.6, 131.8, 133.0, 138.6, 145.7, 145.9 ppm. HRMS calcd. for $C_{17}H_{15}NO_2$ ($M^+ - H_2Br$) 264.1025; found: 264.1027.

1-(2-Bromobenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (8g): The amine was prepared following the general procedure (method B) in toluene at 100 °C for 4.5 h. (88%): $\tilde{\nu}_{max}$ = 3334, 3056, 2931, 1609, 1469, 1439, 1025. ^1H NMR (, 300 MHz, $CDCl_3$, 293 KTMS): δ = 1.72 (1 H, br), 2.78–2.84 (m, 2 H), 2.89–2.98 (m, 2 H), 3.20–3.28 (m, 1 H), 3.39 (dd, 1 H, J = 13.6, 3.3 Hz), 3.78 (s, 3 H), 4.28 (dd, 1 H, J = 10.5, 3.1 Hz), 6.65 (d, 1 H, J = 2.6 Hz), 6.74 (dd, 1 H, J = 8.5, 2.7), 7.08–7.14 (m, 1 H), 7.24–7.27 (m, 3 H), 7.58 (d, 1

H, J = 7.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 30.26, 40.10, 43.06, 54.68, 55.18, 112.15, 113.55, 124.87, 127.37, 127.55, 128.19, 130.94, 131.89, 133.05, 136.41, 138.76, 157.76 ppm. HRMS calcd. for $C_{17}H_{17}BrNO_2$ (M^+ – H) 330.0494; found: 330.0466.

1-(2-Bromobenzyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline (8h): The amine was prepared following the general procedure (method B) in MeCN at 85 °C for 4.5h. (73%): $\tilde{\nu}_{max}$ = 2931, 1611, 1503, 1248, 1040. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 1.64 (br, 1 H), 2.74–2.77 (m, 2 H), 2.91–3.02 (m, 2 H), 3.20–3.28 (m, 1 H), 3.40 (dd, J = 13.6, 3.3 Hz, 1 H), 3.77 (s, 3 H), 4.30 (d, J = 8.9 Hz, 1 H), 6.74 (dd, J = 8.4, 2.6 Hz, 1 H), 6.87 (d, J = 2.5 Hz, 1 H), 7.03 (d, J = 8.4 Hz, 1 H), 7.09–7.14 (m, 1 H), 7.27 (d, J = 4.3 Hz, 1 H), 7.59 (d, J = 7.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 29.0, 34.3, 40.2, 43.0, 55.2, 55.2, 111.6, 112.2, 113.8, 124.8, 127.2, 127.3, 128.2, 129.5, 130.0, 131.9, 133.0, 138.7, 139.6, 157.5 ppm. HRMS calcd. for $C_{17}H_{16}NO$ (M^+ – H_2Br) 250.1232; found: 250.1245.

1-(2-Iodobenzyl)-1,2,3,4-tetrahydroisoquinoline (8j): The amine was prepared following the general procedure (method A). (83%): $\tilde{\nu}_{max}$ = 3421, 3059, 2925, 1672, 1464, 1453, 1435, 1125, 1011. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 2.40 (br, 1 H), 2.80–3.04 (m, 4 H), 3.20–3.28 (m, 1 H), 3.34 (dd, J = 13.7, 3.2 Hz, 1 H), 4.33 (dd, J = 10.5, 2.7 Hz, 1 H), 6.90–6.95 (m, 1 H), 7.08–7.31 (m, 5 H), 7.39–7.42 (m, 1 H), 7.85 (d, J = 7.9 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 29.6, 39.9, 46.8, 54.7, 100.8, 125.5, 126.0, 126.3, 127.9, 128.1, 129.0, 130.9, 134.8, 139.5, 141.4. HRMS calcd. for $C_{16}H_{14}N$ (M^+ – H_2I) 220.1126; found: 220.1084 ppm.

1-(2-Chlorobenzyl)-1,2,3,4-tetrahydroisoquinoline[23] (8k): The amine was prepared following the general procedure (method A). (77%), m.p. 62.9–65.1 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 3333, 3060, 2926, 1672, 1452, 1442, 1121, 1052, 1036. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 1.69 (br, 1 H), 2.79–2.85 (m, 2 H), 2.91–2.99 (m, 2 H), 3.21–3.29 (m, 1 H), 3.42 (dd, J = 13.7, 3.3 Hz, 1 H), 4.32 (dd, J = 10.5, 3.1 Hz, 1 H), 7.09–7.32 (m, 7 H), 7.38–7.41 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 29.8, 40.0, 40.5, 55.1, 125.7, 126.1, 126.4, 126.7, 127.9, 129.2, 129.7, 131.8, 134.3, 135.0, 137.0, 138.6 ppm. HRMS calcd. for $C_{16}H_{15}ClN$ (M^+ – H) 256.0893; found: 256.0894.

4-(2-Bromobenzyl)-1,2,3,4-tetrahydrobenzo[*f*]isoquinoline (8l): The amine was prepared following the general procedure (method A). (68%): $\tilde{\nu}_{max}$ = 3386, 3052, 2930, 1510, 1470, 1440, 1025. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 2.09 (br, 1 H), 2.97–3.14 (m, 4 H), 3.35–3.50 (m, 2 H), 4.45 (d, J = 9.7 Hz, 1 H), 7.09–7.14 (m, 1 H), 7.27–7.28 (m, 2 H), 7.43–7.53 (m, 3 H), 7.60 (d, J = 7.9 Hz, 1 H), 7.68 (d, J = 8.5 Hz, 1 H), 7.80 (d, J = 7.7 Hz, 1 H), 7.94 (d, J = 8.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 26.2, 39.3, 42.3, 55.5, 122.9, 124.8, 125.1, 125.2, 126.0, 126.0, 127.4, 128.2, 128.3, 130.1, 131.9, 132.1, 132.2, 133.0, 135.7, 138.7 ppm. HRMS calcd. for $C_{20}H_{16}N$ (M^+ – H_2Br) 270.1283; found: 270.1270.

1-(2-Bromobenzyl)-1,2,3,4-tetrahydro-7-methylisoquinoline (8m): The amine was prepared following the general procedure (method A). (85%): $\tilde{\nu}_{max}$ = 3297, 1644, 1461, 1238, 1029. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 1.63 (br, 1 H), 2.31 (s, 3 H), 2.69–2.82 (m, 2 H), 2.87–2.97 (m, 2 H), 3.16–3.24 (m, 1 H), 3.39 (d, J = 12.7 Hz, 1 H), 4.29 (d, J = 9.83 Hz, 1 H), 6.94–7.0 (m, 2 H), 7.05–7.14 (m, 2 H), 7.23–7.25 (m, 2 H), 7.55 (d, J = 7.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 21.78, 30.09, 40.74, 43.47, 55.56, 125.39, 127.50, 127.61, 127.85, 128.68, 129.65, 132.46, 132.53, 133.54, 135.59, 138.96, 139.33 ppm. HRMS calcd. for $C_{17}H_{16}N$ (M^+ – H) 234.1283; found: 234.1298.

1-(2-Bromobenzyl)-6-chloro-1,2,3,4-tetrahydroisoquinoline (8n): The amine was prepared following the general procedure (method A); the reaction was heated for 48 h. (98%): $\tilde{\nu}_{max}$ = 3054, 2928, 1597, 1484, 1470, 1128, 1025. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 1.67 (br, 1 H), 2.74–2.79 (m, 2 H), 2.87–2.95 (m, 2 H), 3.16–3.24 (m, 1 H), 3.33 (dd, J = 13.6, 3.4 Hz, 1 H), 4.27 (dd, J = 10.4, 3.2 Hz, 1 H), 7.08–7.13 (m, 3 H), 7.21–7.26 (m, 3 H), 7.57 (dd, J = 7.7, 0.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 29.6, 39.5, 42.7, 54.6, 124.7, 125.8, 127.3, 127.8, 128.2, 128.8, 131.5, 131.8, 132.9, 132.9, 137.0, 138.2 ppm. HRMS calcd. for $C_{16}H_{13}ClBrN$ (M^+) 254.0737; found: 254.0729.

General Procedure for the Synthesis of Carbamates 9a–9n: To a solution of the tetrahydroisoquinoline (1.0 equiv.), diisopropylethylamine (2.0 equiv.) and 1–3 mg of 4-(dimethylamino)pyridine in DCM (0.2 M) was added slowly di-*tert*-butyl dicarbonate (1.2 equiv.) and the resulting mixture was stirred overnight at 23 °C. The reaction was then quenched by adding a solution of NH_4Cl and was extracted with DCM. The crude reaction mixture was then purified by column chromatography on silica gel using Et_2O/hexane mixtures.

***tert*-Butyl 1-(2-Bromo-5-methoxybenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline-2(1*H*)-carboxylate (9b):** The carbamate was prepared following the general procedure (77%), m.p. 125–127 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 2981, 1691, 1519, 1099. ^{1}H NMR analysis revealed the presence of two amide rotamers present in a 5:1 ratio. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS, major rotamer): δ = 1.14 (s, 9 H), 2.62–2.67 (m, 1 H), 2.73–3.06 (m, 2 H), 3.44–3.50 (m, 2 H), 3.72 (s, 3 H), 3.85 (s, 6 H), 4.37 (dd, J = 12.9, 4.7 Hz, 1 H), 5.34 (d, J = 7.8 Hz, 1 H), 6.81 (s, 1 H), 6.58–6.70 (m, 3 H), 7.43 (d, J = 8.7 Hz, 1 H); minor rotamer: 1.36 (s, 9 H), 2.62–2.67 (m, 1 H), 2.73–3.06 (m, 2 H), 3.44–3.50 (m, 2 H), 3.72 (s, 3 H), 3.85 (s, 6 H), 3.93–4.12 (m, 1 H), 5.42 (dd, J = 8.3, 2.9 Hz, 1 H), 6.55 (s, 1 H), 6.58–6.70 (m, 3 H), 7.37 (d, J = 8.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS, major rotamer): δ = 27.6, 27.9, 35.9, 42.5, 53.5, 55.1, 55.5, 55.6, 79.0, 109.5, 111.1, 113.5, 115.3, 117.2, 126.1, 128.5, 132.6, 138.8, 147.1, 147.5, 153.8, 158.6; (peaks corresponding to the minor rotamer were also detected): 27.8, 38.2, 41.7, 53.1, 54.9, 109.8, 110.8, 113.3, 115.6, 116.5, 126.0, 128.4, 138.6, 146.9, 147.4, 153.9, 158.3 ppm. HRMS calcd. for $C_{20}H_{21}BrNO_4$ (M^+ – C_4H_9O) 418.0650; found: 418.0665.

***tert*-Butyl 1-(2-Bromo-5-fluorobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline-2(1*H*)-carboxylate (9c):** The carbamate was prepared following the general procedure (65%), m.p. 117–119 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 2995, 1688, 1519, 13.64, 1166, 1125, 1098. NMR analysis revealed the presence of two amide rotamers present in a 3:1 ratio. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS, major rotamer): δ = 1.16 (s, 9 H), 2.63–2.68 (m, 1 H), 2.78–3.06 (m, 2 H), 3.21–3.29 (m, 2 H), 3.87 (s, 6 H), 4.38 (dd, J = 13.2, 4.6 Hz, 1 H), 5.36 (dd, J = 10.7, 3.2 Hz, 1 H), 6.63 (s, 1 H), 6.80–6.92 (m, 3 H), 7.52 (dd, J = 8.2, 5.2 Hz, 1 H); minor rotamer: 1.35 (s, 9 H), 2.63–2.68 (m, 1 H), 2.78–3.06 (m, 2 H), 3.21–3.29 (m, 1 H), 3.35–3.44 (m, 1 H), 3.78 (s, 3 H), 3.87 (s, 3 H), 4.03 (dt, J = 12.8, 4.8 Hz, 1 H), 5.40 (dd, J = 9.3, 4.6 Hz, 1 H), 6.60 (s, 1 H), 6.80–6.92 (m, 3 H), 7.46 (dd, J = 8.9, 5.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS, major rotamer): δ = 27.8, 28.0, 36.2, 42.6, 53.5, 55.7, 55.8, 79.4, 109.5, 111.3, 115.1 (J_F = 22.6 Hz), 118.5 (J_F = 22.2 Hz), 119.1 (J_F = 3.1 Hz), 126.4, 128.4, 133.4 (J_F = 8.0 Hz), 140.2 (J_F = 7.5 Hz), 147.3, 147.8, 153.9, 161.5 (J_F = 248.3 Hz) ppm. (Peaks corresponding to the minor rotamer were also detected): 27.9, 38.3, 42.0, 53.2, 79.9, 109.8, 111.0, 114.7, 117.8, 118.1, 119.1, 126.2, 140.0, 147.1, 147.6, 154.1, 159.9, 163.1. HRMS calcd. for $C_{19}H_{18}BrFNO_3$ (M^+ – C_4H_9O) 406.0454; found: 406.0404.

***tert*-Butyl 1-[(5-Bromobenzo[*d*][1,3]dioxol-6-yl)methyl]-3,4-dihydro-6,7-dimethoxyisoquinoline-2(1*H*)-carboxylate (9d):** The carbamate was prepared following the general procedure (71%), m.p. 145–146 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 2985, 1688, 1518, 13.64, 1165, 1099, 1038. ^1H NMR analysis revealed the presence of two amide rotamers present in a 4:1 ratio. ^1H NMR (300 MHz, $CDCl_3$, 293 K, TMS, major rotamer): δ = 1.20 (s, 9 H), 2.61–2.66 (m, 1 H), 2.84–2.92 (m, 2 H), 3.14–3.26 (m, 2 H), 3.85 (s, 6 H), 4.36 (d, J = 12.0 Hz, 1 H), 5.28–5.31 (m, 1 H), 5.90 (d, J = 11.7 Hz, 1 H), 6.57 (s, 1 H), 6.62 (s, 1 H), 6.78 (s, 1 H), 7.02 (s, 1 H); minor rotamer: 1.38 (s, 9 H), 2.61–2.66 (m, 1 H), 2.84–2.92 (m, 2 H), 3.14–3.26 (m, 1 H), 3.33–3.41 (m, 1 H), 3.77 (s, 6 H), 4.00–4.09 (m, 1 H), 5.28–5.31 (m, 1 H), 5.90 (d, J = 11.7 Hz, 1 H), 6.57 (s, 1 H), 6.62 (s, 1 H), 6.96 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS, major rotamer): δ = 27.7, 27.9, 35.9, 42.1, 53.6, 55.5, 55.6, 79.0, 101.3, 109.4, 111.0, 111.1, 112.0, 114.9, 126.1, 128.4, 130.9, 146.9, 146.9, 147.0, 147.5, 153.8; (peaks corresponding to the minor rotamer were also detected): 27.8, 28.0, 38.2, 41.6, 53.4, 79.0, 101.1, 109.8, 110.5, 110.8, 115.1, 125.9, 130.8, 146.5, 146.7, 147.3 ppm. HRMS calcd. for $C_{20}H_{19}BrNO_6$ ($M^+ - C_4H_9O$) 432.0450; found: 432.0418.

***tert*-Butyl 1-[(1-Bromonaphth-2-yl)methyl]-3,4-dihydro-6,7-dimethoxyisoquinoline-2(1*H*)-carboxylate (9e):** The carbamate was prepared following the general procedure (87%), m.p. 144–145 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 2933, 1687, 1519, 1391, 1364, 1241, 1165, 1165. NMR analysis revealed the presence of two amide rotamers present in a 5:1 ratio. ^1H NMR (300 MHz, $CDCl_3$, 293 K, TMS, major rotamer): δ = 0.84 (s, 9 H), 2.66–2.71 (m, 1 H), 2.87–2.98 (m, 1 H), 3.17–3.27 (m, 1 H), 3.31–3.41 (m, 1 H), 3.53–3.59 (m, 1 H), 3.82 (s, 3 H), 3.87 (s, 3 H), 4.41 (dd, J = 13.2, 4.5 Hz, 1 H), 5.49 (dd, J = 10.6, 4.0 Hz, 1 H), 6.63 (s, 1 H), 6.82 (s, 1 H), 7.20 (d, J = 8.3 Hz, 1 H), 7.48 (dd, J = 7.0, 7.0 Hz, 1 H), 7.59 (dd, J = 7.0, 7.0 Hz, 1 H), 7.72 (d, J = 8.3 Hz, 1 H), 7.80 (d, J = 8.1 Hz, 1 H), 8.34 (d, J = 8.5 Hz, 1 H); minor rotamer: 1.32 (s, 9 H), 2.66–2.71 (m, 1 H), 2.77–2.82 (m, 1 H), 3.17–3.27 (m, 1 H), 3.31–3.41 (m, 1 H), 3.53–3.59 (m, 1 H), 3.82 (s, 3 H), 3.83 (s, 3 H), 3.95 (dt, J = 13.2, 4.8 Hz, 1 H), 5.49 (m, 1 H), 6.28 (s, 1 H), 6.59 (s, 1 H), 7.37 (d, J = 8.3 Hz, 1 H), 7.42–7.81 (m, 4 H), 8.27 (d, J = 8.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS, major rotamer): δ = 27.5, 28.1, 31.5, 36.3, 43.6, 53.9, 55.8, 79.1, 109.7, 111.3, 124.6, 126.0, 126.4, 126.8, 127.3, 127.3, 127.9, 128.8, 128.9, 132.2, 133.4, 136.3, 147.3, 147.8, 154.1; (peaks corresponding to the minor rotamer were also detected): 28.8, 35.1, 43.5, 54.7, 56.0, 79.9, 110.7, 111.5, 125.6, 126.4, 126.9, 127.6, 128.0, 128.3, 129.0, 133.8, 136.7, 147.4, 148.1, 154.9 ppm. HRMS calcd. for $C_{23}H_{21}BrNO_3$ ($M^+ - C_4H_9O$) 438.0700; found: 438.0656.

***tert*-Butyl 5-(2-Bromobenzyl)-7,8-dihydro-[1,3]dioxolo[4,5-*g*]isoquinoline-6(5*H*)-carboxylate (9f):** The carbamate was prepared following the general procedure (70%), m.p. 131–132 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 2979, 1693, 1481, 1416, 1249, 1166, 1040. ^1H NMR analysis revealed the presence of two amide rotamers present in a 4:1 ratio. ^1H NMR (300 MHz, $CDCl_3$, 293 K, TMS, major rotamer): δ = 1.07 (s, 9 H), 2.60–2.65 (m, 1 H), 2.72–3.07 (m, 2 H), 3.22–3.30 (m, 2 H), 4.36 (dd, J = 13.0, 3.9 Hz, 1 H), 5.36 (dd, J = 11.1, 1.7 Hz, 1 H), 5.91 (s, 2 H), 6.59 (s, 1 H), 6.88 (s, 1 H), 7.06–7.26 (m, 3 H), 7.56 (d, J = 7.7 Hz, 1 H); minor rotamer: 1.31 (s, 9 H), 2.60–2.65 (m, 1 H), 2.72–3.07 (m, 2 H), 3.22–3.30 (m, 2 H), 3.35–3.44 (m, 1 H), 3.94 (dt, J = 13.2, 4.1 Hz, 1 H), 5.42 (d, J = 4.6 Hz, 1 H), 5.92 (s, 2 H), 6.56 (s, 1 H), 6.62 (s, 1 H), 7.06–7.26 (m, 3 H), 7.51 (d, J = 7.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS, major rotamer): δ = 27.7, 28.5, 35.9, 42.6, 53.8, 79.3, 100.8, 106.7, 108.5, 125.2, 127.4, 127.4, 130.1, 131.7, 132.4, 137.9, 146.0, 146.3, 154.0 (peaks corresponding to the minor rotamer were also detected): 28.2, 28.7, 38.5, 42.0, 53.8, 79.2, 100.7, 107.1, 108.2, 126.9, 127.8, 130.0, 131.3, 137.7, 145.8, 146.1, 154.1 ppm. HRMS calcd. for $C_{18}H_{15}BrNO_3$ ($M^+ - C_4H_9O$) 372.0235; found: 372.0224.

***tert*-Butyl 1-(2-Bromobenzyl)-3,4-dihydro-6-methoxyisoquinoline-2(1*H*)-carboxylate (9g):** The carbamate was prepared following the general procedure (86%), m.p. 112–113 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 2999, 1679, 1502, 1461, 1422, 1365, 1239, 1170. NMR analysis revealed the presence of two amide rotamers present in a 5:1 ratio. ^1H NMR (300 MHz, $CDCl_3$, 293 K, TMS, major rotamer): δ = 1.08 (s, 9 H), 2.68–2.75 (m, 1 H), 2.79–3.10 (m, 2 H), 3.23–3.33 (m, 2 H), 3.80 (s, 3 H), 4.39 (dd, J = 13.2, 4.7 Hz, 1 H), 5.42 (dd, J = 10.9, 2.8 Hz, 1 H), 6.68 (d, J = 2.5 Hz, 1 H), 6.81 (dd, J = 8.5, 2.6 Hz, 1 H), 7.01–7.24 (m, 3 H), 7.31 (d, J = 8.5 Hz, 1 H), 7.56 (dd, J = 7.8, 1.0 Hz, 1 H); minor rotamer: 1.32 (s, 9 H), 2.68–2.75 (m, 1 H), 2.79–3.10 (m, 2 H), 3.23–3.33 (m, 1 H), 3.84–3.48 (m, 1 H), 3.78 (s, 3 H), 3.96 (dt, J = 12.9, 5.1 Hz, 1 H), 5.47 (dd, J = 9.6, 5.0 Hz, 1 H), 6.64 (m, 1 H), 6.71 (dd, J = 8.5, 2.4 Hz, 1 H), 7.01–7.24 (m, 4 H), 7.50 (d, J = 7.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS, major rotamer): δ = 27.9, 27.9, 35.9, 42.9, 55.3, 53.5, 79.4, 112.8, 113.3, 125.3, 127.5, 128.1, 128.2, 129.5, 131.8, 132.5, 135.8, 138.2, 154.3, 158.1; (peaks corresponding to the minor rotamer were also detected): 28.3, 29.1, 37.5, 42.5, 53.6, 55.2, 79.4, 112.2, 113.2, 127.0, 127.9, 129.3, 129.5, 130.2, 131.4 ppm. HRMS calcd. for $C_{18}H_{17}BrNO_2$ ($M^+ - C_4H_9O$) 358.0443; found: 358.0393.

***tert*-Butyl 1-(2-Bromobenzyl)-3,4-dihydro-7-methoxyisoquinoline-2(1*H*)-carboxylate (9h):** The carbamate was prepared following the general procedure (57%), m.p. 113–115 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 2999, 1679, 1502, 1461, 1422, 1365, 1239, 1170. NMR analysis revealed the presence of two amide rotamers present in a 5:1 ratio. ^1H NMR (300 MHz, $CDCl_3$, 293 K, TMS, major rotamer): δ = 1.08 (s, 9 H), 2.66–2.73 (m, 1 H), 2.76–3.15 (m, 2 H), 3.24–3.34 (m, 2 H), 3.82 (s, 3 H), 4.38 (dd, J = 13.3, 4.8 Hz, 1 H), 5.44 (dd, J = 11.2, 2.9 Hz, 1 H), 6.78 (dd, J = 8.4, 2.5 Hz, 1 H), 6.93 (d, J = 2.5 Hz, 1 H), 7.00–7.23 (m, 4 H), 7.58 (d, J = 7.9 Hz, 1 H); minor rotamer: 1.32 (s, 9 H), 2.66–2.73 (m, 1 H), 2.76–3.15 (m, 2 H), 3.24–3.34 (m, 1 H), 3.39–3.48 (m, 1 H), 3.71 (s, 3 H), 3.97 (dt, J = 12.6, 5.3 Hz, 1 H), 5.49 (dd, J = 9.7, 5.0 Hz, 1 H),, J = 2.1, 1 H Hz 6.63 (d), 6.74 (dd, J = 8.7, 2.7 Hz, 1 H), 7.00–7.23 (m, 4 H), 7.51 (d, J = 7.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS, major rotamer): δ = 27.7, 27.8, 36.3, 42.7, 54.0, 55.3, 79.4, 112.0, 112.8, 125.3, 126.5, 127.4, 128.2, 130.0, 131.8, 132.5, 138.0, 138.2, 154.2, 157.8; (peaks corresponding to the minor rotamer were also detected): 27.7, 28.3, 38.9, 42.0, 54.2, 55.2, 111.8, 113.0, 127.0, 129.4, 131.4, 137.9, 154.3 ppm. HRMS calcd. for $C_{18}H_{17}BrNO_2$ ($M^+ - C_4H_9O$) 358.0443; found: 358.0417.

***tert*-Butyl 3,4-Dihydro-1-(2-iodobenzyl)isoquinoline-2(1*H*)-carboxylate (9j):** The carbamate was prepared following the general procedure (82%), m.p. 105–107 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 2976, 1690, 1419, 1364, 1245, 1164, 1121. ^1H NMR analysis revealed the presence of two amide rotamers present in a 4:1 ratio. ^1H NMR (300 MHz, $CDCl_3$, 293 K, TMS, major rotamer): δ = 1.07 (s, 9 H), 2.75–2.80 (m, 1 H), 2.95–3.35 (m, 4 H), 4.42 (dd, J = 13.9, 5.2 Hz, 1 H), 5.44 (dd, J = 10.9, 2.7 Hz, 1 H), 6.96 (t, J = 7.8 Hz, 1 H), 7.07–7.29 (m, 5 H), 7.53 (d, J = 7.4 Hz, 1 H), 7.86 (d, J = 7.8 Hz, 1 H); minor rotamer: 1.33 (s, 9 H), 2.75–2.80 (m, 1 H), 2.95–3.35 (m, 4 H), 3.98 (dt, J = 13.1, 4.8 Hz, 1 H), 5.49 (dd, J = 9.3, 5.4 Hz, 1 H), 6.88 (t, J = 7.6 Hz, 1 H), 7.07–7.29 (m, 5 H), 7.53 (d, J = 7.4 Hz, 1 H), 7.78 (d, J = 7.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS, major rotamer): δ = 28.0, 28.6, 36.2, 46.9, 79.5, 101.7, 126.1, 126.8, 127.1, 128.4, 128.4, 129.2, 131.0, 134.5, 137.2, 139.2, 141.2, 154.3; (peaks corresponding to the minor rotamer were also detected): 28.4, 28.8, 38.9, 46.5, 79.3, 101.7, 126.1, 126.7, 127.4, 128.1, 128.3, 129.7, 130.6, 136.9, 154.3 ppm. HRMS calcd. for $C_{17}H_{15}INO$ ($M^+ - C_4H_9O$) 376.0198; found: 376.0231.

***tert*-Butyl 1-(2-Chlorobenzyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (9k):** The carbamate was prepared following the general procedure (75%), m.p. 116–117 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 2976, 1692, 1419, 1165. NMR analysis revealed the presence of two amide rotamers present in a 5:1 ratio. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS, major rotamer): δ = 1.08 (s, 9 H), 2.72–2.78 (m, 1 H), 2.82–3.14 (m, 2 H), 3.14–3.35 (m, 2 H), 4.41 (dd, J = 13.4, 5.3 Hz, 1 H), 5.49 (dd, J = 11.2, 2.8 Hz, 1 H), 7.07–7.26 (m, 6 H), 7.41 (d, J = 7.2 Hz, 1 H), 7.57 (d, J = 7.9 Hz, 1 H); minor rotamer: 1.32 (s, 9 H), 2.72–2.78 (m, 1 H), 2.82–3.14 (m, 2 H), 3.14–3.35 (m, 1 H), 3.41–3.50 (m, 1 H), 3.98 (dt, J = 13.2, 4.8 Hz, 1 H), 5.53 (dd, J = 9.6, 5.0 Hz, 1 H), 7.07–7.26 (m, 7 H), 7.51 (d, J = 7.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS, major rotamer): δ = 27.8, 18.6, 36.0, 42.7, 53.9, 79.4, 125.3, 126.1, 126.6, 127.0, 127.4, 128.2, 129.1, 131.8, 132.5, 134.4, 137.2, 138.1, 154.2; (peaks corresponding to the minor rotamer were also detected): 28.3, 28.7, 38.6, 42.1, 53.9, 79.2, 126.5, 127.3, 127.9, 128.5, 131.4, 137.0, 137.9 ppm. HRMS calcd. for $C_{17}H_{15}ClNO$ ($M^+ - C_4H_9O$) 284.0842; found: 284.0800.

***tert*-Butyl 4-(2-Bromobenzyl)-1,2-dihydrobenzo[*f*]isoquinoline-3(4*H*)-carboxylate (9l):** The carbamate was prepared following the general procedure (67%), m.p. 128–129 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 2979, 1687, 1424, 1366, 1164, 1119, 1027. ^{1}H NMR analysis revealed the presence of two amide rotamers present in a 6.5:1 ratio. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS, major rotamer): δ = 1.07 (s, 9 H), 2.95–3.03 (m, 1 H), 3.08–3.22 (m, 2 H), 3.31–3.48 (m, 2 H), 4.63 (dd, J = 13.3, 4.8 Hz, 1 H), 5.56 (dd, J = 11.1, 2.0 Hz, 1 H), 7.03–7.25 (m, 3 H), 7.37–7.60 (m, 4 H), 7.72 (d, J = 8.5 Hz, 1 H), 7.81 (d, J = 7.6 Hz, 1 H), 7.92 (d, J = 8.3 Hz, 1 H); minor rotamer: 1.31 (s, 9 H), 2.95–3.03 (m, 1 H), 3.08–3.22 (m, 2 H), 3.31–3.48 (m, 2 H), 3.31 (dt, J = 13.0, 2.9 Hz, 1 H), 5.67 (dd, J = 9.9, 3.4 Hz, 1 H), 7.03–7.25 (m, 3 H), 7.37–7.60 (m, 4 H), 7.66 (d, J = 8.6 Hz, 1 H), 7.81 (d, J = 7.6 Hz, 1 H), 7.88–7.91 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS, major rotamer): δ = 25.7, 28.4, 35.9, 42.4, 54.7, 80.0, 123.4, 125.7, 125.8, 126.2, 126.9, 127.0, 128.0, 128.8, 129.0, 130.1, 132.4, 132.5, 132.8, 133.1, 134.9, 138.7, 154.6 (peaks corresponding to the minor rotamer were also detected): 25.8, 28.8, 38.0, 41.9, 54.2, 79.8, 123.3, 126.0, 126.7, 127.6, 128.5, 129.1, 129.9, 131.8, 135.0, 138.4, 154.5 ppm. HRMS calcd. for $C_{21}H_{17}BrNO$ ($M^+ - C_4H_9O$) 378.0494; found: 378.0523.

***tert*-Butyl 1-(2-Bromobenzyl)-3,4-dihydro-7-methylisoquinoline-2(1*H*)-carboxylate (9m):** The carbamate was prepared following the general procedure (82%), m.p. 157–158 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 1683, 1458, 1366, 1246, 1164. ^{1}H NMR analysis revealed the presence of two amide rotamers present in a 6:1 ratio. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS, major rotamer): δ = 1.07 (s, 9 H), 2.37 (s, 3 H), 2.66–2.75 (m, 1 H), 2.78–3.12 (m, 2 H), 3.24–3.33 (m, 2 H), 4.39 (dd, J = 13.4, 5.0 Hz, 1 H), 5.44 (dd, J = 11.4, 2.9 Hz, 1 H), 6.96–7.26 (m, 6 H), 7.58 (dd, J = 7.8, 1.0 Hz, 1 H); minor rotamer: 1.30 (s, 9 H), 2.29 (s, 3 H), 2.66–2.75 (m, 1 H), 2.78–3.12 (m, 2 H), 3.24–3.33 (m, 1 H), 3.38–3.47 (m, 1 H), 3.99 (dt, J = 13.5, 4.6 Hz, 1 H), 5.49 (dd, J = 9.9, 4.8 Hz, 1 H), 6.96–7.26 (m, 6 H), 7.52 (d, J = 8.2 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS, major rotamer): δ = 21.6, 28.3, 28.6, 36.6, 43.1, 54.2, 79.8, 125.7, 127.9, 127.9, 128.0, 128.6, 129.5, 131.8, 132.3, 132.9, 136.1, 137.5, 138.6, 154.7; (peaks corresponding to the minor rotamer were also detected): 28.7, 39.1, 42.5, 79.6, 125.6, 127.7, 128.5, 128.8 ppm. HRMS calculated for $C_{18}H_{17}BrNO$ ($M^+ - C_4H_9O$) 342.0494; found: 342.0500;

***tert*-Butyl 1-(2-Bromobenzyl)-6-chloro-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (9n):** The carbamate was prepared following the general procedure (69%), m.p. 140–142 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 2977, 1691, 1419, 1365, 1163, 1129. ^{1}H NMR analysis revealed the presence of two amide rotamers present in a 4:1 ratio. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS, major rotamer): δ = 1.09 (s, 9 H), 2.69–2.75 (m, 1 H), 2.79–3.11 (m, 2 H), 3.22–3.32 (m, 2 H), 4.39 (dd, J = 13.4, 4.8 Hz, 1 H), 5.44 (dd, J = 11.2, 3.2 Hz, 1 H), 7.01–7.33 (m, 6 H), 7.58 (dd, J = 7.8, 1.0 Hz, 1 H); minor rotamer: 1.33 (s, 9 H), 2.69–2.75 (m, 1 H), 2.79–3.11 (m, 2 H), 3.22–3.32 (m, 1 H), 3.38–3.47 (m, 1 H), 3.97 (dt, J = 13.3, 4.3 Hz, 1 H), 5.49 (dd, J = 9.4, 5.2 Hz, 1 H), 7.01–7.33 (m, 6 H), 7.52 (d, J = 7.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS, major rotamer): δ = 27.8, 28.5, 35.7, 42.7, 53.6, 79.7, 125.3, 126.3, 127.5, 128.4, 128.9, 131.4, 131.8, 132.2, 132.6, 135.6, 136.4, 137.7, 154.1; (peaks corresponding to the minor rotamer were also detected): 28.3, 28.6, 125.3, 126.2, 136.4, 154.2 ppm. HRMS calcd. for $C_{17}H_{14}BrClNO$ (M^+) 361.9947; found: 361.9968.

General Procedure for the Intramolecular Direct Arylation: K_2CO_3 (2 equiv.), ligand (0.1 equiv.), $Pd(OAc)_2$ (0.05 equiv.) and the aryl halide (1 equiv.) are weighed to air and placed in a round-bottomed flask with a magnetic stir bar. The flask is purged with argon (3×). DMA is then added (0.2 M) and the resulting mixture is heated to 130 °C overnight. The reaction mixture is then concentrated and loaded onto a silica gel column for chromatography using ether/hexane mixtures.

***tert*-Butyl 4,5,6a,7-Tetrahydro-1,2,9-trimethoxydibenzo[*de*,*g*]quinoline-6-carboxylate (10b)**: The cyclization was achieved following the general procedure (79%), m.p. 151–152 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 2934, 1688, 1595, 1502, 1409, 1244, 1158, 1107. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 1.50 (s, 9 H), 2.62–2.66 (m, 1 H), 2.78–2.97 (m, 4 H), 3.65 (s, 3 H), 3.85 (s, 3 H), 3.89 (s, 3 H), 4.41 (d, J = 9.9 Hz, 1 H), 4.67 (dd, J = 12.6, 2.1 Hz, 1 H), 6.63 (s, 1 H), 6.81 (d, J = 2.4 Hz, 1 H), 6.86 (dd, J = 8.8, 2.7 Hz, 1 H), 8.39 (d, J = 8.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 29.0, 30.8, 36.3, 39.1, 52.0, 55.6, 46.3, 60.3, 80.3, 111.0, 112.7, 113.9, 124.9126.2, 128.0, 130.2, 130.3, 139.3, 145.4, 152.4, 155.1, 159.2 ppm. HRMS calcd. for $C_{24}H_{29}NO_5$ (M^+) 411.2046; found: 411.2058.

***tert*-Butyl 9-Fluoro-4,5,6a,7-tetrahydro-1,2-dimethoxydibenzo[*de*,*g*]-quinoline-6-carboxylate (10c):** The cyclization was achieved following the general procedure (79%), m.p. 156–158 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 2973, 1692, 1497, 1406, 1242, 1167, 1104. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 1.50 (s, 9 H), 2.63–2.67 (m, 1 H), 2.77–2.97 (m, 4 H), 3.65 (s, 3 H), 3.90 (s, 3 H), 4.42 (d, J = 8.5 Hz, 1 H), 4.67 (dd, J = 13.1, 1.6 Hz, 1 H), 6.67 (s, 1 H), 6.96–7.04 (m, 3 H), 8.42 (dd, J = 8.5, 6.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 28.5, 30.3, 35.5, 38.4, 51.2, 55.8, 59.9, 79.9, 111.2, 113.7 (J_F = 20.5 Hz), 114.8 (J_F = 16.1 Hz), 125.8, 126.8 (J_F = 2.8 Hz), 127.8, 129.9, 130.3 (J_F = 8.3 Hz), 139.6 (J_F = 7.7 Hz), 145.1, 151.9, 154.5, 161.7 (J_F = 248.0 Hz) ppm. HRMS calcd. for $C_{23}H_{26}NO_4F$ (M^+) 399.1846; found: 399.1855.

***tert*-Butyl 4,5,6a,7-Tetrahydro-1,2-dimethoxy-9,11-dioxa-6-azabenzo[*fg*]cyclopenta[*b*]anthracene-6-carboxylate (10d):** The cyclization was achieved following the general procedure (87%), m.p. 176–177 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 2974, 1686, 1487, 1408, 1243, 1166, 1041. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 1.50 (s, 9 H), 2.61–2.96 (m, 5 H), 3.66 (s, 3 H), 3.88 (s, 3 H), 4.41 (d, J = 9.1 Hz, 1 H), 4.63 (d, J = 12.6 Hz, 1 H), 5.97 (s, 2 H), 6.63 (s, 1 H), 6.75 (s, 1 H), 8.00 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 28.4, 30.2, 35.4, 38.4, 51.6, 55.8, 59.9, 79.7, 100.8, 108.2, 108.8, 110.6, 125.0, 125.7, 127.4, 129.6, 131.4, 144.8, 146.4, 146.5, 151.8, 154.5 ppm. HRMS calcd. for $C_{24}H_{27}NO_6$ (M^+) 425.1838; found: 425.1847.

***tert*-Butyl 4,5,6a,7-Tetrahydro-1,2-dimethoxy-6-azadibenzo[*a*,*kl*]-anthracene-6-carboxylate (10e):** The cyclization was achieved fol-

lowing the general procedure (60%), m.p. 189–190 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 2973, 1690, 1408, 1252, 1162. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 1.46 (s, 9 H), 2.68–2.73 (m, 1 H), 2.85–2.98 (m, 4 H), 3.02 (s, 3 H), 3.93 (s, 3 H), 4.48 (d, J = 7.8 Hz, 1 H), 4.60 (dd, J = 12.0, 2.0 Hz, 1 H), 6.76 (s, 1 H), 7.40–7.44 (m, 3 H), 7.78–7.82 (m, 2 H), 7.98–8.01 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 28.4, 30.0, 36.6, 38.5, 51.7, 55.9, 59.9, 79.8, 111.2, 124.9, 124.9, 126.6, 127.3, 127.4, 127.6, 128.2, 128.4, 128.5, 129.0, 129.6, 133.1, 136.2, 144.9, 151.9, 154.7 ppm. HRMS calcd. for $C_{27}H_{29}NO_4$ (M^+) 431.2097; found: 431.2111.

***tert*-Butyl 5,6,7a,8-Tetrahydrobenzo[*g*][1,3]dioxolo[4′,5′:4,5]-benzo[1,2,3-*de*]quinoline-7-carboxylate (10f):** The cyclization was achieved following the general procedure (99%), m.p. 186–188 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 2974, 1690, 1410, 1226, 1160. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 1.50 (s, 9 H), 2.56–2.61 (m, 1 H), 2.74–2.95 (m, 3 H), 3.06 (dd, J = 13.9,3.8 Hz, 1 H), 4.39 (d, J = 10.4 Hz, 1 H), 4.79 (d, J = 11.8 Hz, 1 H), 5.93 (d, J = 1.0 Hz, 1 H), 6.06 (d, J = 1.0 Hz, 1 H), 6.57 (s, 1 H), 7.20–7.34 (m, 3 H), 8.09 (d, J = 7.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 28.5, 30.4, 34.9, 38.7, 51.5, 79.8, 100.8, 107.5, 117.2, 125.9, 126.9, 126.9, 127.0, 127.7, 127.8, 128.3, 130.7, 135.9, 142.8, 146.6, 154.5 ppm. HRMS calcd. for $C_{22}H_{23}NO_4$ (M^+) 365.1627; found: 365.1608.

***tert*-Butyl 2-Methoxy-4,5,6a,7-tetrahydrodibenzo[*de*,*g*]quinoline-6-carboxylate (10g):** The cyclization was achieved following the general procedure (99%), m.p. 111.5–113.8 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 2924, 1676, 1465, 1412, 1173. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 1.51 (s, 9 H), 2.67–3.11 (m, 5 H), 3.86 (s, 3 H), 4.42–4.45 (m, 1 H), 4.80–4.84 (m, 1 H), 6.66 (d, J = 1.91 Hz, 1 H), 7.17–7.35 (m, 4 H), 7.74 (d, J = 7.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 28.58, 30.81, 51.25, 55.38, 79.87, 108.67, 112.41, 123.71, 125.21, 127.28, 128.02, 128.71, 128.74, 128.77, 133.76, 136.04, 136.40, 158.47 ppm. HRMS calculated for $C_{22}H_{25}NO_3$ (M^+); 351.1834; found: 351.1829;

***tert*-Butyl 4,5,6a,7-Tetrahydro-1-methoxydibenzo[*de*,*g*]quinoline-6-carboxylate (10h):** The cyclization was achieved following the general procedure (99%), m.p. 132.6–135.3 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 2924, 1692, 1457, 1406, 1264, 1164. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 1.49 (s, 9 H), 2.66–2.7 (m, 1 H), 2.79–2.98 (m, 4 H), 3.88 (s, 3 H), 4.40–4.43 (m, 1 H), 4.71–4.77 (m, 1 H), 6.89 (d, J = 8.4 Hz, 1 H), 7.08 (d, J = 8.4 Hz, 1 H), 7.18–7.33 (m, 3 H), 8.31 (d, J = 7.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 28.54, 29.75, 35.09, 38.69, 52.09, 55.68, 79.81, 110.53, 122.60, 126.36, 126.52, 127.20, 127.80, 128.42, 128.82, 131.79, 135.16, 136.76, 154.61, 155.27 ppm. HRMS calculated for $C_{18}H_{16}NO_3$ (M^+); 294.1130; found: 294.1115;

***tert*-Butyl 5,6,7a,8-Tetrahydro-7-azadibenzo[*a*,*de*]anthracene-7-carboxylate (10j):** The cyclization was achieved following the general procedure (92%), m.p. 200–201 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 2974, 1690, 1414, 1168. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 1.53 (s, 9 H), 2.94–3.07 (m, 3 H), 3.13 (dd, J = 13.9,4.1 Hz, 1 H), 3.24–3.31 (m, 1 H), 4.57 (d, J = 6.4 Hz, 1 H), 4.79 (dd, J = 12.4, 2.6 Hz, 1 H), 5.93 (d, J = 1.0 Hz, 1 H), 7.27–7.29 (m, 1 H), 7.33–7.39 (m, 1 H), 7.43–7.53 (m, 2 H), 7.84–7.87 (m, 1 H), 7.91–7.96 (m, 1 H), 8.05 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 26.0, 28.5, 34.5, 38.0, 51.9, 79.9, 121.7, 122.8, 124.1, 125.6, 126.2, 127.3, 128.0, 128.3, 128.7, 129.6, 130.1, 130.8, 131.3, 132.3, 133.8, 136.2, 154.5 ppm. HRMS calcd. for $C_{21}H_{16}NO_2$ ($M^+ - C_4H_9$) 314.1181; found: 314.1211.

***tert*-Butyl 4,5,6a,7-Tetrahydro-1-methyldibenzo[*de*,*g*]quinoline-6-carboxylate (10k):** The cyclization was achieved following the general procedure (96%), m.p. 138.3–139.7 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 3001, 1678, 1465, 1364, 1248, 1177. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 1.49 (s, 9 H), 2.59 (s, 3 H), 2.67–2.76 (m, 1 H), 2.85–2.96 (m, 4 H), 4.42–4.46 (m, 1 H), 4.44–4.46 (m, 1 H), 4.65–4.69 (m, 1 H), 7.03 (d, J = 7.8 Hz, 1 H), 7.16 (d, J = 7.8 Hz, 1 H), 7.20–7.33 (m, 3 H), 7.68 (d, J = 7.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 22.91, 28.54, 30.14, 35.35, 38.53, 52.36, 79.81, 126.06, 127.22, 127.51, 128.00, 128.33, 130.48, 131.68, 132.78, 133.52, 133.84, 134.51, 137.92, 154.64 ppm. HRMS calculated for $C_{18}H_{16}NO$ ($M^+ - C_4H_9O$); 262.1298; found: 262.1298;

***tert*-Butyl 2-Chloro-4,5,6a,7-tetrahydrodibenzo[*de*,*g*]quinoline-6-carboxylate (10l):** The cyclization was achieved following the general procedure (86%), m.p. 101–103 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 2976, 1691, 1418, 1163. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 1.51 (s, 9 H), 2.68–2.73 (m, 1 H), 2.80–2.98 (m, 3 H), 3.09 (dd, J = 14.1, 4.4 Hz, 1 H), 4.44 (d, J = 8.8 Hz, 1 H), 4.84 (dd, J = 13.9, 3.8 Hz, 1 H), 7.10 (d, J = 1.6 Hz, 1 H), 7.27–7.37 (m, 3 H), 7.57 (d, J = 1.9 Hz, 1 H), 7.71 (d, J = 7.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 28.5, 30.4, 34.2, 38.5, 51.3, 80.1, 122.5, 123.8, 127.2, 127.5, 128.5, 128.8, 131.1, 132.6, 132.8, 134.8, 135.8, 136.1, 136.9, 154.5 ppm. HRMS calcd. for $C_{17}H_{13}ClNO_3$ ($M^+ - C_4H_9$) 298.0635; found: 298.0669.

***tert*-Butyl 4,5,6a,7-Tetrahydro-2-phenyldibenzo[*de*,*g*]quinoline-6-carboxylate (11a:):** The Suzuki–Miyaura coupling was achieved following the general procedure developed by Buchwald.[16] The aryl chloride (0.1 g, 0.28 mmol, 1.0 equiv.), phenyl boronic acid (0.051 g, 0.42 mmol, 1.5 equiv.), potassium phosphate (0.119 g, 0.56 mmol, 2.0 equiv.), palladium acetate (0.003 g, 0.01 mmol, 0.05 equiv.) and S-Phos (0.014 g, 0.025 mmol, 0.13 equiv.) was placed in a vial and was then purged with argon. Toluene (0.6 mL) was then added and the resulting mixture was heated to 100 °C overnight. The resulting reaction was then purified by chromatography on silica using benzene as the eluent. (90%): $\tilde{\nu}_{max}$ = 2975, 1691, 1409, 1248, 1161. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 1.50 (s, 9 H), 2.63–2.14 (m, 5 H), 4.32–4.58 (m, 1 H), 4.80–4.93 (m, 1 H), 7.06–7.30 (m, 6 H), 7.42–7.68 (m, 4 H), 7.81–7.83 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 28.6, 30.4, 34.5, 38.6, 51.3, 80.1, 123.8, 126.5, 127.1, 127.3, 127.4, 127.5, 128.1, 128.6, 128.8, 131.9, 132.7, 132.8, 133.8, 134.8, 135.5, 135.9, 154.5 ppm. HRMS calcd. for $C_{27}H_{27}NO_2$ ($M^+ - C_4H_9O$) 284.0842; found: 284.0800.

***tert*-Butyl 4,5,6a,7-Tetrahydro-2-(morpholin-4-yl)dibenzo[*de*,*g*]quinoline-6-carboxylate (11b):** The amination coupling was achieved following the general procedure developed by Buchwald.[17] The aryl chloride (0.1 g, 0.28 mmol, 1.0 equiv.), (*o*-biphenyl)$P(Cy)_2$ (0.020 g, 0.06 mmol, 0.2 equiv.), NaO*t*Bu (0.038 g, 0.39 mmol, 1.4 equiv.) and $Pd(OAc)_2$ (0.006 g, 0.03 mmol, 0.1 equiv.) was placed in a vial and was then purged with argon. A solution of morpholine (0.29 mL, 0.34 mmol, 1.2 equiv.) in toluene (1.0 mL) was then added and the resulting mixture was heated to 100 °C overnight. The resulting reaction was then purified by chromatography on silica (50% ether/hexane). (83%), m.p. 171–173 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 2971, 1688, 1609, 1409, 1364, 1251, 1162, 1121. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 1.51 (s, 9 H), 2.65–2.70 (m, 1 H), 2.78–3.12 (m, 4 H), 3.16–3.26 (m, 4 H), 3.89 (t, J = 4.7 Hz, 4 H), 4.43 (d, J = 10.2 Hz, 1 H), 4.32 (dd, J = 13.3, 2.6 Hz, 1 H), 6.68 (s, 1 H), 7.21–7.34 (m, 4 H), 7.75 (d, J = 7.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 28.5, 30.8, 34.6, 38.8, 49.7, 51.1, 66.8, 79.8, 110.4, 115.0, 123.5, 124.9, 127.1, 127.8, 128.7, 134.0, 135.0, 135.9, 136.0, 150.0, 154.6 ppm. HRMS calcd. for $C_{25}H_{30}N_2O_3$ (M^+) 406.2256; found: 406.2277.

***tert*-Butyl 4,5,6a,7-Tetrahydro-2-(2-*tert*-butoxycarbonylvinyl)dibenzo[*de*,*g*]quinoline-6-carboxylate (11c):** The Heck coupling was

achieved using the conditions developed by Fu's group[18] A vial was loaded with the aryl chloride (0.1 g, 0.28 mmol, 1.0 equiv.), P(*t*Bu)$_3$–HBF$_4$ (0.016 g, 0.05 mmol, 0.3 equiv.) and Pd$_2$(dba)$_3$ (0.013 g, 0.01 mmol, 0.05 equiv.) and was purged with argon. To this mixture was added a solution of Cy_2NMe (0.077 mL, 0.36 mmol, 1.3 equiv.), the *tert*-butyl acrylate (0.045 mL, 0.31 mmol, 1.1 equiv.) in dioxane (0.2 mL) and the resulting solution was heated to 100 °C overnight The product was then extracted and purified using chromatography on silica (10% ether/hexane). (54%): $\tilde{\nu}_{max}$ = 2976, 1693, 1409, 1366, 1290, 1221, 1150. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 1.51 (s, 9 H), 1.55 (s, 9 H), 2.72–3.00 (m, 4 H), 3.10 (dd, *J* = 14.0, 4.0 Hz, 1 H), 4.45 (d, *J* = 6.7 Hz, 1 H), 4.89 (dd, *J* = 13.6, 2.8 Hz, 1 H), 6.43 (d, *J* = 16.0 Hz, 1 H), 7.25–7.28 (m, 3 H), 7.31–7.38 (m, 1 H), 7.61 (d, *J* = 16.0 Hz, 1 H), 7.74 (s, 1 H), 7.79 (d, *J* = 7.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 28.7, 29.0, 30.9, 34.6, 39.2, 52.1, 80.5, 81.0, 120.5, 122.2, 124.2, 127.6, 127.9, 128.8, 129.1, 133.6, 133.7, 135.3, 135.4, 136.1, 136.2, 143.8, 155.0, 166.7 ppm. HRMS calcd. for $C_{24}H_{24}NO_4$ ($M^+ - C_4H_9$) 390.1705; found: 390.1787.

***tert*-Butyl 4,5,6a,7-Tetrahydro-2-(1-oxypyridin-2-yl)dibenzo[*de*,*g*]-quinoline-6-carboxylate (11d):** A flask was loaded with the aryl chloride (0.2 g, 0.56 mmol, 1.0 equiv.), P(*t*Bu)$_3$–HBF$_4$ (0.049 g, 0.17 mmol, 0.3 equiv.), K_2CO_3 (0.155 g, 1.12 mmol, 2.0 equiv.) pyridine *N*-oxide (0.054 g, 2.25 mmol, 4.0 equiv.) and Pd(OAc)$_2$ (0.013 g, 0.06 mmol, 0.1 equiv.) and was purged with argon. To the flask was introduced toluene (1.0 mL), and the resulting solution was heated to 110 °C overnight. The product was passed through a short celite pad and then purified directly on chromatography on silica (10%, then 20% acetone/$CHCl_3$). (78%), m.p. 233–235 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 2974, 1688, 1410, 1247, 1162. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 1.52 (s, 9 H), 2.79–3.02 (m, 4 H), 3.11–3.14 (m, 1 H), 4.46–4.48 (m, 1 H), 4.93 (d, *J* = 11.7 Hz, 1 H), 7.24–7.33 (m, 5 H), 7.47 (dd, *J* = 7.7, 1.2 Hz, 1 H), 7.58 (s, 1 H), 7.80 (d, *J* = 7.5 Hz, 1 H), 8.02 (s, 1 H), 8.34 (d, *J* = 5.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 28.4, 30.3, 34.1, 38.6, 51.5, 79.9, 123.1, 123.8, 124.5, 125.7, 127.2, 128.1, 128.3, 128.5, 128.5, 131.1, 133.3, 134.2, 134.4, 135.0, 135.6, 140.4, 149.0, 154.4 ppm. HRMS calcd. for $C_{26}H_{26}N_2O_2$ (M^+ – O) 398.1989; found: 398.1952.

***tert*-Butyl 4,5,6a,7-Tetrahydro-2-(1-oxypyrazin-2-yl)dibenzo[*de*,*g*]-quinoline-6-carboxylate (11f):** A flask was loaded with the aryl chloride (0.1 g, 0.28 mmol, 1.0 equiv.), P(*t*Bu)$_3$–HBF$_4$ (0.012 g, 0.04 mmol, 0.15 equiv.), K_2CO_3 (0.078 g, 0.56 mmol, 2.0 equiv.) pyrazine *N*-oxide (0.054 g, 0.56 mmol, 2.0 equiv.) and Pd(OAc)$_2$ (0.003 g, 0.01 mmol, 0.05 equiv.) and was purged with argon. To the flask was introduced dioxane (1.0 mL) and the resulting solution was heated to 110 °C overnight. The product was purified directly by chromatography on silica (5% acetone/$CHCl_3$). (70%), m.p. 210–212 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 2979, 1688, 1410, 1306, 1161. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 1.52 (s, 9 H), 2.80–3.04 (m, 4 H), 3.12–3.16 (m, 1 H), 4.48–4.55 (m, 1 H), 4.94 (d, *J* = 11.0 Hz, 1 H), 7.29 (m, 1 H), 7.47–7.48 (m, 1 H), 7.55 (s, 1 H), 7.66–7.67 (m, 1 H), 7.79 (d, *J* = 7.1 Hz, 1 H), 8.01 (s, 1 H), 8.24 (s, 1 H), 8.42 (s, 1 H), 8.69 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 28.5, 30.4, 34.1, 38.6, 51.6, 80.1, 123.0, 123.9, 127.4, 128.1, 128.4, 128.7, 131.9, 133.0, 134.5, 135.3, 135.6, 135.6, 144.5, 145.6, 148.3, 154.5 ppm. MS (CI): *m*/*z* (%) = 416 (3), 358 (61), 342 (65), 298 (99), 240 (100).

***tert*-Butyl 4,5,6a,7-Tetrahydro-2-(pyridin-2-yl)dibenzo[*de*,*g*]quinoline-6-carboxylate (11g):** Ammonium formate (0.152g, 2.4 mmol, 10.0 equiv.) was added to a stirring solution of the *N*-oxide (0.1 g, 0.24 mmol, 1.0 equiv.) and Pd/C (0.026 g, 0.002 mmol, 0.1 equiv.) in MeOH (1.5 mL) in a round-bottomed flask. The resulting solution was then purged with argon and left to stir at room temperature for 1.5 h. The product was purified directly by chromatography on silica (100% $CHCl_3$). (82%), m.p. 155–157 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 2974, 1689, 1411, 1161. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 1.52 (s, 9 H), 2.84–3.03 (m, 4 H), 3.13 (dd, *J* = 13.7, 3.0 Hz, 1 H), 4.48–4.49 (m, 1 H), 4.93 (d, *J* = 11.6 Hz, 1 H), 7.24–7.30 (m, 3 H), 7.34–7.38 (m, 1 H), 7.75–7.81 (m, 3 H), 7.93 (d, *J* = 7.7 Hz, 1 H), 8.24 (s, 1 H), 8.72 (d, *J* = 4.7 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 28.6, 30.6, 34.4, 38.8, 51.6, 80.0, 120.5, 121.0, 122.2, 124.0, 126.2, 127.4, 128.1, 128.7, 133.7, 133.8, 134.9, 135.6, 135.8, 136.8, 137.9, 149.6, 154.7, 157.2 ppm. HRMS calcd. for $C_{26}H_{26}N_2O_2$ (M^+) 398.1994; found: 398.2000.

***tert*-Butyl 2-(Benzo[1,3]dioxol-4-yl)-4,5,6a,7-tetrahydrodibenzo-[*de*,*g*]quinoline-6-carboxylate (11h):** A flask was loaded with the aryl chloride (0.1 g, 0.28 mmol, 1.0 equiv.), PMe(*t*Bu)$_2$–HBF$_4$ (0.021 g, 0.08 mmol, 0.3 equiv.), K_2CO_3 (0.078 g, 0.56 mmol, 2.0 equiv.) AgOTf (0.062 g, 0.28 mmol, 1.0 equiv.) and Pd(OAc)$_2$ (0.006 g, 0.02 mmol, 0.1 equiv.) and was purged with argon. To the flask was introduced a solution of 1,3-benzodioxole (0.3 mL, 2.8 mmol, 10.0 equiv.) in DMA (1.0 mL) and the resulting solution was heated to 145 °C overnight. The product was purified directly by chromatography on silica (10% ether/hexane), (65%). $\tilde{\nu}_{max}$ = 2929, 1689, 1365, 1410, 1249, 1162. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 1.52 (s, 9 H), 2.77–3.04 (m, 4 H), 3.09–3.15 (m, 1 H), 4.46–4.48 (m, 1 H), 4.92 (d, *J* = 11.1 Hz, 1 H), 6.03 (d, *J* = 6.2 Hz, 2 H), 6.83 (d, *J* = 7.5 Hz, 1 H), 6.93 (t, *J* = 7.8 Hz, 1 H), 7.09 (d, *J* = 7.7 Hz, 1 H), 7.24–7.37 (m, 3 H), 7.44 (s, 1 H), 7.83 (d, *J* = 7.6 Hz, 1 H), 7.95 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 28.5, 30.5, 34.3, 38.6, 51.5, 79.9, 100.7, 107.7, 121.2, 122.0, 122.0, 122.7, 123.8, 127.1, 127.3, 128.0, 128.7, 132.2, 133.8, 134.4, 134.6, 135.3, 135.8, 144.6, 147.8, 154.6 ppm. HRMS calcd. for $C_{24}H_{18}NO_4$ ($M^+ - C_4H_9$) 384.1236; found: 384.1220.

***tert*-Butyl 4,5,6a,7-Tetrahydro-2-(pyrazin-2-yl)dibenzo[*de*,*g*]quinoline-6-carboxylate (11i):** A flask was loaded with the aryl chloride (0.036 g, 0.09 mmol, 1.0 equiv.), Pd/C (0.009 g, 0.009 mmol, 0.1 equiv.) and MeOH (1.0 mL). The flask was then bubbled with hydrogen gas and the resulting solution was stirred for 1.5 h. The product was purified directly by chromatography on silica (100% $CHCl_3$). (84%), m.p. 137–140 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 2974, 1689, 1409, 1160. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 1.53 (s, 9 H), 2.83–3.04 (m, 4 H), 3.15 (dd, *J* = 14.1, 3.8 Hz, 1 H), 4.50–4.52 (m, 1 H), 4.96 (d, *J* = 12.2 Hz, 1 H), 7.30–7.31 (m, 2 H), 7.36–7.40 (m, 1 H), 7.76 (m, 1 H), 7.92 (d, *J* = 7.7 Hz, 1 H), 8.27 (d, *J* = 1.4 Hz, 1 H), 854 (s, 1 H), 8.66 (s, 1 H), 9.1 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 28.6, 30.7, 34.2, 38.8, 51.7, 80.1, 120.9, 124.0, 126.0, 127.4, 128.5, 128.7, 133.5, 134.8, 135.0, 135.4, 135.8, 136.0, 142.1, 143.0, 144.2, 152.6, 154.6 ppm. HRMS calcd. for $C_{25}H_{25}N_3O_2$ (M^+) 399.1947; found: 399.1942.

(*R*)-1-(2-Bromobenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (8a): Phosphorus oxychloride (6.38 g, 41.6 mmol, 4.0 equiv.) was added to a solution of the 2-(2-bromophenyl)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]acetamide (3.95 g, 10.4 mmol, 1.0 equiv.) in DCM (60 mL) in a round-bottomed flask equipped with a magnetic stirrer and a condenser and the resulting mixture was refluxed overnight. The reaction was then cooled to 0 °C and the solution was neutralized with a saturated solution of 10% NaOH. The resulting mixture was extracted with Et_2O to afford the crude dihydroisoquinoline. The product was found to be pure by NMR and was employed without further purification. The reduction was performed

using Tietze[20] procedure using the 1,2-(*S*,*S*)-*N*-tosyl-1,2-diphenylethylenediamine as the ligand. (99%, 95% *ee*): IR (nujol): $\tilde{\nu}_{max}$ = 3335, 2933, 2832, 1523, 1471, 1254, 1220, 1108, 1025 cm^{-1}. NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 2.67 (t, J = 7.8 Hz, 2 H), 3.73 (t, J = 7.7 Hz, 2 H), 3.79 (s, 3 H), 3.88 (s, 3 H), 4.19 (s, 2 H), 6.66 (s, 1 H), 6.91 (s, 1 H), 7.05 (td, J = 7.4, 1.5 Hz, 1 H), 7.18 (td, J = 7.4, 1.2 Hz, 1 H), 7.28 (dd, J = 7.7, 1.6 Hz, 1 H), 7.57 (dd, J = 8.0, 1.2 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 29.4, 40.0, 43.2, 54.8, 55.8, 55.9, 109.6, 111.6, 124.9, 127.1, 127.4, 128.2, 130.5, 132.0, 133.0, 138.8, 147.0, 147.4 ppm. HRMS calcd. for $C_{18}H_{20}BrNO_2$ ($M^+ - H_2Br$) 280.1338; found: 280.1330. $[a]_D^{22}$ = +41.5 (c = 1, CH_2Cl_2).

(*R*)-Methyl 1-(2-Bromobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline-2(1*H*)-carboxylate (9ab): Methyl chloroformate (0.22 mL, 28.5 mmol, 1.2 equiv.) was added slowly to a solution of (*R*)-1-(2-bromo-benzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (0.86 g, 23.7 mmol, 1.0 equiv.), diisopropylethylamine (0.83 mL, 47.5 mmol, 2.0 equiv.) and 1 mg of 4-(dimethylamino)pyridine in DCM (15 mL) and the resulting mixture was stirred overnight at 23 °C. The reaction was then quenched by adding a solution of NH_4Cl and was extracted with DCM. The crude reaction mixture was then purified by column chromatography on silica gel using 50% Et_2O/hexane. (84%), m.p. 173–175 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 2933, 1693, 1470, 1254, 1098. ^1H NMR analysis revealed the presence of two amide rotamers present in a 2.3:1 ratio. ^1H NMR (ppm, 300 MHz, $CDCl_3$, 293 KTMS): δ = 2.66–2.72 (m, 1 H), 2.78–3.60 (m, 4 H), 3.25 (s, 3 H), 3.79 (s, 3 H), 3.86 (s, 3 H), 4.31 (ddd, 1 H, J = 13.2, 5.3, 2.0 Hz), 5.38 (dd, 1 H, J = 10.2, 4.7 Hz), 6.62 (1 H,s), 6.64 (s, 1 H), 7.04–7.23 (m, 3 H), 7.57 (d, 1 H, J = 7.7 Hz); minor rotamer: 2.66–2.72 (m, 1 H), 2.78–3.60 (m, 4 H), 3.62 (s, 3 H), 3.65 (s, 3 H), 3.84 (s, 3 H), 3.96 (dt, 1 H, J = 13.1, 4.8 Hz), 5.42 (d, 1 H, J = 7.1 Hz), 6.31 (s, 1 H), 6.59 (s, 1 H), 7.04–7.23 (m, 3 H), 7.51 (d, 1 H, J = 8.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS, major rotamer): δ = 27.9, 37.2, 42.5, 51.9, 53.6, 55.7, 55.7, 109.6, 111.1, 124.9, 126.0, 127.1, 128.0, 128.0, 131.5, 132.2, 137.6, 147.1, 147.7, 155.6; (peaks corresponding to the minor rotamer were also detected): 38.6, 41.7, 52.4, 54.5, 55.5, 110.0, 110.8, 125.3, 125.9, 126.9, 127.9, 132.4, 146.8, 147.5 ppm. HRMS calcd. for $C_{13}H_{16}NO_4$ ($M^+ - C_7H_6Br$) 250.1079; found: 250.1096. MS (CI): m/z (%) = 422 (20), 420 (22), 250 (100), 205 (12). $[\alpha]_D^{22}$ = –66.8 (c = 1, CH_2Cl_2).

(*R*)-*tert*-Butyl 1-(2-Bromobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline-2(1*H*)-carboxylate (9aa): The carbamate was prepared following the general procedure (80%), m.p. 108–109 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 3063, 2931, 1686, 1519, 1420, 1228, 1161, 1099. ^1H NMR (300 MHz, [D_6]DMSO, 383 K, TMS): δ = 1.21 (s, 9 H), 2.49–2.80 (m, 2 H), 3.07–3.23 (m, 2 H), 3.32–3.41 (m, 1 H), 3.70 (s, 3 H), 3.76 (s, 3 H), 4.00–4.07 (m, 1 H), 5.29–5.33 (m, 1 H), 6.70 (d, J = 12.9 Hz, 2 H), 7.12–7.29 (m, 3 H), 7.56 (d, J = 7.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO, 383 K): δ = 28.3, 28.7, 38.2, 42.7, 54.8, 57.1, 79.5, 112.9, 114.5, 125.6, 127.8, 128.1, 129.0, 130.1, 132.9, 133.1, 138.9, 148.8, 149.4, 154.5 ppm. HRMS calcd. for $C_{22}H_{28}BrNO_4$ ($M^+ - C_4H_9O$) 388.0548; found: 288.0559. $[a]_D^{22}$ = –81.3 (c = 1, CH_2Cl_2).

Methyl (*R*)-4,5,6a,7-Tetrahydro-1,2-dimethoxydibenzo[*de*,*g*]quinoline-6-carboxylate (10ab): The cyclization was achieved following the general procedure (58%), m.p. 176–177 °C ($CHCl_3$). $\tilde{\nu}_{max}$ = 2953, 1694, 1449, 1405, 1250, 1104. ^1H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 2.64–2.69 (m, 1 H), 2.81–3.05 (m, 4 H), 3.66 (s, 3 H), 3.76 (s, 3 H), 3.90 (s, 3 H), 6.66 (s, 1 H), 6.91 (s, 1 H), 7.05 (td, J = 7.4, 1.5 Hz, 1 H), 7.18 (td, J = 7.4, 1.2 Hz, 1 H), 7.28 (dd, J = 7.7, 1.6 Hz, 1 H), 7.57 (dd, J = 8.0, 1.2 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 30.1, 35.2, 38.8, 51.4, 52.5, 55.8, 59.8, 111.3, 125.9, 126.9, 127.4, 127.5, 128.2, 128.3, 129.5, 131.5, 136.6, 145.6, 151.9, 155.8 ppm. HRMS calcd. for $C_{20}H_{21}NO_4$ (M^+) 339.1471; found: 339.1467. $[a]_D^{22}$ = –132.3 (c = 1, CH_2Cl_2).

(*R*)-Nuciferine (13): $LiAlH_4$ (0.006 g, 0.17 mmol, 1.0 equiv.) was added to a stirred solution of (*R*)-1,2-dimethoxy-4,5,6a,7-tetrahydrodibenzo[*de*,*g*]quinoline-6-carboxylic acid methyl ester (0.057 g, 0.17 mmol, 1.0 equiv.) in dry THF (6 mL) at 0 °C under an argon atmosphere. The temperature was allowed to rise to room temperature. The resulting mixture was stirred at room temperature for 24 h. The reaction was slowly hydrolysed with water and extracted with diethyl ether, dried with $MgSO_4$, filtered, evaporated and then purified by chromatography on column using acetone as the eluent to give the product in 88% yield. The product exhibited the same spectroscopic data as previously reported.[24] $[a]_D^{22}$ = –125.4 (c = 1, EtOH).

***tert*-Butyl (*R*)-4,5,6a,7-Tetrahydro-1,2-dimethoxydibenzo[*de*,*g*]quinoline-6-carboxylate (10aa):** The cyclization was achieved following the general procedure (90%), m.p. 149–151 °C ($CHCl_3$). IR: $\tilde{\nu}_{max}$ = 3070, 2930, 1687, 1406, 1249, 1163, 1106 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ = 1.49 (s, 9 H), 2.63–3.00 (m, 5 H), 3.66 (s, 3 H), 3.89 (s, 3 H), 4.41–4.44 (m, 1 H), 4.64–4.69 (m, 1 H), 6.67 (s, 1 H), 7.21–7.34 (m, 3 H), 8.44 (d, J = 7.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ = 28.8, 30.7, 35.7, 38.7, 51.9, 56.2, 60.3, 80.2, 111.7, 126.8, 127.3, 127.9, 128.0, 128.4, 128.7, 130.1, 132.0, 137.3, 145.8, 152.2, 155.0 ppm. HRMS calculated for $C_{23}H_{27}NO_4$ (M^+) 381.1940; found: 381.1943. $[a]_D^{22}$ = –246.8 (c = 1, CH_2Cl_2).

(*R*)-Nornuciferine (14): Trifluoroacetic acid (0.26 mL, 3.38 mmol, 13.0 equiv.) was added dropwise to a solution of *tert*-butyl (*R*)-4,5,6a,7-tetrahydro-1,2-dimethoxydibenzo[*de*,*g*]quinoline-6-carboxylate (0.1 g, 0.26 mmol, 1.0 equiv.) in dichloromethane (3 mL) and the resulting mixture was stirred at room temperature for 1 h. The solution was removed under reduced pressure and 2 *N* sodium hydroxide solution was added to the residue. The mixture was extracted with chloroform, dried with $MgSO_4$, filtered, evaporated and then purified by chromatography on column using 100% MeOH as the eluent to give the product in 53% yield. The product exhibited the same spectroscopic data as previously reported.[25] $[a]_D^{22}$ = –105.2 (c = 1, EtOH).

Supporting Information (see also the footnote on the first page of this article): ^1H and ^{13}C NMR spectra.

Acknowledgments

We thank the Natural Sciences and Engineering Research Council of Canada (NSERC), the Research Corporation, Tucson, AZ 85712, USA (Cottrell Scholar Award to K. F.), the Ontario Government (Premier's Research Excellence Award to K. F.), the University of Ottawa for support of this work. M. L. thanks the Ontario Government for Ontario Graduate Scholarships and N. B. thanks NSERC for summer undergraduate scholarships.

[1] a) J. L. Ríos, S. Máñez, R. M. Giner, M. C. Recio, *The Alkaloids* (Ed.: G. A. Cordell), Academic: New York, **2000**, vol. *53*, p. 57; b) H. Guinaudeau, M. Leboeuf, A. Cavé, *J. Nat. Prod.* **1994**, *57*, 1033, and references therein.
[2] T. Linnanen, M. Brisander, N. Mohell, A. M. Johansson, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 367.
[3] Y.-C. Chia, K.-S. Chen, Y.-L. Chang, C.-M. Teng, Y.-C. Wu, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3295.

[4] K. Likhitwitaywuid, C. K. Angerhofer, H. Y. Chai, J. M. Pezzuto, G. A. Cordell, N. Ruangrungsi, *Lloydia* **1993**, *56*, 1468.
[5] V. Munoz, M. Sauvain, P. Mollinedo, J. Callapa, I. Rojas, A. Gimenez, A. Velentine, M. Mallie, *Planta Med.* **1999**, *65*, 448.
[6] Y.-C. Wu, F.-R. Chang, Y.-C. Chao, C.-M. Teng, *Phytotherapy Res.* **1998**, *12*, S39.
[7] a) K. Sondergaard, J. L. Kristensen, M. Palner, N. Gillings, G. M. Knudsen, B. L. Roth, M. Begtrup, *Org. Biomol. Chem.* **2005**, *3*, 4077; b) A. Zhang, C. Csutoras, R. Zong, J. L. Neumeyer, *Org. Lett.* **2005**, *7*, 3239, and references therein.
[8] K. Sondergaard, J. L. Kristensen, M. Palner, N. Gillings, G. M. Knudsne, B. L. Roth, M. Begtrup, *Org. Biomol. Chem.* **2005**, *3*, 4077.
[9] For example, see: a) G. D. Cuny, *Tetrahedron Lett.* **2004**, *45*, 5167; b) G. D. Cuny, *Tetrahedron Lett.* **2003**, *44*, 8149; c) A.-E. Gies, M. Pfeffer, C. Sirlin, J. Spencer, *Eur. J. Org. Chem.* **1999**, *8*, 1957; d) D. L. Comins, P. M. Thakker, M. F. Baevsky, M. M. Badawi, *Tetrahedron* **1997**, *53*, 16327; e) M. M. V. Ramana, P. V. Potnis, *Tetrahedron Lett.* **1996**, *37*, 1671; f) S. Wiegand, H. J. Schafer, *Tetrahedron* **1995**, *51*, 534; g) Y. Landais, J. P. Robin, *Tetrahedron* **1992**, *48*, 7185; h) F. Roblot, R. Hocquemiller, A. Cavé, *Bull. Soc. Chim. Fr.* **1990**, *127*, 258; i) S. M. Kupchan, V. Kameswaran, J. W. A. Findlay, *J. Org. Chem.* **1973**, *38*, 405; j) S. M. Kupchan, J. L. Moniot, R. M. Kanojia, J. B. O'Brien, *J. Org. Chem.* **1971**, *36*, 2413; k) S. M. Kupchan, R. M. Kanojia, *Tetrahedron Lett.* **1966**, *44*, 5353.
[10] For reviews, see: a) Handbook of C–H Transformations (Ed.: G. Dyker), Wiley-VCH, Weinheim, **2005**; b) F. Kakiuchi, S. Murai, *Acc. Chem. Res.* **2002**, *35*, 826; c) V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, *102*, 1731; d) M. Miura, M. Nomura, *Top. Curr. Chem.* **2002**, *219*, 211; e) F. Kakiuchi, N. Chatani, *Adv. Synth. Catal.* **2003**, *345*, 1077; f) L. C. Campeau, K. Fagnou, *Chem. Commun.* **2006**, *12*, 1253.
[11] For example, see: a) D. Garcia-Cuadrado, A. A. C. Braga, F. Maseras, A. M. Echavarren, *J. Am. Chem. Soc.* **2006**, *128*, 1066; b) D. Kalyani, N. R. Deprez, L. V. Desai, M. S. Sanford, *J. Am. Chem. Soc.* **2005**, *127*, 7330; c) O. Daugulis, V. G. Zaitsev, *Angew. Chem. Int. Ed.* **2003**, *42*, 4254; d) Q. *Huang*, A. Fazio, G. Dai, M. A. Campo, R. C. Larock, *J. Am. Chem. Soc.* **2004**, *126*, 7460; e) X. Wang, B. S. Lane, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 4996; f) J. C. Lewis, S. H. Wiedemann, R. G. Bergmann, J. A. Ellman, *Org. Lett.* **2004**, *6*, 35; g) C.-H. Park, V. Ryabova, I. V. Seregin, A. W. Sromek, V. Gevorgyan, *Org. Lett.* **2004**, *6*, 1159; h) W. Li, D. P. Nelson, M. S. Jensen, R. S. Hoerrner, G. J. Javadi, D. Cai, R. D. Larsen, *Org. Lett.* **2003**, *5*, 4835; i) T. Okazawa, T. Satoh, M. Miura, M. Nomura, *J. Am. Chem. Soc.* **2002**, *124*, 5286; j) M. S. McClure, B. Glover, E. McSorley, A. Millar, M. H. Osterhout, F. Roschangar, *Org. Lett.* **2001**, *3*, 1677.
[12] M. Lafrance, N. Blaquière, K. Fagnou, *Chem. Commun.* **2004**, *24*, 2874.
[13] a) L.-C. Campeau, M. Parisien, M. Leblanc, K. Fagnou, *J. Am. Chem. Soc.* **2004**, *126*, 9186; b) L.-C. Campeau, M. Parisien, A. Jean, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 581.
[14] N. H. Martin, C. W. Jefford, *Helv. Chim. Acta* **1982**, *65*, 762.
[15] M. R. Netherton, G. C. Fu, *Org. Lett.* **2001**, *3*, 4295.
[16] S. D. Walker, T. E. Barder, J. R. Martinelli, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2004**, *43*, 1871.
[17] J. P. Wolfe, H. Tomori, J. P. Sadighi, J. Yin, S. L. Buchwald, *J. Org. Chem.* **2000**, *65*, 1158.
[18] A. F. Littke, G. C. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 6989.
[19] a) L.-C. Campeau, S. Rousseaux, K. Fagnou, *J. Am. Chem. Soc.* **2005**, *127*, 18020; b) J.-P. Leclerc, K. Fagnou, *Angew. Chem. Int. Ed.* **2006**, *45*, 7781.
[20] L. F. Tietze, N. Rackelmann, G. Sekar, *Angew. Chem. Int. Ed.* **2003**, *42*, 4254.
[21] a) C.-M. Chiou, J.-J. Kang, S.-S. Lee, *J. Nat. Prod.* **1998**, *61*, 46; b) L. Castedo, A. R. de Lera, J. M. Saa, R. Suau, C. Villaverde, *Heterocycles* **1980**, *14*, 1135.
[22] N. Lebegue, G. Bethegnies, P. Berthelot, *Synth. Commun.* **2004**, *34*, 1041.
[23] C. Viel, R. Dorme, P. Rumpf, *Bull. Soc. Chim. Fr.* **1966**, *33*, 1956.
[24] G. D. Cuny, *Tetrahedron Lett.* **2003**, *44*, 8149.
[25] H. Achenbach, C. Renner, I. Addae-Mensah, *Liebigs Ann. Chem.* **1982**, *9*, 1623.

Received: August 1, 2006
Published Online: December 5, 2006

