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Monoligated Pd(0)-catalyzed intramolecular *ortho*- and *para*-arylation of phenols for the synthesis of aporphine alkaloids. Synthesis of (−)-lirinine

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ABSTRACT

An intramolecular palladium(0)-mediated *ortho*-arylation of phenols applied to the synthesis of various substituted aporphines is reported. Most significantly, the efficiency of the transformation was enhanced by the use of monoligated Pd(0) complexes. This methodology was extended to *para*-arylation of phenols and employed in the synthesis of the aporphine alkaloid (−)-lirinine.

1. Introduction

ortho-Arylation of phenols represents a strategy for constructing aryl–aryl bonds. Several approaches have been described in the literature to mediate this process, including Pd-catalyzed,[1] Rh-catalyzed,[2] base-mediated,[3] enzymatic,[4] photochemical,[5] or oxidative reactions,[6] and using the Pinhey–Barton route.[7] Many of these methods have limited applicability due to lack of functional group tolerance to the required harsh reaction conditions, such as strong base or high temperature. Although Pd-mediated methods represent a promising route for intramolecular *ortho*-arylations of phenols, prolonged heating (24–48 h) and high catalyst loadings (20–50 mol %) have previously been necessary for this process, even with aryl iodides.[1]

Aporphine alkaloids are a class of natural products that have demonstrated interesting and assorted biological activities,[8] such as the non-selective dopamine agonist (−)-apomorphine used in the treatment of Parkinson's disease and (−)-lirinine (also known as 3-hydroxynuciferine), which was isolated from the leaves of *Liriodendron tulipifera* and exerts spasmolytic and hypotensive properties (Fig. 1).[9,10] The prominence of aporphines has attracted significant interest by the synthetic organic chemistry community resulting in the development of numerous methods for their preparation.[11] Furthermore, the *ortho*- or *para*-aryl phenol motifs found among many members of the aporphines makes this scaffold interesting for studying intramolecular arylation of phenols. Herein is reported a convenient method for the synthesis of various aporphines using an efficient intramolecular phenol *ortho*-arylation reaction. This process was then extended to *para*-arylation of phenols and applied to the synthesis of the aporphine alkaloid (−)-lirinine.

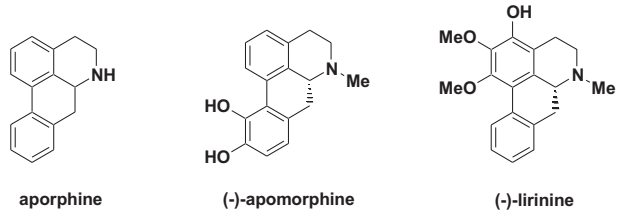

Fig. 1. Aporphine scaffold and examples of aporphine alkaloids.

Buchwald and co-workers recently reported the development of a new class of air- and moisture-stable Pd-precatalysts that are activated under standard reaction conditions and ensure the formation of the monoligated active complex of Pd(0) (Fig. 2).[12] The $L_1Pd(0)$ species generated by the precatalysts presents the advantage to be less sterically hindered and highly reactive, which we hypothesized may be beneficial for mediating the intramolecular *ortho*-arylation of phenols. Thus, the exploration of these precatalysts for the synthesis of aporphines was undertaken.

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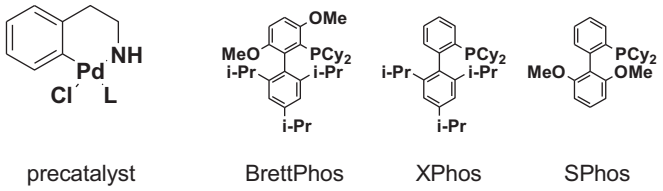
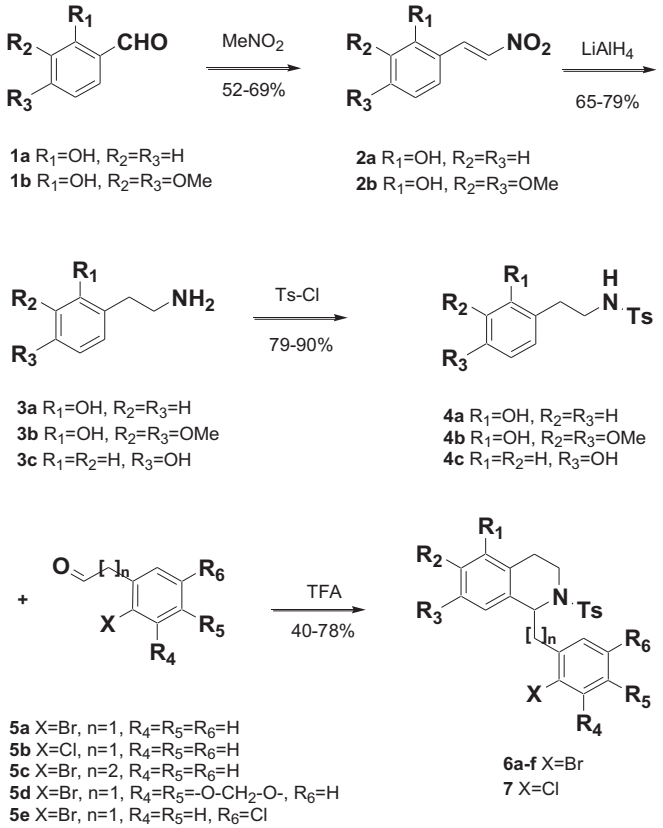


Fig. 2. Structure of Pd-precatalysts and various associated ligands (L).

2. Results and discussion

2.1. Preparation of tetrahydroisoquinolines 6a–f and 7

The sulfonamides **4a**–**c** were obtained in a three-step process involving a Henry reaction of benzaldehydes,[13] followed by reduction of the nitrostyrene and reaction with *p*-toluenesulfonyl chloride (Scheme 1). The substrate tetrahydroisoquinolines **6a**–**f** and **7** were prepared utilizing a Pictet–Spengler cyclization of the sulfonamides **4a**–**c** and acetaldehydes **5a**–**e** under acidic condition. Acetaldehydes **5a**–**e** were synthesized using various methods.

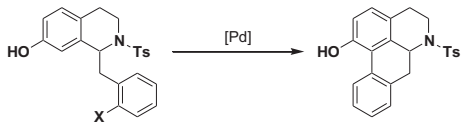


Scheme 1. Synthesis of the tetrahydroisoquinolines using Pictet–Spengler reactions.

2.2. Optimization of phenol *ortho*-arylation conditions

As previously reported, **6a** could be converted to **8a** in moderate yield using a high loading of $Pd(OAc)_2$ and PCy_3 and with prolonged heating (Table 1, entry 1).[1a] However, with the XPhos precatalyst (5 mol %), Cs_2CO_3 (3 equiv) in dimethylacetamide (DMA) at 110 °C for only 1 h aporphine **8a** was obtained in 93% yield (entry 2). For comparison, *ortho*-arylation was not observed using $Pd(OAc)_2$ and XPhos, showing the remarkable effect of the precatalyst (entry 3). Further investigation revealed that the reaction was dependent on the choice of ligand. For example, lower yields were observed with BrettPhos or SPhos (entries 4 and 5). Decreasing the catalyst loading to 1 or 3 mol % also resulted in lower yields of 9% and 60%, respectively (entries 6 and 7). Furthermore, no reaction was observed with chlorine substrate **7** (entry 8).

Table 1
Optimization of the intramolecular *ortho*-arylation of phenols[a]



6a X=Br
7 X=Cl

8a

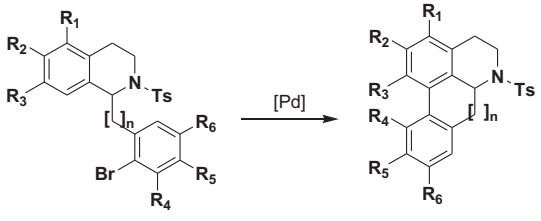
Entry	Substrate	Catalyst	Yield[b] (%)
1	**6a**	$Pd(OAc)_2$ (20%), PCy_3 (40%)	56[c]
2	**6a**	XPhos precat. (5%)	93
3	**6a**	$Pd(OAc)_2$ (5%), XPhos (10%)	0[c]
4	**6a**	BrettPhos precat. (5%)	20[c]
5	**6a**	SPhos precat. (5%)	83
6	**6a**	XPhos precat. (1%)	9[c]
7	**6a**	XPhos precat. (3%)	60[d]
8	**7**	XPhos precat. (5%)	0[c]

[a] Reaction condition: **6a** or **7** (1 equiv), [Pd] (mol %), Cs_2CO_3 (3 equiv), DMA, 110 °C, 1 h.
[b] Isolated yield.
[c] 110 °C for 24 h.
[d] 110 °C for 3 h.

2.3. Substrate scope of intramolecular *ortho*- and *para*-arylation of phenols

With optimized conditions identified, the phenol arylation was extended to the synthesis of various aporphines. As shown in Table 2, electron-donating and electron-withdrawing groups were tolerated in this process and gave the expected aporphines in good yields (entries 1 and 2). Moreover, a homoaporphine, representing a related class of natural products,[14] was also synthesized in 76% yield using the same reaction conditions (entry 3). Next the use of this methodology was extended to *para*-arylation of phenols. Using the same reaction conditions, an aporphine was synthesized via a phenol *para*-arylation in 88% yield (entry 4). However, with a substrate containing a methoxy group *ortho* to the arylation site, the process required 10 mol % of catalyst, presumably due to increased steric hindrance for C–C bond formation (entry 5).

Table 2
Substrate scope and limitations of *ortho*- and *para*-arylation of phenols[a]



6b-f

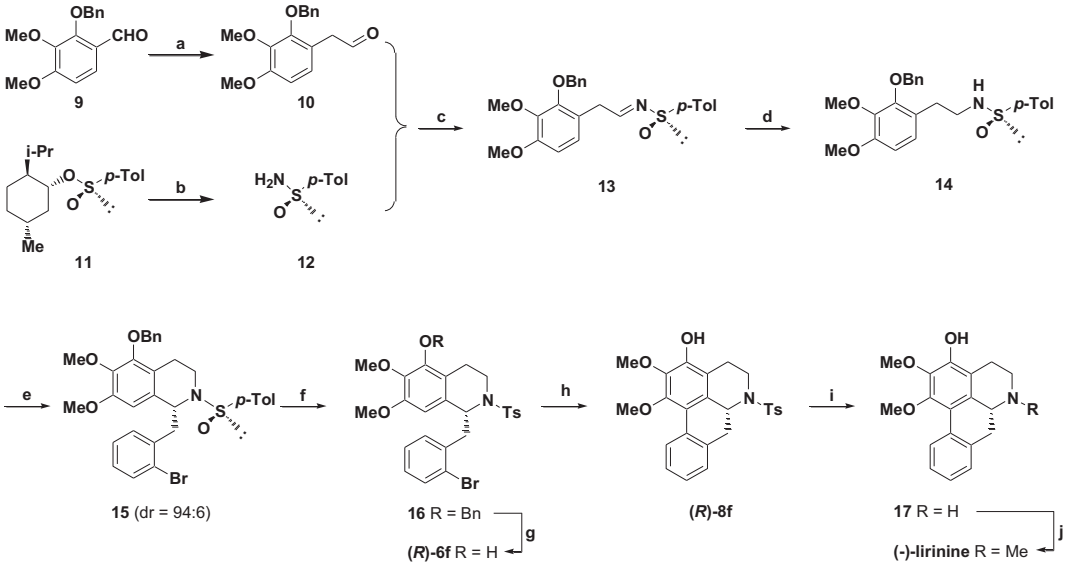
8b-f

Entry	R_1, R_2, R_3	R_4, R_5, R_6	*n*	Product	Yield[b] (%)
1	H, H, OH	–O–CH_2–O–, H	1	**8b**	78
2	H, H, OH	H, H, Cl	1	**8c**	77
3	H, H, OH	H, H, H	2	**8d**	76
4	OH, H, H	H, H, H	1	**8e**	88
5	OH, OMe, OMe	H, H, H	1	**8f**	98[c]

[a] Reaction condition: **6b**–**f** (1 equiv), XPhos precat. (5 mol %), Cs_2CO_3 (3 equiv), DMA, 110 °C, 1 h.
[b] Isolated yield.
[c] XPhos precat. (10 mol %).

2.4. Synthesis of the aporphine alkaloid (−)-lirinine

With the methodology established for the intramolecular *para*-arylation of phenols, this process was applied to the synthesis of the aporphine alkaloid (−)-lirinine (Scheme 2). The key steps in the synthetic strategy were to prepare and use an enantiomerically pure *N*-sulfinylamine tetrahydroisoquinoline intermediate in the Pictet–Spengler reaction.[15]



Scheme 2. Synthesis of (−)-lirinine. Reagents and conditions: (a) 1. $ClPh_3PCH_2OCH_3$, KO^{t}Bu; 2. HCl, 83% over two steps; (b) LiHMDS, 91%; (c) $Ti(OEt)_4$, 64%; (d) $NaBH_4$, 80%; (e) **5a**, $BF_3{\cdot}Et_2O$, 53%, dr: 94:6; (f) *m*-CPBA, 99%; (g) HCl, 64%; (h) XPhos precat. (10 mol %), 98%; (i) Na/Naphthalene, 94%; (j) CH_2O, then $NaBH_4$, 95%.

Homologation of benzaldehyde **9** was performed by a Wittig reaction, followed by enol ether hydrolysis in 83% yield over two steps. Acetaldehyde **10** was converted to the chiral sulfinylamide **14** by addition of (−)-sulfinylamine **10** in the presence of $Ti(OEt)_4$ in 64% yield, followed by imine reduction with $NaBH_4$ in 80% yield. Then, a diastereoselective Pictet–Spengler reaction between **14** and 2-bromophenylacetaldehyde **5a** gave the tetrahydroisoquinoline **15** in 53% yield and with good diastereomeric selectivity (dr=94:6 as determined by ^{1}H NMR). This selectivity was notably higher than a similar reported substrate, which lacked the *ortho*-bromine.[15] Tetrahydroisoquinoline **15** (dr=94:6) was quantitatively oxidized with *m*-CPBA to the corresponding *N*-tosyl tetrahydroisoquinoline **16**. Then, removal of the benzyl group under acidic conditions furnished the phenol intermediate (*R*)-**6f**. The intramolecular *para*-arylation was performed with Xphos precatalyst (10 mol %) to give (*R*)-**8f** in 98% yield. The *N*-tosyl group was removed under sodium naphthalide conditions to give **17** in 94% yield and 89% ee.[16] Finally, reductive amination furnished (−)-lirinine in 95% yield. NMR spectral data for the synthetic material was in agreement with that previously reported for the isolated natural product.[9a,11f,17]

3. Conclusion

In summary, a monoligated Pd(0) catalyst has shown remarkable reactivity in the *ortho*-arylation of phenols. Low catalyst loading (5 mol %) and short reaction times (1–3 h) were sufficient to perform this process for most substrates generating various aporphines in good to excellent yields. The methodology was extended for the first time to the *para*-arylation of phenols for the construction of aporphines and used for the synthesis of (−)-lirinine.

4. Experimental section

4.1. General information and materials

All reactions were carried out under an atmosphere of argon in flame dried or oven-dried glassware with magnetic stirring. Purification of products was performed on an automated system using disposable silica gel columns. Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and ninhydrin solution, $KMnO_4$ or anisaldehyde staining followed by heating. ^{1}H NMR spectra were recorded on a 400 or 500 MHz spectrometer and are reported in parts per million using solvent as the internal standard ($CDCl_3$ at 7.26 ppm or DMSO-d_6 at 2.54 ppm). Data are reported as: (br=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet; integration; coupling constant(s) in hertz). ^{13}C NMR spectra were recorded on a 100 or 125 MHz spectrometer. Chemical shifts are reported in ppm from tetramethylsilane, with the solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm or DMSO-d_6 at 39.0 ppm). High-resolution mass spectra were obtained on MALDI-FT-ICR MS, using 150 mg/mL 2,5-dihydroxybenzoic acid dissolved in MeOH/H_2O (50:50) as matrix.

All reagents and solvents were purchased from commercial sources and used without further purification. The following starting materials were made according to literature procedures: 2-(2-nitrovinyl)phenol **2a**,[18] 2,3-dimethoxy-6-(2-nitrovinyl)-phenol **2b**,[19] *N*-(4-hydroxy phenethyl)-*p*-toluenesulfonamide **4c**,[1a] 2-(2-bromophenyl)acetaldehyde **5a**,[20] 2-(2-chlorophenyl)-acetaldehyde **5b**,[21] 3-(2-bromo-phenyl)propanal **5c**,[22] 1-(2-bromobenzyl)-2-*p*-toluenesulfonamide-1,2,3,4-tetrahydroisoquinolin-7-ol **6a**,[1a] 2-(benzyloxy)-3,4-dimethoxybenzaldehyde **9**,[13] (*S*)-(+)-*p*-toluenesulfinamide **12**.[23]

4.2. Synthesis of amines 3a and b

*4.2.1. 2-(2-Aminoethyl)phenol (**3a**)*[24]. A solution of 2-(2-nitrovinyl) phenol **2a** (860 mg, 5.21 mmol) in THF (12 mL) was added dropwise (over 1 h) to a stirred and cooled (0 °C) suspension of $LiAlH_4$ (479 mg, 17.18 mmol) in THF (6 mL). Stirring was continued for 2 h at room temperature. The reaction mixture was cooled to 0 °C and then water was added. The organic solvent was removed in vacuo. The residue

was dissolved in HCl (10%, 40 mL) and washed twice with EtOAc (20 mL). The combined organic layers were extracted twice with HCl (10%, 20 mL). The combined aqueous layers were treated with tartaric acid (4 equiv) and the pH was adjusted to >10 with concd NH_3 and the aqueous layers were extracted three times with chloroform (30 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by chromatography on silica gel using 3–10% 2 M NH_3 in MeOH in CH_2Cl_2 to yield **3a** as a white solid (464 mg, 3.38 mmol, 65%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.12 (ddd, J=8.0, 8.0, 1.5 Hz, 1H), 6.99 (dd, J=7.5, 1.5 Hz, 1H), 6.90 (dd, J=8.0, 1.0 Hz, 1H), 6.76 (ddd, J=7.5, 7.5, 1.0 Hz, 1H), 5.40 (br, 1H), 3.09–3.07 (m, 2H), 2.80–2.78 (m, 2H).

*4.2.2. 6-(2-Aminoethyl)-2,3-dimethoxyphenol (**3b**).* The same procedure as for **3a** was used. The residue was purified by chromatography on silica gel 3–10% 2 M NH_3 in MeOH in CH_2Cl_2 to yield **3b** as a white solid (739 mg, 3.75 mmol, 78%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.70 (d, J=8.5 Hz, 1H), 6.36 (d, J=8.5 Hz, 1H), 5.11 (br, 3H), 3.89 (s, 3H), 3.84 (s, 3H), 3.04–3.01 (m, 2H), 2.78–2.73 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.2, 150.3, 137.8, 124.8, 121.5, 102.7, 55.9, 42.3, 60.6, 35.4. HRMS (MALDI-TOF) $C_{10}H_{16}NO_3$ $[M+H]^+$: 198.1125; found: 198.1128.

4.3. Synthesis of sulfonamides 4a and b

*4.3.1. N-(2-Hydroxyphenethyl)-p-toluenesulfonamide (**4a**).* To a solution of **3a** (370 mg, 2.70 mmol) in 6 mL of DMF at 0 °C under argon was added tosyl chloride (540 mg, 2.80 mmol) followed by diisopropylethylamine (473 μL, 2.80 mmol). The solution was stirred at room temperature for 4 h. The reaction was concentrated, and then diluted in HCl 1 N (10 mL), extracted twice with EtOAc (20 mL). The organic layers were combined, washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by chromatography on silica gel using CH_2Cl_2/cyclohexane/EtOAc (60/35/5) to give **4a** (620 mg, 2.13 mmol, 79%) as an orange oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, J=8.0 Hz, 2H), 7.24 (d, J=8.0 Hz, 2H), 7.09 (ddd, J=8.0, 8.0, 1.5 Hz, 1H), 6.98 (dd, J=7.5, 1.5 Hz, 1H), 6.82 (ddd, J=8.0, 8.0, 1.0 Hz, 1H), 6.75 (dd, J=7.5, 1.0 Hz, 1H), 5.50 (br, 1H), 4.86 (t, J=6.0 Hz, 1H), 3.21 (q, J=6.5 Hz, 2H), 2.79 (t, J=6.5 Hz, 2H), 2.40 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.0, 143.6, 136.8, 131.2, 129.9, 128.4, 127.3, 124.6, 121.3, 115.8, 43.7, 30.7, 21.7. HRMS (MALDI-TOF) $C_{15}H_{17}NNaO_3S$ $[M+Na]^+$: 314.0821; found: 314.0835.

*4.3.2. N-(2-Hydroxy-3,4-dimethoxyphenethyl)-p-toluenesulfonamide (**4b**).* The same procedure as for **4a** was used. The residue was purified by chromatography on silica gel using 25–50% EtOAc in cyclohexane to give **4b** (319 mg, 0.91 mmol, 90%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, J=8.5 Hz, 2H), 7.25 (d, J=8.5 Hz, 2H), 6.66 (d, J=8.5 Hz, 1H), 6.37 (d, J=8.5 Hz, 1H), 5.87 (s, 1H), 4.59 (t, J=6.0 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.20 (q, J=6.5 Hz, 2H), 2.71 (t, J=6.5 Hz, 2H), 2.41 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.5, 147.5, 143.3, 137.2, 135.6, 129.8, 127.2, 125.1, 117.1, 103.9, 61.1, 56.0, 43.3, 30.1, 21.7. HRMS (MALDI-TOF) $C_{17}H_{21}NNaO_5S$ $[M+Na]^+$: 374.1033; found: 374.1046.

4.4. Preparation of phenylacetaldehydes 5d and e

A solution under argon of methoxymethyl-triphenylphosphonium chloride (2.2 equiv) in dry THF (4 mL) at 0 °C was treated dropwise with a solution of KO^{t}Bu 1 M in THF (2 equiv). The resulting mixture was allowed to warm to room temperature and stirred under argon for 30 min, then treated with a solution of aldehyde (1 equiv) in dry THF (4 mL) and stirred at room temperature for 3 h. The reaction was quenched by the addition of brine (10 mL), extracted with EtOAc (3×10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel using 0–10% EtOAc in cyclohexane to give the corresponding vinyl ether.

The vinyl ether was dissolved in THF (5 mL) and cooled to 0 °C, then treated with 6 M H_2SO_4 (2.5 mL). The resulting mixture was heated to 50 °C for 4 h. After cooling, the reaction was added dropwise in a saturated solution of $NaHCO_3$ (20 mL) and extracted twice with EtOAc (20 mL). The organic layers were combined, washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated.

*4.4.1. (2-Bromo-3,4-methylenedioxyphenyl)acetaldehyde (**5d**).* The residue was purified by chromatography on silica gel using 0–10% EtOAc in cyclohexane to give **5d** (244 mg, 1.0 mmol, 78%) as a moderately unstable white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.74 (t, J=1.5 Hz, 1H), 7.08 (d, J=8.5 Hz, 1H), 6.67 (d, J=8.5 Hz, 1H), 6.00 (s, 2H), 3.82 (d, J=1.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.4, 147.9, 147.0, 125.4, 116.3, 114.9, 109.1, 102.1, 44.2.

*4.4.2. (2-Bromo-5-chlorophenyl)acetaldehyde (**5e**)[25].* The residue was purified by chromatography on silica gel using 0–10% EtOAc in cyclohexane to give **5e** (276 mg, 1.2 mmol, 70%) as moderately unstable a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.76 (t, J=1.5 Hz, 1H), 7.54 (d, J=8.5 Hz, 1H), 7.24 (d, J=2.5 Hz, 1H), 7.18 (dd, J=8.5, 2.5 Hz, 1H), 3.85 (d, J=1.5 Hz, 2H).

4.5. Preparation of tetrahydroisoquinolines 6b–f and 7, exemplified for 1-(2-chlorobenzyl)-2-*p*-toluenesulfonyl-1,2,3,4-tetrahydroisoquinolin-7-ol (7)

Into a flask was added aldehyde **5b** (80 mg, 0.51 mmol), sulfonamide **4c** (100 mg, 0.34 mmol), and TFA (1 mL). The solution was heated to 70 °C for 5 h. After cooling, the reaction mixture was diluted with water (10 mL) and neutralized with saturated $NaHCO_3$. The mixture was extracted twice with EtOAc (20 mL). The organic extracts were combined, washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by chromatography on silica gel using 10–30% EtOAc in cyclohexane to give **7** (103 mg, 0.24 mmol, 70%) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 (d, J=8.0 Hz, 2H), 7.29 (dd, J=7.5, 1.5 Hz, 1H), 7.20–7.10 (m, 3H), 7.04 (d, J=8.0 Hz, 2H), 6.86 (d, J=3.0 Hz, 1H), 6.63 (dd, J=5.5, 2.5 Hz, 1H), 6.47 (d, J=2.5 Hz, 1H), 5.23 (dd, J=5.5, 4.0 Hz, 1H), 4.52 (s, 1H), 3.88–3.83 (m, 1H), 3.67–3.56 (m, 1H), 3.23–3.11 (m, 2H), 2.74–2.68 (m, 1H), 2.60–2.55 (m, 1H). 2.32 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.7, 142.9, 137.1, 136.9, 135.5, 134.5, 132.1, 130.1, 126.7, 129.4, 129.3, 128.1, 127.1, 125.1, 114.6, 113.5, 56.1, 41.0, 39.3, 26.9, 26.1, 21.4. HRMS (MALDI-TOF) $C_{23}H_{22}ClNNaO_3S$ $[M+Na]^+$: 450.0901; found: 450.0904.

*4.5.1. 1-(2-Bromo-3,4-methylenedioxybenzyl)-2-p-toluenesulfonyl-1,2,3,4-tetrahydroisoquinolin-7-ol (**6b**).* The same procedure as for **7** was used. The crude product was purified by chromatography on silica gel using 10–30% EtOAc in cyclohexane to give **6b** (158 mg, 0.31 mmol, 61%) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, J=8.0 Hz, 2H), 7.04 (d, J=8.0 Hz, 2H), 6.97 (d, J=8.0 Hz, 1H), 6.89 (d, J=8.5 Hz, 1H), 6.70 (d, J=2.5 Hz, 1H), 3.91–3.87 (m, 1H), 6.65 (dd, J=5.5, 2.5 Hz, 1H), 6.56 (d, J=8.0 Hz, 1H), 5.84 (d, J=1.5 Hz, 1H), 5.80 (d, J=1.5 Hz, 1H), 5.29 (dd, J=7.0, 4.0 Hz, 1H), 4.74 (br, 1H), 3.70–3.64 (m, 1H), 3.25–3.20 (m, 1H), 2.97 (dd, J=10.0, 4.0 Hz, 1H), 2.82–2.75 (m, 1H), 2.60–2.56 (m, 1H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.9, 148.1, 146.7, 143.0, 137.7, 137.4, 130.5, 129.5, 127.1, 125.5, 125.1, 119.9, 116.6, 114.9, 113.5, 108.3, 106.8, 101.7, 55.2, 39.2, 37.2, 26.6, 21.6. HRMS (MALDI-TOF) $C_{24}H_{22}BrNNaO_5S$ $[M+Na]^+$: 538.0294; found: 538.0291.

*4.5.2. 1-(2-Bromo-5-chlorobenzyl)-2-p-toluenesulfonyl-1,2,3,4-tetrahydroisoquinolin-7-ol (**6c**).* The same procedure as for **7** was

used. The crude product was purified by chromatography on silica gel using 10–30% EtOAc in cyclohexane to give **6c** (126 mg, 0.25 mmol, 50%) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.30 (m, 3H), 7.07–7.01 (m, 4H), 6.90 (d, J=8.0 Hz, 1H), 6.65 (dd, J=5.5, 2.5 Hz, 1H), 6.61 (d, J=7.5 Hz, 1H), 4.79 (br, 1H), 5.22 (dd, J=5.5, 4.5 Hz, 1H), 3.95–3.91 (m, 1H), 3.59–3.53 (m, 1H), 3.18–3.03 (m, 2H), 2.84–2.77 (m, 1H), 2.63–2.58 (m, 1H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.0, 143.2, 139.1, 137.1, 136.8, 133.9, 133.3, 132.0, 130.4, 129.6, 128.6, 127.2, 125.4, 123.1, 115.0, 113.5, 56.0, 43.4, 39.6, 26.5, 21.7. HRMS (MALDI-TOF) $C_{23}H_{21}BrClNNaO_3S$ $[M+Na]^+$: 528.0006; found: 528.0025.

*4.5.3. 1-(2-Bromophenethyl)-2-p-toluenesulfonyl-1,2,3,4-tetrahydroisoquinolin-7-ol (**6d**).* The same procedure as for **7** was used. The crude product was purified by chromatography on silica gel using 10–30% EtOAc in cyclohexane to give **6d** (87 mg, 0.18 mmol, 52%) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, J=8.0 Hz, 2H), 7.50 (dd, J=8.0, 1.0 Hz, 1H), 7.27 (ddd, 1H, J=8.0, 8.0, 2.0 Hz, 1H), 7.22 (ddd, 1H, J=7.5, 7.5, 1.0 Hz, 1H), 7.12 (d, J=8.5 Hz, 2H), 7.04 (ddd, J=7.5, 7.5, 1.5 Hz, 1H), 6.73 (d, J=8.0 Hz, 1H), 6.55 (dd, J=8.0, 2.5 Hz, 1H), 6.52 (d, J=2.5 Hz, 1H), 5.02 (dd, 1H, J=5.5, 4.5 Hz, 1H), 4.55 (br, 1H), 3.95–3.90 (m, 1H), 3.56–3.50 (m, 1H), 3.02–2.83 (m, 2H), 2.46–2.43 (m, 2H), 2.33 (s, 3H), 2.13–1.95 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.9, 143.3, 141.3, 138.0, 137.7, 133.0, 130.7, 130.2, 129.6, 127.9, 127.7, 127.2, 124.8, 124.5, 114.5, 113.4, 56.8, 39.3, 37.7, 33.8, 27.1, 25.5, 21.6. HRMS (MALDI-TOF) $C_{24}H_{24}BrNNaO_3S$ $[M+Na]^+$: 508.0552; found: 508.0558.

*4.5.4. 1-(2-Bromobenzyl)-2-tosyl-1,2,3,4-tetrahydroisoquinolin-5-ol (**6e**).* Into a flask was added **5a** (90 mg, 0.45 mmol), sulfonamide **4a** (88 mg, 0.30 mmol), and TFA (1 mL). The solution was stirred at room temperature for 1 h. Then, the reaction mixture was diluted with water (10 mL) and neutralized with saturated $NaHCO_3$. The mixture was extracted twice with EtOAc (20 mL). The organic extracts were combined, washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by chromatography on silica gel using 10–30% EtOAc in cyclohexane to give **6e** (57 mg, 0.12 mmol, 40%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (dd, J=7.5, 1.0 Hz, 1H), 7.37 (d, J=8.0 Hz, 2H), 7.19 (ddd, J=7.5, 7.5, 1.0 Hz, 1H), 7.14–7.07 (m, 2H), 7.04–6.98 (m, 3H), 6.72 (d, J=7.5 Hz, 1H), 6.59 (d, J=8.0 Hz, 1H), 5.32 (dd, J=10.0, 5.0 Hz, 1H), 4.65 (br, 1H), 4.03–3.98 (m, 1H), 3.63–3.57 (m, 1H), 3.24–3.11 (m, 2H), 2.64–2.61 (m, 2H), 2.32 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.3, 143.0, 137.5, 137.3, 132.9, 132.3, 129.5, 128.5, 127.5, 127.3, 126.7, 125.3, 120.3, 119.7, 113.2, 55.8, 43.3, 38.5, 27.1, 21.6, 21.2. HRMS (MALDI-TOF) $C_{23}H_{22}BrNNaO_3S$ $[M+Na]^+$: 494.0396; found: 494.0419.

*4.5.5. 1-(2-Bromobenzyl)-6,7-dimethoxy-2-p-toluenesulfon-yl-1,2,3,4-tetrahydroisoquinolin-5-ol (**6f**).* Into a flask was added aldehyde **5a** (255 mg, 1.28 mmol), sulfonamide **4b** (300 mg, 0.84 mmol), and TFA (2 mL). The solution was stirred at room temperature for 1 h. The reaction mixture was diluted with water (20 mL) and neutralized with saturated $NaHCO_3$. The mixture was extracted twice with EtOAc (40 mL). The organic extracts were combined, washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by chromatography on silica gel using CH_2Cl_2/cyclohexane/EtOAc (60:35:5) to give **6f** (353 mg, 0.66 mmol, 78%) as a yellowish solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (dd, J=8.0, 1.0 Hz, 1H), 7.43 (d, J=8.0 Hz, 2H), 7.19 (ddd, J=7.5, 7.5, 1.0 Hz, 1H), 7.12–7.07 (m, 2H), 7.05 (d, J=8.0 Hz, 2H), 6.01 (s, 1H), 5.74 (s, 1H), 5.22 (t, J=8.0 Hz, 1H), 3.97–3.93 (m, 1H), 3.84 (s, 3H), 3.67 (s, 3H), 3.60–3.54 (m, 1H), 3.21–3.13 (m, 2H), 2.64–2.53 (m, 2H), 2.32 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.0, 146.5, 142.8, 137.3, 133.9, 132.7, 132.2, 131.2, 129.3, 128.3, 127.3, 127.1, 125.2, 112.9, 102.2, 61.0, 55.7, 43.1, 38.3, 26.9, 21.4, 20.7. HRMS (MALDI-TOF) $C_{25}H_{26}BrNNaO_5S$ $[M+Na]^+$: 554.0607; found: 554.0626.

4.6. General procedure for the *ortho*- and *para*-arylation of phenols

A reaction tube was charged with tetrahydroisoquinoline **8a**–**f** (1 equiv), Xphos precat. (1–10 mol %) and Cs_2CO_3 (3 equiv). The tube was evacuated and backfilled with argon (three times), and then dry DMA (1 mL/0.1 mmol of starting material) was added. The mixture was sparged with argon for 5 min and then heated at 110 °C for 1 h. After cooling at room temperature, the reaction mixture was quenched with 1 N HCl. The reaction mixture was extracted three times with ethyl acetate. The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by chromatography on silica gel using CH_2Cl_2/cyclohexane/EtOAc (60:35:5) as eluent to yield a white solid.

*4.6.1. 5,6,6a,7-Tetrahydro-6-p-toluenesulfonyl-4H-dibenzo-[de,g] quinolin-1-ol (**8a**).* ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (d, J=8.0 Hz, 1H), 7.69 (d, J=8.0 Hz, 2H), 7.38–7.34 (m, 2H), 7.29–7.28 (m, 1H), 7.23 (d, J=8.0 Hz, 2H), 6.85 (d, J=8.5 Hz, 1H), 6.74 (d, J=8.5 Hz, 1H), 5.19 (s, 1H), 4.11–4.07 (m, 1H), 4.66 (dd, J=14.0, 4.5 Hz, 1H), 3.27–3.21 (m, 1H), 3.16 (dd, J=14.0, 4.5 Hz, 1H), 3.02 (t, J=14.0 Hz, 1H), 2.48–2.43 (m, 1H), 2.38 (s, 3H), 2.36–2.31 (m, 1H).

*4.6.2. 10,11-Methylenedioxy-5,6,6a,7-tetrahydro-6-p-toluenesulfonyl-4H-dibenzo[de,g]-quinolin-1-ol (**8b**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J=8.5 Hz, 2H), 7.64 (d, J=8.5 Hz, 1H), 7.25–7.23 (m, 2H), 6.82 (d, J=8.0 Hz, 1H), 6.74 (d, J=8.0 Hz, 1H), 6.07 (d, J=1.5 Hz, 1H), 6.01 (d, J=1.5 Hz, 1H), 5.27 (s, 1H), 5.30 (s, 1H), 4.66 (dd, J=14.0, 4.5 Hz, 1H), 4.10–4.06 (m, 1H), 3.36 (dd, J=14.0, 4.5 Hz, 1H), 3.25–3.19 (m, 1H), 2.69 (t, J=14.0 Hz, 1H), 2.47–2.43 (m, 1H), 2.38 (m, 3H), 2.36–2.32 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.1, 146.9, 143.5, 138.3, 133.2, 130.1, 128.4, 127.1, 125.9, 125.8, 121.2, 120.7, 118.1, 116.1, 106.8, 101.6, 53.2, 41.1, 30.2, 28.3, 21.7. HRMS (MALDI-TOF) $C_{24}H_{21}NNaO_5S$ $[M+Na]^+$: 458.1033; found: 458.1043.

*4.6.3. 9-Chloro-5,6,6a,7-tetrahydro-6-p-toluenesulfonyl-4H-dibenzo [de,g]quinolin-1-ol (**8c**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, J=9.5 Hz, 1H), 7.69 (d, J=8.5 Hz, 2H), 3.00 (t, J=14.0 Hz, 1H), 7.32–7.29 (m, 2H), 7.24 (d, J=8.5 Hz, 2H), 6.85 (d, J=8.0 Hz, 1H), 6.69 (d, J=8.0 Hz, 1H), 5.19 (s, 1H), 4.64 (dd, J=14.0, 4.5 Hz, 1H), 4.11–4.07 (m, 1H), 3.25–3.19 (m, 1H), 3.14–3.10 (m, 1H), 2.48–2.44 (m, 1H), 2.38 (s, 3H), 2.35–2.31 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.4, 143.6, 138.4, 138.1, 134.0, 133.1, 130.1, 129.3, 129.1, 128.7, 127.3, 127.1, 126.0, 120.5, 116.2, 53.4, 41.2, 37.4, 28.3, 21.7. HRMS (MALDI-TOF) $C_{23}H_{20}ClNNaO_3S$ $[M+Na]^+$: 448.0745; found: 448.0762.

*4.6.4. 4,5,6,6a,7,8-Hexahydro-6-p-toluenesulfonyl-benzo [6,7] cyclohept[1,2,3-ij] isoquinoline-1-ol (**8d**).* ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (d, J=8.0 Hz, 2H), 7.37–7.44 (m, 4H), 7.11 (d, J=8.0 Hz, 2H), 6.88–6.84 (m, 2H), 5.26 (s, 1H), 4.63 (dd, J=11.0, 6.5 Hz, 1H), 3.95–3.90 (m, 1H), 3.45–3.39 (m, 1H), 2.68–2.61 (m, 1H), 2.58–2.5 (m, 2H), 2.45–2.38 (m, 2H), 2.34 (s, 3H), 2.24–2.18 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.0, 143.2, 140.5, 138.2, 133.4, 130.0, 129.8, 129.6, 129.3, 128.1, 127.7, 127.0, 124.4, 115.1, 52.9, 38.9, 38.4, 30.5, 27.1, 21.6. HRMS (MALDI-TOF) $C_{24}H_{23}NNaO_3S$ $[M+Na]^+$: 428.1291; found: 428.1302.

*4.6.5. 5,6,6a,7-Tetrahydro-6-p-toluenesulfonyl-4H-dibenzo [de,g]quinolin-3-ol (**8e**).* ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, J=8.5 Hz, 2H), 7.66 (d, J=8.0 Hz), 7.47 (d, 1H, J=8.0 Hz), 7.33–7.28 (m, 2H), 7.25–7.22 (m, 3H), 6.71 (d, 1H, J=8.5 Hz, 1H), 4.77 (dd, J=14.0, 5.0 Hz, 1H), 4.70 (s, 1H), 4.17–4.13 (m, 1H), 3.30–3.23 (m, 2H), 3.09 (t, J=14.0 Hz, 1H), 2.76–2.72 (m, 1H), 2.38 (s, 3H), 2.16–2.10 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 152.3, 143.6, 138.1, 134.7, 133.9, 133.5, 130.1, 129.2, 127.8, 127.5, 127.1, 123.4, 123.1, 121.1, 113.6, 53.3, 40.8, 37.1, 22.2, 21.7. HRMS (MALDI-TOF) $C_{23}H_{21}NNaO_3S$ $[M+]^+$: 414.1134; found: 414.1142.

*4.6.6. 1,2-Dimethoxy-5,6,6a,7-tetrahydro-6-p-toluenesulfonyl-4H-dibenzo[de,g] quinolin-3-ol (**8f**).* ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (d, *J*=8.0 Hz, 1H), 7.69 (d, *J*=8.5 Hz, 2H), 7.32–7.28 (m, 2H), 7.24–7.20 (m, 3H), 5.83 (s, 1H), 4.58 (dd, *J*=14.0, 4.5 Hz, 1H), 4.12–4.08 (m, 1H), 3.96 (s, 3H), 3.68 (s, 3H), 3.26–3.20 (m, 1H), 3.14–3.11 (m, 1H), 3.02 (t, *J*=14.0 Hz, 1H), 2.77–2.73 (m, 1H), 2.38 (s, 3H), 2.14–2.07 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.3, 145.9, 143.4, 139.0, 138.2, 135.9, 131.7, 130.1, 129.5, 128.7, 127.6, 127.2, 127.1, 120.1, 116.3, 61.2, 60.3, 53.4, 40.5, 37.7, 22.1, 21.7. HRMS (MALDI-TOF) $C_{25}H_{25}NNaO_5S$ $[M+Na]^+$: 474.1346; found: 474.1353.

4.7. Synthesis of (−)-lirinine

*4.7.1. 2-(2-(Benzyloxy)-3,4-dimethoxyphenyl)acetaldehyde (**10**)*[26]. A solution under argon of methoxymethyl-triphenylphosphonium chloride (3.50 g, 9.9 mmol) in dry THF (12 mL) at 0 °C was treated dropwise with KO^{t}Bu (1 M in THF, 9.9 mL, 9.9 mmol). The resultant mixture was allowed to warm to room temperature and stirred for 30 min, then treated with a solution of benzaldehyde **9** (1.29 g, 4.7 mmol) in dry THF (6 mL) and stirred at room temperature under argon for 14 h. The reaction was quenched by the addition of brine (10 mL), extracted with EtOAc (3×20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel using 0–10% EtOAc in cyclohexane to afford the enol ether (1.41 g, 4.7 mmol, 100%) as a pale yellow solid.

The enol ether (1.41 g, 4.7 mmol) was dissolved in acetone (10 mL) and cooled at 0 °C, then treated with a solution HCl (6 N, 10 mL). The resultant mixture was stirred for 1 h at room temperature, extracted with EtOAc (4×30 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel using 0–10% EtOAc in cyclohexane to afford **10** (1.13 g, 3.94 mmol, 83%) as a moderately unstable colorless oil (stored under argon at 0 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.54 (t, *J*=2.0 Hz, 1H), 7.41–7.31 (m, 5H), 6.81 (d, *J*=8.5 Hz, 1H), 6.68 (d, *J*=8.5 Hz, 1H), 5.08 (s, 2H), 3.90 (s, 3H), 3.88 (s, 3H), 3.51 (d, *J*=2.0 Hz, 2H).

*4.7.2. (R)-N-2-(2-(Benzyloxy)-3,4-dimethoxyphenyl)ethyl-idene]-p-toluene sulfinamide (**13**).* To a solution of acetaldehyde **10** (1.02 g, 3.56 mmol) in CH_2Cl_2 (35 mL) under argon was added sulfinamide **12** (553 mg, 3.56 mmol) and $Ti(OEt)_4$ (3.73 mL, 17.81 mmol). The reaction mixture was refluxed 4 h, and then cooled to 0 °C and quenched with H_2O (10 mL). The turbid solution was filtered through Celite, and the filter cake was washed with CH_2Cl_2 (2×10 mL). The phases were separated and the aqueous layer was washed with CH_2Cl_2 (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by chromatography on silica gel using 0–20% EtOAc in cyclohexane to afford **13** (1.03 g, 2.44 mmol, 69%) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (t, *J*=5.0 Hz, 1H), 7.51 (d, *J*=8.0 Hz, 2H), 7.35–7.30 (m, 5H), 7.24 (d, *J*=8.0 Hz, 2H), 6.79 (d, *J*=8.5 Hz, 1H), 6.64 (d, *J*=8.5 Hz, 1H), 4.98 (s, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.65 (t, *J*=5.0 Hz, 1H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.3, 150.9, 142.6, 141.7, 141.6, 137.5, 129.7, 128.4, 128.2, 128.0, 124.8, 124.6, 121.2, 107.6, 75.2, 60.9, 56.1, 36.6, 21.4. HRMS (MALDI-TOF) $C_{24}H_{26}NO_4S$ $[M+H]^+$: 424.1577; found: 424.1593. $[\alpha]_D^{20}$ +229 (*c* 0.3, $CHCl_3$).

*4.7.3. (R)-N-2-(2-(Benzyloxy)-3,4-dimethoxyphenyl)ethyl]-p-toluene sulfinamide (**14**).* To a solution of **13** (100 mg, 0.24 mmol) in CH_3OH (2 mL) under argon at 0 °C was added sodium borohydride (18 mg, 0.47 mmol). After stirring for 30 min, acetone (2 mL) was added and the reaction was stirred another 5 min. The solvent was removed in vacuo and the residue was dissolved in EtOAc (10 mL), washed with water (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by chromatography on silica gel using 10–30% EtOAc in cyclohexane to afford **14** (80 mg, 0.19 mmol, 80%) as a thick pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, *J*=8.0 Hz, 2H), 7.42–7.31 (m, 5H), 7.23 (d, *J*=8.0 Hz, 2H), 6.79 (d, *J*=8.5 Hz, 1H), 6.62 (d, *J*=8.5 Hz, 1H), 5.05–4.99 (m, 2H), 4.08 (t, *J*=6.0 Hz, 1H), 3.86 (s, 6H), 3.30–3.24 (m, 1H), 2.99–2.92 (m, 1H), 2.70 (t, *J*=7.0 Hz, 2H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.9, 151.1, 142.7, 141.5, 141.2, 137.9, 130.3, 129.7, 128.7, 128.3, 128.2, 126.2, 125.0, 124.8, 124.7, 107.7, 75.4, 61.1, 56.3, 41.8, 31.2, 21.5. HRMS (MALDI-TOF) $C_{24}H_{27}NNaO_4S$ $[M+Na]^+$: 448.1559; found: 448.1574. $[\alpha]_D^{20}$ +41.5 (*c* 0.2, $CHCl_3$).

*4.7.4. (+)-1-(2-Bromobenzyl)-5-benzyloxy-6,7-dimethoxy-2-p-toluenesulfinyl-1,2,3,4-tetrahydroisoquinoline (**15**).* A solution of **14** (185 mg, 0.43 mmol) and aldehyde **5a** (173 mg, 0.87 mmol) in dry CH_2Cl_2 (4 mL) under argon was cooled to −78 °C. $BF_3{\cdot}Et_2O$ (110 μL, 0.87 mmol) was added, and the reaction mixture was stirred at −78 °C for 18 h. The reaction was quenched with triethylamine (121 μL, 0.87 mmol), and then the solvent was removed in vacuo. The residue was purified by chromatography on silica gel using 10–40% EtOAc in cyclohexane to give **15** (139 mg, 0.23 mmol, 53%) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, *J*=8.5 Hz, 2H), 7.40–7.31 (m, 4H), 7.24 (d, *J*=8.5 Hz, 2H), 7.16 (ddd, *J*=7.5, 7.5, 1.5 Hz, 1H), 7.09–7.03 (m, 3H), 6.89 (dd, 1H, *J*=7.5, 1.5 Hz), 6.09 (s, 1H), 5.04 (s, 2H), 4.74 (t, *J*=7.0 Hz, 1H), 3.85 (s, 3H), 3.72–3.64 (m, 2H), 3.62 (s, 3H), 3.15–3.04 (m, 2H), 2.79–2.76 (m, 2H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.1, 141.1, 140.8, 140.2, 138.1, 137.7, 133.0, 132.7, 129.6, 128.6, 128.4, 128.2, 127.3, 126.0, 125.4, 120.6, 106.2, 74.8, 61.1, 55.8, 55.0, 43.7, 41.3, 23.5, 21.6. HRMS (MALDI-TOF) $C_{32}H_{32}BrNNaO_4S$ $[M+Na]^+$: 628.1128; found: 628.1147. $[\alpha]_D^{20}$ +51.0 (*c* 0.2, $CHCl_3$).

*4.7.5. (R)-1-(2-Bromobenzyl)-5-benzyloxy-6,7-dimethoxy-2-p-toluenesulfonyl-1,2,3,4-tetrahydroisoquinoline (**16**).* To a solution of **15** (130 mg, 0.21 mmol) in dry CH_2Cl_2 (3 mL) under argon at 0 °C was added *m*-CPBA (71 mg, 0.32 mmol), and the reaction mixture was stirred at this temperature for 1 h. Next, a solution of saturated aqueous $NaHCO_3$ (3 mL) was added and the resulting solution was vigorously stirred for 30 min. The reaction mixture was diluted with CH_2Cl_2 (10 mL). The organic phase was separated, washed with H_2O (5 mL), brine (5 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography on silica gel using 10–40% EtOAc in cyclohexane to give **16** (132 mg, 0.21 mmol, 99%) as a white solid. ^{1}HH NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J*=7.5 Hz, 1H), 7.45 (d, *J*=8.5 Hz, 2H), 7.39–7.31 (m, 5H), 7.20 (ddd, *J*=7.5, 7.5, 1.0 Hz, 1H), 7.10 (d, *J*=7.5 Hz, 2H), 7.06 (d, *J*=8.5 Hz, 2H), 6.15 (s, 1H), 5.20 (t, *J*=7.5 Hz, 1H), 4.87 (AB, 2H, *J*=108.0, 11.0 Hz, 2H), 3.83 (s, 3H), 3.82–3.77 (m, 1H), 3.66 (s, 3H), 3.54–3.47 (m, 1H), 3.17 (d, *J*=7.5 Hz, 2H), 2.59–2.46 (m, 2H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.7, 150.0, 143.1, 141.3, 137.8, 137.5, 132.9, 132.4, 131.0, 129.5, 128.5, 128.3, 127.6, 127.4, 125.5, 120.2, 106.4, 74.9, 61.1, 56.3, 56.0, 43.4, 39.1, 21.6. HRMS (MALDI-TOF) $C_{32}H_{32}BrNNaO_5S$ $[M+Na]^+$: 644.1077; found: 644.1089. $[\alpha]_D^{20}$ −70.3 (*c* 0.3, $CHCl_3$).

*4.7.6. (R)-1-(2-Bromobenzyl)-6,7-dimethoxy-2-p-toluenesulfonyl-1,2,3,4-tetrahydroisoquinolin-5-ol [(R)-**6f**].* To a solution of **16** (180 mg, 0.29 mmol) in DME (2 mL) was added dropwise concd HCl (2 mL). The mixture was heated to 80 °C for 1 h. After cooling, the reaction mixture was poured in a saturated solution of $NaHCO_3$ (10 mL), extracted with EtOAc (2×10 mL). The organic layers were

combined, washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography on silica gel using 10–30% EtOAc in cyclohexane gave (*R*)-**6f** (98 mg, 0.18 mmol, 64%) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (dd, 1H, *J*=8.0, 1.0 Hz), 7.43 (d, *J*=8.0 Hz, 2H), 7.19 (dt, *J*=7.5, 1.0 Hz, 1H), 7.12–7.07 (m, 2H), 7.05 (d, *J*=8.0 Hz, 2H), 6.01 (s, 1H), 5.74 (s, 1H), 5.22 (t, *J*=8.0 Hz, 1H), 3.99–3.91 (m, 1H), 3.85 (s, 3H), 3.67 (s, 3H), 3.60–3.51 (m, 1H), 3.21–3.12 (m, 2H), 2.62–2.51 (m, 2H), 2.33 (s, 3H). $[\alpha]_D^{20}$ −129 (*c* 0.3, $CHCl_3$).

*4.7.7. (R)-1,2-Dimethoxy-5,6,6a,7-tetrahydro-6-p-toluenesulfonyl-4H-dibenzo[de,g] quinolin-3-ol [(R)-**8f**].* A reaction tube was charged with (*R*)-**6f** (53 mg, 0.1 mmol), Xphos precatalyst (7.4 mg, 0.01 mmol), Cs_2CO_3 (97 mg, 0.3 mmol). The tube was evacuated and backfilled with argon (three times), and then dry DMA (1 mL/0.1 mmol of starting material) was added. The mixture was sparged with argon for 5 min and then heated at 110 °C for 1 h. The reaction mixture was allowed to cool, and then quenched with 1 N HCl (5 mL), extracted with ethyl acetate (3×10 mL). The organic extracts were combined, washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography on silica gel using CH_2Cl_2/cyclohexane/EtOAc (60/35/5) to give (*R*)-**8f** (44 mg, 0.097 mmol, 98%) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (d, *J*=8.0 Hz, 1H), 7.69 (d, *J*=8.5 Hz, 2H), 7.32–7.27 (m, 2H), 7.24–7.20 (m, 3H), 5.83 (s, 1H), 4.59 (dd, *J*=14.0, 4.5 Hz, 1H), 4.12–4.07 (m, 1H), 3.96 (s, 3H), 3.68 (s, 3H), 3.26–3.19 (m, 1H), 3.14–3.10 (m, 1H), 3.02 (t, *J*=14.0 Hz, 1H), 2.77–2.72 (m, 1H), 2.38 (s, 3H), 2.14–2.06 (m, 1H). $[\alpha]_D^{20}$ −238 (*c* 0.3, $CHCl_3$).

*4.7.8. (R)-1,2-Dimethoxy-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinolin-3-ol (**17**).* A solution of sodium naphthalenide in DME was prepared by adding DME (5 mL) to a mixture of sodium (150 mg, 6.5 mmol) and naphthalene (1.1 g, 8.6 mmol) and stirring the resulting mixture at room temperature for 2 h. A solution of tosylamide (*R*)-**8f** (45 mg, 0.1 mmol) in dry DME (2 mL) was cooled in a dry ice-isopropyl alcohol bath. The sodium naphthalenide solution was added dropwise to the well-stirring tosylamide solution until a light green color persisted. The reaction was quenched by addition of saturated $NaHCO_3$ (100 μL). Anhydrous K_2CO_3 (547 mg) was added, and the mixture was stirred for 24 h. The mixture was filtered and the precipitates were rinsed with ether (3×10 mL). The combined filtrates were concentrated under reduced pressure. The residue was purified by chromatography on silica gel and eluted with 5% 2 M NH_3 in MeOH in CH_2Cl_2 to give **17** (28 mg, 0.094 mmol, 94%) as a pale yellow solid. The %ee was determined to be 89%.[16] ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.98 (s, 1H), 8.08 (d, *J*=8.0 Hz, 1H), 7.26–7.20 (m, 2H), 7.13 (ddd, *J*=8.0, 8.0, 1.0 Hz, 1H), 3.76 (s, 3H), 3.65 (s, 3H), 3.52 (dd, *J*=14, 4.5 Hz, 1H), 3.25–3.16 (m, 2H), 2.76–2.67 (m, 2H), 2.58–2.54 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7, 146.5, 138.6, 135.4, 133.1, 132.4, 127.7, 127.3, 126.9, 126.4, 118.5, 116.2, 61.1, 60.3, 54.0, 42.8, 37.4, 23.6. HRMS (MALDI-TOF) $C_{18}H_{20}NO_3$ $[M+H]^+$: 298.1438; found: 298.1439. $[\alpha]_D^{20}$ −35.0 (*c* 0.1, $CHCl_3$).

4.7.9. (R)-1,2-Dimethoxy-5,6,6a,7-tetrahydro-6-methyl-4H-dibenzo [de,g]quinolin-3-ol; (−)-lirinine. Into a round bottom flask was added **17** (15 mg, 0.05 mmol), MeOH (1 mL) and CH_2O 37% in water (10 drops). The solution was stirred at room temperature for 30 min and then $NaBH_4$ (38 mg, 1 mmol) was added. Stirring was continued for another hour at room temperature. The reaction mixture was concentrated, dissolved in water (5 mL), and extracted with EtOAc (3×10 mL). The organic layers were combined, washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by chromatography on silica gel and eluted using 3% 2 M NH_3 in MeOH in CH_2Cl_2 to give (−)-lirinine (15 mg, 0.048 mmol, 95%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, *J*=8.0 Hz, 1H), 7.28 (ddd, *J*=8.0, 7.5, 1.0 Hz, 1H), 7.24 (d, *J*=7.5 Hz, 1H), 7.18 (ddd, *J*=7.5, 7.5, 1.0 Hz, 1H), 5.86 (br, 1H), 3.98 (s, 3H), 3.72 (s, 3H), 3.11–3.08 (m, 2H), 3.01 (dd, *J*=13.5, 3.0 Hz, 1H), 2.92–2.88 (m, 1H), 2.78 (dd, *J*=17.0, 4.0 Hz, 1H), 2.60 (t, *J*=13.5 Hz, 1H), 2.55 (s, 3H), 2.45 (ddd, *J*=12.0, 12.0, 4.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7, 146.0, 138.5, 135.6, 132.2, 127.8, 127.3, 126.9, 126.4, 118.9, 116.0, 62.6, 61.1, 60.3, 52.9, 44.0, 34.8, 23.3. HRMS (MALDI-TOF) $C_{19}H_{22}NO_3$ $[M+H]^+$: 312.1594; found: 312.1598. $[\alpha]_D^{20}$ −52.0 (*c* 0.1, $CHCl_3$), [lit.[11f] −83.7 (*c* 1.0, $CHCl_3$)].

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Supplementary data

Description of the general experimental procedures and NMR spectra of the compounds is provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.12.022.

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