Transition-Metal-Free Arylation of *N*-Alkyl-tetrahydroisoquinolines under Oxidative Conditions: A Convenient Synthesis of C1-Arylated Tetrahydroisoquinoline Alkaloids

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Abstract: A simple protocol for the C1 arylation of tetrahydroisoquinolines with aryl Grignard reagents via diethyl azodicarboxylate (DEAD) mediated oxidative C–H activation under metal-free conditions has been developed. The target compounds, including some naturally occurring alkaloids, were obtained in moderate to good yields.

Key words: arylation, tetrahydroisoquinoline, C–H activation, alkaloids, metal-free

The tetrahydroisoquinoline motif forms the basic framework of many naturally occurring alkaloids of pharmaceutical importance.[1] In particular, 1-aryl-1,2,3,4-tetrahydroisoquinolines are of wide biological significance as they exhibit anti-HIV,[2a,b] antitumor,[2c,d] and antibacterial activity.[2e] Various analogues of C1-arylated tetrahydroisoquinolines (Figure 1) act as dopamine D_1 like receptor antagonists[3a,b] and they are neuroprotective agents for the treatment of Alzheimer's and Parkinson's type diseases.[3c,d] Solifenacin (Figure 1) has been investigated as a bladder-selective muscarinic M_3 receptor antagonist.[4] Other naturally occurring alkaloids such as cryptostylines I, II, and III (Figure 1) belong to this family and show interesting pharmacological properties.[5] The synthesis of 1-aryl-tetrahydroisoquinolines is an attractive area of research due to their applicability in the areas of pharmaceutics and medicine. Earlier reported methods for the synthesis of 1-aryl-tetrahydroisoquinolines include Pictet–Spengler condensation,[6] Bischler–Napieralski cyclization,[7] and a modified Pummerer reaction.[8] Apart from these common procedures, a number of other methods have also been developed.[9]

In the recent past, direct C–H bond activation under oxidative conditions has attracted much attention as it provides efficient routes for the synthesis of biologically active natural products.[10] Enormous efforts have been made for the modification of known methods and to develop new procedures for the synthesis of C–H arylated heterocyclic compounds.[11] Metal-catalyzed arylation of (un)protected tetrahydroisoquinolines at C1 has been demonstrated by Schnürch and co-workers using *tert*-butyl hydroperoxide (TBHP) as an oxidant.[11d] Li and co-workers have used copper salts as catalysts to couple 2-phenyl-1,2,3,4-tetrahydroisoquinolines and other N-protected tetrahydroisoquinolines with indole,[12a–d] 2-naphthol,[12e] and arylboronic acids.[12f] One drawback here is that removal of the phenyl group from the nitrogen is difficult and further functionalization cannot be pursued.[13] Klussmann and Schweitzer-Chaput described a two-step *tert*-butyl hydroperoxide mediated C1 arylation of *N*-Cbz-, *N*-Boc-, and *N*-benzyl-protected tetrahydroisoquinolines catalyzed by a Brønsted acid.[14] A one-step C1 arylation of *N*-Cbz-protected tetrahydroisoquinolines using triphenylcarbenium perchlorate has been achieved by Xie et al.[15] It was also noted that such arylation reactions did not succeed with *N*-methyl-tetrahydroisoquinoline and only overoxidation products were detected.[14] Recently Li and co-workers reported α-sp^3 C–H arylation reactions of *N*-

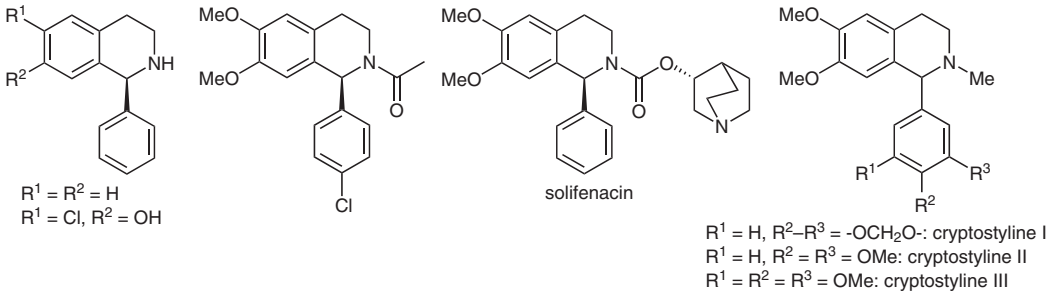

Figure 1 C1-Arylated tetrahydroisoquinolines

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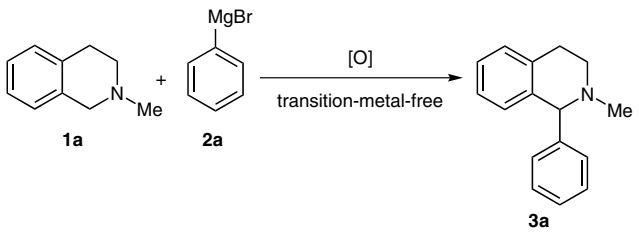
(4-methoxyphenyl) (*N*-PMP) and benzyl-protected tetrahydroisoquinolines using aryl Grignard reagents in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or hypervalent iodine(III) as oxidants under metal-free conditions.[16a,b] The latest report describes the arylation of *N*-carbamoyl-protected tetrahydroisoquinolines using sodium persulfate.[16c] In all these reports, *N*-aryl-tetrahydroisoquinolines or N-protected tetrahydroisoquinolines were used as substrates and, therefore, these procedures could not be used for the one-step synthesis of α-arylated *N*-methyl-tetrahydroisoquinolines. Some other related coupling reactions of tertiary amines with different nucleophiles have also been reported.[17]

We recently reported our findings on the direct arylation of a C–H bond in *N*-methyl-tetrahydroisoquinolines involving the reactions of amino carbanions[18] with in situ generated benzyne intermediates.[19] In continuation of our interest in exploring new oxidative coupling reactions, involving dithiolanes with ketones and indoles,[20a] formamides with diphenyl diselenides,[20b] and our earlier finding on the use of readily available diethyl azodicarboxylate as a suitable oxidant in the regioselective alkynylation of *N*-methyl-tetrahydroisoquinolines[20c] or unactivated aliphatic tertiary amines,[21] the direct coupling of the α-position in *N*-alkyl tetrahydroisoquinolines with aryl Grignard reagents in the presence of diethyl azodicarboxylate seemed a viable option. This article describes the outcome of these investigations, which also resulted in a convenient and direct route for the synthesis of 2-alkyl-1-aryl-1,2,3,4-tetrahydroisoquinolines under transition-metal-free conditions.

Initially, we reacted 2-methyl-1,2,3,4-tetrahydroisoquinoline (**1a**) with phenylmagnesium bromide (2 equiv) using diethyl azodicarboxylate (1.1 equiv) in tetrahydrofuran at room temperature for two hours under a nitrogen atmosphere. The desired product 2-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**3a**) was obtained in 20% yield (Table 1, entry 1). Use of four and six equivalents of Grignard reagent increased the yield of **3a** to 42% and 65%, respectively (entries 2 and 3). A further increase in the amount of the Grignard reagent to eight equivalents did not improve the yield (entry 4). Solvents like *N*,*N*-dimethylformamide and toluene gave inferior results (entries 5 and 6) while in case of chloroform and diethyl ether **3a** was obtained in 60–62% yield (entries 7 and 8). Among the other oxidants which were investigated, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone[22] afforded the product in 22% yield (entry 9) while cerium ammonium nitrate (CAN) and 3-chloroperoxybenzoic acid, were ineffective (entries 10 and 11). With the *tert*-butyl hydroperoxide/iodine[23] system, the arylation reaction occurred to a lesser extent (entry 12). Increasing the reaction time did not improve the yield of **3a** (entry 13), but decreasing the reaction time somewhat lowered the yield (entry 14). No improvement in the yield of **3a** was observed with the use of copper(I) iodide as a catalyst (entry 16). Using a higher reaction temperature did not affect the reaction (entry 15). The use of 0.5 equivalents of diethyl azodicarboxylate decreased the product yield as expected, (entry 17). Increasing the amount of oxidant to 2.2 equivalents only marginally changed the yield of **3a** (entry 18). Surprisingly, further increase in the amount of the oxidant to 3.3 equivalents depressed the yield (entry 19). Thus, the optimized conditions for the coupling of **1a** used 6 equivalents of Grignard's reagent in tetrahydrofuran using diethyl

Table 1 Optimization of Reaction Conditions[a]

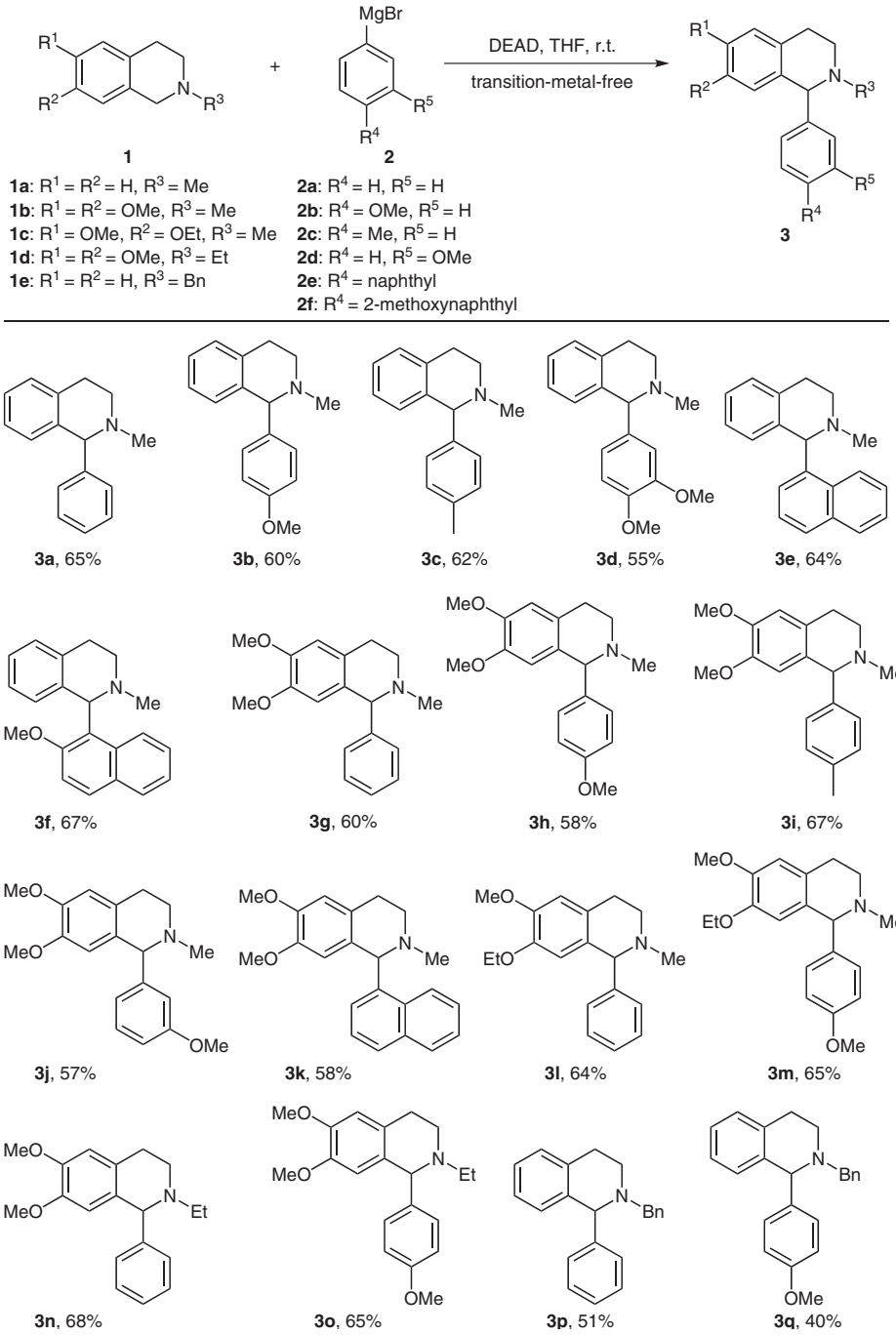


Entry	Grignard (equiv)	Oxidant	Solvent	Yield[b] (%)
1	2	DEAD	THF	20
2	4	DEAD	THF	42
3	6	DEAD	THF	65
4	8	DEAD	THF	64
5[c]	6	DEAD	DMF	48
6[c]	6	DEAD	toluene	56
7[c]	6	DEAD	$CHCl_3$	60
8	6	DEAD	Et_2O	62
9	6	DDQ	THF	22
10	6	CAN	THF	trace
11	6	MCPBA	THF	trace
12	6	TBHP/I_2	THF	28
13[d]	6	DEAD	THF	64
14[e]	6	DEAD	THF	60
15[f]	6	DEAD	THF	66
16[g]	6	DEAD	THF	65
17[h]	6	DEAD	THF	35
18[i]	6	DEAD	THF	66
19[j]	6	DEAD	THF	40

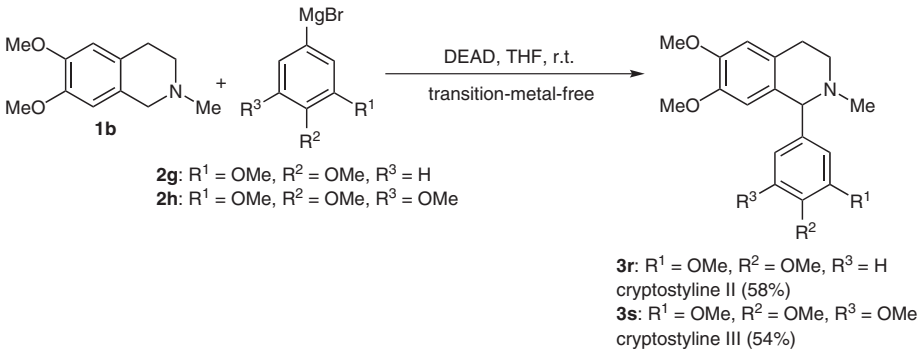
[a] Reaction conditions: **1a** (1 equiv), oxidant (1.1 equiv), solvent (2 mL), r.t., 2 h.
[b] Isolated yield.
[c] The Grignard reagent was prepared in THF and the iminium cation was generated in DMF, toluene or $CHCl_3$.
[d] 3 h.
[e] 1 h.
[f] Refluxing THF.
[g] CuI (5 mol%) was used as a catalyst.
[h] DEAD (0.5 equiv).
[i] DEAD (2.2 equiv).
[j] DEAD (3.3 equiv).

azodicarboxylate as the oxidant and without the use of a metal salt (entry 3).

To investigate the scope and generality of the reaction, various arylmagnesium bromides were reacted with differently substituted *N*-methyl-tetrahydroisoquinolines under the optimized conditions. Tetrahydroisoquinolines **1a**–**c** coupled well with Grignard reagents **2a**–**f** to give the desired products **3a**–**m** in moderate to good yields (55–67%) (Scheme 1). The reaction tolerated methoxy/methyl substituents on the phenyl rings of the coupling partners. Even *meta*-substituted aryl Grignard reagent **2d** worked well to afford **3j** in 57% yield. 1-Naphthylmagnesium bromide (**2e**) and 2-methoxy-1-naphthylmagnesium bromide (**2f**) also coupled effectively to give the corresponding products **3e**,**f**,**k** in 58–67% yields. 2-Ethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**1d**) was also evaluated and the C1-arylated products **3n**,**o** were obtained in good yields. However, 2-benzyl-1,2,3,4-tetrahydroisoquinoline (**1e**) coupled to a lesser extent with **2a** and **2b** to furnish the products **3p** and **3q** in 51% and 40% yields, respectively.



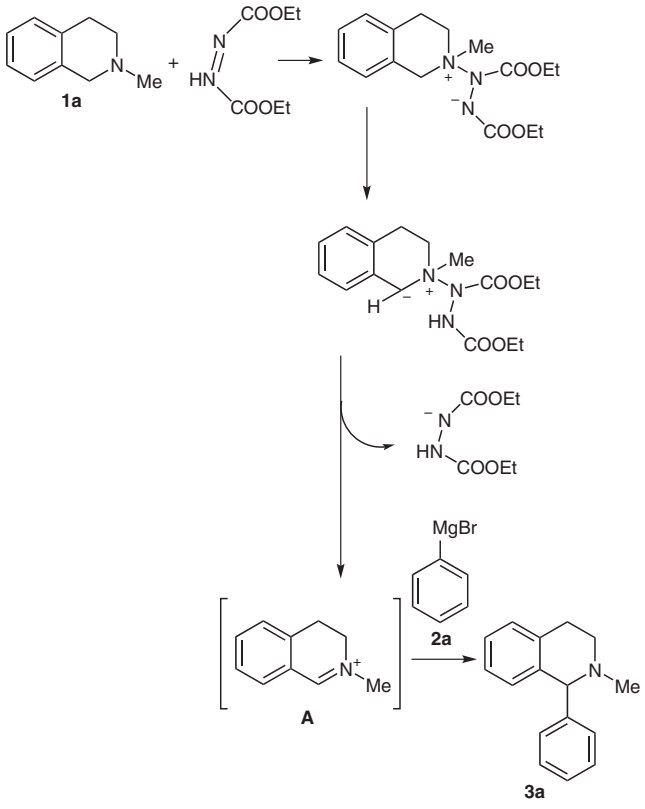
Scheme 1 Substrate scope in oxidative C1 arylation of tetrahydroisoquinoline with Grignard reagents. *Reagents and conditions*: **1a** (1 equiv), DEAD (1.1 equiv), aryl Grignard reagent (6 equiv), THF (2 mL), r.t., 2 h; isolated yield based on **1**.



Scheme 2 Synthesis of cryptostyline alkaloids

With the aim of demonstrating the utility of this procedure for the synthesis of naturally occurring alkaloids, we applied these metal-free conditions to the synthesis of cryptostyline II (**3r**) and cryptostyline III (**3s**). The coupling of **1b** with **2g** and **2h** afforded the products **3r** and **3s** in 58% and 54% yield, respectively (Scheme 2).

This arylation procedure may be compared with that described by Costa and Radesca in which they used triphenylcarbenium tetrafluoroborate to generate iminium cation for further reaction with Grignard reagent.[9b,24] It may be pointed out that triphenylcarbenium tetrafluoroborate is a corrosive and air-sensitive reagent that requires very careful handling. Furthermore, the yields of the products are significantly lower in many cases using this reagent.[9b]



Scheme 3 Plausible mechanism

A plausible mechanism for the coupling of **1a** and **2a** is depicted in Scheme 3. As already established,[14,20c,21,25] iminium ion **A** is formed during oxidation of tetrahydroisoquinoline with diethyl azodicarboxylate. Subsequent attack of the nucleophile **2a** on iminium ion **A** furnishes the arylated product **3a**.

In summary, a direct and convenient procedure for the synthesis of 1-aryl-2-methyl-tetrahydroisoquinoline via oxidative coupling of *N*-alkyltetrahydroisoquinolines and Grignard reagents using diethyl azodicarboxylate under metal-free conditions has been developed. Moreover, the synthesis of naturally occurring alkaloids cryptostyline II and III has also been achieved.

Melting points were taken in open capillaries and are uncorrected. ^{1}H NMR spectra were recorded on Bruker 400 MHz spectrometer in $CDCl_3$ solution relative to internal standard TMS. ^{13}C NMR spectra were obtained at 100 MHz and referenced to the internal solvent signals (δ = 77.00). MS and HRMS data were obtained on Q-Tof Micro™ Mass Spectrometer. Differently substituted starting amines were prepared according to literature procedure.[26] Products were isolated and purified by column chromatography (silica gel, hexane–EtOAc).

2-Methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (3a);[7e,27]
Typical Procedure

To a flame-dried two-necked round-bottom flask, charged with 1-methyl-1,2,3,4-tetrahydroisoquinoline (**1a**, 0.2 mL, 1.36 mmol) in THF (2 mL) was added DEAD (0.267 mL, 1.49 mmol) dropwise at 5–10 °C and the mixture was stirred for 15 min under N_2. To this was added phenylmagnesium bromide (**2a**, 8.16 mmol) in THF slowly and the mixture was stirred at r.t. for 2 h. The reaction was quenched with 10% HCl (20–25 mL), basified with Na_2CO_3, and extracted with EtOAc (2 × 25 mL). The solvent was evaporated and the residue was purified by column chromatography (silica gel, 230–400 mesh, EtOAc–hexane) to afford **3a** (197 mg, 65%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$–CCl_4): δ = 7.23–7.16 (m, 5 H), 7.01–6.85 (m, 3 H), 6.53 (d, *J* = 7.8 Hz, 1 H), 4.13 (s, 1 H), 3.19–3.01 (m, 2 H), 2.76–2.52 (m, 2 H), 2.14 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$–CCl_4): δ = 144.0, 138.5, 134.1, 129.7, 128.6, 128.3, 127.3, 125.9, 125.7, 71.6, 52.4, 44.4, 29.6.

1-(4-Methoxyphenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (3b)
Yellow solid; yield: 206 mg (60%); mp 76–78 °C (Lit.[19b] 78–80 °C).

^{1}H NMR (400 MHz, $CDCl_3$–CCl_4): δ = 7.09–7.05 (m, 2 H), 7.00–6.95 (m, 2 H), 6.89–6.85 (m, 1 H), 6.75–6.71 (m, 2 H), 6.54 (d, *J* = 7.8 Hz, 1 H), 4.08 (s, 1 H), 3.71 (s, 3 H), 3.21–3.12 (m, 1 H), 3.04–2.99 (m, 1 H), 2.74–2.69 (m, 1 H), 2.56–2.50 (m, 1 H), 2.13 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$–CCl_4): δ = 158.8, 138.8, 135.9, 134.1, 130.5, 128.5, 128.2, 125.8, 125.6, 113.5, 70.9, 55.0, 52.4, 44.3, 29.5.

2-Methyl-1-(*p*-tolyl)-1,2,3,4-tetrahydroisoquinoline (3c)
Yellow oil; yield: 200 mg (62%).

^{1}H NMR (400 MHz, $CDCl_3$–CCl_4): δ = 7.13–7.02 (m, 6 H), 6.95–6.91 (m, 1 H), 6.60 (d, *J* = 7.8 Hz, 1 H), 4.17 (s, 1 H), 3.29–3.21 (m, 1 H), 3.12–3.08 (m, 1 H), 2.82–2.77 (m, 1 H), 2.64–2.58 (m, 1 H), 2.33 (s, 3 H), 2.21 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$–CCl_4): δ = 140.8, 138.6, 136.6, 134.0, 129.9, 129.5, 128.9, 128.5, 128.2, 125.8, 125.6, 71.2, 52.3, 44.3, 29.5, 21.2.

HRMS (ES^+): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{20}N$: 237.1517; found: 238.1564.

1-(3,4-Dimethoxyphenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (3d)[19b]
Yellow solid; yield: 211 mg (55%); mp 76–78 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.05–7.01 (m, 2 H), 6.94–6.89 (m, 1 H), 6.79–6.70 (m, 3 H), 6.60 (d, *J* = 7.8 Hz, 1 H), 4.11 (s, 1 H), 3.81 (s, 3 H), 3.74 (s, 3 H), 3.24–3.17 (m, 1 H), 3.11–3.06 (m, 1 H), 2.77–2.53 (m, 2 H), 2.18 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.0, 148.2, 134.0, 131.4, 128.3, 128.2, 125.9, 125.6, 122.1, 111.8, 110.2, 71.4, 55.8, 55.7, 52.5, 44.3, 29.3.

2-Methyl-1-(naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline (3e)
Yellow solid; yield: 237 mg (64%); mp 111–112 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 8.5 Hz, 1 H), 7.72 (t, *J* = 8.7 Hz, 2 H), 7.39–7.21 (m, 4 H), 7.09 (t, *J* = 8.8 Hz, 1 H), 6.98 (t, *J* = 7.4 Hz, 1 H), 6.77 (t, *J* = 7.5 Hz, 1 H), 6.47 (d, *J* = 7.8 Hz, 1 H), 4.70 (s, 1 H), 3.37–3.28 (m, 1 H), 3.17–3.12 (m, 1 H), 2.83–2.79 (m, 1 H), 2.64–2.57 (m, 1 H), 2.09 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.0, 138.6, 134.3, 133.8, 131.6, 128.9, 128.4, 128.3, 128.2, 127.4, 125.9, 125.8, 125.5, 125.3, 125.0, 53.3, 44.5, 29.3.

HRMS (ES^+): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{20}N$: 273.1517; found: 274.1534.

1-(2-Methoxynaphthalen-1-yl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (3f)[28]
Yellow solid; yield: 138 mg (67%); mp 107–108 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 7.3 Hz, 1 H), 7.72–7.60 (m, 2 H), 7.24 (d, *J* = 9.1 Hz, 1 H), 7.13–7.05 (m, 3 H), 6.96 (t, *J* = 7.3 Hz, 1 H), 6.76 (t, *J* = 7.5 Hz, 1 H), 6.42 (d, *J* = 7.8 Hz, 1 H), 5.37 (s, 1 H), 3.89 (s, 3 H), 3.45–3.37 (m, 1 H), 3.19–3.16 (m, 1 H), 2.83 (d, *J* = 16 Hz, 1 H), 2.67–2.60 (m, 1 H), 2.07 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.4, 139.2, 134.0, 129.6, 128.1, 127.9, 126.7, 126.5, 125.8, 125.4, 123.3, 113.1, 62.2, 57.0, 54.4, 44.1, 29.9.

6,7-Dimethoxy-2-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (3g)[29]
Yellow oil; yield: 162 mg (60%).

^{1}H NMR (400 MHz, $CDCl_3$–CCl_4): δ = 7.23–7.16 (m, 5 H), 6.48 (s, 1 H), 5.97 (s, 1 H), 4.07 (s, 1 H), 3.76 (s, 3 H), 3.47 (s, 3 H), 3.13–2.98 (m, 2 H), 2.66–2.49 (m, 2 H), 2.14 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$–CCl_4): δ = 147.5, 147.2, 144.0, 130.5, 129.6, 128.3, 127.4, 126.4, 111.6, 110.9, 71.2, 55.8, 55.7, 52.4, 44.4, 29.1.

6,7-Dimethoxy-1-(4-methoxyphenyl)-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (3h)
Yellow solid; yield: 174 mg (58%); mp 93–95 °C (Lit.[30] 96–97 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 (d, *J* = 8.6 Hz, 2 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 6.59 (s, 1 H), 6.11 (s, 1 H), 4.20 (s, 1 H), 3.84 (s, 3 H), 3.80 (s, 3 H), 3.58 (s, 3 H), 3.20–3.08 (m, 2 H), 2.78–2.60 (m, 2 H), 2.25 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8, 147.3, 146.9, 135.1, 131.4, 130.5, 130.1, 126.2, 114.5, 113.5, 111.3, 110.5, 70.0, 55.7, 55.1, 51.8, 43.9, 28.6.

6,7-Dimethoxy-2-methyl-1-(*p*-tolyl)-1,2,3,4-tetrahydroisoquinoline (3i)
Yellow oil; yield: 191 mg (67%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15–7.12 (m, 4 H), 6.60 (s, 1 H), 6.12 (s, 1 H), 4.20 (s, 1 H), 3.84 (s, 3 H), 3.57 (s, 3 H), 3.17–3.07 (m, 2 H), 2.77–2.60 (m, 2 H), 2.33 (s, 3 H), 2.24 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.2, 146.8, 140.0, 136.8, 130.0, 129.7, 129.3, 128.8, 128.6, 126.2, 111.3, 110.5, 70.3, 55.6, 51.7, 43.9, 28.6, 21.0.

HRMS (ES^+): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{24}NO_2$: 297.1729; found: 298.1798.

6,7-Dimethoxy-1-(3-methoxyphenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (3j)[19b]
Yellow oil; yield: 170 mg (57%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16–7.14 (m, 1 H), 6.80–6.73 (m, 3 H), 6.53 (s, 1 H), 6.07 (s, 1 H), 4.16 (br s, 1 H), 3.78 (s, 3 H), 3.71 (s, 3 H), 3.51 (s, 3 H), 3.09–3.05 (m, 2 H), 2.71–2.58 (m, 2 H), 2.21 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7, 147.6, 147.1, 129.2, 126.2, 122.2, 115.0, 113.0, 111.3, 110.7, 100.0, 55.9, 55.8, 55.3, 52.0, 44.1, 28.6.

6,7-Dimethoxy-2-methyl-1-(naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline (3k)
Yellow solid; yield: 185 mg (58%); mp 139–140 °C (Lit.[31] 140–142 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 8.4 Hz, 1 H), 7.74–7.69 (m, 2 H), 7.35–7.25 (m, 4 H), 6.57 (s, 1 H), 5.97 (s, 1 H), 4.70 (br s, 1 H), 3.76 (s, 3 H), 3.30 (s, 3 H), 3.27–3.11 (m, 2 H), 2.78–2.73 (m, 1 H), 2.64–2.58 (m, 1 H), 2.14 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.4, 147.1, 134.3, 130.3, 128.4, 128.2, 126.1, 125.5, 125.3, 110.8, 110.6, 55.6, 52.7, 44.3, 28.4.

7-Ethoxy-6-methoxy-2-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (3l)[19b]
Yellow oil; yield: 170 mg (64%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.16 (m, 5 H), 6.53 (s, 1 H), 6.02 (s, 1 H), 4.10 (s, 1 H), 3.76–3.62 (m, 5 H), 3.05–3.01 (m, 2 H), 2.68–2.54 (m, 2 H), 2.16 (s, 3 H), 1.19 (t, *J* = 7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.7, 145.1, 142.8, 129.2, 128.5, 127.2, 126.2, 125.5, 112.1, 109.8, 70.0, 63.1, 54.8, 51.2, 43.2, 27.9, 13.5.

7-Ethoxy-6-methoxy-1-(4-methoxyphenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (3m)
Creamy solid; yield: 190 mg (65%); mp 85–87 °C (Lit.[19b] 87–89 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10–7.07 (m, 2 H), 6.79–6.75 (m, 2 H), 6.52 (s, 1 H), 6.04 (s, 1 H), 4.08 (s, 1 H), 3.79–3.64 (m, 8 H), 3.09–2.99 (m, 2 H), 2.69–2.51 (m, 2 H), 2.16 (s, 3 H), 1.21 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8, 147.7, 146.2, 130.5, 130.4, 126.4, 113.5, 113.1, 110.8, 70.2, 64.2, 55.8, 55.2, 52.1, 44.1, 28.8, 14.6.

2-Ethyl-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (3n)
Yellow solid; yield: 201 mg (68%); mp 73–74 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.13 (m, 5 H), 6.52 (s, 1 H), 6.09 (s, 1 H), 4.46 (s, 1 H), 3.77 (s, 3 H), 3.51 (s, 3 H), 3.09–3.04 (m, 1 H), 2.96–2.89 (m, 1 H), 2.74–2.68 (m, 1 H), 2.58–2.49 (m, 2 H), 2.35–2.26 (m, 1 H), 0.99–0.96 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.3, 146.9, 144.0, 130.1, 129.4, 128.0, 127.0, 126.8, 111.6, 110.7, 67.2, 55.7, 48.0, 46.3, 28.1, 11.6.

HRMS (ES^+): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{24}NO_2$: 297.1729; found: 298.1802.

2-Ethyl-6,7-dimethoxy-1-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (3o)
Yellow solid; yield: 182 mg (65%); mp 66–68 °C (Lit.[32] 64–66 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10–7.06 (m, 2 H), 6.77–6.74 (m, 2 H), 6.52 (s, 1 H), 6.10 (s, 1 H), 4.43 (s, 1 H), 3.77 (s, 3 H), 3.72 (s, 3 H), 3.53 (s, 3 H), 3.09–3.03 (m, 1 H), 2.92–2.88 (m, 1 H), 2.74–2.69 (m, 1 H), 2.57–2.51 (m, 2 H), 2.33–2.28 (m, 1 H), 1.00–0.97 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.6, 147.4, 147.0, 130.5, 126.8, 113.4, 111.7, 110.8, 99.9, 66.6, 55.8, 55.2, 47.9, 46.2, 28.1, 11.6.

2-Benzyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (3p)[33]
White solid; yield: 136 mg (51%); mp 118–120 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.28 (m, 2 H), 7.24–7.10 (m, 8 H), 7.03–7.00 (m, 2 H), 6.92 (t, *J* = 7.8 Hz, 1 H), 6.65 (d, *J* = 7.5 Hz, 1 H), 4.52 (s, 1 H), 3.74 (d, *J* = 13.5 Hz, 1 H), 3.18 (d, *J* = 13.5 Hz, 1 H), 3.04–2.94 (m, 2 H), 2.71–2.65 (m, 1 H), 2.43–2.39 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.4, 139.6, 138.5, 134.8, 129.7, 128.9, 128.8, 128.5, 128.3, 128.2, 127.3, 126.8, 125.9, 125.7, 68.9, 58.8, 47.3, 29.2.

2-Benzyl-1-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (3q)[33]
White solid; yield: 117 mg (40%); mp 148–150 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22–7.13 (m, 7 H), 7.04–6.99 (m, 2 H), 6.95–6.87 (m, 1 H), 6.80–6.76 (m, 2 H), 6.66 (d, *J* = 7.8 Hz, 1 H), 4.50 (s, 1 H), 3.76 (s, 1 H), 3.71 (s, 3 H), 3.18–3.15 (m, 1 H), 3.00 (br s, 2 H), 2.71–2.67 (m, 1 H), 2.44 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 130.8, 128.9, 128.5, 128.2, 126.9, 125.7, 113.7, 67.9, 59.5, 55.2, 47.2, 29.7.

1-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (3r)[34]
Yellow oil; yield: 181 mg (58%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.78–6.69 (m, 3 H), 6.53 (s, 1 H), 6.06 (s, 1 H), 4.07 (br s, 1 H), 3.82 (s, 3 H), 3.78 (s, 3 H), 3.75 (s, 3 H), 3.51 (s, 3 H), 3.12–3.06 (m, 2 H), 2.69–2.55 (m, 2 H), 2.18 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.1, 148.5, 147.1, 126.1, 122.3, 111.9, 111.3, 110.6, 110.3, 70.9, 56.2, 56.0, 55.8, 52.3, 44.1, 28.7.

6,7-Dimethoxy-2-methyl-1-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (3s)
White solid; yield: 193 mg (54%); mp 139–141 °C (Lit.[35] 140–141 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.53–6.45 (m, 3 H), 6.09 (s, 1 H), 4.11 (br s, 1 H), 3.78 (s, 6 H), 3.74 (s, 6 H), 3.54 (s, 3 H), 3.11 (br s, 2 H), 2.69–2.58 (m, 2 H), 2.22 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.0, 147.4, 146.9, 139.3, 137.1, 129.9, 126.3, 111.2, 110.6, 106.3, 71.6, 60.8, 56.1, 55.9, 55.7, 52.5, 44.4, 28.7.

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