Synthesis of Tetrahydroisoquinolines via Cascade Reductive Amination of Isochromenylium Tetrafluoroborate with Primary Amines

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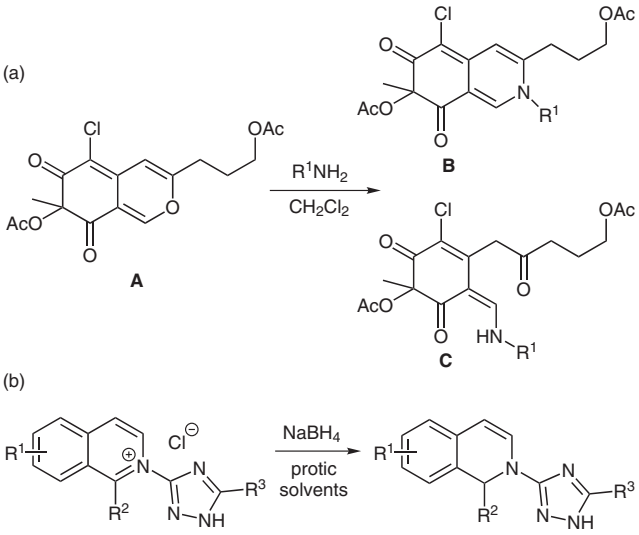
Abstract: Reactions of isochromenylium tetrafluoroborates with various primary amines have been investigated under reductive amination conditions. The established cascade methodology provides a convenient one-step synthesis of various tetrahydroisoquinoline derivatives under mild conditions.

Key words: isochromenylium, reductive amination, tetrahydroisoquinoline, heterocycle, cascade reaction

The isochromenylium cation is a type of non-classical reactive intermediate.[1–6] They were reported to be inseparable intermediates in many cascade transformations[7–10] until the air- and moisture-stable crystalline isochromenylium tetrafluoroborates (ICTBs) were prepared and fully characterized by our group recently.[11–13] In one of our previous works we found that the azaphilone derivative **A** could smoothly react with some primary amines to afford the corresponding vinylogous γ-pyridones **B** or stable enamines **C** (Scheme 1a).[14] Prauda and coworkers also showed that some *N*-aryl isoquinolinium salts could be reduced with sodium borohydride in protic solvents to afford dihydroisoquinolines (Scheme 1b).[15] These studies suggested to us that ICTBs (**1**) might be able to react with amines, generating isoquinoline derivatives through similar addition/reductive-opening/cyclization mechanisms. Following such an idea, we explored the 'formal' one-step transformations of ICTBs into nitrogenous heterocycles, which would be of value in the synthesis of many biologically important alkaloids.[16] Herein, we wish to report our recent results on the application of stable ICTBs of type **1** to the synthesis of a variety of tetrahydroisoquinolines via a direct reductive amination process.

4-Methylaniline (**2i**) was initially employed as the amine substrate to examine the reaction with ICTB **1a** in the presence of sodium borohydride and potassium carbonate in 1,2-dichloroethane (DCE). Here, the base potassium carbonate was used to neutralize HBF_4, the acid produced in this reaction. According to our initial analysis and to the previous report,[15] this reaction might finally give the dihydroisoquinoline derivative **1′** (Scheme 2a). The ICTB **1a** is thought to undergo an insertion reaction with amine **2i**, providing an *N*-aryl isoquinolinium salt. Further reduction of this salt with sodium borohydride affords the dihydroisoquinoline derivative **1′**. However, the amino alcohol **3** was finally afforded upon completion of the reaction. A possible mechanism is proposed in Scheme 2b. Nucleophilic addition of the primary amine **2i** to the electrophilic C-1 carbon atom results in the formation of aminal intermediate **A**, which is then opened to furnish imine **B**. Both imine and ketone functionalities of **B** are finally reduced with sodium borohydride to provide the amino alcohol **3**.



Scheme 1 (a) Reaction of azaphilone with primary amines, and (b) reduction of *N*-aryl isoquinolinium salts with sodium borohydride

Clearly, reaction of ITCB **1a** with amine **2i** did not followed the previously known process involving an *N*-aryl isoquinolinium intermediate (Scheme 1b and Scheme 2a).[15] According to a mechanistic analysis, the stronger reducing power of sodium borohydride is thought to be a major reason for the production of the unexpected amino alcohol **3** rather than isoquinoline derivatives **1′**. To overcome such problems, use of a weaker reducing agent, sodium cyanoborohydride, was then considered (Scheme 3). In this case, after similar treatment, the tetrahydroisoquinoline derivative **4i**, instead of the expected dihydroisoquinoline derivative, was obtained in 60% isolated yield. An explanation is proposed in

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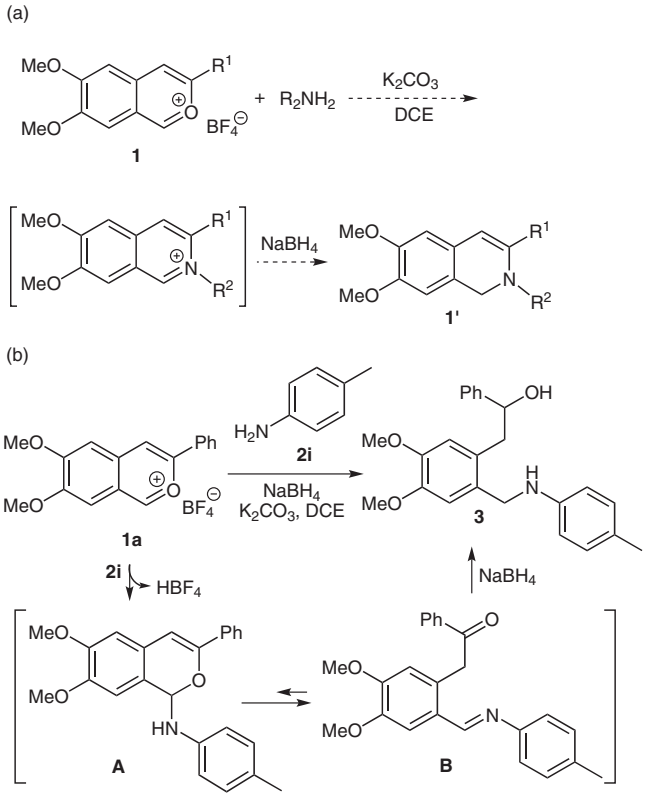
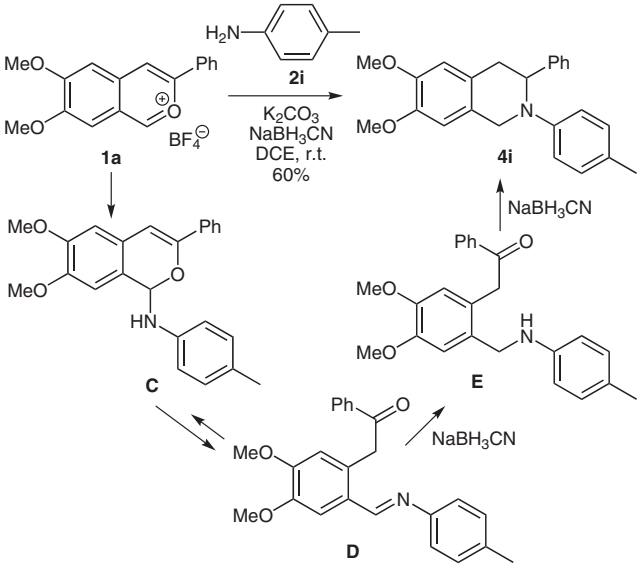


Scheme 2 (a) Reductive amination of ICTBs **1** with primary amines, and (b) the observed reaction of ICTB **1a** with aniline **2i** in the presence of sodium borohydride

Scheme 3. First, nucleophilic addition of the primary amine **2i** takes place at the C-1 carbon atom of ICTB **1a**, giving the aminal intermediate **C**. Subsequent ring-opening, followed by sodium cyanoborohydride mediated reduction provides the secondary amine **E**. Intramolecular enamine cyclization of **E** and reductive amination mediated by sodium cyanoborohydride finally provides the tetrahydroisoquinoline product **4i**. In this reaction, it is believed that the *N*-aryl isoquinolinium intermediate[15] was not formed.

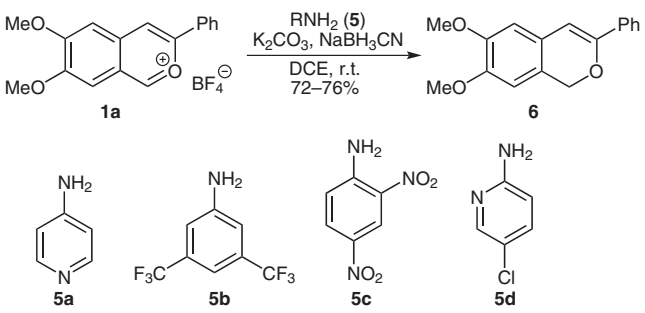
To explore the substrate scope, a variety of primary amines were then examined under the above conditions (Table 1). In these experiments, ICTB **1a** was successively treated with primary amine **2** (1.0 equiv), potassium carbonate (2.0 equiv) and sodium cyanoborohydride (4.0 equiv) in anhydrous dichloroethane, and the reaction was stirred at room temperature for 1.5 hours. The progress of the reaction could be roughly judged by the color change that occurred during the reaction; when the color became either yellow or colorless from orange, the reaction was approximately complete. Primary amines applied in this type of reaction included aliphatic amines (Table 1, entries 1–4), benzylic-type amines and allylamine (entries 5–7 and 17), methoxyamine (entry 8), aryl amines (entries 9–12), and amino acid esters (entries 13–16). In all cases, the corresponding tetrahydroisoquinolines **4** were afforded in moderate to satisfactory yields. Reactions with 1*H*-indazol-5-amine (**2l**, entry 12) and tryptophan methyl ester (**2p**, entry 16) indicate that the existence of additional



Scheme 3 Reaction of ICTB **1a** with amine **2i** in the presence of sodium cyanoborohydride

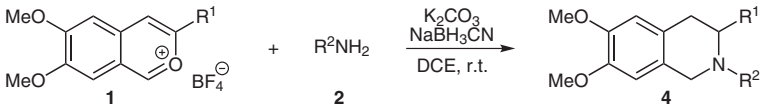
less nucleophilic amino group(s) did not affect the results of reductive amination reactions. When the reaction was performed with optically pure amino acid methyl esters, a diastereoisomeric mixture of two tetrahydroisoquinolines, which varied at the C-3 position, was usually afforded (according to ^{1}H NMR analysis; entries 13–16). Compared with the less bulky amino acid ester **2n** (dr = 1.5:1, entry 14), the use of tryptophan methyl ester **2p** (dr = 3.9:1, entry 16) achieved a better diastereomeric ratio of products.

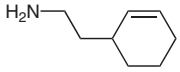
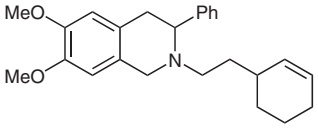
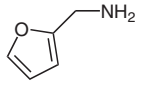
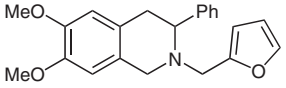
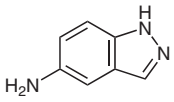
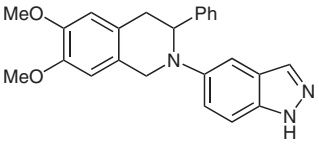
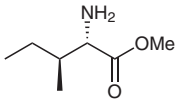
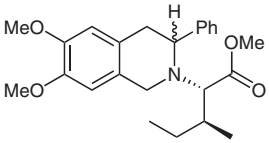
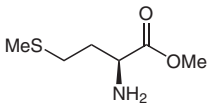
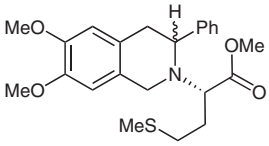
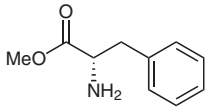
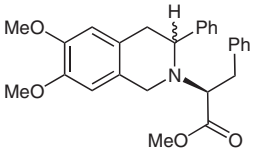
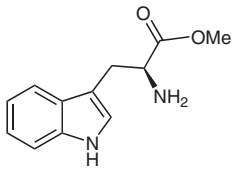
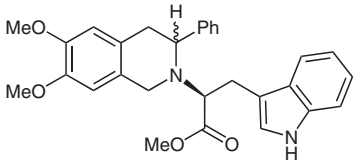
Reactions with several electron-deficient aniline or other aromatic amines **5a–d** were also attempted under the same conditions (Scheme 4). However, 1*H*-isochromene **6**, which formed from direct reduction of ICTB **1a**,[13] was provided in 72–76% yields, and no expected tetrahydroisoquinoline derivatives were detected. It is speculated that the nucleophilicity of these amines is too weak to enable attack on ICTB **1a**, whereas competitive hydride addition by sodium cyanoborohydride to the C-1 carbon of ICTB **1a** is favorable under such conditions. In addition, the reaction with bulky *tert*-butyl amine was also found to give a ring-opening product similar to **3** (Scheme 2), because of the failure to form an enamine or semi-acetal, which is essential for the second reductive amination.



Scheme 4 Reaction of ICTB **1a** with electron-deficient aromatic amines **5a–d**. *Reagents and conditions*: ICTB **1a** (0.5 mmol), primary amine **5** (0.5 mmol), K_2CO_3 (1 mmol), $NaBH_3CN$ (2 mmol), anhydrous DCE (10 mL), r.t. (see the experimental section for details).

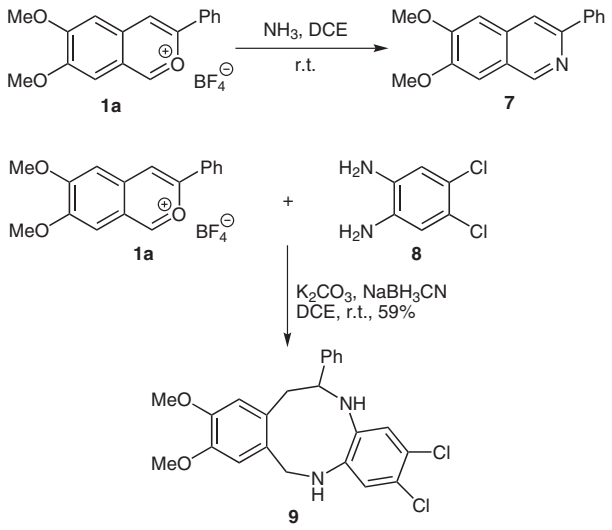
Table 1 Direct Reductive Amination of ICTBs **1** with Primary Amines **2**[a]



Entry	1	R^1	2	R^2NH_2	Product 4	Yield (%)[b]
1	**1a**	Ph	**2a**	*n*-$BuNH_2$	**4a**	61
2	**1a**	Ph	**2b**	$HOCH_2CH_2NH_2$	**4b**	62
3	**1a**	Ph	**2c**		**4c** 	67[c]
4	**1a**	Ph	**2d**	*c*-$HexNH_2$	**4d**	43
5	**1a**	Ph	**2e**	$BnNH_2$	**4e**	74
6	**1a**	Ph	**2f**		**4f** 	70
7	**1a**	Ph	**2g**	$allylNH_2$	**4g**	67
8	**1a**	Ph	**2h**	$MeONH_2$	**4h**	52
9	**1a**	Ph	**2i**	4-$MeC_6H_4NH_2$	**4i**	60
10	**1a**	Ph	**2j**	4-$MeOC_6H_4NH_2$	**4j**	59
11	**1a**	Ph	**2k**	1-$naphthylNH_2$	**4k**	52
12	**1a**	Ph	**2l**		**4l** 	64
13[d]	**1a**	Ph	**2m**		**4m** 	72[e] (dr = 1.1:1)
14[d]	**1a**	Ph	**2n**		**4n** 	62[e] (dr = 1.5:1)
15[d]	**1a**	Ph	**2o**		**4o** 	76[e] (dr = 1.7:1)
16[d]	**1a**	Ph	**2p**		**4p** 	67[e] (dr = 3.9:1)
17	**1b**	*n*-C_6H_{13}	**2g**	$allylNH_2$	**4q**	67

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), K_2CO_3 (1 mmol), $NaBH_3CN$ (2 mmol), anhydrous DCE (10 mL), r.t. (see the experimental section for details).
[b] Isolated yield.
[c] Product **4c** was formed as an inseparable diastereomeric mixture and could be detected by ^{13}C NMR analysis.
[d] Diastereomeric ratio of products were assessed based on the isolated yields; the absolute configuration of new stereogenic center was not determined.
[e] Combined yield of two diastereoisomers.

Reaction of ICTB **1a** with ammonia (bubbling gas) was also investigated (Scheme 5). In contrast to the previous examples, the stable isoquinoline derivative **7** was isolated under these conditions, with or without the addition of potassium carbonate and sodium cyanoborohydride. Furthermore, reaction of **1a** with 1,2-diamine **8** afforded the nine-membered-ring product **9**. In this reaction, a diimine intermediate might be formed before the reductive amination.



Scheme 5 Reactions of ICTB **1a** with ammonia and 1,2-diamine **8**

In summary, reductive amination of ICTBs **1** has been studied with a variety of primary amines under mild conditions. The developed methodology provides a new, direct route to various tetrahydroisoquinoline derivatives. Reasonable interpretations of the reaction mechanisms were proposed and discussed. Further applications of this methodology to the synthesis of biologically interesting alkaloids and tetrahydroisoquinoline-containing heterocycles[16] are underway in this laboratory and will be reported in due course.

All reactions were conducted using oven-dried glassware. DMF and DCE were distilled from CaH_2. CH_2Cl_2, petroleum ether and EtOAc were obtained from commercial suppliers and used without further purification. All melting points are uncorrected. IR spectra were recorded with a Bio-Rad FTS 185 FT-IR instrument. ^{1}H NMR spectra were recorded at 400 MHz, and ^{13}C NMR spectra were recorded at 75 MHz or 100 MHz with Varian EM-390 or Bruker AMX-300 spectrometers; shifts (δ) are given in ppm relative to residual protonated solvent [$CHCl_3$: δ = 7.26 (^{1}H) and 77.0 (^{13}C) ppm. For acetone-d_6: δ = 2.17 (^{1}H), 205.9 and 30.6 (^{13}C) ppm]. Flash column chromatography was performed on silica gel H (10–40 μm).

Tetrahydroisoquinoline Derivatives 4a–p; General Procedure

To a solution of isochromenylium tetrafluoroborate **1a** (174 mg, 0.5 mmol) in anhydrous DCE (10 mL), primary amine **2** (0.5 mmol) was added at r.t. The reaction was stirred for 15 min and then K_2CO_3 (139 mg, 1.0 mmol) was added at r.t. After the starting material **2** was consumed, $NaBH_3CN$ (130 mg, 2.0 mmol) was added. After the reaction reached completion (approx. 2 h, monitored by TLC), the mixture was filtered to remove the solid and the organic solution was washed with brine (3 × 10 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 8:1) to afford the pure product.

2-Butyl-6,7-dimethoxy-3-phenyl-1,2,3,4-tetrahydroisoquinoline (4a)

Yellow oil.

IR (KBr): 2961, 1610, 1519, 1253, 1241, 1139, 1002, 851, 738, 703 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.26–7.36 (m, 5 H), 6.60 (s, 1 H), 6.58 (s, 1 H), 3.98 (d, *J* = 10.2 Hz, 1 H), 3.86 (s, 3 H), 3.84 (s, 3 H), 3.67 (dd, *J* = 3.9, 6.9 Hz, 1 H), 3.54 (d, *J* = 11.4 Hz, 1 H), 2.98–3.03 (m, 2 H), 2.51–2.58 (m, 1 H), 2.10–2.16 (m, 1 H), 1.50–1.53 (m, 2 H), 1.20–1.30 (m, 2 H), 0.85 (t, *J* = 5.7 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 147.4, 147.2, 142.7 (×2), 128.2 (×2), 127.8, 127.0, 126.4, 126.1, 110.7, 109.1, 64.2, 55.8, 55.7, 53.9, 53.8, 36.8, 29.1, 20.4, 13.9.

ESI-MS: *m*/*z* = 326 [M + H$^+$].

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $C_{21}H_{28}NO_2$: 326.2120; found: 326.2122.

2-[6,7-Dimethoxy-3-phenyl-3,4-dihydroisoquinolin-2(1*H*)-yl]ethanol (4b)

Yellow oil.

IR (KBr): 2935, 1613, 1519, 1356, 1132, 772, 710 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.18–7.28 (m, 5 H), 6.53 (s, 1 H), 6.50 (s, 1 H), 3.75–3.88 (m, 2 H), 3.77 (s, 3 H), 3.78 (s, 3 H), 3.42–3.64 (m, 3 H), 2.98 (d, *J* = 6.3 Hz, 2 H), 2.64–2.71 (m, 2 H), 2.28–2.32 (m, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 147.6, 147.3, 141.5, 128.5 (×2), 128.0 (×2), 127.4, 125.8, 125.6, 110.8, 109.0, 63.5, 58.2, 55.8 (×2), 54.5, 52.6, 35.2.

ESI-MS: *m*/*z* = 314 [M + H$^+$].

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $C_{19}H_{24}NO_3$: 314.1756; found: 314.1749.

2-[2-(Cyclohex-2-enyl)ethyl]-6,7-dimethoxy-3-phenyl-1,2,3,4-tetrahydroisoquinoline (4c)[17]

Inseparable diastereomeric mixture (1:1); yellow oil.

IR (KBr): 2916, 2834, 1607, 1505, 1464, 1264, 1108, 738, 702 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.25–7.33 (m, 5 H), 6.58 (s, 1 H), 6.56 (s, 1 H), 5.58–5.61 (m, 1 H), 5.41–5.46 (m, 1 H), 3.96 (d, *J* = 15.2 Hz, 1 H), 3.85 (s, 3 H), 3.83 (s, 3 H), 3.65–3.70 (m, 1 H), 3.55 (d, *J* = 14.8 Hz, 1 H), 2.92–3.06 (m, 2 H), 2.55–2.65 (m, 1 H), 2.14–2.23 (m, 1 H), 2.01 (br s, 1 H), 1.91 (br s, 1 H), 1.47–1.65 (m, 5 H), 1.26 (m, 1 H), 1.01–1.15 (m, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 147.5, 147.3, 147.2, 142.6 (×2), 132.0, 131.6, 128.3, 127.9, 127.1, 126.9, 126.8, 126.7, 126.4, 126.1, 110.0, 110.8, 109.2, 64.2, 64.2, 55.8 (×2), 53.8 (×2), 36.9, 36.7, 33.5, 33.3, 33.2, 33.1, 29.2, 28.7, 25.2, 21.3, 21.2.

ESI-MS: *m*/*z* = 378 [M + H$^+$].

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{25}H_{31}NO_2$: 377.2355; found: 377.2357.

2-Cyclohexyl-6,7-dimethoxy-3-phenyl-1,2,3,4-tetrahydroisoquinoline (4d)

Pale-yellow solid; mp 126–127 °C (petroleum ether and EtOAc).

IR (KBr): 2929, 2853, 1517, 1450, 1245, 1135, 844, 702 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.20–7.38 (m, 5 H), 6.60 (s, 1 H), 6.54 (s, 1 H), 3.93–3.96 (m, 1 H), 3.85 (s, 3 H), 3.81 (s, 3 H), 2.88–

3.03 (m, 2 H), 2.48–2.54 (m, 1 H), 1.63–1.74 (m, 4 H), 1.47–1.53 (m, 2 H), 1.23–1.30 (m, 3 H), 1.01–1.12 (m, 2 H), 0.83–0.89 (m, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 147.7, 147.2, 143.4, 128.4 (×2), 127.9 (×2), 127.5, 126.9, 126.5, 110.8, 109.3, 61.4, 58.3, 55.9, 55.8, 47.3, 38.1, 31.7, 26.4, 26.3, 25.6, 25.1.

ESI-MS: *m*/*z* = 352 [M + H$^+$].

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{23}H_{29}NO_2$: 351.2198; found: 351.2200.

2-Benzyl-6,7-dimethoxy-3-phenyl-1,2,3,4-tetrahydroisoquinoline (4e)
Pale-yellow solid; mp 119–120 °C (petroleum ether and EtOAc).

IR (KBr): 2932, 2832, 1610, 1517, 1463, 1251, 1136, 1117, 1028, 738, 701 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.44–7.46 (m, 2 H), 7.34–7.37 (m, 4 H), 7.21–7.30 (m, 4 H), 6.59 (s, 1 H), 6.46 (s, 1 H), 3.83 (s, 3 H), 3.79 (s, 3 H), 3.75–3.85 (m, 3 H), 3.45 (d, *J* = 15.2 Hz, 1 H), 2.99–3.11 (m, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 174.5, 174.3, 142.9, 139.4, 128.6 (×2), 128.5 (×2), 128.2 (×2), 127.8 (×2), 127.3, 126.8, 126.4, 126.1, 110.8, 109.1, 64.3, 58.7, 55.9, 55.8, 54.0, 36.9.

ESI-MS: *m*/*z* = 360 [M + H$^+$].

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{24}H_{25}NO_2$: 359.1885; found: 359.1890.

2-(Furan-2-ylmethyl)-6,7-dimethoxy-3-phenyl-1,2,3,4-tetrahydroisoquinoline (4f)
Yellow oil.

IR (KBr): 2932, 2832, 1557, 1250, 1131, 1003, 768, 736, 703 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.24–7.44 (m, 6 H), 6.55 (s, 1 H), 6.52 (s, 1 H), 6.29–6.30 (m, 1 H), 6.13–6.14 (m, 1 H), 3.86 (d, *J* = 15.2 Hz, 1 H), 3.81 (s, 6 H), 3.71–3.75 (m, 2 H), 3.62 (d, *J* = 15.2 Hz, 1 H), 3.37 (d, *J* = 14.0 Hz, 1 H), 2.90–3.00 (m, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 152.3, 147.5, 147.3, 142.3, 141.9, 128.5 (×2), 127.9 (×2), 127.3, 126.1, 125.9, 110.7, 109.9, 109.1, 108.4, 63.6, 55.8 (×2), 53.9, 50.6, 37.2.

ESI-MS: *m*/*z* = 350 [M + H$^+$].

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{22}H_{23}NO_3$: 349.1678; found: 349.1682.

2-Allyl-6,7-dimethoxy-3-phenyl-1,2,3,4-tetrahydroisoquinoline (4g)
Yellow oil.

IR (KBr): 2935, 2791, 1612, 1519, 1251, 1134, 1003, 703 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.25–7.36 (m, 5 H), 6.56 (s, 2 H), 5.80–5.94 (m, 1 H), 5.10–5.17 (m, 2 H), 3.91 (d, *J* = 15.3 Hz, 1 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 3.67 (dd, *J* = 5.4, 8.7 Hz, 1 H), 3.50 (d, *J* = 15.0 Hz, 1 H), 3.23 (dd, *J* = 5.4, 13.5 Hz, 1 H), 2.97–3.04 (m, 2 H), 2.72 (dd, *J* = 7.8, 13.8 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 147.4, 147.2, 142.2, 135.6, 128.3 (×2), 127.7 (×2), 127.1, 126.2, 125.9, 117.1, 110.7, 109.0, 63.8, 57.3, 55.7 (×2), 53.7, 36.8.

ESI-MS: *m*/*z* = 310 [M + H$^+$].

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $C_{20}H_{24}NO_2$: 310.1807; found: 310.1798.

2,6,7-Trimethoxy-3-phenyl-1,2,3,4-tetrahydroisoquinoline (4h)
Yellow oil.

IR (KBr): 1609, 1517, 1338, 1260, 1111, 1018, 852, 702 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.28–7.49 (m, 5 H), 6.60 (s, 1 H), 6.59 (s, 1 H), 4.38 (d, *J* = 14.4 Hz, 1 H), 3.98 (br s, 2 H), 3.87 (s, 3 H), 3.84 (s, 3 H), 3.37 (s, 3 H), 3.25 (br s, 1 H), 2.95 (dd, *J* = 4.2, 16.2 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.2, 147.9, 142.1, 128.5 (×2), 128.1 (×2), 127.6, 125.8, 125.2, 110.9, 109.6, 60.6 (×2), 57.3, 56.2, 56.1, 38.0.

ESI-MS: *m*/*z* = 300 [M + H$^+$].

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $C_{18}H_{22}NO_3$: 300.1600; found: 300.1608.

6,7-Dimethoxy-3-phenyl-2-*p*-tolyl-1,2,3,4-tetrahydroisoquinoline (4i)
White solid; mp 68–70 °C (petroleum ether and EtOAc).

IR (KBr): 1612, 1517, 1462, 1120, 705 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.01–7.17 (m, 7 H), 6.75 (d, *J* = 6.6 Hz, 2 H), 6.71 (s, 1 H), 6.57 (s, 1 H), 5.06–5.08 (m, 1 H), 4.44 (d, *J* = 14.4 Hz, 1 H), 4.32 (d, *J* = 14.4 Hz, 1 H), 3.87 (s, 3 H), 3.81 (s, 3 H), 3.39 (dd, *J* = 5.4, 15.0 Hz, 1 H), 3.03 (d, *J* = 15.6 Hz, 1 H), 2.24 (s, 3 H).

EI-MS: *m*/*z* = 359 [M]$^+$.

Anal. Calcd for $C_{24}H_{25}NO_2$: C, 80.19; H, 7.01; N, 3.90. Found: C, 80.12; H, 6.96; N, 3.84.

6,7-Dimethoxy-2-(4-methoxyphenyl)-3-phenyl-1,2,3,4-tetrahydroisoquinoline (4j)
Yellow solid; mp 77–79 °C (petroleum ether and EtOAc).

IR (KBr): 2795, 1610, 1521, 1235, 1119, 1037, 823, 705 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.08–7.18 (m, 5 H), 6.77–6.84 (m, 4 H), 6.67 (s, 1 H), 6.59 (s, 1 H), 4.94 (t, *J* = 4.2 Hz, 1 H), 4.32 (d, *J* = 14.7 Hz, 1 H), 4.23 (d, *J* = 14.4, 1 H), 3.86 (s, 3 H), 3.80 (s, 3 H), 3.73 (s, 3 H), 3.36 (dd, *J* = 5.7, 9.9 Hz, 1 H), 3.03 (dd, *J* = 3.3, 15.6 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 152.7, 147.7, 147.4, 144.2, 142.5, 128.1 (×2), 126.9 (×2), 126.8, 126.7, 125.7, 117.1 (×2), 114.5 (×2), 111.2, 109.2, 59.6, 55.9, 55.8, 55.6, 48.7, 35.1.

EI-MS: *m*/*z* = 375 [M]$^+$.

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $C_{24}H_{26}NO_3$: 376.1913; found: 376.1915.

6,7-Dimethoxy-2-(naphthalen-2-yl)-3-phenyl-1,2,3,4-tetrahydroisoquinoline (4k)
White solid; mp 82–86 °C (petroleum ether and EtOAc).

IR (KBr): 2833, 1463, 1247, 1218, 1116, 776, 700 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.49 (d, *J* = 6.8 Hz, 1 H), 7.80 (d, *J* = 8.0 Hz, 1 H), 7.44–7.53 (m, 3 H), 7.20–7.24 (m, 2 H), 7.08 (br s, 4 H), 6.87 (br s, 1 H), 6.72 (s, 1 H), 6.54 (s, 1 H), 4.82 (br s, 1 H), 4.31 (d, *J* = 13.6 Hz, 1 H), 3.99 (d, *J* = 14.8 Hz, 1 H), 3.89 (s, 3 H), 3.82 (s, 3 H), 3.55–3.17 (m, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.0, 147.7, 147.4, 134.7, 128.3 (×2), 127.9 (×2), 127.5, 126.9, 126.8, 126.1, 125.7 (×2), 125.5 (×4), 123.7, 123.6, 111.1, 108.9, 61.6, 55.9 (×3), 53.4.

ESI-MS: *m*/*z* = 396 [M + H$^+$].

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{27}H_{25}NO_2$: 395.1885; found: 395.1884.

2-(1*H*-Indazol-5-yl)-6,7-dimethoxy-3-phenyl-1,2,3,4-tetrahydroisoquinoline (4l)
Green soild; mp 208–211 °C (petroleum ether and EtOAc).

IR (KBr): 3373, 2927, 1518, 1506, 1454, 1571, 1217, 1113, 1026, 943, 857, 701 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.91 (s, 1 H), 7.35 (d, *J* = 8.8 Hz, 1 H), 7.06–7.23 (m, 7 H), 6.69 (s, 1 H), 6.64 (s, 1 H), 5.05–5.08 (m, 1 H), 4.35 (d, *J* = 14.8 Hz, 1 H), 4.26 (d, *J* = 14.8 Hz, 1 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 3.42 (dd, *J* = 5.6, 15.6 Hz, 1 H), 3.10 (dd, *J* = 3.2, 16.0 Hz, 1 H); one NH proton was not found in the spectrum.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 147.8, 147.5, 145.1, 141.8, 135.6, 134.3, 128.2 (×2), 127.1 (×2), 126.9, 126.8, 125.7, 124.1, 120.6, 111.2, 110.2, 109.2, 105.5, 60.3, 60.0, 55.9, 49.0, 34.7.

ESI-MS: *m*/*z* = 386 [M + H^+].

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{24}H_{23}N_3O_2$: 385.1790; found: 385.1786.

Methyl-2-[6,7-dimethoxy-3-phenyl-3,4-dihydroisoquinolin-2(1*H*)-yl]-3-methylpentanoate (4m)

Major product; pale-yellow solid; mp 96–97 °C (petroleum ether and EtOAc); $[\alpha]_D^{25}$ +140.5 (*c* 0.39, $CHCl_3$).

IR (KBr): 2952, 2867, 2834, 1731, 1615, 1519, 1464, 1362, 1253, 1241, 1150, 1029, 1002, 847, 737, 703 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.32–7.38 (m, 4 H), 7.25–7.30 (m, 1 H), 6.61 (s, 1 H), 6.55 (s, 1 H), 4.06 (dd, *J* = 4.0, 10.4 Hz, 1 H), 3.98 (d, *J* = 14.8 Hz, 1 H), 3.89 (d, *J* = 14.8 Hz, 1 H), 3.86 (s, 3 H), 3.82 (s, 3 H), 3.61 (s, 3 H), 3.38 (dd, *J* = 7.2, 8.0 Hz, 1 H), 3.07 (dd, *J* = 10.2, 16.0 Hz, 1 H), 2.83 (dd, *J* = 3.6, 16.0 Hz, 1 H), 1.55–1.74 (m, 3 H), 0.81 (d, *J* = 6.8 Hz, 3 H), 0.74 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 173.4, 147.4, 147.3, 142.8. 128.4 (×2), 128.3 (×2), 127.5, 126.9, 126.5, 110.7, 109.1, 62.9, 59.4, 55.9 (×2), 50.7, 48.0, 39.0, 38.9, 24.3, 23.0, 22.1.

ESI-MS: *m*/*z* = 398 [M + H^+].

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{24}H_{31}NO_4$: 397.2253; found: 397.2258.

Methyl-2-[6,7-dimethoxy-3-phenyl-3,4-dihydroisoquinolin-2(1*H*)-yl]-4-(methylthio)butanoate (4n)

Major product; yellow oil; $[\alpha]_D^{25}$ –102.0 (*c* 0.63, $CHCl_3$).

IR (KBr): 2948, 2834, 1728, 1610, 1517, 1493, 1453, 1351, 1255, 1241, 1158, 1029, 1000, 849, 738, 770, 703 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.26–7.36 (m, 5 H), 6.60 (s, 1 H), 6.55 (s, 1 H), 4.12 (dd, *J* = 4.0, 10.4 Hz, 1 H), 3.96 (d, *J* = 12.0 Hz, 1 H), 3.86 (s, 3 H), 3.83 (s, 3 H), 3.78 (d, *J* = 10.4 Hz, 1 H), 3.64 (s, 3 H), 3.49 (t, *J* = 15.2 Hz, 1 H), 3.07 (dd, *J* = 10.4, 15.6 Hz, 1 H), 2.84 (dd, *J* = 4.0, 16.0 Hz, 1 H), 2.52–2.63 (m, 1 H), 2.40–2.47 (m, 1 H), 2.03 (s, 3 H), 1.99–2.05 (m, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.8, 147.5, 147.4, 142.5, 128.5 (×4), 127.6, 126.5, 126.4, 110.8, 109.1, 62.9, 60.1, 55.9 (×2), 51.0, 48.0, 39.0, 30.8, 28.9, 15.3.

ESI-MS: *m*/*z* = 416 [M + H^+].

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{23}H_{29}NO_4S$: 415.1817; found: 415.1815.

Methyl-2-[6,7-dimethoxy-3-phenyl-3,4-dihydroisoquinolin-2(1*H*)-yl]-3-phenylbutanoate (4o)

Major product; yellow oil; $[\alpha]_D^{25}$ –5.4 (*c* 0.88, $CHCl_3$).

IR (KBr): 2836, 1730, 1612, 1519, 1255, 1002, 737, 701 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.17–7.23 (m, 6 H), 6.99–7.05 (m, 4 H), 6.66 (s, 1 H), 6.52 (s, 1 H), 4.17 (d, *J* = 14.8 Hz, 1 H), 4.02 (dd, *J* = 4.0, 10.4 Hz, 1 H), 3.89 (s, 3 H), 3.81 (s, 3 H), 3.76 (d, *J* = 14.8 Hz, 1 H), 3.62 (s, 3 H), 3.58 (dd, *J* = 6.8, 8.4 Hz, 1 H), 3.08 (dd, *J* = 6.8, 13.6 Hz, 1 H), 2.88–2.99 (m, 2 H), 2.76 (dd, *J* = 4.0, 16.0 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 172.5, 147.4, 147.2, 142.4, 138.6, 129.6 (×2), 128.2 (×2), 127.9 (×2), 127.3 (×2), 126.4, 126.2, 126.0 (×2), 110.6, 109.0, 63.1 (×2), 55.9, 55.8, 50.9, 48.3, 39.1, 35.8.

ESI-MS: *m*/*z* = 432 [M + H^+].

HRMS (ESI): *m*/*z* [M + H^+] calcd for $C_{27}H_{30}NO_4$: 432.2175; found: 432.2160.

Methyl-2-[6,7-dimethoxy-3-phenyl-3,4-dihydroisoquinolin-2(1*H*)-yl]-3-(1*H*-indol-3-yl)propanoate (4p)

Major product; yellow oil; $[\alpha]_D^{25}$ –18.2 (*c* 0.99, $CHCl_3$).

IR (KBr): 3377, 2947, 1729, 1611, 1517, 1456, 1109, 740, 702 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.90 (br s, 1 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 7.20 (s, 5 H), 7.13 (t, *J* = 8.0 Hz, 1 H), 6.97–7.01 (m, 2 H), 6.66 (s, 1 H), 6.55 (s, 1 H), 4.21 (d, *J* = 14.8 Hz, 1 H), 4.02 (dd, *J* = 4.0, 10.4 Hz, 1 H), 3.88 (s, 3 H), 3.83 (s, 3 H), 3.82 (d, *J* = 14.8 Hz, 1 H), 3.75 (dd, *J* = 6.8, 8.4 Hz, 1 H), 3.58 (s, 3 H), 3.39 (dd, *J* = 8.8, 14.4 Hz, 1 H), 2.98–3.08 (m, 2 H), 2.84 (dd, *J* = 4.0, 14.8 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 172.5, 147.5, 147.3, 142.7, 135.9, 128.4 (×2), 128.3 (×2), 127.5, 127.4, 126.5, 126.4, 123.1, 121.7, 119.0, 118.8, 112.3, 110.8, 110.7, 109.1, 63.3, 62.0, 55.9, 50.8, 48.6, 39.2, 29.7, 26.1.

ESI-MS: *m*/*z* = 471 [M + H^+].

HRMS (ESI): *m*/*z* [M + H^+] calcd for $C_{29}H_{31}N_2O_4$: 471.2284; found: 471.2295.

2-Allyl-3-hexyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (4q)

Yellow oil.

IR (KBr): 2926, 2428, 1611, 1516, 1416, 1255, 1106, 996, 916, 849 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 6.57 (s, 1 H), 6.51 (s, 1 H), 5.88–5.98 (m, 1 H), 5.13–5.21 (m, 2 H), 3.83 (s, 3 H), 3.79 (s, 3 H), 3.74 (d, *J* = 16.0 Hz, 1 H), 3.66 (d, *J* = 15.6 Hz, 1 H), 3.14–3.21 (m, 2 H), 2.94 (br s, 1 H), 2.83 (dd, *J* = 8.8, 16.0 Hz, 1 H), 2.53 (dd, *J* = 5.6, 16.0 Hz, 1 H), 1.60–1.63 (m, 1 H), 1.26–1.39 (m, 9 H), 0.88 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 147.3, 147.1, 136.2, 125.7, 125.6, 117.1, 111.7, 109.3, 56.5, 55.7 (×2), 54.6, 50.7, 31.7, 30.2, 29.6, 29.4, 26.5, 22.5, 14.0.

ESI-MS: *m*/*z* = 318 [M + H^+].

HRMS (ESI): *m*/*z* [M + H^+] calcd for $C_{20}H_{32}NO_2$: 318.2433; found: 318.2434.

2-{4,5-Dimethoxy-2-[(*p*-tolylamino)methyl]phenyl}-1-phenylethanol (3)

To a solution of ICTB **1a** (174 mg, 0.5 mmol) in anhydrous DCE (10 mL), primary amine **2i** (0.5 mmol) was added at r.t. The reaction was stirred for 15 min and then K_2CO_3 (139 mg, 1.0 mmol) was added at r.t. After the amine was consumed, $NaBH_4$ (130 mg, 2.0 mmol) was added and, after being stirred for 2 h, the mixture was filtered to remove the solid and then washed with brine (3 × 10 mL). The organic solution was dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 3:2) to afford **3**.

Yield: 155 mg (82%); yellow oil.

IR (KBr): 3388, 2933, 2856, 1614, 1517, 1463, 1274, 1103, 910, 759 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.25–7.31 (m, 5 H), 7.03 (d, *J* = 8.1 Hz, 2 H), 6.85 (s, 1 H), 6.64 (d, *J* = 8.1 Hz, 2 H), 6.62 (s, 1 H), 4.91 (t, *J* = 6.3 Hz, 1 H), 4.16 (d, *J* = 12.3 Hz, 1 H), 4.08 (d,

J = 12.3 Hz, 1 H), 3.83 (s, 3 H), 3.79 (s, 3 H), 3.02 (d, J = 6.3 Hz, 2 H), 2.90–3.10 (br m, 2 H), 2.27 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.2, 147.6, 145.7, 144.3, 129.8 (×2), 129.0, 128.4 (×2), 127.8, 127.4 (×2), 125.8 (×2), 113.9 (×2), 113.7, 112.9, 75.2, 55.9, 55.8, 47.0, 42.2, 20.5.

ESI-MS: m/z = 378 [M + H$^+$].

HRMS (ESI): m/z [M + Na$^+$] calcd for $C_{24}H_{27}NO_3Na$: 400.1889; found: 400.1883.

6,7-Dimethoxy-3-phenyl-1*H*-isochromene (6)[13]

A solution of isochromenylium tetrafluoroborate **1a** (174 mg, 0.5 mmol) in anhydrous DCE (10 mL), with or without primary amine **5** (0.5 mmol), was stirred at r.t. for 15 min. K_2CO_3 (139 mg, 1.0 mmol) and $NaBH_3CN$ (130 mg, 2.0 mmol) were then added at r.t., successively. Upon completion of the reaction, the solid was filtered off and the organic solution was washed with brine (3 × 10 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 8:1) to afford pure product **6**.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.71 (d, J = 7.2 Hz, 2 H), 7.26–7.40 (m, 3 H), 6.67 (s, 1 H), 6.64 (s, 1 H), 6.40 (s, 1 H), 5.17 (s, 2 H), 3.90 (s, 3 H), 3.89 (s, 3 H).

6,7-Dimethoxy-3-phenylisoquinoline (7)[18]

To a solution of ICTB **1a** (174 mg, 0.5 mmol) in anhydrous DCE (10 mL) was bubbled ammonia at r.t. for 10 s. After 10 min, the mixture was filtered to remove the solid, and H_2O (5 mL) was added. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 4:1) to afford **7**.

Yield: 89 mg (67%); yellow solid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.13 (s, 1 H), 8.09 (d, J = 7.2 Hz, 2 H), 7.95 (s, 1 H), 7.50 (t, J = 7.2 Hz, 2 H), 7.40 (t, J = 6.9 Hz, 1 H), 7.23 (s, 1 H), 7.13 (s, 1 H), 4.06 (s, 6 H).

EI-MS: m/z = 265 [M]$^+$.

2,3-Dichloro-8,9-dimethoxy-12-phenyl-6,11,12,13-tetrahydro-5*H*-dibenzo[*b*,*f*][1,4]diazonine (9)

To a solution of ICTB **1a** (174 mg, 0.5 mmol) in anhydrous DCE (10 mL) was added diamine **9** (0.5 mmol) at r.t. The reaction was stirred at r.t. for the 15 min, and then K_2CO_3 (139 mg, 1.0 mmol) was added. After the amine was consumed, $NaBH_3CN$ (260 mg, 4.0 mmol) was added and the reaction was stirred for an additional 2 h. The mixture was filtered to remove the solid and the organic solution was then washed with brine (3 × 10 mL), dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 5:1) to afford **9**.

Yield: 125 mg (59%); yellow solid; mp 118–121 °C (petroleum ether and EtOAc).

IR (KBr): 1608, 1487, 1464, 1262, 1245, 1224, 1187, 1122, 878, 856, 701 cm^{-1}.

^{1}H NMR (acetone-d_6, 400 MHz): δ = 7.14 (d, J = 7.6 Hz, 2 H), 7.06 (t, J = 7.2 Hz, 2 H), 6.99 (t, J = 7.2 Hz, 1 H), 6.79 (s, 1 H), 6.73 (s, 1 H), 6.63 (s, 1 H), 6.58 (s, 1 H), 5.02–5.04 (m, 2 H), 4.41 (t, J = 6.4 Hz, 1 H), 3.99 (d, J = 14.8 Hz, 1 H), 3.68 (d, J = 14.8 Hz, 1 H), 3.66 (s, 3 H), 3.65 (s, 3 H), 2.93–2.95 (m, 2 H).

^{13}C NMR (acetone-d_6, 100 MHz): δ = 150.2, 150.0, 146.3 (×2), 144.2, 138.9, 130.0 (×2), 129.3, 129.1, 128.9, 128.3, 128.0, 127.2, 119.4, 116.8, 113.6, 111.4, 62.7, 57.2 (×2), 55.7, 39.7.

ESI-MS: m/z = 429 [M + H$^+$].

HRMS (ESI): m/z [M + Na$^+$] calcd for $C_{23}H_{22}N_2O_2Cl_2Na$: 451.0956; found: 451.0951.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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