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Silver- and Gold-Mediated Intramolecular Cyclization to Substituted Tetracyclic Isoquinolizinium Hexafluorostilbates

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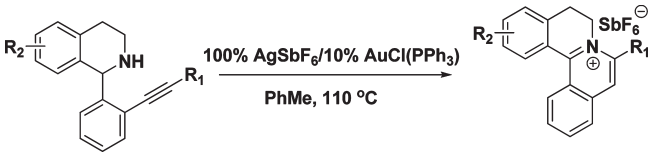

A convenient route for the synthesis of various charged tetracyclic isoquinolizinium hexafluorostilbates was developed using $AgSbF_6/AuCl(PPh_3)$ for the intramolecular addition of amine to alkyne. The described process is tolerant of a variety of functional groups and broadens the diversity of substrates with the use of 8-substituted tetracyclic isoquinolizinium salts.

Introduction

Dihydroisoquinolino[1,2-*a*]isoquinolizinium-type cations[1] are versatile heterocyclic compounds found in many natural[2] and synthetic products and are well-known for their potent biological activities. Heterocyclic compounds, especially protoberberine alkaloids (palmatine,[3a] jateorrhizine,[3b] epiberberine,[3c] coptisine,[3d] groenlandicine,[3e] and berberine[3f]) have attracted considerable attention from chemists due to their variety of activities, including a strong inhibitory potency against Alzheimer's disease[4] (Figure 1). Therefore, the synthesis and functionalization of these alkaloids have invoked considerable interest during recent years, and many potential routes for the synthesis of such compounds have been developed.[5] However, the classical methods are limited in the diversity of the configuration of the tetracyclic compounds, and it is difficult to construct distinct substituted heterocycles.[6] The construction of different configurations of heterocyclic cations, which are the analogues of protoberberine alkaloids that possibly retain their potential bioactivities, especially the substitution on the isoquinolizinium-type cations, remains a challenge for chemists. Therefore, the development of improved methodologies to synthesize new alkaloids with different backbone structures still remains highly desirable.

In recent years, transition-metal homogeneous catalysis has been considered as one of the most promising routes to a wide range of chemical processes,[7] especially, homogeneous silver and gold catalysis have emerged as powerful tools to synthesize many *N*-heterocycles.[8] Unlike the catalysts used in classical methods, silver and gold catalysts used in our

[§] These authors contributed equally to this work.

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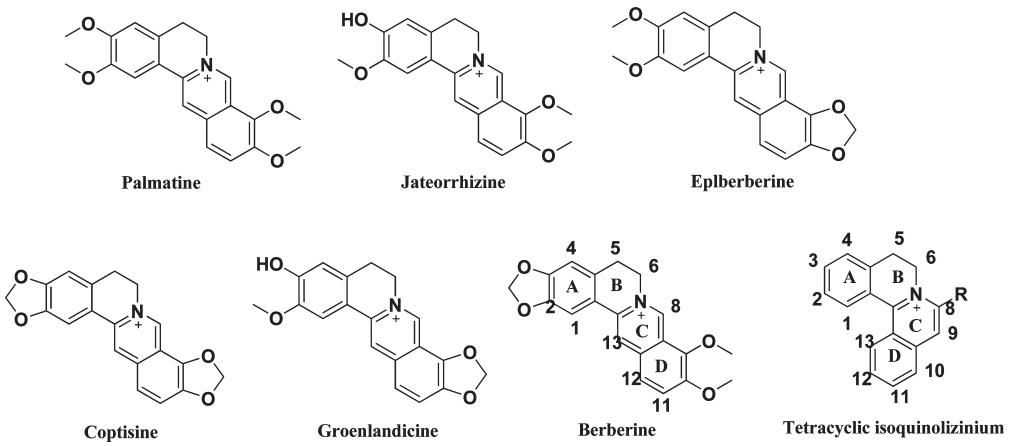
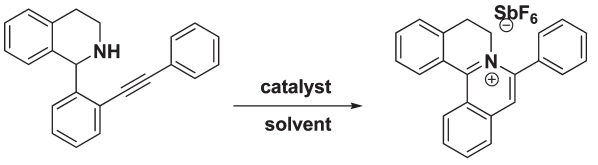


FIGURE 1. Representative dihydroisoquinolizinium-type cations in medicinal chemistry and natural products.

method are very effective and popular in reactions involving intermolecular and intramolecular nucleophilic substitutions on alkynes, owing to their exceptional ability to activate π-systems.[9] Our long-term interests in novel synthesis of biologically active heterocyclic compounds using transition-metal catalysts[10] led us to investigate the cyclization of tetracyclic isoquinolizinium. Herein, we report in detail the construction of novel cationic alkaloids in the presence of silver and gold salts.

Conventional routes to alkaloids are long and complicated;[11] moreover, the substrates are limited in the diversity of the configuration of tetracycles and the low substitution possibility on the C-ring. Our method can be used to construct diverse and new 8-substituted dihydroisoquinolino[1,2-*a*]isoquinolizinium cationic alkaloids under mild conditions using silver and gold salts as catalysts. This new configuration of tetracyclic compounds is similar to the protoberberine alkaloids and is expected to exhibit similar biological activities.[12] The interesting 8-substituted isoquinolizinium will widen the category and quantity of alkaloid derivatives that can be formed. To the best of our knowledge, the synthesis of such substituted heterocyclic compounds has not yet been reported. The process has several distinguished features: (1) this is the first report on the synthesis of new dihydroisoquinolino[1,2-*a*]isoquinolizinium cations, and these diverse analogues of cationic alkaloids can be obtained in moderate to good yields; (2) this study provides an efficient method for the metal-mediated synthesis of new tetraheterocycles via the intramolecular addition of amines to alkynes, unlike that in the classical methods.

TABLE 1. Optimization of the Reaction Conditions[a]



1a 2a

entry	catalyst	solvent	time (h)	yield[b] (%)
1		PhMe	24	0
2	20%CuI	PhMe	24	0
3	20%$PdCl_2$	PhMe	24	0
4	20%$RuCl_3.xH_2O$	PhMe	24	0
5	20%K_2PtCl_4	PhMe	24	0
6	20% AgOTf	PhMe	24	0
7	20% AgOAc	PhMe	24	0
8	20% Ag_2CO_3	PhMe	24	0
9	20% $AgSbF_6$	PhMe	24	20
10	20% $AgSbF_6$	PhMe	48	21
11	20% $AgSbF_6$	DMF	24	0
12	20% $AgSbF_6$	CH_2Cl_2	24	< 10
13	20% $AgSbF_6$	THF	24	trace
14	20% $AgSbF_6$	CH_3CN	24	0
15	50% $AgSbF_6$	PhMe	24	38
16	50% $AgSbF_6$	PhMe	48	40
17	100% $AgSbF_6$	PhMe	24	65
18	100% $AgSbF_6$	PhMe	48	67
19	100% $AgSbF_6$/10% AuCl	PhMe	12	64
20	100% $AgSbF_6$/10%$AuCl_3$	PhMe	12	66
21	100% $AgSbF_6$/10% AuCl(PPh_3)	PhMe	12	78
22	100% $AgSbF_6$/20% AuCl(PPh_3)	PhMe	12	77
23	100% $AgSbF_6$/10% AuCl(PPh_3)	PhMe	48	75
24[c]	100% $AgSbF_6$/10% AuCl(PPh_3)	PhMe	48	15
25	100% TfOH/10% AuCl(PPh_3)	PhMe	48	0
26	100% AuCl(PPh_3)	PhMe	48	0
27[d]	100% $AgSbF_6$/10% AuCl(PPh_3)	PhMe	0.5	55
28[e]	**100% $AgSbF_6$/10% AuCl(PPh_3)**	**PhMe**	**12**	**76**

[a]The reaction was carried out in the presence of catalysts in anhydrous solvent at 110 °C under argon protection unless otherwise noted. [b]Yields of isolated products based on **1**. [c]The reaction was carried out at 80 °C. [d]The reaction was carried out under microwave irradiation (The temperature was measured by fiber optics inside the reaction vial). [e]The reaction was carried out without argon protection.

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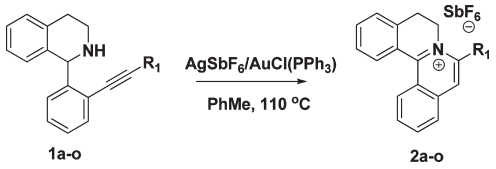
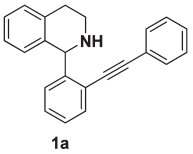
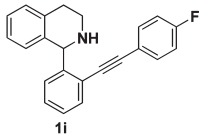
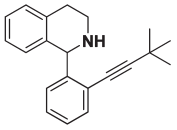
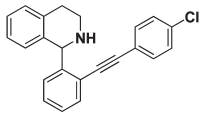
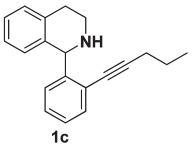
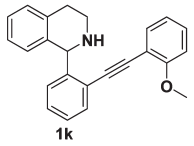
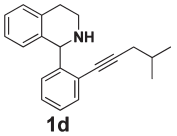
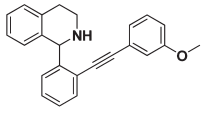
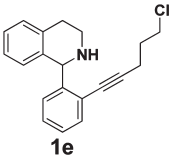
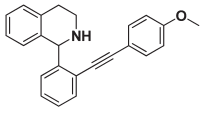
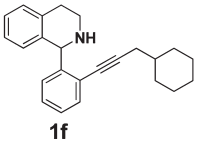
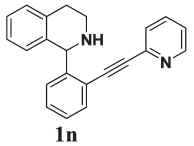
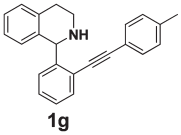
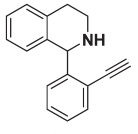
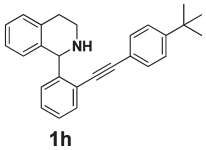
TABLE 2. Synthesis of Tetracyclic Isoquinolizinium Hexafluorostilbates with R^1 Substitutents[a]



1a-o 2a-o

entry	substrate **1**	product **2**: yield (%)[b]	entry	substrate **1**	product **2**: yield (%)[b]
1	 1a	**2a: 76**	9	 1i	**2i: 70**
2	 1b	**2b:trace**[c]	10	 1j	**2j: 62**
3	 1c	**2c: 71**	11	 1k	**2k:74**
4	 1d	**2d: 63**	12	 1*l*	**2*l*:70**
5	 1e	**2e:58**	13	 1m	**2m: 75**
6	 1f	**2f: 65**	14	 1n	**2n:0**[c]
7	 1g	**2g: 70**	15	 1o	**2o:0**
8	 1h	**2h:56**			

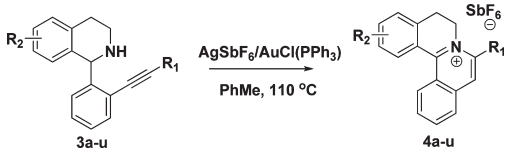
[a]The reaction was carried out in the presence of $AgSbF_6$ (100 mol %) and $AuCl(PPh_3)$ (10 mol %) in anhydrous toluene at 110 °C unless otherwise noted. [b]Yields of isolated products based on **1**. [c]The reactant was recovered.

Results and Discussion

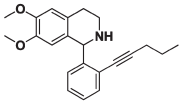
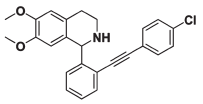
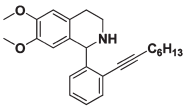
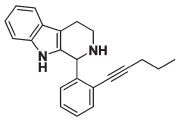
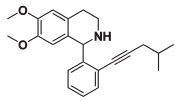
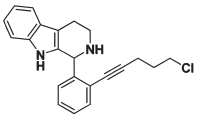
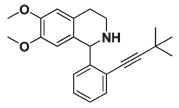
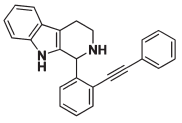
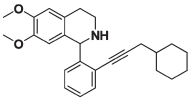
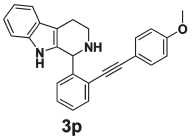
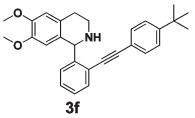
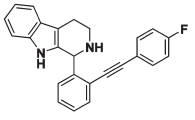
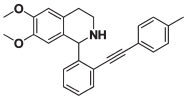
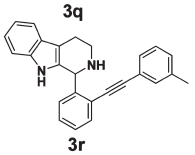
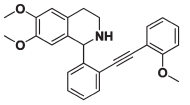
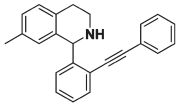
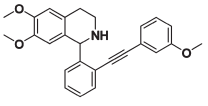
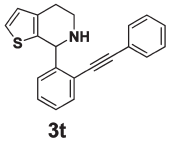
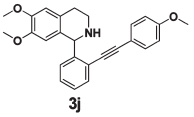
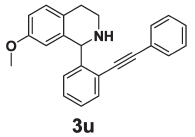
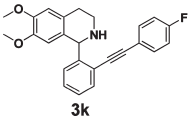
The optimal conditions were determined using **1a**[13] as a model substrate and by varying the concentrations of catalysts (different equivalents) and solvents. As shown in Table 1, under catalyst-free conditions the reaction did not occur, and only the starting material **1a** was recovered (entry 1, Table 1). Similarly, the reactions did not occur in the presence of CuI, $PdCl_2$, $RuCl_3 \cdot xH_2O$, K_2PtCl_4, AgOTf, AgOAc, and Ag_2CO_3 (entries 2−8, Table 1). Product **2a** was obtained

(13) For the synthesis of **1a**, see the Experimental Section.

TABLE 3. Synthesis of Tetracyclic Isoquinolizinium Hexafluorostilbates with R^1 and/or R^2 Substitutents[a]

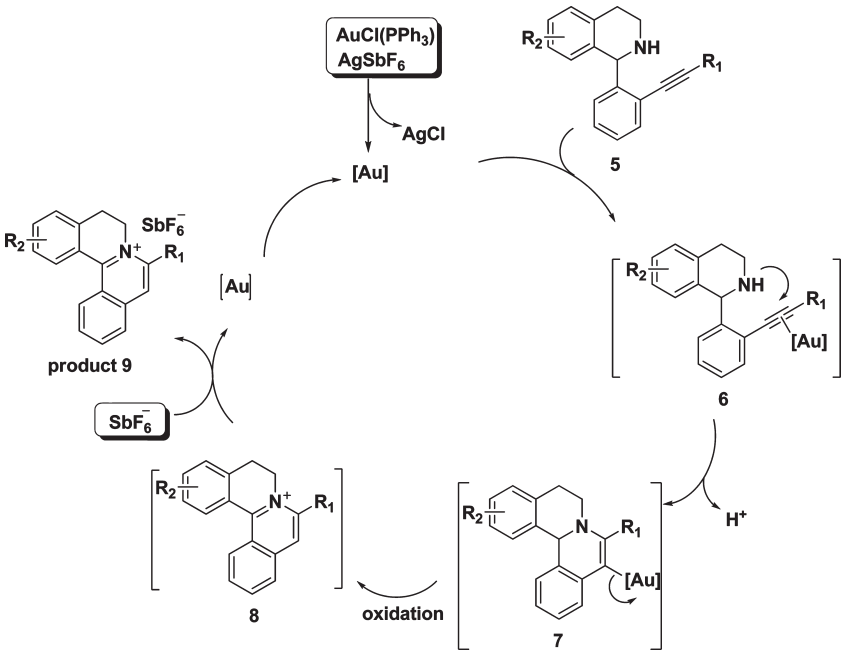


3a-u 4a-u

entry	substrate **3**	product **4**: yield (%)[b]	entry	substrate **3**	product **4**: yield (%)[b]
1	 **3a**	**4a: 71**	12	 ***3l***	***4l*: 76**
2	 **3b**	**4b: 74**	13	 **3m**	**4m: 74**
3	 **3c**	**4c: 67**	14	 **3n**	**4n: 69**
4	 **3d**	**4d: trace**[c]	15	 **3o**	**4o: 71**
5	 **3e**	**4e: 72**	16	 **3p**	**4p: 72**
6	 **3f**	**4f:74**	17	 **3q**	**4q: 71**
7	 **3g**	**4g: 64**	18	 **3r**	**4r: 74**
8	 **3h**	**4h:83**	19	 **3s**	**4s:72**
9	 **3i**	**4i:80**	20	 **3t**	**4t:74**
10	 **3j**	**4j: 84**	21	 **3u**	**4u:70**
11	 **3k**	**4k: 72**			

[a]The reaction was carried out in the presence of $AgSbF_6$ (100 mol %) and $AuCl(PPh_3)$ (10 mol %) in anhydrous toluene at 110 °C unless otherwise noted. [b]Yields of isolated products based on **1**. [c]The reactant was recovered.

SCHEME 1. Plausible Mechanism for the Cyclization



in 20% yield when 0.2 equiv of $AgSbF_6$ dissolved in anhydrous toluene was used at 110 °C for 24 h (entry 9, Table 1). Increasing the reaction time to 48 h did not improve the product yield (entry 10, Table 1). Polar solvents were found to have a detrimental effect on the reaction, and anhydrous toluene was confirmed to be the optimum solvent (entries 11−14, Table 1). When a stoichiometric amount of $AgSbF_6$ was used, the yield of product **2a** obviously increased to 65% (entry 17, Table 1). However, prolonging the reaction time did not substantially improve the yield (entries 16 and 18, Table 1). To accelerate the reaction, we used various cocatalysts (entries 19−24, Table 1). The addition of 10% $AuCl(PPh_3)$ could noticeably promote the intramolecular cyclization and decrease the reaction time, affording **2a** in 78% yield (entry 21, Table 1). Similar yields were obtained even when the amount of cocatalysts was increased or the reaction time was prolonged (entries 22 and 23, Table 1). In addition, the reaction temperature was found to play an important role in the process. For example, the yield of compound **2a** was only 10% when the temperature was reduced to 80 °C (entry 24, Table 1). We have done control experiments with 100% TfOH and 10% $AuCl(PPh_3)$; it did not work (entry 25, Table 1). We have also done control experiments with 100% $AuCl(PPh_3)$ only, and it did not work (entry 26, Table 1). We also performed the reaction under microwave irradiation at 110 °C for 30 min and could obtain only 55% the yield (entry 27, Table1), indicating that the classical heating method is more effective. Last, we performed the reaction without argon protection, and a similar yield (76%) was obtained (entries 21 and 28, Table 1).

The structure of **2a** is confirmed by ^1H nuclear magnetic resonance (NMR) spectroscopy, ^{13}C NMR spectroscopy, mass spectroscopy, and X-ray crystallography (see the Supporting Information).[14]

(14) CCDC 762577 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Under the optimized reaction conditions (1.0 equiv of $AgSbF_6$, 0.1 equiv of $AuCl(PPh_3)$, PhMe, 110 °C, 12 h, as shown in entry 28, Table 1), we then examined the generality of the process. The results are summarized in Tables 2 and 3. A variety of alkynes, including aliphatic, aromatic, and heterocyclic substitutents, were investigated (Table 2). The aliphatic alkynes generated the desired products in moderate yields (entries 3−6, Table 2). Steric hindrance strongly affected the reaction, and only a trace amount of **2b** was obtained (entry 2, Table 2). However, the alkynes with aromatic substituents produced higher yields (entries 7−13, Table 2). Better results were observed with electron-donating substitutents on the aromatic ring, presumably due to the electronic effect (entries 7, 8, and 11−13, Table 2). The ortho, meta, or para substitution on the aromatic ring of R_1 did not significantly affect the yields (entries 11−13, Table 2). Substrate **1n** with a heterocyclic substituted alkyne and **1o** with a terminal alkyne did not generate the desired products under the optimized conditions (entries 14 and 15, Table 2).

To further broaden the scope of this method, we also examined the influence of substitution on the A ring. As shown in Table 3, corresponding product yields increased greatly when the A ring was substituted by electron-donating groups. Similarly, substrates with aliphatic substituted alkyne moieties generated moderate to good yields (entries 1−5, Table 3). Steric hindrance strongly affected the reaction, and only a trace amount of **4d** was observed (entry 4, Table 3). We also examined the steric and electron effects of various substitutents on the aromatic alkyne. We found that the steric and electron effects did not significantly influence the reaction, and moderate product yields were obtained (entries 6−12, Table 3). The indole-substituted substrates could generate moderate yields of corresponding products (entries 13−18, Table 3). When the A ring was fused with a benzene or thiofuran ring or methoxyl phenyl moieties, **4s**, **4t**, and **4u** could be generated in 72%, 74%, and 70% yields, respectively (entries 19−21, Table 3).

On the basis of the above-mentioned findings, a plausible mechanism was proposed in Scheme 1. As has been postulated for other Au-catalyzed nucleophilic additions, the catalyst used in our method is a cationic gold complex typically precipitated from $AgSbF_6$ and $AuCl(PPh_3)$.[15] Initial activation of the gold catalyst to the alkyne function allows the formation of a transient intermediate (**6**). Intramolecular nucleophilic addition of the amine on the activated alkyne affords the intermediate **7**,[16] which on subsequent oxidative aromatization (**8**) and complexation with hexafluoro antimonate anion generates the tetracyclic isoquinoline hexafluorostilbates **9** and metallic gold. Product **9** is stable due to the conjugated system.

Conclusion

In summary, we have developed a mild strategy to synthesize a class of tetracyclic isoquinolizinium salts in moderate to good yields via silver- and gold-cocatalyzed intramolecular cyclization. Because of the biological activities of isoquinoline alkaloids, it is speculated that these new biologically intriguing structures will find broad applications in medicinal chemistry programs. Further studies to elucidate the precise mechanism underlying these reactions and to extend the scope of their synthetic utilities are in progress in our laboratory.

Experimental Section

Typical Procedure for the Synthesis of 1-(2-(Phenylethynyl)-phenyl)-1,2,3,4-tetrahydroisoquinoline (1a). To a solution of EDCI (1.2 mmol) and 2-iodobenzoic acid (1 mmol) in CH_2Cl_2 (20 mL) was added triethylamine (1.2 mmol), followed by addition of amines (1 mmol) 1 h later. The resulting mixture was stirred overnight under room temperature. When the starting materials were completely consumed as monitored with TLC, the reaction mixture was diluted with CH_2Cl_2, washed successively with water, aqueous HCl, saturated $NaHCO_3$, and brine, and dried by anhydrous Na_2SO_4. Evaporation of the solvent followed by chromatography on a short silica gel column with petroleum ether (PE)/EtOAc (4/1, v/v) as eluent afforded crude product 2-iodobenzamides. To a solution of the corresponding 2-iodophenylacetamides (1.0 mmol) in acetonitrile was added phosphoryl trichloride (5.0 mmol), and the resulting mixture was stirred for 2 h at 80 °C and monitored by TLC to establish completion. When the reaction was complete, the solvent was removed under reduced pressure. The residue was washed with $NaHCO_3$, the solvent was removed under reduced pressure, the residue was dissolved in CH_3OH, and $NaBH_4$ (5.0 mmol) was added for 2 h at room temperature. The solvent was removed under reduced pressure, and the residue was washed with NH_4Cl; when the solvent was removed under reduced pressure, the residue was dissolved in 1,4-dioxnne/2 N NaOH aq, $(Boc)_2O$ (5.0 mmol) was added for 1 h at 80 °C, and the reaction was monitored by TLC to establish completion. When the reaction was complete, the solvent was removed under reduced pressure, and the residue was purified by column chromatography. To a solution of the residue (1.0 mmol) and the terminal alkyne (1.2 mmol) in Et_3N (5 mL) were added $Pd(PPh_3)_2Cl_2$ (0.02 mmol) and CuI (0.01 mmol). The resulting mixture was then heated under an argon atmosphere at 80 °C. The reaction was monitored by TLC to establish completion. When the reaction was complete, the mixture was allowed to cool to room temperature, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel with petroleum ether (PE)/EtOAc (8/1, v/v) as eluent to afford the corresponding compounds. Then compound from the above procedure (1.0 mmol) was diluted in 10 mL of a TFA/CH_2Cl_2 1:1 mixture. After the mixture was stirred at room temperature for 1 h, the solvent was evaporated to afford **1a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, J = 7.2 Hz, 1H), 7.52−7.49 (m, 2H), 7.39−7.31 (m, 5H), 7.22 (d, J = 7.5 Hz, 1H), 7.17−7.13 (m, 3H), 7.77 (d, J = 7.8 Hz, 1H), 6.16 (s, 1H), 3.59 (br s, 1H), 3.20 (br s, 1H), 2.80 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2 132.8 132.2 131.8 130.0 129.2 128.9 128.8 128.3 128.0 127.1 124.1 122.2 117.9 95.7 85.4 57.2 39.9 25.6; MS (EI, m/z) 309 $[M]^+$; HRMS (EI) calcd for $C_{23}H_{19}N$ $[M]^+$ 309.1517, found 309.1520.

1-(2-(Pent-1-ynyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (1c): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, J = 8.4 Hz, 1H), 7.19−7.18 (m, 3H), 7.14−7.10 (m, 3H), 6.93 (t, J = 7.8 Hz, 1H), 6.19 (s, 1H), 4.28 (br s, 1H), 3.36 (t, J = 7.5 Hz, 1H), 2.99−2.96 (m, 1H), 2.89 (s, 1H), 2.43 (t, J = 7.8 Hz, 2H), 1.81−1.73 (m, 2H), 0.77 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.3 139.6 135.2 135.0 128.7 128.6 128.6 127.9 126.7 126.2 100.7 80.3 61.8 40.0 36.5 29.4 26.8 23.4; MS (EI, m/z) 275 $[M]^+$; HRMS (EI) calcd for $C_{20}H_{21}N$ $[M]^+$ 275.1674, found 275.1660.

1-(2-(4-Methylpent-1-ynyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (1d): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, J = 7.2 Hz, 2H), 7.21 (t, J = 7.5 Hz, 2H), 7.19−7.12 (m, 2H), 6.91 (t, J = 7.5 Hz, 2H), 5.70 (s, 1H), 3.82 (br s, 1H), 3.37 (br s, 1H), 2.77 (br, 2H), 2.35 (d, J = 4.8 Hz, 2H), 1.93−1.88 (m, 1H), 1.03 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.4 144.0 139.7 135.3 128.8 128.7 128.4 128.0 126.8 126.3 100.8 80.4 61.9 40.1 31.3 29.5 28.6 22.5; MS (EI, m/z) 289 $[M]^+$; HRMS (EI) calcd for $C_{21}H_{23}N$ $[M]^+$ 289.1830, found 289.1851.

1-(2-(5-Chloropent-1-ynyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (1e): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, J = 7.2 Hz, 1H), 7.36 (d, J = 7.2 Hz, 2H), 7.20 (t, J = 7.5 Hz, 2H), 6.99 (t, J = 7.2 Hz, 2H), 6.91 (t, J = 7.2 Hz, 1H), 5.81 (s, 1H), 4.20 (br, 2H), 3.69 (t, J = 6.3 Hz, 2H), 2.99−2.95 (m, 2H), 2.66 (t, J = 6.9 Hz, 2H), 2.10−2.02 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.0 139.6 136.0 135.0 134.5 132.3 128.7 128.5 127.8 126.7 126.6 100.7 79.9 61.9 43.6 36.5 31.3 29.4 17.1; MS (EI, m/z) 309 $[M]^+$; HRMS (EI) calcd for $C_{20}H_{20}ClN$ $[M]^+$ 309.1284, found 309.1296.

1-(2-(3-Cyclohexylprop-1-ynyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (1f): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, J = 7.5 Hz, 1H), 7.43−7.41 (m, 1H), 7.21 (t, J = 7.2 Hz, 2H), 7.15−7.13 (m, 2H), 6.92 (t, J = 8.4 Hz, 2H), 6.10 (s, 1H), 4.12 (br, 2H), 2.93−2.88 (m, 2H), 2.34 (d, J = 6.6 Hz, 2H), 1.23−1.11 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.6 136.2 135.3 128.8 128.7 128.4 128.0 126.7 126.4 126.3 100.7 80.4 62.0 40.0 37.4 32.7 29.5 27.4 26.2 26.1; MS (EI, m/z) 329 $[M]^+$; HRMS (EI) calcd for $C_{24}H_{27}N$ $[M]^+$ 329.2143, found 329.2147.

1-(2-(*p*-Tolylethynyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (1g): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, J = 7.5 Hz, 1H), 7.52−7.49 (m, 2H), 7.52−7.39 (m, 5H), 7.22 (s, 1H), 7.14 (d, J = 7.8 Hz, 2H), 6.77 (d, J = 7.8 Hz, 1H), 6.16 (s, 1H), 4.21 (br, 1H), 3.37 (br, 1H), 3.01−2.96 (m, 2H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.2 139.6 138.4 136.2 135.3 135.0 134.4 132.3 131.5 129.0 128.8 128.7 128.4 128.0 126.7 126.3 120.0 100.7 80.4 61.9 40.0 29.5 21.5; MS (EI, m/z) 323 $[M]^+$; HRMS (EI) calcd for $C_{24}H_{21}N$ $[M]^+$ 323.1674, found 323.1675.

1-(2-((4-*tert*-Butylphenyl)ethynyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (1h): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, J = 7.2 Hz, 1H), 7.56−7.52 (m, 3H), 7.37−7.34 (m, 3H), 7.17−7.09 (m, 4H),

(15) (a) Toullec, P. Y.; Genin, E.; Leseurre, L.; Genet, J. P.; Michelet, V. *Angew. Chem., Int. Ed.* **2006**, *45*, 7427. (b) Asao, N.; Aikawa, H.; Tago, S.; Umetsu, K. *Org. Lett.* **2007**, *9*, 4299.

(16) (a) Asao, N; Yudha, S. S.; Nogami, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 5526. (b) Asao, N.; Iso, K.; Yudha, S. S. *Org. Lett.* **2006**, *8*, 4149. (c) Huo, Z.; Yamamoto, Y. *Tetrahedron Lett.* **2009**, *50*, 3651.

7.01 (d, J = 8.7 Hz, 1H), 6.10 (s, 1H), 3.79 (br, 1H), 3.37 (br, 1H), 2.93−2.89 (m, 1H), 2.79 (br, 1H), 1.36 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.0 147.2 140.0 136.2 135.3 135.1 131.3 128.8 128.7 128.4 128.0 126.8 125.3 120.3 100.8 80.4 62.0 40.1 31.1 29.5 28.2; MS (EI, m/z) 365 $[M]^+$; HRMS (EI) calcd for $C_{27}H_{27}N$ $[M]^+$ 365.2143, found 365.2157.

1-(2-((4-Fluorophenyl)ethynyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (1i): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61−7.58 (m, 3H), 7.42 (d, J = 7.2 Hz, 2H), 7.24−7.16 (m, 5H), 7.05 (t, J = 8.7 Hz, 2H), 6.21 (s, 1H), 4.21 (br, 1H), 3.70 (br, 1H), 3.03−3.00 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1 139.6 136.0 135.0 134.5 133.5 132.3 128.7 128.6 128.0 127.8 126.7 126.4 126.3 122.4 119.4 115.6 115.4 100.7 80.0 61.9 40.1 29.5; MS (EI, m/z) 327 $[M]^+$; HRMS (EI) calcd for $C_{23}H_{18}FN$ $[M]^+$ 327.1423, found 327.1434.

1-(2-((4-Chlorophenyl)ethynyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (1j): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, J = 7.5 Hz, 1H), 7.31 (s, 2H), 7.25−7.23 (m, 4H), 7.18−7.16 (m, 4H), 6.93 (d, J = 8.1 Hz, 1H), 6.00 (s, 1H), 4.31−4.18 (br, 2H), 3.02−2.98 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1 139.6 136.0 135.3 134.5 134.2 132.8 132.4 128.7 128.6 128.5 128.0 127.8 126.8 126.7 126.5 126.3 121.8 100.7 80.0 61.9 36.6 24.6; MS (EI, m/z) 343 $[M]^+$; HRMS (EI) calcd for $C_{23}H_{18}ClN$ $[M]^+$ 343.1128, found 343.1130.

1-(2-((2-Methoxyphenyl)ethynyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (1k): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, J = 8.4 Hz, 1H), 7.43−7.41 (m, 1H), 7.21 (t, J = 7.5 Hz, 2H), 7.15−7.13 (m, 3H), 6.92 (t, J = 8.4 Hz, 3H), 6.62 (d, J = 8.1 Hz, 2H), 6.10 (s, 1H), 4.12 (br s, 2H), 3.84 (s, 3H), 2.91−2.88 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5 152.2 140.5 138.9 138.5 136.0 134.0 133.0 131.6 131.0 130.2 128.1 127.7 126.6 125.8 125.0 124.0 115.8 90.0 80.2 62.2 56.2 40.0 27.6; MS (EI, m/z) 339 $[M]^+$; HRMS (EI) calcd for $C_{24}H_{21}NO$ $[M]^+$ 339.1623, found 339.1626.

1-(2-((3-Methoxyphenyl)ethynyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (1l): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 8.1 Hz, 2H), 7.70 (s, 1H), 7.56−7.50 (m, 1H), 7.23−7.18 (m, 3H), 6.91 (t, J = 7.8 Hz, 3H), 6.75 (d, J = 8.7 Hz, 2H), 6.09 (s, 1H), 4.09 (br s, 2H), 3.80 (s, 3H), 3.10 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6 148.4 138.7 138.5 136.0 134.0 133.0 131.5 131.0 130.2 128.1 127.7 126.6 125.6 125.0 124.0 120.1 110.8 98.2 90.0 60.1 55.5 42.0 27.6; MS (EI, m/z) 339 $[M]^+$; HRMS (EI) calcd for $C_{24}H_{21}NO$ $[M]^+$ 339.1623, found 339.1620.

1-(2-((4-Methoxyphenyl)ethynyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (1m): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58−7.48 (dd, J = 14.1, 6.9 Hz, 3H), 7.32 (s, 1H), 7.22−7.20 (m, 3H), 7.16−7.14 (m, 3H), 6.88 (d, J = 8.7 Hz, 2H), 5.94 (s, 1H), 4.17 (br, 2H), 3.82 (s, 3H), 3.00 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2 139.0 136.2 132.9 132.0 131.4 129.4 129.2 127.3 126.4 122.1 121.8 119.6 119.4 118.2 118.1 111.0 110.6 95.1 80.2 62.0 55.4 41.2 21.2; MS (EI, m/z) 339 $[M]^+$; HRMS (EI) calcd for $C_{24}H_{21}NO$ $[M]^+$ 339.1623, found 339.1627.

6,7-Dimethoxy-1-(2-(pent-1-ynyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (3a): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44−7.41 (m, 1H), 7.15 (br, 2H), 6.92 (t, J = 7.5 Hz, 1H), 6.64 (s, 1H), 6.62 (s, 1H), 5.95 (s, 1H), 4.11 (br, 1H), 3.84 (s, 3H), 3.71 (s, 3H), 3.37 (br, 1H), 2.95−2.87 (m, 2H), 2.66 (t, J = 6.9 Hz, 3H), 2.07 (t, J = 6.9 Hz, 2H), 0.91−0.84 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8 147.4 132.2 128.7 128.2 128.0 127.3 127.1 126.7 111.2 111.0 110.4 100.0 82.3 63.9 55.9 55.8 43.7 36.6 31.3 28.2 17.1; MS (EI, m/z) 335 $[M]^+$; HRMS (EI) calcd for $C_{22}H_{25}NO_2$ $[M]^+$ 335.1885, found 335.1890.

6,7-Dimethoxy-1-(2-(oct-1-ynyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (3b): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.34 (m, 2H), 7.21 (t, J = 7.2 Hz, 1H), 6.92 (t, J = 7.5 Hz, 1H), 6.64 (s, 2H), 6.08(s, 1H), 4.15 (br s, 1H), 3.85 (s, 3H), 3.73 (s, 3H), 3.36 (br s, 1H), 2.92−2.89 (m, 1H), 2.77 (br s, 1H), 1.50−1.26 (m, 11H), 0.90−0.84 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8 147.4 140.0 139.1 135.2 129.2 128.7 128.4 127.2 127.0 111.0 110.7 100.3 80.3 61.5 55.9 55.8 46.1 32.1 30.2 27.1 26.1 26.0 22.2 16.0; MS (EI, m/z) 377 $[M]^+$; HRMS (EI) calcd for $C_{25}H_{31}NO_2$ $[M]^+$ 377.2335, found 377.2340.

6,7-Dimethoxy-1-(2-(4-methylpent-1-ynyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (3c): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−741 (m, 1H), 7.21 (t, J = 7.2 Hz, 1H), 6.91 (t, J = 7.5 Hz, 2H), 6.63 (s, 2H), 5.80 (s, 1H), 4.13 (br s, 1H), 3.83 (s, 3H), 3.71 (s, 3H), 3.38 (br s, 1H), 2.77 (br, 2H), 2.35 (d, J = 5.7 Hz, 2H), 1.93−1.89 (m, 1H), 1.03 (d, J = 1.8 Hz, 3H), 1.02 (d, J = 1.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8 147.4 140.0 135.3 128.7 128.4 128.2 127.2 127.0 111.2 111.0 110.7 100.3 80.3 61.6 55.8 55.7 40.9 32.1 28.9 28.5 22.2; MS (EI, m/z) 349 $[M]^+$; HRMS (EI) calcd for $C_{23}H_{27}NO_2$ $[M]^+$ 349.2042, found 349.2045.

1-(2-(3-Cyclohexylprop-1-ynyl)phenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (3e): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (br s, 1H), 7.21 (t, J = 7.5 Hz,1H), 7.15−7.13 (m, 1H), 6.92 (t, J = 8.4 Hz, 1H), 6.64 (s, 1H), 6.61 (s, 1H), 5.70 (s, 1H), 4.13 (br s, 1H), 3.84 (d, J = 5.4 Hz, 3H), 3.71(d, J = 5.7 Hz, 3H), 3.37 (br s, 1H), 2.93−2.88 (m, 2H), 2.35 (d, J = 6.6 Hz, 1H), 2.16 (s, 1H), 1.84 (br, 1H), 1.25−0.99 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8 147.4 140.0 128.7 128.2 127.2 127.0 126.4 111.2 111.0 110.7 110.5 100.3 80.3 61.5 55.8 55.7 50.0 39.4 34.0 29.2 28.9 27.2 26.0; MS (EI, m/z) 389 $[M]^+$; HRMS (EI) calcd for $C_{26}H_{31}NO_2$ $[M]^+$ 389.2355, found 389.2360.

1-(2-((4-*tert*-Butylphenyl)ethynyl)phenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (3f): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J = 7.2 Hz, 1H), 7.43−7.33 (m, 3H), 7.20 (d, J = 7.5 Hz, 2H), 6.93 (t, J = 8.4 Hz, 2H), 6.65 (s, 2H), 5.92 (s, 1H), 4.17 (br s, 1H), 3.86 (s, 3H), 3.74 (s, 3H), 3.36 (br s, 1H), 2.93−2.90 (m, 1H), 2.79 (br, 1H), 1.36 (br s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.0148.3 135.6 133.8 131.3 130.4 130.0 128.3 128.0 136.4 125.0 124.7 124.4 118.9 115.9 114.1 121.0 110.8 100.3 80.3 61.6 56.7 42.0 31.1 30.1 27.2; MS (EI, m/z) 425 $[M]^+$; HRMS (EI) calcd for $C_{29}H_{31}NO_2$ $[M]^+$ 425.2355, found 425. 2361.

6,7-Dimethoxy-1-(2-(*p*-tolylethynyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (3g): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.44 (br, 2H), 7.14 (d, J = 7.8 Hz, 3H), 6.92 (t, J = 7.5 Hz, 2H), 6.95 (s, 1H), 6.62 (s, 1H), 5.97 (s, 1H), 4.13 (br, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.37 (br, 1H), 2.92 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.7 147.3 144.0 140.0 138.4 131.3 129.0 128.7 128.3 128.0 127.1 127.0 126.6 120.0 116.0 111.1 110.0 110.6 100.2 80.2 61.5 55.8 55.7 41.1 29.1 21.4; MS (EI, m/z) 383 $[M]^+$; HRMS (EI) calcd for $C_{26}H_{25}NO_2$ $[M]^+$ 383.1885, found 383.1882.

6,7-Dimethoxy-1-(2-((2-methoxyphenyl)ethynyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (3h): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 8.1 Hz, 1H), 7.62 (d, J = 8.1 Hz, 1H), 7.39 (br s, 2H), 7.21 (d, J = 7.2 Hz, 2H), 7.07−7.02 (m, 1H), 6.93 (t, J = 7.5 Hz, 1H), 6.65 (s, 2H), 6.11 (s, 1H), 4.13 (br, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.74 (s, 3H), 3.39 (br, 1H), 2.92 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0 152.7 152.0 148.3 143.6 138.8 135.7 134.5 133.3 131.4 130.7 130.7 130.3 128.1 124.9 121.8 121.0 118.4 115.4 96.1 84.1 64.2 56.9 56.7 55.8 41.0 27.0; MS (EI, m/z) 399 $[M]^+$; HRMS (EI) calcd for $C_{26}H_{25}NO_3$ $[M]^+$ 399.1834, found 399.1837.

6,7-Dimethoxy-1-(2-((3-methoxyphenyl)ethynyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (3i): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71−7.67 (m, 1H), 7.59 (s, 1H), 7.35 (d, J = 7.2 Hz, 1H), 7.20 (t, J = 7.2 Hz, 1H), 7.10−7.06 (m, 2H), 6.90 (t, J = 8.1 Hz, 1H), 6.80 (d, J = 7.2 Hz, 1H), 6.64 (s, 2H), 6.08 (s, 1H), 4.15 (br s, 2H), 3.85 (s, 3H), 3.72 (s, 3H), 3.56 (s, 3H), 2.77 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0 148.1 147.8 143.6 141.1 138.6 135.5 133.9 133.5 130.4 128.1 125.0 124.4 121.9 118.9 117.4 116.0 115.0 96.0 82.1 63.0 56.8 56.7 56.0 40.0 27.2; MS (EI, m/z) 399 $[M]^+$; HRMS (EI) calcd for $C_{26}H_{25}NO_3$ $[M]^+$ 399.1834, found 399.1831.

6,7-Dimethoxy-1-(2-((4-methoxyphenyl)ethynyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (3j): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, J = 8.1 Hz, 1H), 7.45 (d, J = 7.2 Hz, 1H), 7.35 (d, J = 7.2 Hz, 1H), 7.21 (t, J = 7.2 Hz, 2H), 6.98 (t, J = 7.8 Hz, 1H), 6.91 (t, J = 7.2 Hz, 2H), 6.63 (s, 2H), 5.83 (s, 1H), 4.16 (br s, 1H), 3.85 (s, 4H), 3.72 (s, 5H), 3.35 (br s, 1H), 2.75 (br, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4 147.8 147.5 140.5 138.7 135.6 133.7 131.7 130.4 130.2 128.1 124.8 124.6 124.2 118.8 115.6 114.8 111.0 100.3 80.4 60.6 59.7 55.6 42.0 27.3; MS (EI, m/z) 399 $[M]^+$; HRMS (EI) calcd for $C_{26}H_{25}NO_3$ $[M]^+$ 399.1834, found 399.1840.

1-(2-((4-Fluorophenyl)ethynyl)phenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (3k): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.49 (d, J = 8.1 Hz, 1H), 7.27−7.20 (m, 3H), 7.07−7.01 (m, 1H), 6.93 (t, J = 7.8 Hz, 2H), 6.65 (s, 2H), 5.63 (s, 1H), 4.14 (br s,1H), 3.87 (s, 3H), 3.74 (s, 3H), 3.37 (br s, 1H), 2.94 (br, 1H), 2.79 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5 147.7 147.3 140.0 138.8 135.0 128.7 128.2 128.0 127.5 127.1 126.7 113.1 111.1 110.6 100.2 80.2 61.4 55.8 55.7 41.1 28.4; MS (EI, m/z) 387 $[M]^+$; HRMS (EI) calcd for $C_{25}H_{22}FNO_2$ $[M]^+$ 387.1635, found 387.1637.

1-(2-((4-Chlorophenyl)ethynyl)phenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (3l): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, J = 7.8 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.21 (t, J = 7.2 Hz, 3H), 7.02 (br s, 1H), 6.91 (t, J = 7.8 Hz, 2H), 6.64 (s, 2H), 5.92 (s, 1H), 4.16 (br s, 1H), 3.85 (s, 3H), 3.72 (s, 3H), 3.36 (br s, 1H), 2.92−2.89 (m, 1H), 2.78−2.73 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8 147.4 138.8 134.0 130.4 130.0 129.3 128.9 128.4 128.0 127.4 126.5 125.0 124.4 118.9 116.0 111.4 111.1 100.3 80.3 61.6 55.8 55.7 40.0 28.0; MS (EI, m/z) 403 $[M]^+$; HRMS (EI) calcd for $C_{25}H_{22}ClNO_2$ $[M]^+$ 403.1339, found 403.1342.

1-(2-(Pent-1-ynyl)phenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]-indole (3m): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59−7.54 (m, 3H), 7.36−7.33 (m, 2H), 7.16−7.12 (m, 3H), 6.01 (s, 1H), 4.20 (br s, 1H), 3.71 (br s, 1H), 299 (br s, 2H), 1.85 (t, J = 7.2 Hz, 2H), 1.01 (t, J = 7.2 Hz, 3H), 0.88−0.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.2 134.5 132.4 131.6 128.6 128.3 127.9 126.7 126.5 126.4 123.3 93.6 80.1 61.9 44.1 29.2 24.1 22.0 17.6; MS (EI, m/z) 314 $[M]^+$; HRMS (EI) calcd for $C_{22}H_{22}N_2$ $[M]^+$ 314.1783, found 314.1785.

1-(2-(5-Chloropent-1-ynyl)phenyl)-2,3,4,9-tetrahydro-1*H*-pyrido-[3,4-*b*]indole (3n): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67−7.64 (m, 1H), 7.56 (s, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.30−7.27 (m, 4H), 7.00 (t, J = 8.1 Hz, 1H), 5.90 (s, 1H), 4.30−4.21 (br, 2H), 3.69 (t, J = 6.3 Hz, 2H), 2.97 (s, 2H), 2.66 (t, J = 6.9 Hz, 2H), 2.10−2.04 (m, 2H); ^{13}C NMR (75 MHz, DMSO) δ 146.0 140.6 136.6 132.5 131.9 130.4 129.3 128.6 126.7 122.0 119.3 118.5 112.0 109.2 100.3 80.4 60.0 48.6 44.4 32.0 31.4 30.6; MS (EI, m/z) 348 $[M]^+$; HRMS (EI) calcd for $C_{22}H_{21}ClN_2$ $[M]^+$ 348.1393, found 348.1396.

1-(2-(Phenylethynyl)phenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]-indole (3o): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56−7.54 (m, 3H), 7.37−7.34 (m, 3H), 7.30−7.27 (m, 3H), 7.15−7.10 (m, 3H), 6.99 (t, J = 7.8 Hz, 1H), 5.89 (s, 1H), 4.08- 3.85 (br, 1H), 3.25 (br s, 1H), 2.64 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.2 140.0 136.2 132.8 132.0 131.5 129.4 128.8 128.5 127.3 126.4 122.1 121.9 119.6 119.4 118.2 118.2 111.0 110.9 87.6 81.0 60.0 42.3 24.5; MS (EI, m/z) 348 $[M]^+$; HRMS (EI) calcd for $C_{25}H_{20}N_2$ $[M]^+$ 348.1626, found 348.1632.

1-(2-((4-Methoxyphenyl)ethynyl)phenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (3p): ^{1}H NMR (300 MHz,$CDCl_3$) δ 7.65−7.62 (m, 1H), 7.55−7.49 (m, 5H), 7.24 (s, 1H), 7.15−7.10 (m, 2H), 6.83 (d, J = 8.7 Hz, 3H), 5.82 (s, 1H), 4.22 (br s, 1H), 3.84 (s, 3H), 3.62 (br s, 1H), 2.96 (s, 2H); ^{13}C NMR (75 MHz, DMSO) δ 159.5 155.0 140.0 136.2 133.2 132.6 132.4 131.4 128.7 127.9 126.3 128.2 121.2 118.6 117.8 114.6 114.1 111.4 108.6 94.3 86.3 79.3 55.2 46.2 28.0; MS (EI, m/z) 378 $[M]^+$; HRMS (EI) calcd for $C_{26}H_{22}N_2O$ $[M]^+$ 378.1732, found 378.1738.

1-(2-((4-Fluorophenyl)ethynyl)phenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (3q): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.53 (d, J = 8.1 Hz, 1H), 7.67−7.64 (m, 1H), 7.55 (d, J = 7.2 Hz, 3H), 7.15 (t, J = 8.1 Hz, 3H), 7.08−6.96 (m, 3H), 5.70 (s, 1H), 4.01 (br s, 1H), 3.54 (br s, 1H), 2.94 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2 144.1 140.0 136.2 136.1 133.5 132.7 132.0 129.4 128.8 127.4 126.5 122.1 122.0 119.5 118.3 115.9 111.0 110.9 109.4 87.3 80.2 60.2 41.0 21.0; MS (EI, m/z) 366 $[M]^+$; HRMS (EI) calcd for $C_{25}H_{19}FN_2$ $[M]^+$ 366.1532, found 366.1542.

1-(2-(*m*-Tolylethynyl)phenyl)-2,3,4,9-tetrahydro-1*H*-pyrido-[3,4-*b*]indole (3r): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.66 (d, J = 7.2 Hz, 1H), 7.46 (d, J = 7.5 Hz, 3H), 7.19−7.11 (m, 6H), 7.00 (t, J = 7.5 Hz, 1H), 5.98 (s, 1H), 4.19−3.99 (br, 1H), 3.22 (br s, 1H), 2.69 (s, 2H), 2.19 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 137.0 136.9 134.0 132.8 131.9 130.6 129.0 128.9 128.6 128.4 128.3 126.4 125.3 123.0 115.5 115.1 114.9 114.0 113.9 113.1 94.8 82.4 60.0 47.6 32.1 28.1; MS (EI, m/z) 362$[M]^+$; HRMS (EI) calcd for $C_{26}H_{22}N_2$ $[M]^+$ 362.1783, found 362.1780.

7-Methyl-1-(2-(phenylethynyl)phenyl)-1,2,3,4-tetrahydroiso-quinoline (3s): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, J = 7.5 Hz, 2H), 7.44 (s, 1H), 7.22−7.20 (m, 4H), 7.14 (d, J = 7.5 Hz, 3H), 6.92 (t, J = 7.2 Hz, 2H), 6.11 (s, 1H), 3.38 (br s, 2H), 2.92 (s, 2H), 2.17(s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.2 139.6 136.2 135.3 135.0 128.7 128.6 128.4 128.0 126 126.3 100.7 80.4 61.9 40.0 29.5 22.1; MS (EI, m/z) 323 $[M]^+$; HRMS (EI) calcd for $C_{24}H_{21}N$ $[M]^+$ 323.1674, found 323.1678.

7-(2-(Phenylethynyl)phenyl)-4,5,6,7-tetrahydrothieno[2,3-*c*]-pyridine (3t): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70−7.54 (m, 1H), 7.53 (d, J = 7.2 Hz, 2H), 7.36 (d, J = 7.2 Hz, 2H), 7.21 (t, J = 7.2 Hz, 2H), 6.98 (t, J = 6.9 Hz, 1H), 6.91 (t, J = 7.5 Hz, 2H), 6.81 (d, J = 6.9 Hz, 1H), 6.07 (s, 1H), 3.63 (br, 2H), 2.92−2.90 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.2 132.0 129.4 128.8 128.6 128.5 128.4 128.3 126.4 125.6 123.7 122.1 119.5 118.2 111.0 100.1 80.5 65.5 44.3 29.1; MS (EI, m/z) 315 $[M]^+$; HRMS (EI) calcd for $C_{21}H_{17}NS$ $[M]^+$ 315.1082, found 315.1087.

7-Methoxy-1-(2-(phenylethynyl)phenyl)-1,2,3,4-tetrahydroiso-quinoline (3u): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 6.9 Hz, 1H), 7.80 (d, J = 7.2 Hz, 1H), 7.71−7.67 (m, 1H), 7.45 (d, J = 7.2 Hz, 1H), 7.37−7.33 (m, 2H), 7.21 (t, J = 7.5 Hz, 2H), 6.99 (t, J = 6.9 Hz, 1H), 6.92 (t, J = 7.2 Hz, 2H), 6.75 (s, 1H), 6.08 (s, 1H), 4.15 (br, 1H), 3.85 (s, 3H), 3.36 (br, 1H), 2.92−2.88 (m, 1H), 2.78 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1 150.4 150.0 146.0 144.0 139.1 135.7 135.1 133.3 131.4 130.7 130.4 128.2 125.9 122.1 121.9 119.0 116.0 96.1 94.0 61.0 55.8 41.2 28.0; MS (EI, m/z) 339 $[M]^+$; HRMS (EI) calcd for $C_{24}H_{21}NO$ $[M]^+$ 339.1623, found 339.1630.

Typical Procedure for the Synthesis of 8-Phenyl-5,6-dihydro-isoquinolino[1,2-*a*]isoquinolizinium Hexafluorostilbate (2a). A mixture of **1a** (0.1 mmol) and $AgSbF_6$ (0.1 mmol)/$AuCl(PPh_3)$ (0.01 mmol) in 5 mL of anhydrous toluene was heated at 110 °C in a sealed tube for 12 h. After the reaction was cooled to ambient temperature, the solvent was removed under reduced pressure. The residue was purified by column chromatography with CH_2Cl_2/MeOH (20/1, v/v) to yield **2a** as a yellow solid (yield 76%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (d, J = 8.7 Hz, 1H), 8.08 (t, J = 7.5 Hz, 2H), 8.00 (s, 1H), 7.95 (d, J = 8.1 Hz, 1H), 7.88 (t, J = 7.2 Hz, 2H), 7.72 (d, J = 7.2 Hz, 2H), 7.60 (t, J = 7.2 Hz, 3H), 7.48 (d, J = 7.2 Hz, 2H), 4.69 (s, 2H), 3.53 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8 148.2 139.0 138.3 136.1 134.0 133.2 132.2 131.0 129.8 128.5 128.4 128.0 126.5 125.9 46.0 27.5; MS (EI, m/z) 308 $[M]^+$; HRMS (EI) calcd for $C_{23}H_{18}N$ $[M]^+$ 308.1434, found 308.1438.

8-Propyl-5,6-dihydroisoquinolino[1,2-*a*]isoquinolizinium Hexafluorostilbate (2c). In the same manner as described in the preparation of **2a**, **2c** was obtained as a yellow solid after purification by column chromatography with CH_2Cl_2/MeOH (20/1, v/v) (yield 71%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (d, J = 8.7 Hz, 1H), 8.10−8.05 (m, 2H), 7.95 (s, 1H), 7.86 (d, J = 7.8 Hz,

1H), 7.82 (d, J = 6.9 Hz, 1H), 7.68 (d, J = 7.5 Hz, 1H), 7.59 (t, J = 7.8 Hz, 2H), 3.44 (t, J = 5.7 Hz, 2H), 3.35 (t, J = 6.0 Hz, 2H), 1,80−1.66 (m, 4H), 1.20 (br s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4 147.1 139.4 138.8 135.7 133.9 132.7 130.3 130.0 128.3 127.4 127.3 126.6 125.4 124.5 50.0 41.4 37.0 32.9 25.9; MS (EI, m/z) 274 $[M]^+$; HRMS (EI) calcd for $C_{20}H_{20}N$ $[M]^+$ 274.1590, found 274.1593.

8-Isobutyl-5,6-dihydroisoquinolino[1,2-*a*]isoquinolizinium hexafluorostilbate (2d). In the same manner as described in the preparation of **2a**, **2d** was obtained as a yellow solid after purification by column chromatography with CH_2Cl_2/MeOH (20/1, v/v) (yield 63%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (d, J = 6.3 Hz, 1H), 8.08 (d, J = 6.0 Hz, 1H), 8.03 (t, J = 5.1 Hz, 1H), 7.96 (s, 1H), 7.83 (t, J = 5.7 Hz, 2H), 7.67 (t, J = 5.4 Hz, 1H), 7.61 (d, J = 5.4 Hz, 1H), 7.53 (t, J = 6.0 Hz, 1H), 3.55 (s, 2H), 3.49 (d, J = 4.8 Hz, 2H), 1.69 (s, 2H), 1.09 (s, 3H), 1.08 (s, 3H), 0.89−0.83 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4 148.0 139.9 138.9 135.4 133.8 132.5 130.1 128.4 127.4 127.2 126.6 125.3 124.5 53.4 50.5 42.9 30.9 27.9 27.7; MS (EI, m/z) 288 $[M]^+$; HRMS (EI) calcd for $C_{21}H_{22}N$ $[M]^+$ 288.1747, found 288.1751.

8-(3-Chloropropyl)-5,6-dihydroisoquinolino[1,2-*a*]isoquinolizinium Hexafluorostilbate (2e). In the same manner as described in the preparation of **2a**, **2e** was obtained as a yellow solid after purification by column chromatography with CH_2Cl_2/MeOH (20/1, v/v) (yield 58%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (d, J = 8.7 Hz, 1H), 8.10 (d, J = 7.5 Hz, 1H), 7.87 (d, J = 8.7 Hz, 2H), 7.66 (d, J = 7.2 Hz, 1H), 7.59 (d, J = 7.8 Hz, 2H), 7.59 (d, J = 7.8 Hz, 2H), 3.82 (t, J = 5.7 Hz, 2H), 3.60 (t, J = 7.5 Hz, 2H), 3.40 (t, J = 5.7 Hz, 2H), 2.42 (t, J = 6.9 Hz, 2H), 2.29−2.18 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.2 146.0 141.1 137.9 135.6 130.6 128.5 127.2 127.1 126.8 123.9 122.3 121.3 57.1 47.1 32.0 28.2 25.1; MS (ESI, m/z) 308 $[M]^+$; HRMS (ESI) calcd for $C_{20}H_{19}ClN$ $[M]^+$ 308.1201, found 308.1196.

8-(Cyclohexylmethyl)-5,6-dihydroisoquinolino[1,2-*a*]isoquinolizinium Hexafluorostilbate (2f). In the same manner as described in the preparation of **2a**, **2f** was obtained as a yellow solid after purification by column chromatography with CH_2Cl_2/MeOH (20/1, v/v) (yield 65%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, J = 8.7 Hz, 1H), 8.09 (s, 1H), 7.95 (d, J = 8.1 Hz, 1H), 7.89 (t, J = 7.2 Hz, 2H), 7.72 (t, J = 6.6 Hz, 1H), 7.60 (t, J = 6.3 Hz, 2H), 7.49 (d, J = 7.2 Hz, 1H), 4.75 (t, J = 6.0 Hz, 2H), 3.53 (t, J = 7.0 Hz, 2H), 2.93 (d, J = 6.5 Hz, 2H), 2.09−1.94 (m, 1H), 1.19−1.14 (m, 4H), 1.07−0.98 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.3 140.4 139.2 138.4 136.0 134.1 133.0 130.5 130.1 129.6 129.0 128.1 126.8 126.5 124.6 49.0 43.6 35.1 29.7 29.0 27.3 21.5 19.1; MS (EI, m/z) 328 $[M]^+$; HRMS (EI) calcd for $C_{24}H_{26}N$ $[M]^+$ 328.2060, found 328.2070.

8-*p*-Tolyl-5,6-dihydroisoquinolino[1,2-*a*]isoquinolizinium Hexafluorostilbate (2g). In the same manner as described in the preparation of **2a**, **2g** was obtained as a yellow solid after purification by column chromatography with CH_2Cl_2/MeOH (20/1, v/v) (yield 70%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, J = 8.7 Hz, 1H), 8.17 (t, J = 8.1 Hz, 1H), 8.00 (s, 1H), 7.98 (d, J = 7.5 Hz, 1H), 7.87 (t, J = 8.7 Hz, 1H), 7.70−7,62 (m, 4H), 7.56 (t, J = 6.9 Hz, 2H), 7.38 (d, J = 7.8 Hz, 2H), 4.65 (t, J = 5.7 Hz, 2H), 3.28 (t, J = 6.0 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4 146.7 141.2 138.9 135.8 133.8 133.0 130.8 130.3 130.2 130.1 129.3 128.3 127.5 126.7 125.9 125.1 52.2 27.8 21.5; MS (EI, m/z) 322 $[M]^+$; HRMS (EI) calcd for $C_{24}H_{20}N$ $[M]^+$ 322.1590, found 322.1597.

8-(4-*tert*-Butylphenyl)-5,6-dihydroisoquinolino[1,2-*a*]isoquinolizinium Hexafluorostilbate (2h). In the same manner as described in the preparation of **2a**, **2h** was obtained as yellow solid after purification by column chromatography with CH_2Cl_2/MeOH (20/1, v/v) (yield 56%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (d, J = 6.6 Hz, 1H), 8.16−8.01 (m, 4H), 7.89 (t, J = 6.0 Hz, 2H), 7.68−7.54 (m, 6H), 4.59 (s, 2H), 3.22 (s, 2H), 1.38 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5 154.3 146.4 138.8 138. Six 135.5 133.8 133.2 130.9 130.3 129.8 129.7 129.3 128.6 128.1 127.6 126.7 126.3 126.1 125.9 125.2 52.1 31.1 29.6 27.6; MS (ESI, m/z) 364 $[M]^+$; HRMS (ESI) calcd for $C_{27}H_{26}N$ $[M]^+$ 364.2060, found 364.2057.

8-(4-Fluorophenyl)-5,6-dihydroisoquinolino[1,2-*a*]isoquinolizinium Hexafluorostilbate (2i). In the same manner as described in the preparation of **2a**, **2i** was obtained as yellow solid after purification by column chromatography with CH_2Cl_2/MeOH (20/1, v/v) (yield 70%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (d, J = 8.4 Hz, 1H), 8.06 (s, 1H), 7.92 (t, J = 8.4 Hz, 2H), 7.78 (t, J = 7.5 Hz, 2H), 7.62−7.50 (m, 7H), 3.79 (d, J = 5.8 Hz, 2H), 3.39 (d, J = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, DMSO) δ 164.1 156.1 147.1 144.1 135.8 133.7 133.0 130.8 130.2 130.1 130.0 129.2 128.2 127.5 126.7 125.9 119.5 56.1 28.0; MS (ESI, m/z) 326 $[M]^+$; HRMS (ESI) calcd for $C_{23}H_{17}FN$ $[M]^+$ 326.1340, found 326.1334.

8-(4-Chlorophenyl)-5,6-dihydroisoquinolino[1,2-*a*]isoquinolizinium Hexafluorostilbate (2j). In the same manner as described in the preparation of **2a**, **2j** was obtained as yellow solid after purification by column chromatography with CH_2Cl_2/MeOH (20/1, v/v) (yield 62%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, J = 6.6 Hz, 1H), 8.08 (t, J = 6.3 Hz, 2H), 8.00 (s, 1H), 7.95 (d, J = 6.0 Hz, 1H), 7.96 (d, J = 6.0 Hz, 2H), 7.72 (t, J = 5.4 Hz, 1H), 7.60 (t, J = 5.7 Hz, 3H), 7.53 (d, J = 2.4 Hz, 2H), 3.31 (s, 2H), 3.26 (d, J = 5.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1 155.1 147.1 144.1 135.8 133.7 133.0 130.8 130.2 130.1 130.0 129.2 128.2 127.5 126.7 125.8 122.5 56.4 28.1; MS (ESI, m/z) 342 $[M]^+$; HRMS (ESI) calcd for $C_{23}H_{17}ClN$ $[M]^+$ 342.1044, found 342.1044.

8-(2-Methoxyphenyl)-5,6-dihydroisoquinolino[1,2-*a*]isoquinolizinium Hexafluorostilbate (2k). In the same manner as described in the preparation of **2a**, **2k** was obtained as yellow solid after purification by column chromatography with CH_2Cl_2/MeOH (20/1, v/v) (yield 74%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (d, J = 6.0 Hz, 1H), 8.18 (d, J = 6.3 Hz, 1H), 8.11 (t, J = 6.3 Hz, 2H), 8.01 (d, J = 6.0 Hz, 1H), 7.93 (t, J = 6.3 Hz, 1H), 7.73−7.56 (m, 5H), 7.12 (d, J = 6.9 Hz, 2H), 4.65 (t, J = 4.7 Hz, 2H), 3.90 (s, 3H), 3.21 (t, J = 4.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5 151.1 145.4 138.8 138.4 136.0 133.9 132.9 131.6 130.9 130.2 128.1 127.7 126.5 125.8 124.9 124.0 115.8 56.1 51.9 27.6; MS (EI, m/z) 338 $[M]^+$; HRMS (EI) calcd for $C_{24}H_{20}NO$ $[M]^+$ 338.1539, found 338.1536.

8-(3-Methoxyphenyl)-5,6-dihydroisoquinolino[1,2-*a*]isoquinolizinium Hexafluorostilbate (2l). In the same manner as described in the preparation of **2a**, **2l** was obtained as yellow solid after purification by column chromatography with CH_2Cl_2/MeOH (20/1, v/v) (yield 70%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (d, J = 6.0 Hz, 1H), 8.18 (d, J = 6.3 Hz, 1H), 8.11 (t, J = 6.6 Hz, 2H), 8.00 (d, J = 5.7 Hz, 1H), 7.93 (t, J = 5.7 Hz, 1H), 7.72 (t, J = 5.7 Hz, 1H), 7.67−7.61 (m, 3H), 7.57 (d, J = 5.4 Hz, 1H), 7.11 (d, J = 6.6 Hz, 2H), 4.65 (t, J = 4.5 Hz, 2H), 3.90 (s, 3H), 3.20 (t, J = 4.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6 156.4 148.4 138.6 138.4 136.0 133.9 132.9 131.5 130.9 130.2 128.1 127.7 126.5 125.8 124.9 124.0 110.8 55.5 51.9 27.6; MS (EI, m/z) 338 $[M]^+$; HRMS (EI) calcd for $C_{24}H_{20}NO$ $[M]^+$ 338.1539, found 338.1540.

8-(4-Methoxyphenyl)-5,6-dihydroisoquinolino[1,2-*a*]isoquinolizinium Hexafluorostilbate (2m). In the same manner as described in the preparation of **2a**, **2m** was obtained as yellow solid after purification by column chromatography with CH_2Cl_2/MeOH (20/1, v/v) (yield 75%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (d, J = 6.3 Hz, 1H), 8.18 (d, J = 6.0 Hz, 1H), 8.11 (t, J = 6.6 Hz, 2H), 8.10 (d, J = 5.7 Hz, 1H), 7.93 (t, J = 5.4 Hz, 1H), 7.71 (t, J = 5.4 Hz, 1H), 7.67−7.61 (m, 3H), 7.57 (d, J = 5.7 Hz, 1H), 7.12 (d, J = 6.6 Hz, 2H), 4.65 (t, J = 4.2 Hz, 2H), 3.90 (s, 3H), 3.20 (t, J = 4.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6 154.4 146.4 138.8 138.4 136.0 133.9 132.9 131.6 130.9 130.2 128.1 127.7 126.5 125.8 124.9 124.0 114.8 55.5 51.9 27.6; MS (EI, m/z) 338 $[M]^+$; HRMS (EI) calcd for $C_{24}H_{20}NO$ $[M]^+$ 338.1539, found 338.1534.

2,3-Dimethoxy-8-propyl-5,6-dihydroisoquinolino[1,2-*a*]isoquinolizinium Hexafluorostilbate (4a). In the same manner as described in the preparation of **2a**, **4a** was obtained as yellow solid after purification by column chromatography with CH_2Cl_2/MeOH (20/1, v/v) (yield 71%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (t, J = 8.4 Hz, 1H), 7.93 (s, 1H), 7.74 (d, J = 6.6 Hz, 1H), 7.64 (d, J = 5.7 Hz, 1H), 7.42 (d, J = 6.6 Hz, 1H), 7.30 (s, 1H), 7.15 (s, 1H), 4.02 (d, J = 6.6 Hz, 2H), 3.95 (s, 3H), 3.92 (s, 3H), 3.42 (t, J = 3.0 Hz, 2H), 2.45 (t, J = 8.0 Hz, 2H), 1.27−1.14 (m, 2H), 0.79 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2 148.6 148.1 147.6 138.9 135.4 134.0 130.4 129.8 127.5 124.1 122.5 118.5 115.4 110.8 56.6 56.5 49.2 35.3 27.1 21.4 13.7; MS (EI, m/z) 334 $[M]^+$; HRMS (EI) calcd for $C_{22}H_{24}NO_2$ $[M]^+$ 334.1802, found 334.1790.

8-Hexyl-2,3-dimethoxy-5,6-dihydroisoquinolino[1,2-*a*]isoquinolizinium Hexafluorostilbate (4b). In the same manner as described in the preparation of **2a**, **4b** was obtained as yellow solid after purification by column chromatography with CH_2Cl_2/MeOH (20/1, v/v) (yield 74%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J = 7.5 Hz, 1H), 7.87 (s, 1H), 7.65 (d, J = 7.5 Hz, 1H), 7.64−7.47 (m, 2H), 7.30 (s, 1H), 7.13 (s, 1H), 4.01 (s, 2H), 3.94 (s, 3H), 3.92 (s, 3H), 3.39 (t, J = 6.3 Hz, 2H), 2.80 (t, J = 5.7 Hz, 2H), 1.54−1.35 (m, 8H), 0.90 (t, J = 3.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2 148.1 147.9 147.3 138.9 135.3 134.0 130.7 129.9 127.4 124.1 122.3 118.6 115.4 56.5 56.0 49.1 33.4 31.5 28.1 27.1 25.7 22.4 14.0; MS (EI, m/z) 376 $[M]^+$; HRMS (EI) calcd for $C_{25}H_{30}NO_2$ $[M]^+$ 376.2271, found376.2284.

8-Isobutyl-2,3-dimethoxy-5,6-dihydroisoquinolino[1,2-*a*]isoquinolizinium Hexafluorostilbate (4c). In the same manner as described in the preparation of **2a**, **4c** was obtained as yellow solid after purification by column chromatography with CH_2Cl_2/MeOH (20/1, v/v) (yield 67%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51(d, J = 8.4 Hz, 1H), 8.08−8.01 (m, 2H), 7.86−7.81 (m, 2H), 7.31(s, 1H), 7.17 (s, 1H), 4.07 (s, 3H), 3.93 (s, 3H), 3.46 (t, J = 6.6 Hz, 2H), 3.37 (d, J = 6.7 Hz, 2H), 2.21−2.15 (m, 3H), 1.12 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3 148.1 146.9 138.7 135.4 134.3 129.9 129.8 127.4 124.2 123.9 118.6 115.4 110.9 56.6 56.5 49.7 42.7 29.2 27.7 27.3 22.4; MS (EI, m/z) 348 $[M]^+$; HRMS (EI) calcd for $C_{23}H_{26}NO_2$ $[M]^+$ 348.1958, found 348.1962.

8-(Cyclohexylmethyl)-2,3-dimethoxy-5,6-dihydroisoquinolino-[1,2-*a*]isoquinolizinium Hexafluorostilbate (4e). In the same manner as described in the preparation of **2a**, **4e** was obtained as yellow solid after purification by column chromatography with CH_2Cl_2/MeOH (20/1, v/v) (yield 72%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, J = 9.0 Hz, 1H), 8.03 (m, 2H), 7.86−7.81 (m, 2H), 7.31 (s, 1H), 7.19 (s, 1H), 4.07 (s, 3H), 4.01 (s, 1H), 3.97 (s, 1H), 3.96 (s, 3H), 3.44 (d, J = 6.6 Hz, 2H), 3.40 (d, J = 5.1 Hz, 2H), 1.82−1.58 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3 148.1 146.2 138.6 135.4 134.1 129.9 128.0 127.4 124.2 124.1 118.5 115.3 110.8 56.6 56.5 49.6 41.4 36.9 33.3 32.9 27.1 25.9; MS (EI, m/z) 388 $[M]^+$; HRMS (EI) calcd for $C_{26}H_{30}NO_2$ $[M]^+$ 388.2271, found 388.2280.

8-(4-*tert*-Butylphenyl)-2,3-dimethoxy-5,6-dihydroisoquinolino-[1,2-*a*]isoquinolizinium Hexafluorostilbate (4f). In the same manner as described in the preparation of **2a**, **4f** was obtained as yellow solid after purification by column chromatography with CH_2Cl_2/MeOH (20/1, v/v) (yield 74%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, J = 7.5 Hz, 1H), 7.94 (d, J = 7.2 Hz, 1H), 7.65 (d, J = 4.5 Hz, 4H), 7.47 (s, 1H), 7.33−7.29 (m, 3H), 7.19 (s, 1H), 4.08 (s, 3H), 3.97 (s, 3H), 3.88 (s, 2H), 3.64 (s, 2H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5 138.7 135.5 133.7 131.3 130.3 129.7 128.2 128.0 126.4 124.9 124.6 124.4 118.8 115.8 111.0 110.2 56.7 51.7 31.1 29.6 27.2; MS (ESI, m/z) 424 $[M]^+$; HRMS (ESI) calcd for $C_{29}H_{30}NO_2$ $[M]^+$ 424.2271, found 424.2269.

2,3-Dimethoxy-8-*p*-tolyl-5,6-dihydroisoquinolino[1,2-*a*]isoquinolizinium Hexafluorostilbate (4g). In the same manner as described in the preparation of **2a**, **4g** was obtained as yellow solid after purification by column chromatography with CH_2Cl_2/MeOH (20/1, v/v) (yield 64%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (d, J = 6.6 Hz, 1H), 8.12−8.06 (m, 2H), 7.94 (s, 1H), 7.90 (t, J = 6.3 Hz, 1H), 7.61 (d, J = 6.3 Hz, 2H), 7.46 (s, 1H), 7.41 (d, J = 5.7 Hz, 2H), 7.15 (s, 1H), 4.62 (t, J = 4.5 Hz, 2H), 4.06 (s, 3H), 3.96 (s, 3H), 3.23 (t, J = 4.8 Hz, 2H), 2.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5 148.4 146.4 141.4 138.7 135.5 133.7 130.4 130.3 130.0 129.8 128.3 128.0 124.8 124.3 118.8 115.9 111.0 56.7 56.6 51.8 29.2 27.2; MS (EI, m/z) 382 $[M]^+$; HRMS (EI) calcd for $C_{26}H_{24}NO_2$ $[M]^+$ 382.1802, found 382.1823.

2,3-Dimethoxy-8-(2-methoxyphenyl)-5,6-dihydroisoquinolino-[1,2-*a*]isoquinolizinium Hexafluorostilbate (4h). In the same manner as described in the preparation of **2a**, **4h** was obtained as yellow solid after purification by column chromatography with CH_2Cl_2/MeOH (20/1, v/v) (yield 83%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (d, J = 6.6 Hz, 1H), 8.17−8.12 (m, 2H), 7.98−7.95 (m, 2H), 7.64 (t, J = 6.0 Hz, 1H), 7.50 (d, J = 6.0 Hz, 1H), 7.46 (s, 1H), 7.33 (s, 1H), 7.23 (t, J = 5.7 Hz, 1H), 7.12 (d, J = 6.2 Hz, 1H), 4.51 (s, 1H), 4.43 (s, 1H), 4.10 (s, 3H), 3.98 (s, 3H), 3.83 (s, 3H), 3.31 (t, J = 4.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9 154.7 153.9 148.3 143.6 138.8 135.7 134.4 133.3 131.3 130.7 130.3 128.1 124.8 121.8 120.9 118.4 115.4 111.4 111.2 56.8 56.6 55.8 50.4 26.8; MS (EI, m/z) 398 $[M]^+$; HRMS (EI) calcd for $C_{26}H_{24}NO_3$ $[M]^+$ 398.1751, found 398.1747.

2,3-Dimethoxy-8-(3-methoxyphenyl)-5,6-dihydroisoquinolino-[1,2-*a*]isoquinolizinium Hexafluorostilbate (4i). In the same manner as described in the preparation of **2a**, **4i** was obtained as yellow solid after purification by column chromatography with CH_2Cl_2/MeOH (20/1, v/v) (yield 80%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (d, J = 9.0 Hz, 1H), 8.11−8.01 (m, 2H), 7.92 (s, 1H), 7.87 (t, J = 8.1 Hz, 1H), 7.46 (t, J = 6.3 Hz, 2H), 7.36 (s, 1H), 7.18 (d, J = 6.9 Hz, 2H), 7.09 (d, J = 6.6 Hz, 1H), 4.58 (br s, 2H), 4.03 (s, 3H), 3.95 (s, 3H), 3.90 (s, 3H), 3.24 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0 154.5 154.3 148.2 145.9 138.6 135.4 133.8 133.5 130.3 128.1 125.0 124.3 121.8 118.8 117.3 115.9 114.9 111.1 56.8 56.7 56.0 51.8 27.2; MS (ESI, m/z) 398 $[M]^+$; HRMS (ESI) calcd for $C_{26}H_{24}NO_3$ $[M]^+$ 398.1751, found 398.1766

2,3-Dimethoxy-8-(4-methoxyphenyl)-5,6-dihydroisoquinolino-[1,2-*a*]isoquinolizinium Hexafluorostilbate (4j). In the same manner as described in the preparation of **2a**, **4j** was obtained as yellow solid after purification by column chromatography with CH_2Cl_2/MeOH (20/1, v/v) (yield 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, J = 6.6 Hz, 1H), 8.02−8.10 (dd, J = 12.9 Hz, J = 5.7 Hz, 2H), 7.93 (s, 1H), 7.84 (t, J = 5.4 Hz, 1H), 7.67 (br s, 2H), 7.42 (s, 1H), 7.11−7.06 (m, 3H), 4.62 (s, 2H), 4.00 (s, 3H), 3.91 (s, 3H), 3.84 (s, 3H), 3.21 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5 154.3 148.3 146.2 138.7 135.5 133.6 131.6 130.4 130.1 128.0 124.7 124.5 124.2 118.8 115.6 114.8 110.9 56.6 55.5 53.7 51.5 27.2; MS (EI, m/z) 398 $[M]^+$; HRMS (EI) calcd for $C_{26}H_{24}NO_3$ $[M]^+$ 398.1751, found 398.1725.

8-(4-Fluorophenyl)-2,3-dimethoxy-5,6-dihydroisoquinolino[1,2-*a*]-isoquinolizinium Hexafluorostilbate (4k). In the same manner as described in the preparation of **2a**, **4k** was obtained as yellow solid after purification by column chromatography with CH_2Cl_2/MeOH (20/1, v/v) (yield 72%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, J = 6.2 Hz, 1H), 7.90 (d, J = 6.0 Hz, 1H), 7.50 (s, 1H), 7.50−7.33 (m, 5H), 7.20 (t, J = 5.1 Hz, 2H),7.10 (t, J = 6.0 Hz, 1H), 4.06 (s, 2H), 3.97 (s, 6H), 3.89 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3 148.3 145.2 138.6 135.5 134.2 133.4 132.6 132.5 130.4 130.3 128.4 128.1 125.0 124.6 118.9 116.7 116.4 115.9 110.6 56.6 56.5 51.6 27.2; MS (EI, m/z) 386 $[M]^+$; HRMS (EI) calcd for $C_{25}H_{21}FNO_2$ $[M]^+$ 386.1551, found 386.1543.

8-(4-Chlorophenyl)-2,3-dimethoxy-5,6-dihydroisoquinolino[1,2-*a*]-isoquinolizinium Hexafluorostilbate (4l). In the same manner as described in the preparation of **2a**, **4l** was obtained as yellow solid after purification by column chromatography with

CH_2Cl_2/MeOH (20/1, v/v) (yield 76%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, J = 6.3 Hz, 2H), 7.42 (d, J = 6.6 Hz, 2H), 7.23−7.03 (m, 5H), 7.02 (d, J = 5.7 Hz, 2H), 3.82 (s, 6H), 3.19 (t, J = 4.8 Hz, 2H), 3.12 (t, J = 4.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5 146.5 138.7 135.5 133.8 130.4 129.7 128.3 128.8 128.4 128.0 127.3 126.4 125.0 124.4 118.8 115.9 111.4 111.1 56.7 55.8 41.8 29.3; MS (ESI, m/z) 402 $[M]^+$; HRMS (ESI) calcd for $C_{25}H_{21}ClNO_2$ $[M]^+$ 402.1255, found 402.1262.

9-Propylindole[2,3-*c*]-2,3-dihydropyridine[1,2-*a*]isoquinolizinium Hexafluorostilbate (4m). In the same manner as described in the preparation of **2a**, **4m** was obtained as yellow solid after purification by column chromatography with CH_2Cl_2/MeOH (20/1, v/v) (yield 74%): ^{1}H NMR (300 MHz, DMSO) δ 12.34 (s, 1H), 8.96 (d, J = 9.0 Hz, 1H), 8.20 (d, J = 7.5 Hz, 1H, 8.17 (s, 1H), 8.04 (t, J = 8.4 Hz, 1H), 7.89 (d, J = 8.1 Hz, 1H), 7.68 (d, J = 8.1 Hz, 2H), 7.47 (t, J = 6.9 Hz, 1H), 7.26 (t, J = 6.0 Hz, 1H), 3.42 (t, J = 5.4 Hz, 2H), 3.23 (t, J = 5.7 Hz, 2H), 1.85 (t, J = 7.5 Hz, 2H), 1.11 (t, J = 7.2 Hz, 3H), 0.90−0.80 (m, 2H); ^{13}C NMR (75 MHz, DMSO) δ 147.2 146.2 141.0 137.8 135.3 130.4 129.4 127.2 127.0 126.8 123.8 122.9 122.3 121.8 121.2 113.3 49.4 35.0 20.9 18.7 13.5; MS (ESI, m/z) 313 $[M]^+$; HRMS (ESI) calcd for $C_{22}H_{21}N_2$ $[M]^+$ 313.1699, found 313.1685.

9-Chloropropylindole[2,3-*c*]-2,3-dihydropyridine[1,2-*a*]isoquinolizinium Hexafluorostilbate (4n). In the same manner as described in the preparation of **2a**, **4n** was obtained as yellow solid after purification by column chromatography with CH_2Cl_2/MeOH (20/1, v/v) (yield 69%): ^{1}H NMR (300 MHz, DMSO) δ 12.36 (s, 1H), 8.96 (d, J = 8.1 Hz, 1H), 8.21 (d, J = 5.7 Hz, 1H), 8.18 (s, 1H), 7.89 (d, J = 7.8 Hz, 2H), 7.68 (d, J = 8.4 Hz, 2H), 7.48 (t, J = 6.9 Hz, 1H), 7.28 (d, J = 6.9 Hz, 1H), 4.83 (t, J = 6.3 Hz, 2H), 3.87 (t, J = 6.6 Hz, 2H), 3.49 (t, J = 4.8 Hz, 2H), 2.30 (t, J = 6.9 Hz, 2H), 0.91−0.80 (m, 2H); ^{13}C NMR (75 MHz, DMSO) δ 146.5 146.0 141.1 137.9 135.4 130.5 129.4 127.2 127.1 126.8 123.8 123.0 122.4 122.1 113.3 49.6 44.3 30.7 30.4 29.6; MS (ESI, m/z) 347 $[M]^+$; HRMS (ESI) calcd for $C_{22}H_{20}ClN_2$ $[M]^+$ 347.1370, found 347.1326.

9-Phenylindole[2,3-*c*]-2,3-dihydropyridine[1,2-*a*]isoquinolizinium Hexafluorostilbate (4o). In the same manner as described in the preparation of **2a**, **4o** was obtained as yellow solid after purification by column chromatography with CH_2Cl_2/MeOH (20/1, v/v) (yield 71%): ^{1}H NMR (300 MHz, DMSO) δ 12.48 (s, 1H), 9.06 (d, J = 8.4 Hz, 1H), 8.33−8.13 (m, 3H), 7.84−7.69 (m, 6H), 7.50−7.27 (m, 2H), 7.25 (t, J = 8.1 Hz, 2H), 4.57 (d, J = 5.1 Hz, 2H), 2.11 (d, J = 5.4 Hz, 2H); ^{13}C NMR (75 MHz, DMSO) δ 146.1 145.9 141.2 138.7 137.7 135.6 133.7 131.1 130.3 129.5 129.1 127.8 127.2 126.8 123.8 123.6 123.3 122.8 121.1 114.5 113.4 55.8 18.6; MS (ESI, m/z) 347 $[M]^+$; HRMS (ESI) calcd for $C_{25}H_{19}N_2$ $[M]^+$ 347.1543, found 347.1542.

9-Methoxyphenylindole[2,3-c]-2,3-dihydropyridine[1,2-*a*]isoquinolizinium Hexafluorostilbate (4p). In the same manner as described in the preparation of **2a**, **4p** was obtained as yellow solid after purification by column chromatography with CH_2Cl_2/MeOH (20/1, v/v) (yield 72%): ^{1}H NMR (300 MHz, DMSO) δ 12.47 (s, 1H), 9.04 (d, J = 8.4 Hz, 1H), 8.26−8.14 (m, 3H), 8.11 (t, J = 6.9 Hz, 1H), 7.85−7.75 (m, 4H), 7.45 (t, J = 7.8 Hz, 1H), 7.25 (t, J = 7.5 Hz, 3H), 4.60 (t, J = 6.3 Hz, 2H), 3.90 (s, 3H), 2.89 (s, 1H), 2.73 (s, 1H); ^{13}C NMR (75 MHz, DMSO) δ 160.0 146.0 141.1 137.7 135.3 134.6 134.5 131.2 130.5 130.3 128.5 127.7 127.1 126.8 125.8 123.8 123.2 122.7 121.3 121.1 117.2 114.4 113.3 55.5 52.3 28.8; MS (ESI, m/z) 377 $[M]^+$; HRMS (ESI) calcd for $C_{26}H_{21}N_2O$ $[M]^+$ 377.1648, found 377.1632.

9-Fluorophenylindole[2,3-*c*]-2,3-dihydropyridine[1,2-*a*]isoquinolizinium Hexafluorostilbate (4q). In the same manner as described in the preparation of **2a**, **4q** was obtained as yellow solid after purification by column chromatography with CH_2Cl_2/MeOH (20/1, v/v) (yield 71%): ^{1}H NMR (300 MHz, DMSO) δ 12.50 (s, 1H), 9.06 (d, J = 8.1 Hz, 1H), 8.28 (s, 1H), 8.23 (t, J = 7.8 Hz, 2H), 7.82 (t, J = 8.4 Hz, 3H), 7.71 (d, J = 8.7 Hz, 2H), 7.59−7.53 (m, 3H), 7.26 (t, J = 7.2 Hz, 1H), 4.57 (t, J = 4.2 Hz, 2H), 3.45 (t, J = 4.8 Hz, 2H); ^{13}C NMR (75 MHz, DMSO) δ 161.8 146.1 145.0 141.2 137.6 135.7 132.2 132.1 131.1 130.6 130.1 129.5 128.1 127.8 127.2 123.8 123.3 122.8 121.3 121.2 116.3 116.0 113.4 52.4 18.5; MS (ESI, m/z) 365 $[M]^+$; HRMS (ESI) calcd for $C_{25}H_{18}FN_2$ $[M]^+$ 365.1449, found 365.1449.

9-*m*-tolylindole[2,3-*c*]-2,3-dihydropyridine[1,2-*a*]isoquinolizinium Hexafluorostilbate (4r). In the same manner as described in the preparation of **2a**, **4r** was obtained as yellow solid after purification by column chromatography with CH_2Cl_2/MeOH (20/1, v/v) (yield 74%): ^{1}H NMR (300 MHz, DMSO) δ 12.48 (s, 1H), 9.06 (d, J = 8.4 Hz, 1H), 8.25 (d, J = 7.2 Hz, 2H), 8.22 (s, 1H), 8.13 (t, J = 8.4 Hz, 1H), 7.83 (d, J = 7.8 Hz, 2H), 7.71 (d, J = 8.4 Hz, 2H), 7.57 (t, J = 6.6 Hz, 3H), 7.26 (t, J = 6.9 Hz, 1H), 4.60 (t, J = 6.3 Hz, 2H), 3.49 (t, J = 6.6 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 146.1 141.2 138.5 137.7 133.7 131.0 130.5 130.4 129.9 129.6 128.9 127.8 127.2 126.8 126.6 123.8 123.6 123.3 122.8 121.3 121.2 113.4 52.5 21.0 18.6; MS (ESI, m/z) 361 $[M]^+$; HRMS (ESI) calcd for $C_{26}H_{21}N_2$ $[M]^+$ 361.1699, found 361.1680.

2-Methyl-8-phenyl-5,6-dihydroisoquinolino[1,2-*a*]isoquinolizinium Hexafluorostilbate (4s). In the same manner as described in the preparation of **2a**, **4s** was obtained as yellow solid after purification by column chromatography with CH_2Cl_2/MeOH (20/1, v/v) (yield 72%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48−8.57 (dd, J = 12 Hz, J = 8.1 Hz, 1H), 8.08 (s, 1H), 7.90 (t, J = 7.5 Hz, 1H), 7.78−7.62 (m, 7H), 7.43 (s, 1H), 7.03 (d, J = 6.6 Hz, 2H), 4.59 (t, J = 5.1 Hz, 2H), 3.18 (t, J = 5.7 Hz, 2H), 2.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6 146.2 138.7 137.9 137.3 134.6 131.5 131.0 130.2 129.8 129.5 129.3 128.9 128.5 127.5 126.6 125.8 125.1 52.4 27.2 21.3; MS (ESI, m/z) 322 $[M]^+$; HRMS (ESI) calcd for $C_{24}H_{20}N$ $[M]^+$ 322.1590, found 322.1599.

7-Phenylthieno[2,3-*c*]-2,3-dihydropyridine[1,2-*a*]isoquinolizinium Hexafluorostilbate (4t). In the same manner as described in the preparation of **2a**, **4t** was obtained as yellow solid after purification by column chromatography with CH_2Cl_2/MeOH (20/1, v/v) (yield 74%): ^{1}H NMR (300 MHz, DMSO) δ 8.96 (d, J = 9.0 Hz, 1H), 8.18 (d, J = 8.1 Hz, 3H), 8.04 (t, J = 8.4 Hz, 1H), 7.89 (d, J = 8.1 Hz, 2H), 7.68 (d, J = 8.1 Hz, 2H), 7.47 (t, J = 7.8 Hz, 2H), 7.26 (t, J = 7.8 Hz, 1H), 4.83 (t, J = 5.4 Hz, 2H), 3.23 (t, J = 4.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1 147.1 146.2 141.6 138.4 136.0 132.6 131.0 130.8 129.7 129.5 129.3 128.5 127.9 125.9 124.9 124.4 52.3 22.7; MS (ESI, m/z) 314 $[M]^+$; HRMS (ESI) calcd for $C_{21}H_{16}NS$ $[M]^+$ 314.0998, found 314.1007.

2-Methoxy-8-phenyl-5,6-dihydroisoquinolino[1,2-*a*]isoquinolizinium Hexafluorostilbate (4u). In the same manner as described in the preparation of **2a**, **4u** was obtained as yellow solid after purification by column chromatography with CH_2Cl_2/MeOH (20/1, v/v) (yield 70%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (d, J = 9.3 Hz, 1H), 8.18 (d, J = 9.0 Hz, 1H), 8.09 (s, 2H), 7.79 (d, J = 6.6 Hz, 3H), 7.60−7,44 (m, 6H), 4.60 (s, 2H), 3.89 (s, 3H), 3.16 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5 154.4 146.4 138.8 135.8 132.2 130.8 130.7 130.6 130.3 130.1 129.3 129.2 128.4 127.5 126.1 125.3 119.4 118.8 56.0 52.8 26.9; MS (ESI, m/z) 338 $[M]^+$; HRMS (ESI) calcd for $C_{24}H_{20}NO$ $[M]^+$ 338.1539, found 338.1540.

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Supporting Information Available: Detailed experimental procedures, characterization data, copies of ^{1}H and ^{13}C NMR spectra for all products, and X-ray data for **2a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.