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Ring Expansion of 1,2,3,4-Tetrahydroisoquinolines to Dibenzo[*c*,*f*]azonines. An Unexpected [1,4]-Sigmatropic Rearrangement of Nitrile-Stabilized Ammonium Ylides

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Supporting Information

ABSTRACT: When the products of a Strecker reaction of 1,2,3,4-tetrahydroisoquinolines with aromatic aldehydes are quaternized with alkyl triflates and subsequently treated with base, a ring expansion to 6,7,8,13-tetrahydro-5*H*-dibenzo[*c*,*f*]-azonine-5-carbonitriles takes place. The nine-membered cyclic products can be obtained in good yields (78−89%) in a process involving the [1,4]-sigmatropic rearrangement of a nitrile-stabilized ammonium ylide. The reaction sequence provides a new, simple, and efficient method for the synthesis of these unusual N-heterocycles.

INTRODUCTION

Azonines are prototypical representatives of medium-sized saturated N-heterocycles and constitute the backbone of several natural products.[1−5] Their biological properties range from antihypertensive, antimalarial, and antiproliferative to analgetic.[6−11] In contrast, their [*c*,*f*]dibenzo-annulated derivatives have been much less investigated, although they possess a promising potential as CNS stimulants, anti-inflammatory drugs, and modulators of NO synthase.[12−14] Moreover, they bear similarity to the scaffolds of known GPCR receptor ligands.

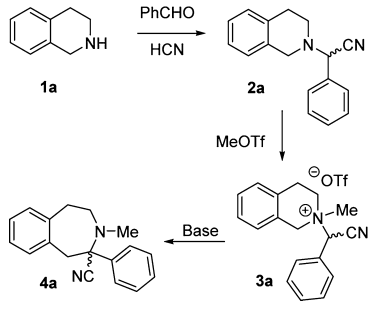
However, synthetic efforts toward the preparation of dibenzo[*c*,*f*]azonines are rather limited. The first approach to this compound class was reported by Zugna and co-workers, who treated 2,2′-bisbromomethyldiphenylmethane with sodium cyanamide or benzylamine to give the ring-closed substitution products.[15] Manning and Houlihan patented the synthesis of dibenzo[*c*,*f*]azonines from isoindolo[1,2-*a*]isoquinolinum salts by reduction with sodium in liquid ammonia to cleave the central bond between C-12b and nitrogen.[12,13] A Sommelet−Hauser rearrangement of 1-phenyltetrahydroisoquinolinium methylides to dibenzo[*c*,*f*]azonines was reported by Sato et al.[16] The latest report on this class of heterocycles is a patent by Dreux and co-workers describing a sequential reduction, hydrolysis, and intramolecular cyclocondensation of ethyl-3-(3-methoxybenzylamino)-4-(3,4-dimethoxyphenyl)-2-butenoate.[14]

Herein, we report a novel and broadly applicable method for the preparation of 6,7,8,13-tetrahydro-5*H*-dibenzo[*c*,*f*]-azonines starting from 1,2,3,4-tetrahydroisoquinolines. To the best of our knowledge, this represents the first direct ring expansion of ammonium ylides via [1,4]-sigmatropic rearrangement as well as the first efficient protocol for the preparation of dibenzo[*c*,*f*]azonines from simple starting materials.

RESULTS AND DISCUSSION

Recently, our research group has developed methodology which takes advantage of the chemistry of α-aminonitriles and their conversion to nitrile-stabilized ammonium ylides as precursors for efficient [1,2]-Stevens rearrangements.[17,18] Motivated by these results, we decided to explore the application of this process in the synthesis of other classes of N-heterocycles. Thus, we sought to develop a strategy for the synthesis of 2-substituted benzo[*d*]azepines (**4a**) from 1,2,3,4-tetrahydroisoquinolines via Strecker reaction and subsequent quaternization to the ammonium salts (**2a**) which should be followed by [1,2]-Stevens rearrangement of the nitrile-stabilized ammonium ylides obtained by deprotonation (Scheme 1). Related methodologies have been described using ester derivatives instead of nitriles.[19] Soldatova and co-workers explored α-aminonitrile-derived starting materials for the ring expansion of 1-benzyl-1,2,3,4-tetrahydroisoquinolines but reported only moderate yields.[20] We

Scheme 1. Proposed Synthesis of a Benzo[*d*]azepine by [1,2]-Stevens Rearrangement



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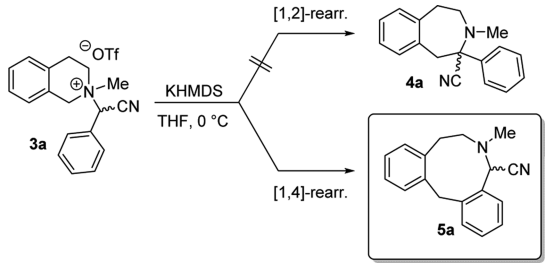
anticipated a better outcome if the negative charge in the ammonium ylide is stabilized by an adjacent aryl group. This should increase the acidity of the α-proton and suppress the competing formation of Hofmann elimination products.

Along these lines, compound **4a** should be available in three steps from 1,2,3,4-tetrahydroisoquinoline (**1a**). We found that when **1a** and benzaldehyde are treated under Knoevenagel–Bucherer conditions,[21] α-aminonitrile **2a** is obtained in higher yield compared to other reported methods.[22] N-Methylation of **1a** with methyl triflate leads to the formation of tetrahydroisoquinolinium salt **3a** in 98% yield. The use of methyl iodide is not recommended because halide anions are capable of nucleopilic N-dealkylation.

When compound **3a** was treated with KHMDS in THF at 0 °C over 3 h (Scheme 2), the formation of a single product

Scheme 2. Unexpected [1,4]-Sigmatropic Rearrangement to Dibenzo[*c*,*f*]azonines 5a

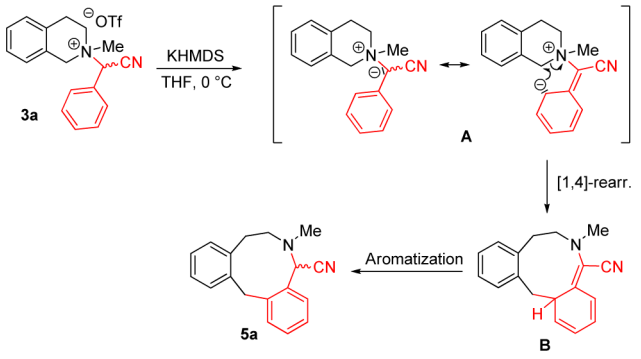


was observed. LC-MS analysis indicated a molecular mass matching that of the expected benzo[*d*]azepine. Chromatographic purification afforded the corresponding compound in 50% yield. However, NMR analysis revealed that one of the aromatic proton resonances was missing and showed an unexpected broadening of the signals in the aliphatic region. Variable temperature NMR indicated that an optimal resolution of the signals can be obtained at 70 °C where ring inversion is fast enough to give sharp resonances (Figure 1).

With this, we were able to identify the product as the dibenzo[*c*,*f*]azonine carbonitrile **5a**. The structure was further confirmed by X-ray crystallography (see Supporting Information).

The surprising formation of aminonitrile **5a** indicated that a [1,4]-sigmatropic rearrangement of the ammonium ylide derived from tetrahydroisoquinolinium salt **3a** had taken place (Scheme 3). This reaction involves a six-electron

Scheme 3. [1,4]-Sigmatropic Rearrangement of the Tetrahydroisoquinolinium Salt 3a



aromatic transition state with suprafacial–suprafacial characteristics.[23,24] Migrations of this kind have been observed before as competing reactions of the common [1,2]- and [2,3]-sigmatropic rearrangements of ammonium benzylides as well as of allylic ammonium ylides.[24−29]

To explore the scope of the reaction, eight new α-aminonitriles, compounds **2b–i**, were prepared via Knoevenagel–Bucherer-type Strecker reaction of 1,2,3,4-tetrahydroisoquinoline (**1a**) or 6,7-dimethoxytetrahydroisoquinoline (**1b**) in 80–94% yield. They were quaternized with alkyl triflates to form 10 new ammonium triflates **3b–j** in moderate to high yields (Table 1).

For the preparation of dibenzo[*c*,*f*]azonines **5**, compound **3a** was chosen as a model substrate for the optimization of the reaction conditions (Table 2). Shorter reaction times as well as higher yields were achieved when DBU was used as a base in conjunction with acetonitrile as solvent at room temperature. Recrystallization turned out to be the method of choice for the purification of the products. Remarkably, no competing rearrangements were observed as judged by LC-MS analysis of the reaction mixtures.

By applying these optimized reaction conditions to compounds **3b–j**, we prepared nine new dibenzo[*c*,*f*]azonines

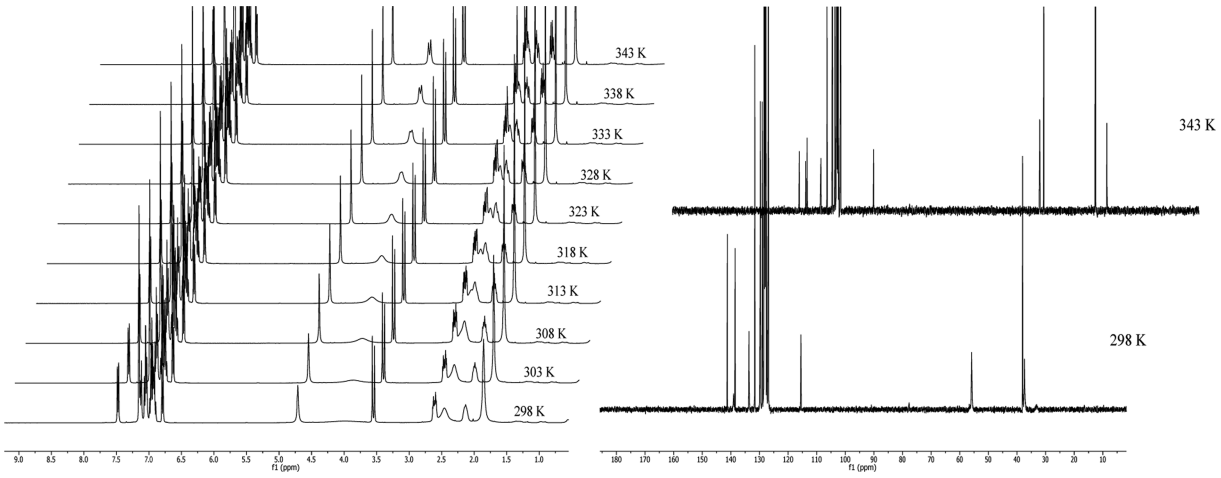


Figure 1. ^{1}H and ^{13}C spectra of compound **5a** at variable temperatures (K) in C_6D_6.

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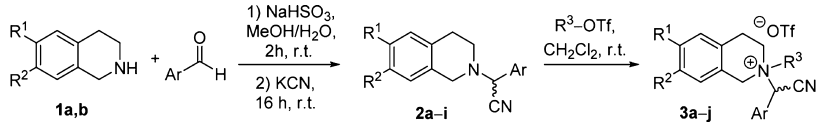
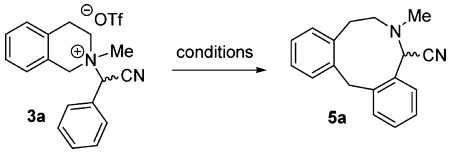
Table 1. Synthesis of 1,2,3,4-Tetrahydroisoquinolinium 3a–j Salts from α-Aminonitriles 2a–i



entry	THIQ	R^1	R^2	Ar	Aminonitrile	Yield (%)	R^3	Salt	Yield (%)
1	**1a**	H	H		**2a**	83	Me	**3a**	98
2	**1a**	H	H		**2b**	90	Me	**3b**	96
3	**1a**	H	H		**2c**	94[a]	Me	**3c**	94
4	**1a**	H	H		**2d**	90	Me	**3d**	91
5	**1a**	H	H		**2e**	93	Me	**3e**	99
6	**1a**	H	H		**2f**	80	Me	**3f**	96
7	**1a**	H	H		**2g**	87	Me	**3g**	93
8	**1b**	OCH_3	OCH_3		**2h**	82	Me	**3h**	98
9	**1b**	OCH_3	OCH_3		**2i**	84	Me	**3i**	99
10	**1a**	H	H		**2e**	93	*n*-Bu	**3j**	27[b]

[a]Used in the next step without further purification. [b]N-Debenzylation of the aminonitrile with TfOH produced by β-elimination of the electrophile occurred. The addition of scavenger bases led, however, to problems with the chromatographic workup.

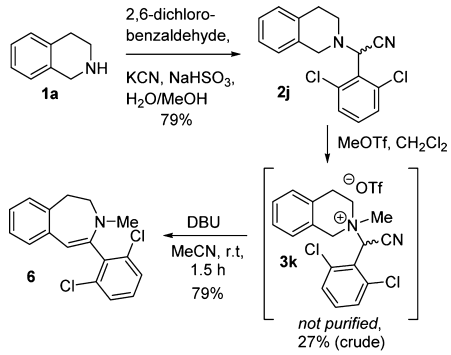
Table 2. Optimization of the Reaction Conditions for Preparation of Dibenzo[*c*,*f*]azonine 5a



entry	base	equiv	solvent	temp	time (h)	yield (%)
1	KHMDS	1.2	THF	0 °C	3	50[a]
2	KHMDS	1.2	THF	rt	1.5	60[a]
3	KHMDS	1.3	PhMe	reflux	6	65[b]
4	DBU	1.2	MeCN	rt	1	87[b]
5	DBU	1.2	THF	rt	15	45[c]
6	DBU	1.3	DMF	rt	1.5	77[b]
7	KOH	2	H_2O	70 °C	48	no reaction

[a]Purification by flash chromatography. [b]Purification by recrystallization. [c]Incomplete consumption of the starting material.

Scheme 4. Synthesis of 4-(2,6-Dichlorophenyl)-3-methyl-2,3-dihydro-1*H*-benzo[*d*]azepine 6



(**5b–j**) in 78–89% yield (Table 3). It was observed that substituents in the aryl ring directly involved in the rearrangement have a strong influence on the rates but not on the outcome of the reaction. Derivatives with electron-withdrawing groups reacted faster than derivatives with electron-donating groups. Whether or not the abstraction of the α-proton is the rate-determining step remains to be elucidated.

When both ortho-positions in the benzylic moiety are blocked (derivative **3k**), the initially expected [1,2]-Stevens rearrangement followed by an in situ dehydrocyanation occurred to produce compound **6** in high yield (Scheme 4).

This class of dibenzo[*c*,*f*]azonines also revealed another remarkable issue. The crystal structure of compounds **5a** and **5h** showed that, although both azonine rings adopt a different conformation, the lone pair at the pyramidal ring nitrogen is oriented antiperiplanar to the nitrile group in both cases (see Supporting Information). This should make dibenzazonine carbonitriles of type **5** suitable candidates for substitutions of cyanide in elimination/addition reactions, such as the Bruylants reaction or reductive decyanations.[30,31]

To test this hypothesis, compound **5a** was treated with $LiAlH_4$ to obtain the decyanated dibenzo[*c*,*f*]azonine **7** in 84% yield (Scheme 5).

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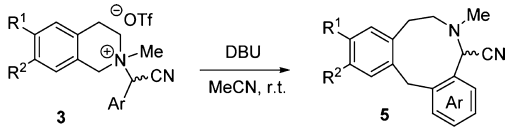
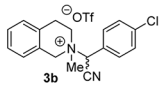
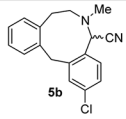
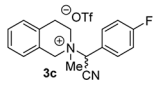
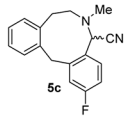
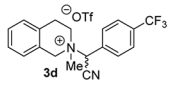
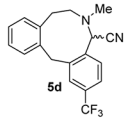
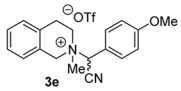
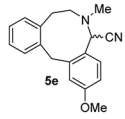
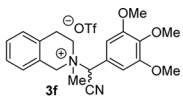
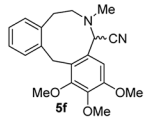
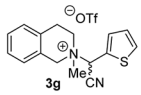
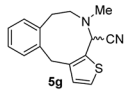
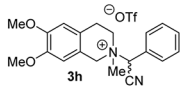
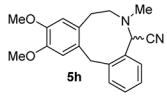
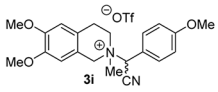
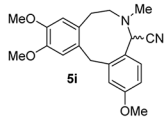
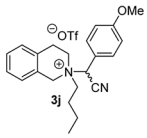
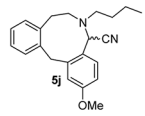
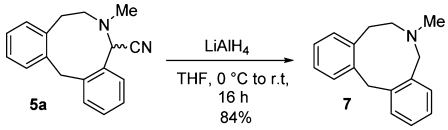
Table 3. Preparation of Dibenzo[c,f]azonines 5b–j by [1,4]-Sigmatropic Rearrangement



entry	Salt	Time (h)	Product	Yield (%)
1		0.67		84
2		0.67		85
3		0.5		89
4		1.5		81
5		3.7		87
6		1		78
7		1		84
8		2		83
9		1.5		80

Scheme 5. Synthesis of 6-Methyl-6,7,8,13-tetrahydro-5*H*-dibenzo[c,f]azonine 7 by Reductive Decyanation



CONCLUSIONS

In summary, we have found a novel method for the straightforward preparation of 6,7,8,13-tetrahydro-5*H*-dibenzo-[c,f]azonines from simple starting materials as well as the first example of a direct ring expansion via [1,4]-sigmatropic rearrangement. In the case of 2,6-disubstitution of the benzylic N-substituent, a benzo[b]azepine was formed instead. At present, we are investigating suitable substrates and reaction conditions to induce the [1,2]-Stevens rearrangement selectively.

EXPERIMENTAL SECTION

Anhydrous reactions were performed in dried glassware under argon atmosphere. Temperatures ≤0 °C were produced using a water/ice or a dry ice/acetone cooling bath. All reagents and solvents were obtained from commercial suppliers without further purification. 6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline (**1b**) and *n*-butyl triflate were synthesized according to known procedures.[18,32−34] Anhydrous THF was distilled from potassium/benzophenone under argon and collected over activated 4 Å molecular sieves. Anhydrous acetonitrile was obtained from distillation from P_2O_5 and collected over activated 4 Å molecular sieves. Melting points were determined in open capillary tubes and are uncorrected. FTIR spectra were recorded using a diamond ATR unit and are reported in terms of frequency of absorption (ν, cm^{-1}). A 400 MHz (400 MHz ^1H and 100.6 MHz

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^{13}C) or a 600 MHz (600 MHz ^{1}H and 150.9 MHz ^{13}C) spectrometer equipped with 5 mm inverse probeheads with *z*-gradient coils were used to record the corresponding NMR spectra. The signals were referenced to the residual solvent signal ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm; C_6D_6: δ_H = 7.16 ppm, δ_C = 128.06 ppm).[35] ESI-HRMS spectra were recorded on a Q-TOF instrument with a dual source and a suitable external calibrant. Thin-layer chromatography was carried out on 0.2 mm silica gel plates with a fluorescence indicator. Substance bands were detected by illumination with UV light (254 and 360 nm).

General Procedure for the One-Pot Synthesis of α-Aminonitriles (2a–h). To a turbid solution of the respective aldehyde (1.0 equiv) in water/methanol (4:1, 7 mL/mmol) was added $NaHSO_3$ (1.0 equiv) in one portion at room temperature. The reaction mixture was stirred vigorously for 2 h, and then the corresponding amine (1.0 equiv) was added, followed by KCN (2.0 equiv) in one portion. The mixture again turned turbid, and the stirring was continued for an additional 16 h. The reaction mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were washed with water and brine, dried over Na_2SO_4, and filtered. The solvent was removed under reduce pressure, and the crude products were either purified by recrystallization or used without further purification where indicated.

2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-2-phenylacetonitrile (2a). Following the general procedure, compound **2a** was prepared from 1,2,3,4-tetrahydroisoquinoline **1a** (952 μL, 7.51 mmol), benzaldehyde (766 μL, 7.51 mmol), $NaHSO_3$ (781 mg, 7.51 mmol), and KCN (978 mg, 15.02 mmol). The crude product was recrystallized from methanol to afford the title compound (1.54 g, 6.20 mmol, 83%) as colorless crystals: mp 84.9–85.3 °C (lit.[22] mp 77–80 °C); R_f = 0.62 (cyclohexane/EtOAc, 3:2); IR (ATR) ν = 3063, 3028, 2922, 2816, 2756, 2227, 1602, 1585, 1495, 1450, 1091, 937, 740, 711 cm^{-1}; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.66–7.59 (m, 2H, H-2′6′), 7.49–7.37 (m, 3H, H-3′,5′, H-4′), 7.19–7.09 (m, 3H, H-5, H-6, H-7), 7.05–6.97 (m, 1H, H-8), 5.09 (s, 1H, CHCN), 3.82 (d, *J* = 14.4 Hz, 1H, H-1), 3.77 (d, *J* = 14.4 Hz, H-1), 3.05–2.79 (m, 4H, 2H-3, 2H-4) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 133.8 (C4a), 133.7 (C8a), 133.1 (C1′), 129.1 (C4′), 129.0 (2C, C3′,5′), 128.8 (C5), 127.9 (2C, C2′,6′), 126.7 (C8), 126.5 (C6), 125.9 (C7), 115.4 (CN), 62.3 (C–CN), 52.5 (C1), 47.6 (C3), 29.4 (C4) ppm; ESI-MS (*m*/*z*) 249.1 (100) $[M + H]^+$; ESI-HRMS calcd for $[C_{17}H_{17}N_2]^+$ 249.1392, found 249.1397.

2-(4-Chlorophenyl)-2-(3,4-dihydroisoquinolin-2(1*H*)-yl)-acetonitrile (2b). Following the general procedure, compound **2b** was prepared from 1,2,3,4-tetrahydroisoquinoline **1a** (952 μL, 7.51 mmol), *p*-chlorobenzaldehyde (1.05 g, 7.51 mmol), $NaHSO_3$ (781 mg, 7.51 mmol), and KCN (978 mg, 15.02 mmol). The crude product was recrystallized from methanol to afford the title compound (1.91 g, 6.75 mmol, 90%) as colorless crystals: mp 62.5–63.4 °C; R_f = 0.56 (cyclohexane/EtOAc, 3:2); IR (ATR) ν = 3065, 3025, 2922, 2819, 2758, 2228, 1597, 1490, 1090, 1015, 937, 840, 787, 740 cm^{-1}; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.57 (d, *J* = 8.4 Hz, 2H, H-2′,6′), 7.41 (d, *J* = 8.4 Hz, 2H, H-3′,5′), 7.20–7.09 (m, 3H, H-5, H-6, H-7), 7.02–6.94 (m, 1H, H-8), 5.06 (s, 1H, CHCN), 3.81 (d, *J* = 14.4 Hz, 1H, H-1), 3.75 (d, *J* = 14.4 Hz, 1H, H-1), 3.04–2.80 (m, 4H, 2H-3, 2H-4) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 135.3 (C4′), 133.6 (C4a), 133.3 (C8a), 131.5 (C1′), 129.4 (2C, C2′,6′), 129.3 (2C, C3′,5′), 128.9 (C5), 126.7 (2C, C6, C8), 126.1 (C7), 115.0 (CN), 61.7 (C–CN), 52.5 (C1″), 47.7 (C3), 29.3 (C4) ppm; ESI-MS (*m*/*z*) 283.1 (100) $[M + H]^+$; ESI-HRMS calcd for $[C_{17}H_{16}ClN_2]^+$ 283.1002, found 283.1008.

2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-2-(4-fluorophenyl)-acetonitrile (2c). Following the general procedure, compound **2c** was prepared from 1,2,3,4-tetrahydroisoquinoline **1a** (952 μL, 7.51 mmol), *p*-fluorobenzaldehyde (810 μL, 7.51 mmol), $NaHSO_3$ (781 g, 7.51 mmol), and KCN (978 mg, 15.02 mmol). The title compound (1.88 g, 7.06 mmol, 94%) was obtained as a yellow oil and was used without further purification: R_f = 0.79 (cyclohexane/EtOAc, 3:2); IR (ATR) ν = 3067, 3025, 2924, 2818, 2759, 2227, 1670, 1604, 1508, 1455, 1226, 1159, 1089, 938, 843, 785, 741 cm^{-1}; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.60 (dd, *J* = 8.7, 5.2 Hz, 2H, H-2′,6′), 7.22–7.07 (m, 5H, H-3′,5′, H-5, H-6, H-7), 7.06–6.98 (m, 1H, H-8), 5.04 (s, 1H, CHCN), 3.80 (d, *J* = 14.4 Hz, 1H, H-1), 3.75 (d, *J* = 14.4 Hz, 1H, H-1), 3.09–2.74 (m, 4H, 2H-3, 2H-4) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 163.1 (d, *J* = 248.2 Hz, C4′), 133.7 (C4a), 133.6 (C8a), 129.7 (d, *J* = 8.2 Hz, 2C, C2′,6′), 129.0 (d, *J* = 3.1 Hz, C1′), 128.8 (C5), 126.7 (C8), 126.6 (C6), 126.0 (C7), 115.9 (d, *J* = 21.7 Hz, 2C, C3′,5′), 115.3 (CN), 61.6 (C–CN), 52.4 (C1), 47.6 (C3), 29.3 (C4) ppm; ESI-MS (*m*/*z*) 267.1 (100) $[M + H]^+$; ESI-HRMS calcd for $[C_{17}H_{16}FN_2]^+$ 267.1298, found 267.1302.

2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-2-(4-(trifluoromethyl)-phenyl)acetonitrile (2d). Following the general procedure, compound **2d** was prepared from 1,2,3,4-tetrahydroisoquinoline **1a** (952 μL, 7.51 mmol), *p*-trifluoromethylbenzaldehyde (1.03 mL, 7.51 mmol), $NaHSO_3$ (781 g, 7.51 mmol), and KCN (978 mg, 15.02 mmol). The title compound (2.15 g, 6.80 mmol, 90%) was obtained as a slightly yellow solid after purification by flash column chromatography (Isolera Flash Purification System, cyclohexane/EtOAc, gradient 0–28%): R_f = 0.63 (cyclohexane/EtOAc, 3:2); IR (ATR) ν = 3067, 3026, 2926, 2820, 2227, 1620, 1499, 1413, 1326, 1166, 1126, 1092, 1019, 882, 753 cm^{-1}; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.78 (d, *J* = 8.3 Hz, 2H, H-2′,6′), 7.70 (d, *J* = 8.3 Hz, 2H, H-3′,5′), 7.22–7.11 (m, 3H, H-5, H-6, H-7), 7.06–6.97 (m, 1H, H-8), 5.12 (s, 1H, CHCN), 3.84 (d, *J* = 14.4 Hz, 1H, H-1), 3.77 (d, *J* = 14.4 Hz, 1H, H-1), 3.06–2.88 (m, 2H, 2H-4), 2.90–2.85 (m, 2H, 2H-3) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 137.2 (C1′), 133.6 (C4a), 133.4 (C8a), 131.5 (q, *J* = 32.9 Hz, C4′), 128.9 (C5), 128.2 (2C, C2′,6′), 126.7 (C8), 126.6 (C6), 126.1 (C7), 126.0 (q, *J* = 3.8 Hz, 2C, C3′,5′), 126.0 (q, *J* = 272.4 Hz, CF_3), 114.8 (CN), 61.9 (C–CN), 52.6 (C1), 47.7 (C3), 29.3 (C4) ppm; ESI-MS (*m*/*z*) 317.1 (100) $[M + H]^+$; ESI-HRMS calcd for $[C_{18}H_{15}F_3N_2]^+$ 317.1266, found 317.1275.

2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-2-(4-methoxyphenyl)-acetonitrile (2e). Following the general procedure, compound **2e** was prepared from 1,2,3,4-tetrahydroisoquinoline **1a** (952 μL, 7.51 mmol), *p*-anisaldehyde (921 μL, 7.51 mmol), $NaHSO_3$ (781 g, 7.51 mmol), and KCN (978 mg, 15.02 mmol). The crude product was recrystallized from diethyl ether to afford the title compound (1.94 g, 6.97 mmol, 93%) as colorless crystals: mp 98.5–99.1 °C; R_f = 0.56 (cyclohexane/EtOAc, 3:2); IR (ATR) ν = 3065, 3023, 2932, 2835, 2757, 2225, 1611, 1585, 1511, 1463, 1250, 1176, 1088, 1032, 937, 839, 799, 741 cm^{-1}; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.52 (d, *J* = 8.6 Hz, 2H, H-2′,6′), 7.20–7.07 (m, 3H, H-5, H-6, H-7), 7.03–6.96 (m, 1H, H-8), 6.94 (d, *J* = 8.6 Hz, 2H, H-3′,5′), 5.03 (s, 1H, CHCN), 3.84 (s, 3H, OCH_3-4′), 3.79 (d, *J* = 14.8 Hz, 1H, H-1), 3.75 (d, *J* = 14.8 Hz, 1H, H-1), 3.11–2.68 (m, 4H, 2H-3, 2H-4) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 160.3 (C4′), 133.7 (C4a), 133.6 (C8a), 129.4 (2C, C2′,6′), 128.9 (C5), 126.8 (C8), 126.6 (C6), 126.0 (C7), 124.8 (C1′), 115.6 (CN), 114.3 (2C, C3′,5′), 61.7 (C–CN), 55.5 (OMe-4′), 52.4 (C1), 47.6 (C3), 29.3 (C4) ppm; ESI-MS (*m*/*z*) 279.1 (100) $[M + H]^+$; ESI-HRMS calcd for $[C_{18}H_{19}N_2O]^+$ 279.1497, found 279.1498.

2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-2-(3,4,5-trimethoxy-phenyl)acetonitrile (2f). Following the general procedure, compound **2f** was prepared from 1,2,3,4-tetrahydroisoquinoline **1a** (952 μL, 7.51 mmol), 3,4,5-trimethoxybenzaldehyde (1.47 g, 7.51 mmol), $NaHSO_3$ (781 mg, 7.51 mmol), and KCN (978 mg, 15.02 mmol). The crude product was recrystallized from diethyl ether to afford the title compound (2.03 g, 6.00 mmol, 80%) as colorless crystals: mp 126.9–127.5 °C; R_f = 0.51 (cyclohexane/EtOAc, 3:2); IR (ATR) ν = 3065, 3001, 2938, 2835, 2755, 2228, 1691, 1591, 1505, 1456, 1331, 1233, 1125, 1051, 935, 842, 741 cm^{-1}; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.21–7.10 (m, 3H, H-5, H-6, H-7), 7.06–7.01 (m, 1H, H-8), 6.84 (s, 2H, H-2′,6′), 5.01 (s, 1H, CHCN), 3.88 (s, 6H, OMe-3′,5′), 3.87 (s, 3H, OMe-4′), 3.84 (d, *J* = 14.7 Hz, 1H, H-1), 3.79 (d, *J* = 14.7 Hz, 1H, H-1), 3.02–2.85 (m, 3H, 2H-3, H-4), 2.85–2.74 (m, 1H, H-4) ppm; ^{13}C NMR, HMBC, HSQC

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(100.6 MHz, $CDCl_3$) δ = 153.6 (2C, C3′,5′), 138.4 (C4′), 133.8 (C4a), 133.7 (C8a), 128.9 (C5), 128.7 (C1′), 126.7 (C8), 126.6 (C6), 126.0 (C7), 115.5 (CN), 104.7 (2C, C2′,6′), 62.3 (C−CN), 61.0 (OMe-4′), 56.4 (2C, OMe-3′,5′), 52.8 (C1), 47.3 (C3), 29.4 (C4) ppm; ESI-MS (m/z) 206.0 (100) $[M - C_9H_{10}N]^+$, 339.1 (38) $[M + H]^+$; ESI-HRMS calcd for $[C_{20}H_{23}N_2O_3]^+$ 339.1709, found 339.1711.

2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-2-(thiophen-2-yl)acetonitrile (2g). Following the general procedure, compound **2g** was prepared from 1,2,3,4-tetrahydroisoquinoline **1a** (952 μL, 7.51 mmol), 2-thiophene carbaldehyde (702 μL, 7.51 mmol), $NaHSO_3$ (781 g, 7.51 mmol), and KCN (978 g, 15.02 mmol). The crude product was recrystallized from methanol to afford the title compound (1.66 g, 6.53 mmol, 87%) as a slightly yellow solid: mp 79.6−80.2 °C; R_f = 0.62 (cyclohexane/EtOAc, 3:2); IR (ATR) ν = 3066, 3024, 2922, 2819, 2756, 2229, 1584, 1498, 1455, 1355, 1267, 1139, 1088, 934, 844, 739, 703 cm^{-1}; ^1H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.38 (d, J = 5.2 Hz, 1H, H-5′), 7.38−7.32 (m, 1H, H-3′), 7.21−7.09 (m, 3H, H-5, H-6, H-7), 7.07−6.99 (m, 2H, H-4′, H-8), 5.23 (s, 1H, CHCN), 3.88 (t, 2H, 2H-1), 3.06−2.93 (m, 3H, 2H-3, H-4), 2.90−2.75 (m, 1H, H-4) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 137.0 (C2′), 133.7 (C4a), 133.2 (C8a), 128.9 (C5), 127.7 (C5′), 127.5 (C3′), 126.9 (C4′), 126.7 (2C, C6, C8), 126.1 (C7), 114.8 (CN), 58.0 (C−CN), 52.7 (C1), 47.4 (C3), 29.3 (C4) ppm; ESI-MS (m/z) 255.1 (100) $[M + H]^+$; ESI-HRMS calcd for $[C_{15}H_{15}N_2S]^+$ 255.0956, found 255.0957.

2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-phenylacetonitrile (2h). Following the general procedure with a subtle modification, compound **2h** was prepared from 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **1b** (1.00 g, 5.17 mmol, dissolved in 3 mL of methanol before addition), benzaldehyde (527 μL, 5.17 mmol), $NaHSO_3$ (538 mg, 5.17 mmol), and KCN (673 mg, 10.34 mmol). The crude product was recrystallized from diethyl ether to afford the title compound (1.30 g, 4.21 mmol, 82%) as colorless crystals: mp 101.6−102.3 °C; R_f = 0.38 (cyclohexane/EtOAc, 3:2); IR (ATR) ν = 3062, 2998, 2935, 2835, 2225, 1611, 1517, 1463, 1257, 1223, 1124, 1013, 980, 855, 726, 697 cm^{-1}; ^1H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.65−7.57 (m, 2H, H-2′,6′), 7.48−7.37 (m, 3H, H-3′,5′, H-4′), 6.60 (s, 1H, H-5), 6.48 (s, 1H, H-8), 5.07 (s, 1H, CHCN), 3.84 (s, 3H, OMe-6), 3.81 (s, 3H, OMe-7), 3.72 (d, J = 14.0 Hz, 1H, H-1), 3.67 (d, J = 14.0 Hz, 1H, H-1), 2.95−2.76 (m, 4H, 2H-3, 2H-4) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 147.8 (C6), 147.5 (C7), 133.1 (C1′), 129.1 (C4′), 129.0 (2C, C3',5'), 128.0 (2C, C2',6'), 125.6 (C4a), 125.4 (C8a), 115.5 (CN), 111.5 (C5), 109.5 (C8), 62.3 (C−CN), 56.0 (2C, OMe-6, OMe-7), 52.0 (C1), 47.9 (C3), 29.0 (C4) ppm; ESI-MS (m/z) 309.1 (100) $[M + H]^+$; ESI-HRMS calcd for $[C_{19}H_{21}N_2O_2]^+$ 309.1603, found 309.1613.

2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-(4-methoxyphenyl)acetonitrile (2i). Following the general procedure with a subtle modification, compound **2i** was prepared from 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **1b** (979 mg, 5.07 mmol, dissolved in 3 mL of methanol before addition), *p*-anisaldehyde (622 μL, 5.07 mmol), $NaHSO_3$ (527 mg, 5.07 mmol), and KCN (660 g, 10.14 mmol). The crude product was recrystallized from diethyl ether to afford the title compound (1.44 g, 4.26 mmol, 84%) as colorless crystals: mp 117.3−117.7 °C; R_f = 0.39 (cyclohexane/EtOAc, 3:2); IR (ATR) ν = 3059, 2999, 2935, 2836, 2226, 1611, 1585, 1511, 1463, 1250, 1223, 1175, 1123, 1030, 940, 819, 780, 733 cm^{-1}; ^1H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.51 (d, J = 8.6 Hz, 2H, H-2′, 6′), 6.94 (d, J = 8.8 Hz, 2H, H-3′,5′), 6.60 (s, 1H, H-5), 6.48 (s, 1H, H-8), 5.01 (s, 1H, CHCN), 3.84 (s, 3H, OMe-6), 3.83 (s, 3H, OMe-7), 3.81 (s, 3H, OMe-4′), 3.70 (d, J = 14.0 Hz, 1H, H-1), 3.65 (d, J = 14.0 Hz, 1H, H-1), 2.99−2.71 (m, 4H, 2H-3, 2H-4) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 160.2 (C4′), 147.8 (C6), 147.5 (C7), 129.3 (2C, C2′,6′), 125.6 (C4a), 125.4 (C8a), 125.0 (C1′), 115.7 (CN), 114.3 (2C, C3′,5′), 111.4 (C5), 109.5 (C8), 61.7 (C−CN), 56.0 (2C, OMe-6, OMe-7), 55.5 (OMe-4′), 51.9 (C1), 47.8 (C3), 28.9 (C4) ppm; ESI-MS (m/z) 339.2 (100) $[M + H]^+$; ESI-HRMS calcd for $[C_{20}H_{23}N_2O_3]^+$ 339.1709, found 339.1712.

2-(2,6-Dichlorophenyl)-2-(3,4-dihydroisoquinolin-2(1*H*)-yl)-acetonitrile (2j). Following the general procedure, compound **2j** was prepared from 1,2,3,4-tetrahydroisoquinoline (**1a**, 952 μL, 7.51 mmol), 2,6-dichlorobenzaldehyde (1.31 g, 7.51 mmol), $NaHSO_3$ (781 g, 7.51 mmol), and KCN (978 mg, 15.02 mmol). The crude product (1.88 g, 5.93 mmol, 79%) was obtained as a yellow oil and was used without further purification: R_f = 0.56 (cyclohexane/EtOAc, 3:2); IR (ATR) ν = 3066, 3025, 2922, 2814, 2758, 2243, 1673, 1563, 1202, 1095, 133, 781, 749 cm^{-1}; ^1H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.43−7.38 (m, 2H, H-3′,5′), 7.29 (dd, J = 8.8, 7.3 Hz, 1H, H-4′), 7.15−7.06 (m, 3H, H-5, H-6, H-7), 7.06−6.98 (m, 1H, H-8), 5.46 (s, 1H, CHCN), 3.96 (d, J = 14.4 Hz, 1H, H-1), 3.85 (d, J = 14.4 Hz, 1H, H-1), 3.13−2.86 (m, 4H, 2H-3, 2H-4) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 136.6 (2C, C2′,6′), 133.7 (C4a), 133.5 (C8a), 130.9 (C4′), 129.7 (2C, C3′,5′), 129.0 (C1′), 128.8 (C5), 126.8 (C8), 126.6 (C6), 126.0 (C7), 115.5 (CN), 56.7 (C−CN), 52.3 (C1), 48.4 (C3), 29.2 (C4) ppm; ESI-MS (m/z) 317.1 (100) $[M + H]^+$; ESI-HRMS calcd for $[C_{17}H_{15}Cl_2N_2]^+$ 317.0612, found 317.0624.

General Procedure for the Preparation of 2-(Cyano(aryl)-methyl)-2-alkyl-1,2,3,4-tetrahydroisoquinolin-2-ium Trifluoromethanesulfonate (3a−j). Alkyl triflate (1.2−2.0 equiv) was added to a stirred solution of the corresponding α-aminonitrile **2a−i** (1.0 equiv) in dry dichloromethane (6 mL). The stirring was continued at room temperature for a determined period of time (TLC monitoring). Removal of the solvent under reduce pressure provided a crude material which was purified by flash column chromatography (Isolera Flash Purification System, chloroform/methanol, gradient 0−16%) to afford the title compouds.

2-(Cyano(phenyl)methyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-2-ium Trifluoromethanesulfonate (3a). According to the general procedure described above, α-aminonitrile **2a** (733 mg, 2.94 mmol) and methyl triflate (387 μL, 3.54 mmol) were allowed to react overnight in order to obtain compound **3a** as a diastereomeric mixture in a 51:49 ratio (^1H NMR) in the form of a white foam (1.19 g, 2.88 mmol, 98%): R_f = 0.33 (chloroform/methanol, 10:1); IR (ATR) ν = 3060, 2934, 1588, 1459, 1253, 1224, 1155, 1029, 874, 745, 637 cm^{-1}; (*Major diastereomer*) ^1H NMR, COSY, NOESY (400 MHz, $CDCl_3$) δ = 7.88 (d, J = 6.8 Hz, 2H, H-2′,6′), 7.70−7.58 (m, 3H, H-3′,5′ H-4′), 7.41−7.20 (m, 3H, H-5, H-6, H-7), 7.18 (d, J = 7.6 Hz, 1H, H-8), 6.76 (s, 1H, CHCN), 4.88 (t, J = 14.7 Hz, 1H, H-1), 4.65 (dd, J = 14.7, 1.8 Hz, 1H, H-1), 4.09−3.97 (m, 1H, H-3), 3.94−3.86 (m, 1H, H-3), 3.39−3.25 (m, 2H, H-4), 3.28 (s, 3H, N−Me) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 133.4 (C4′), 132.6 (2C, C2′,6′), 130.4 (2C, C3′,5″), 129.9 (C5), 129.1 (C6), 128.5 (C7), 128.0 (C4a), 127.7 (C8), 124.5 (C8a), 123.8 (q, J = 319.6 Hz, OTf), 123.3 (C1′), 112.8 (CN), 68.6 (C−CN), 60.4 (C1), 56.4 (C3), 44.0 (N−Me), 23.9 (C4) ppm; (*Minor diastereomer*) ^1H NMR, COSY, NOESY (400 MHz, $CDCl_3$) δ = 7.85 (d, J = 6.8 Hz, 2H, H-2′,6′), 7.70−7.58 (m, 3H, H-3′,5′ H-4′), 7.41−7.21 (m, 3H, H-5, H-6, H-7), 7.15 (d, J = 7.6 Hz, 1H, H-8), 6.65 (s, 1H, CHCN), 4.88 (t, J = 14.7 Hz, 1H, H-1), 4.54 (dd, J = 14.7, 1.2 Hz, 1H, H-1), 4.28−4.15 (m, 1H, H-3), 3.88−3.75 (m, 1H, H-3), 3.39−3.25 (m, 2H, H-4), 3.26 (s, 3H, N−Me) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 133.3 (C4′), 132.5 (2C, C2′,6′), 130.4 (2C, C3′,5′), 129.8 (C5), 129.2 (C6), 128.5 (C7), 127.9 (C4a), 127.8 (C8), 124.5 (C8a), 123.8 (q, J = 319.6 Hz, OTf), 123.1 (C1′), 112.7 (CN), 67.7 (C−CN), 60.2 (C1), 57.0 (C3), 44.4 (N−Me), 23.9 (C4) ppm; ESI-MS (m/z) 263.1 (100) $[M]^+$; ESI-HRMS calcd for $[C_{18}H_{20}N_2]^+$ 264.1626, found 264.1617.

2-((4-Chlorophenyl)(cyano)methyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-2-ium Trifluoromethanesulfonate (3b). According to the general procedure described above, α-aminonitrile **2b** (1.00 g, 3.54 mmol) and methyl triflate (463 μL, 4.24 mmol) were allowed to react overnight in order to obtain compound **3b** as a diastereomeric mixture in a 52:48 ratio (^1H NMR) in the form of a white foam (1.52 g, 3.40 mmol, 96%): R_f = 0.37 (chloroform/

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methanol, 10:1); IR (ATR) ν = 3057, 2933, 1596, 1495, 1251, 1156, 1028, 875, 754, 637 cm^{-1}; (*Major diastereomer*) ^1H NMR, COSY, NOESY (400 MHz, $CDCl_3$) δ = 7.85 (d, J = 8.6 Hz, 2H, H-2′,6′), 7.58 (d, J = 8.6 Hz, 2H, H-3′,5′), 7.41−7.21 (m, 3H, H-5, H-6, H-7), 7.14 (d, J = 7.6 Hz, 1H, H-8), 6.73 (s, 1H, CHCN), 4.91 (d, J = 14.5 Hz, 1H, H-1), 4.50 (dd, J = 14.5, 2.3 Hz, 1H, H-1), 4.04−3.95 (m, 1H, H-3), 3.93−3.78 (m, 1H, H-3), 3.36−3.25 (m, 2H, H-4), 3.25 (s, 3H, N−Me) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 140.2 (C4′), 133.7 (2C, C2′,6′), 130.7 (2C, C3′,5′), 129.9 (C5), 129.2 (C6), 128.5 (C7), 127.9 (C4a), 127.8 (C8), 124.4 (C8a), 121.6 (C1′), 120.6 (q, J = 319.7 Hz, OTf), 112.5 (CN), 67.0 (C−CN), 60.4 (C1), 57.1 (C3), 44.2 (N−Me), 23.8 (C4) ppm; (*Minor diastereomer*) ^1H NMR, COSY, NOESY (400 MHz, $CDCl_3$) δ = 7.84 (d, J = 8.6 Hz, 2H, H-2′,6′), 7.58 (d, J = 8.6 Hz, 2H, H-3′,5′), 7.41−7.21 (m, 3H, H-5, H-6, H-7), 7.17 (d, J = 7.6 Hz, 1H, H-8), 6.80 (s, 1H, CHCN), 4.85 (d, J = 14.5 Hz, 1H, H-1), 4.64 (dd, J = 14.5, 2.0 Hz, 1H, H-1), 4.21−4.12 (m, 1H, H-3), 3.93−3.78 (m, 1H, H-3), 3.36−3.25 (m, 2H, H-4), 3.25 (s, 3H, N−Me) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 140.1 (C4′), 134.0 (2C, C2′,6′), 130.7 (2C, C3′,5′), 129.8 (C5), 129.1 (C6), 128.4 (C7), 128.0 (C4a), 127.9 (C8), 124.5 (C8a), 121.8 (C1′), 120.6 (q, J = 319.7 Hz, OTf), 112.5 (CN), 67.8 (C−CN), 60.5 (C1), 56.4 (C3), 43.9 (N−Me), 23.9 (C4) ppm; ESI-MS (m/z) 297.1 (100) $[M]^+$; ESI-HRMS calcd for $[C_{18}H_{18}ClN_2]^+$ 297.1159, found 297.1164.

2-(Cyano(4-fluorophenyl)methyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-2-ium Trifluoromethanesulfonate (3c). According to the general procedure described above, α-aminonitrile **2c** (1.23 g, 4.62 mmol) and methyl triflate (606 μL, 5.54 mmol) were allowed to react overnight in order to obtain compound **3c** as a diastereomeric mixture in a 52:48 ratio (^1H NMR) in the form of a slightly yellow foam (1.86 g, 4.32 mmol, 94%): R_f = 0.37 (chloroform/methanol, 10:1); IR (ATR) ν = 3071, 2933, 1606, 1512, 1250, 1164, 1029, 845, 755, 637 cm^{-1}; (*Major diastereomer*) ^1H NMR, COSY, NOESY (400 MHz, $CDCl_3$) δ = 7.94−7.82 (m, 2H, H-2′,6′), 7.35−7.18 (m, 5H, H-5, H-6, H-7, H-3′,5′), 7.11 (d, J = 7.5 Hz, 1H, H-8), 6.59 (s, 1H, CHCN), 4.84 (t, J = 13.9 Hz, 1H, H-1), 4.46 (dd, J = 13.9, 2.2 Hz, 1H, H-1), 4.15−4.05 (m, 1H, H-3), 3.98−3.75 (m, 1H, H-3), 3.35−3.23 (m, 2H, H-4), 3.17 (s, 3H, N−Me) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 165.3 (d, J = 256.5 Hz, C4′), 134.9 (d, J =9.3 Hz, 2C, C2′,4′), 129.7 (C5), 129.1 (C6), 128.3 (C7), 128.1 (C4a), 127.7 (C8), 124.5 (C8a), 120.6 (q, J = 319.7 Hz, OTf), 119.2 (d, J = 3.4 Hz, C1′), 117.7 (d, J = 22.3 Hz, 2C, C3′,5″), 112.6 (CN), 66.9 (C−CN), 60.5 (C1), 57.0 (C3), 44.0 (N−Me), 23.7 (C4) ppm; (*Minor diastereomer*) ^1H NMR, COSY, NOESY (400 MHz, $CDCl_3$) δ = 7.94−7.82 (m, 2H, H-2′,6′), 7.35−7.18 (m, 5H, H-5, H-6, H-7, H-3′,5′), 7.15 (d, J = 7.5 Hz, 1H, H-8), 6.66 (s, 1H, CHCN), 4.84 (t, J = 13.9 Hz, 1H, H-1), 4.62 (dd, J = 13.9, 2.3 Hz, 1H, H-1), 3.98−3.75 (m, 2H, H-3), 3.35−3.23 (m, 2H, H-4), 3.20 (s, 3H, N−Me) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 165.3 (d, J = 256.5 Hz, C-4′), 134.1 (d, J =9.3 Hz, 2C, C2′,6′), 129.6 (C5), 129.0 (C6), 128.3 (C7), 128.2 (C4a), 127.8 (C8), 124.6 (C8a), 120.6 (q, J = 319.7 Hz, OTf), 119.3 (d, J = 3.4 Hz, C1′), 117.7 (d, J = 22.3 Hz, 2C, C3′,5′), 112.5 (CN), 67.7 (C−CN), 60.6 (C1), 56.2 (C3), 43.8 (N−CH_3), 23.7 (C4) ppm; ESI-MS (m/z) 281.1 (100) $[M]^+$; ESI-HRMS calcd for $[C_{18}H_{18}FN_2]^+$ 281.1454, found 281.1452.

2-(Cyano(4-(trifluoromethyl)phenyl)methyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-2-ium Trifluoromethanesulfonate (3d). According to the general procedure described above, α-aminonitrile **2d** (1.00 g, 3.16 mmol) and methyl triflate (415 μL, 3.79 mmol) were allowed to react overnight in order to obtain compound **3d** as a diastereomeric mixture in a 51:49 ratio (^1H NMR) and in the form of a white foam (1.38 g, 2.87 mmol, 91%): R_f = 0.39 (chloroform/methanol, 10:1); IR (ATR) ν = 3037, 2935, 2253, 1501, 1457, 1326, 1251, 1164, 1133, 1070, 1029, 851, 756, 638 cm^{-1}; (*Major diastereomer*) ^1H NMR, COSY, NOESY (400 MHz, $CDCl_3$) δ = 8.07 (d, J = 8.3 Hz, 2H, H-2′,6′), 7.84 (d, J = 8.3 Hz, 2H, H-3′,5′), 7.39−7.19 (m, 3H, H-5, H-6, H-7), 7.13 (d, J = 7.6 Hz, 1H, H-8), 6.74 (s, 1H, CHCN), 4.89 (t, J = 14.7 Hz, 1H, H-1), 4.66 (dd, J = 14.7, 2.4 Hz, 1H, H-1), 4.03−3.93 (m, 1H, H-3), 3.94−3.81 (m, 1H, H-3), 3.37−3.21 (m, 2H, H-4), 3.23 (s, 3H, N−Me) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 135.0 (q, J = 33.1 Hz, C4′), 133.2 (2C, C2′,6′), 129.9 (C5), 129.1 (C6), 128.4 (C7), 128.0 (C4a), 127.8 (C8), 127.3 (q, J = 4.0 Hz, 2C, C3′,5′), 127.1 (C1′), 124.4 (C8a), 123.2 (q, J = 273.2 Hz, CF_3), 120.6 (q, J = 319.6 Hz, OTf), 112.3 (CN), 66.8 (C−CN), 60.9 (C1), 57.4 (C3), 44.3 (N−Me), 23.8 (C4) ppm; (*Minor diastereomer*) ^1H NMR, COSY, NOESY (400 MHz, $CDCl_3$) δ = 8.04 (d, J = 8.3 Hz, 2H, H-2′,6′), 7.84 (d, J = 8.3 Hz, 2H, H-3′,5′), 7.39−7.19 (m, 3H, H-5, H-6, H-7), 7.16 (d, J = 7.6 Hz, 1H, H-8), 6.81 (s, 1H, CHCN), 4.89 (t, J = 14.7 Hz, 1H, H-1), 4.51 (dd, J = 14.7, 2.4 Hz, 1H, H-1), 4.21−3.11 (m, 1H, H-3), 3.94−3.81 (m, 1H, H-3), 3.37−3.21 (m, 2H, H-4), 3.25 (s, 3H, N−Me) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 135.0 (q, J = 33.1 Hz, C4′), 133.3 (2C, C2′,6′), 129.8 (C5), 129.0 (C6), 128.3 (C7), 127.9 (C4a), 127.7 (C8), 127.3 (q, J = 4.0 Hz, 2C, C3′,5′), 127.0 (C1′), 124.3 (C8a), 123.2 (q, J = 273.2 Hz, CF_3), 120.6 (q, J = 319.6 Hz, OTf), 112.2 (CN), 67.6 (C−CN), 60.8 (C1), 57.7 (C3), 44.1 (N−Me), 23.8 (C4) ppm; ESI-MS (m/z) 331.2 (100) $[M]^+$; ESI-HRMS calcd for $[C_{19}H_{18}F_3N_2]^+$ 331.1422, found 331.1431.

2-(Cyano(4-methoxyphenyl)methyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-2-ium Trifluoromethanesulfonate (3e). According to the general procedure described above, α-aminonitrile **2e** (1.00 g, 3.59 mmol) and methyl triflate (471 μL, 4.31 mmol) were allowed to react overnight in order to obtain compound **3e** as a diastereomeric mixture in a 52:48 ratio (^1H NMR) in the form of a white foam (1.60 g, 3.58 mmol, 99%): R_f = 0.37 (chloroform/methanol, 10:1); IR (ATR) ν = 3041, 2938, 2844, 1609, 1515, 1254, 1157, 1028, 842, 755, 637 cm^{-1}; (*Major diastereomer*) ^1H NMR, COSY, NOESY (400 MHz, $CDCl_3$) δ = 7.77 (d, J = 8.8 Hz, 2H, H-2′,6′), 7.41−7.21 (m, 3H, H-5, H-6, H-7), 7.15 (d, J = 7.7 Hz, 1H, H-8), 6.61 (s, 1H, CHCN), 4.85 (t, J = 14.7 Hz, 1H, H-1), 4.50 (dd, J = 14.7, 1.6 Hz, 1H, H-1), 4.03−3.94 (m, 1H, H-3), 3.93−3.82 (m, 1H, H-3), 3.87 (s, 3H, OMe-4′), 3.35−3.24 (m, 2H, H-4), 3.25 (s, 3H, N−Me) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 163.3 (C4′), 134.3 (2C, C2′,6′), 129.9 (C-5), 129.2 (C6), 128.5 (C7), 128.1 (C4a), 127.8 (C8), 124.7 (C8a), 120.7 (q, J = 319.3 Hz, OTf), 115.7 (2C, C3′,5′), 114.7 (C-1′), 112.9 (CN), 67.7 (C−CN), 59.7 (C1), 55.9 (2C, C3, OMe-4′), 44.1 (N−Me), 23.9 (C4) ppm; (*Minor diastereomer*) ^1H NMR, COSY, NOESY (400 MHz, $CDCl_3$) δ = 7.80 (d, J = 8.9 Hz, 2H, H-2′,6′), 7.41−7.21 (m, 3H, H-5, H-6, H-7), 7.17 (d, J = 7.9 Hz, 1H, H-8), 6.71 (s, 1H, CHCN), 4.85 (t, J = 14.7 Hz, 1H, H-1), 4.60 (dd, J = 14.7, 1.9 Hz, 1H, H-1), 4.23−4.12 (m, 1H, H-3), 3.83−3.71 (m, 1H, H-3), 3.87 (s, 3H, OMe-4′), 3.35−3.24 (m, 2H, H-4), 3.23 (s, 3H, N−Me) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 163.3 (C-4′), 134.1 (2C, C2′,6′), 129.8 (C5), 129.1 (C6), 128.4 (C7), 128.0 (C4a), 127.9 (C8), 124.7 (C8a), 120.7 (q, J = 319.3 Hz, OTf), 115.7 (2C, C3′,5′), 114.5 (C-1′), 112.9 (CN), 68.5 (C−CN), 60.0 (C1), 56.5 (C3, OMe-4′), 55.9 (OCH_3-4′), 43.6 (N−Me), 24.0 (C-4) ppm; ESI-MS (m/z) 293.2 (100) $[M]^+$; ESI-HRMS calcd for $[C_{19}H_{21}N_2O]^+$ 293.1654, found 293.1653.

2-(Cyano(3,4,5-trimethoxyphenyl)methyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-2-ium (3f). According to the general procedure described above, α-aminonitrile **2f** (500 mg, 1.47 mmol) and methyl triflate (192 μL, 4.31 mmol) were allowed to react overnight in order to obtain compound **3f** as a diastereomeric mixture in a 51:49 ratio (^1H NMR) in the form of a white foam (708 mg, 1.41 mmol, 96%): R_f = 0.46 (chloroform/methanol, 10:1); IR (ATR) ν = 3058, 2943, 2843, 1593, 1508, 1466, 1246, 1126, 1028, 829, 732, 636 cm^{-1}; (*Major diastereomer*) ^1H NMR, COSY, NOESY (400 MHz, $CDCl_3$) δ = 7.39−7.19 (m, 3H, H-5, H-6, H-7), 7.15 (t, J = 7.2 Hz, 1H, H-8), 7.03 (s, 2H, H-2′H-6′), 6.59 (s, 1H, CHCN), 4.84 (d, J = 14.7 Hz, 1H, H-1), 4.67 (dd, J = 14.7, 2.1 Hz, 1H, H-1), 4.21−4.11 (m, 1H, H-3), 4.02−3.76 (m, 1H, H-3), 3.91 (s, 6H, OMe-3″,5′), 3.87 (s, 3H, OMe-4′), 3.34−3.26 (m, 2H, H-4), 3.26 (s, 3H, N−Me) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 154.3 (2C, C3′,5′), 141.8 (C4′), 129.7 (C5), 129.0 (C6), 128.2 (C7), 128.1 (C4a), 127.8 (C8), 124.7 (C8a), 120.6 (q, J

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= 319.9 Hz, OTf), 118.0 (C1′), 112.9 (CN), 109.8 (2C, C2′,6′), 69.0 (C−CN), 61.0 (2C, OMe-3′,5′), 60.3 (C1), 56.8 (Me-4″), 56.1 (C3), 44.0 (N−Me), 23.8 (C4) ppm; (*Minor diastereomer*) ^{1}H NMR, COSY, NOESY (400 MHz, $CDCl_3$) δ = 7.39−7.19 (m, 3H, H-5, H-6, H-7), 7.15 (t, J = 7.2 Hz, 1H, H-8), 7.07 (s, 2H, H-2′,6′), 6.49 (s, 1H, CHCN), 4.91 (d, J = 14.8 Hz, 1H, H-1), 4.50 (dd, J = 14.8, 1.9 Hz, 1H, H-1), 4.02−3.76 (m, 2H, H-3), 3.90 (s, 6H, OMe-3′,5′), 3.88 (s, 3H, OMe-4′), 3.34−3.26 (m, 2H, H-4), 3.25 (s, 3H, N−Me) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 154.3 (2C, C3′,5′), 141.8 (C4′), 129.8 (C5), 129.1 (C6), 128.3 (C7), 128.0 (C4a), 127.7 (C8), 124.7 (C8a), 120.6 (q, J = 319.9 Hz, OTf), 117.9 (C1′), 112.7 (CN), 109.8 (2C, C2′, C6′), 68.0 (C−CN), 61.1 (2C, OMe-3′,5′), 60.6 (C-1), 56.9 (OMe-4′), 57.1 (C3), 44.3 (N−Me), 23.8 (C4) ppm; ESI-MS (m/z) 206.0 (100) $[M - C_{10}H_{13}N]^+$, 353.2 (89) $[M]^+$; ESI-HRMS calcd for $[C_{21}H_{25}N_2O_3]^+$ 353.1865, found 353.1864.

2-(Cyano(thiophen-2-yl)methyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-2-ium Trifluoromethanesulfonate (3g). According to the general procedure described above, α-aminonitrile **2g** (501 mg, 1.97 mmol) and methyl triflate (258 μL, 2.36 mmol) were allowed to react overnight in order to obtain compound **3g** as a diastereomeric mixture in a 53:47 ratio (^{1}H NMR) in the form of a brown foam (768 mg, 1.83 mmol, 93%): R_f = 0.43 (chloroform/methanol, 10:1); IR (ATR) ν = 3090, 2921, 1476, 1422, 1248, 1155, 1028, 845, 730, 636 cm^{-1}; (*Major diastereomer*) ^{1}H NMR, COSY, NOESY (400 MHz, $CDCl_3$) δ = 7.82 (dd, J = 3.7, 1.2 Hz, 1H, H-5′), 7.73 (d, J = 1,2 Hz, 1H, H-3′), 7.38−7.20 (m, 4H, H-4′, H-5, H-6, H-7), 7.13 (d, J = 7.6 Hz, 1H, H-8), 7.03 (s, 1H, CHCN), 4.94 (d, J = 14.9 Hz, 1H, H-1), 4.52 (dd, J = 14.9, 2.2 Hz, 1H, H-1), 4.03−3.81 (m, 2H, H-3), 3.43−3.25 (m, 2H, H-4), 3.27 (s, 3H, N−Me) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 137.4 (C5′), 133.4 (C3′), 129.9 (C5), 129.1 (2C, C6, C4′), 128.4 (C7), 128.2 (C4a), 127.8 (C8), 124.5 (C8a), 123.4 (C2′), 120.6 (q, J = 319.8 Hz, OTf), 112.3 (CN), 62.9 (C−CN), 60.2 (C1), 56.9 (C3), 44.0 (N−Me), 23.9 (C4) ppm; (*Minor diastereomer*) ^{1}H NMR, COSY, NOESY (400 MHz, $CDCl_3$) δ = 7.84 (dd, J = 3.7, 1.2 Hz, 1H, H-5′), 7.74 (d, J = 1,2 Hz, 1H, H-3′), 7.38−7.20 (m, 4H, H-4′, H-5, H-6, H-7), 7.17 (d, J = 7.6 Hz, 1H, H-8), 7.10 (s, 1H, CHCN), 4.89 (d, J = 14.9 Hz, 1H, H-1), 4.69 (dd, J = 14.9, 2.2 Hz, 1H, H-1), 4.24−4.11 (m, 1H, H-3), 4.03−3.81 (m, 1H, H-3), 3.43−3.25 (m, 2H, H-4), 3.28 (s, 3H, N−Me) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 137.7 (C5′), 133.5 (C3′), 129.7 (C5), 129.2 (2C, C6, C4′), 128.3 (C7), 128.1 (C4a), 127.8 (C7), 124.6 (C8a), 123.5 (C2′), 120.6 (q, J = 319.8 Hz, OTf), 112.2 (CN), 63.7 (C−CN), 60.5 (C1), 56.1 (C3), 44.0 (N−Me), 23.9 (C4) ppm; ESI-MS (m/z) 269.1 (100) $[M]^+$; ESI-HRMS calcd for $[C_{16}H_{17}N_2S]^+$ 269.1112, found 269.1105.

2-(Cyano(phenyl)methyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-2-ium Trifluoromethanesulfonate (3h). According to the general procedure described above, α-aminonitrile **2h** (848 mg, 2.75 mmol) and methyl triflate (361 μL, 3.30 mmol) were allowed to react overnight in order to obtain compound **3h** as a diastereomeric mixture in a 51:49 ratio (^{1}H NMR) in the form of a slightly yellow foam (1.28 g, 2.71 mmol, 98%): R_f = 0.37 (chloroform/methanol, 10:1); IR (ATR) ν = 3061, 2940, 2841, 1613, 1521, 1461, 1252, 1157, 1119, 1028, 730, 700, 636 cm^{-1}; (*Major diastereomer*) ^{1}H NMR, COSY, NOESY (400 MHz, $CDCl_3$) δ = 7.85 (d, J = 7.3 Hz, 2H, H-2′,6′), 7.66−7.53 (m, 3H, H-3′,5′, H-4′), 6.86 (s, 1H, H-5), 6.63 (s, 1H, CHCN), 6.59 (s, 1H, H-8), 4.79 (d, J = 14.4 Hz, 1H, H-1), 4.54 (d, J = 14.4 Hz, 1H, H-1), 4.10−4.05 (m, 1H, H-3), 3.82−3.67 (m, 1H, H-3), 3.82 (s, 3H, OMe-6), 3.80 (s, 3H, OMe-7), 3.29−3.12 (m, 2H, H-4), 3.22 (s, 3H, N−Me) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 150.0 (C6), 149.2 (C7), 133.2 (C4′), 132.6 (2C, C2′,6′), 130.3 (2C, C3′,5′), 123.3 (C-1′), 120.6 (q, J = 319.8 Hz, OTf), 120.0 (C4a), 116.3 (C8a), 112.7 (CN), 110.9 (C5), 109.8 (C8), 68.5 (C−CN), 60.3 (C1), 57.2 (C3), 56.2 (2C, OMe-6, OMe-7), 43.8 (N−Me), 23.6 (C4) ppm; (*Minor diastereomer*) ^{1}H NMR, COSY, NOESY (400 MHz, $CDCl_3$) δ = 7.80 (d, J = 7.5 Hz, 2H, H-2′,6′), 7.66−7.53 (m, 3H, H-3′,5′, H-4′), 6.68 (s, 1H, H-5), 6.58 (s, 1H, H-8), 6.52 (s, 1H, CHCN), 4.79 (d, J = 14.4 Hz, 1H, H-1), 4.42 (d, J = 14.4 Hz, 1H, H-1), 4.0−3.90 (m, 1H, H-3), 3.83 (s, 3H, OMe-6), 3.82−3.67 (m, 1H, H-3), 3.81 (s, 3H, OMe-7), 3.29−3.12 (m, 2H, H-4), 3.22 (s, 3H, N−Me) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 150.1 (C6), 149.1 (C7), 133.2 (C4′), 132.4 (2C, C2′,6′), 130.3 (2C, C3′,5′), 123.2 (C1′), 120.6 (q, J = 319.8 Hz, OTf), 120.1 (C4a), 116.2 (C8a), 112.7 (CN), 111.0 (C5), 109.7 (C8), 67.4 (C−CN), 60.1 (C1), 56.5 (C3), 56.2 (2C, OMe-6, OMe-7), 44.2 (N−Me), 23.6 (C4) ppm; ESI-MS (m/z) 323.2 (100) $[M]^+$; ESI-HRMS calcd for $[C_{20}H_{23}N_2O_2]^+$ 323.1760, found 323.1764.

2-(Cyano(4-methoxyphenyl)methyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-2-ium Trifluoromethanesulfonate (3i). According to the general procedure described above, α-aminonitrile **2i** (500 mg, 1.48 mmol) and methyl triflate (194 μL, 1.77 mmol) were allowed to react overnight in order to obtain compound **3i** as a diastereomeric mixture in a 51:49 ratio (^{1}H NMR) in the form of a white foam (650 mg, 1.47 mmol, 99%): R_f = 0.48 (chloroform/methanol, 10:1); IR (ATR) ν = 3008, 2940, 2842, 1610, 1520, 1467, 1258, 1159, 1120, 1029, 842, 811, 638 cm^{-1}; (*Major diastereomer*) ^{1}H NMR, COSY, NOESY (400 MHz, $CDCl_3$) δ = 7.75 (d, J = 9.0 Hz, 2H, H-2′,6′), 7.06 (dd, J = 9.0, 2.3 Hz, 2H, H-3′,5′), 6.67 (s, 1H, H-5), 6.59 (s, 1H, H-8), 6.56 (s, 1H, CHCN), 4.78 (t, J = 14.5 Hz, 1H, H-1), 4.41 (d, J = 14.5 Hz, 1H, H-1), 4.14−4.05 (m, 1H, H-3), 3.82−3.65 (m, 1H, H-3), 3.86 (s, 3H, OMe-6), 3.85 (s, 3H, OMe-7), 3.83 (s, 3H, OMe-4′), 3.31−3.12 (m, 2H, H-4), 3.21 (s, 3H, N−Me) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 163.2 (C-4′), 150.1 (C6), 149.2 (C7), 134.1 (2C, C2′, C6′), 120.7 (q, J = 319.7 Hz, OTf), 120.1 (C4a), 116.4 (C8a), 115.7 (2C, C3′, C5′), 114.6 (C1′), 112.9 (CN), 111.0 (C5), 109.7 (C8), 67.3 (C−CN), 59.6 (C1), 56.6 (C3), 56.2 (2C, OMe-6, OMe-7), 55.8 (OMe-4′), 43.9 (N−Me), 23.6 (C4) ppm; (*Minor diastereomer*) ^{1}H NMR, COSY, NOESY (400 MHz, $CDCl_3$) δ = 7.79 (d, J = 9.0 Hz, 2H, H-2′,6′), 7.06 (dd, J = 9.0, 2.3 Hz, 2H, H-3′,5′), 6.66 (s, 1H, H-5), 6.64 (s, 1H, CHCN), 6.52 (s, 1H, H-8), 4.78 (t, J = 14.5 Hz, 1H, H-1), 4.52 (dd, J = 14.5, 2.3 Hz, 1H, H-1), 4.00−3.87 (m, 1H, H-3), 3.82−3.65 (m, 1H, H-3), 3.86 (s, 3H, OMe-6), 3.85 (s, 3H, OMe-7), 3.83 (s, 3H, OMe-4′), 3.31−3.12 (m, 2H, H-4), 3.22 (s, 3H, N−Me) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 163.3 (C4′), 150.2 (C6), 149.3 (C7), 134.2 (2C, C2′,6′), 120.7 (q, J = 319.7 Hz, OTf), 119.9 (C4a), 116.5 (C8a), 115.7 (2C, C3′, C5′), 114.8 (C1′), 113.0 (CN), 110.9 (C5), 109.8 (C8), 68.3 (C−CN), 59.8 (C1), 55.9 (C3), 56.2 (2C, OMe-6, OMe-7), 55.8 (OMe-4′), 43.5 (N−Me), 23.7 (C4) ppm; ESI-MS (m/z) 353.2 (100) $[M]^+$; ESI-HRMS calcd for $[C_{21}H_{25}N_2O_3]^+$ 353.1865, found 353.1864.

2-Butyl-2-(cyano(4-methoxyphenyl)methyl)-1,2,3,4-tetrahydroisoquinolin-2-ium Trifluoromethanesulfonate (3j). According to the general procedure described above, α-aminonitrile **2e** (1.00 g, 3.59 mmol) and butyl triflate (1.48 g, 7.18 mmol) were allowed to react over 3 days in order to obtain compound **3j** as a diastereomeric mixture in a 52:48 ratio (^{1}H NMR) in the form of a slightly yellow foam (463 mg, 955 μmol, 27%): R_f = 0.41 (chloroform/methanol, 10:1); IR (ATR) ν = 3062, 2965, 2878, 2845, 1608, 1515, 1225, 1156, 1029, 838, 754, 637 cm^{-1}; (*Major diastereomer*) ^{1}H NMR, COSY, NOESY (400 MHz, $CDCl_3$) δ = 7.77 (d, J = 8.9 Hz, 2H, H-2′,6′), 7.39−7.16 (m, 4H, H-5, H-6, H-7, H-8), 7.05 (d, J = 8.9 Hz, 2H, H-3′,5′), 6.45 (s, 1H, CHCN), 4.70 (d, J = 15.0 Hz, 1H, H-1), 4.53 (dd, J = 15.0, 2.1 Hz, 1H, H-1), 4.35−4.24 (m, 1H, H-3), 3.84 (s, 3H, OMe-4′), 3.76−3.54 (m, 1H, H-3), 3.48−3.14 (m, 4H, 2H-4, 2H-1″), 2.18−1.85 (m, 2H, H-2″), 1.39−1.17 (m, 2H, H-3″), 0.94 (t, J = 7.4 Hz, 3H, H-4″) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 163.2 (C-4′), 134.1 (2C, C2′,6′), 129.7 (C5), 129.1 (C6), 128.5 (C7), 128.3 (C4a), 127.8 (C8), 124.7 (C8a), 120.8 (q, J = 319.8 Hz, OTf), 115.7 (2C, C3′,5′), 114.5 (C1′), 113.0 (CN), 65.2 (C−CN), 58.7 (C1), 57.9 (C1″), 55.8 (OMe-4″), 53.7 (C3), 24.4 (C2″), 19.8 (C3″), 13.3 (C4″) ppm; (*Minor diastereomer*) ^{1}H NMR, COSY, NOESY (400 MHz, $CDCl_3$) δ = 7.83 (d, J = 8.8 Hz, 2H, H-2′,6′), 7.39−7.16 (m, 4H, H-5, H-6, H-7, H-8), 7.05 (d, J = 8.8 Hz, 2H, H-3′,5′), 6.52 (s, 1H, CHCN), 4.76 (dd, J = 15.3, 2.4 Hz, 1H, H-1), 4.54 (d, J = 15.3

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Hz, 1H, H-1), 4.15−4.04 (m, 1H, H-3), 3.83 (s, 3H, OMe-4′), 3.76−3.54 (m, 1H, H-3), 3.48−3.14 (m, 4H, 2H-4, 2H-1″), 2.18−1.85 (m, 2H, H-2″), 1.39−1.17 (m, 2H, H-3″), 0.89 (t, J = 7.3 Hz, 3H, H-4″) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 163.1 (C-4′), 134.2 (2C, C2′,6′), 129.6 (C5), 128.8 (C6), 128.4 (C7), 128.2 (C4a), 128.0 (C8), 125.0 (C8a), 120.8 (q, J = 319.8 Hz, OTf), 115.6 (2C, C3′,5′), 114.7 (C1′), 113.1 (CN), 64.8 (C−CN), 56.9 (C1), 56.8 (C1″), 55.8 (OMe-4′), 55.0 (C3), 24.2 (C2″), 23.8 (C4), 20.0 (C3″), 13.2 (C4″) ppm; ESI-MS (m/z) 335.2 (100) $[M]^+$; ESI-HRMS calcd for $[C_{22}H_{27}N_2O]^+$ 335.2123, found 335.2126.

General Procedure for the Synthesis of Azonines (5a−i). DBU (1.2 equiv) was added dropwise to a stirred solution of the corresponding salt **3a−j** (1.0 equiv) in dry acetonitrile (26 mL/mmol) at room temperature. The reaction mixture was stirred for an estimated period of time (monitoring by TLC). After consumption of the starting material, the solvent was removed from the reaction by distillation under reduced pressure and the crude product was redissolved in dichloromethane. The organic layer was washed two times with water, and then the water layer was extracted once with dichloromethane. Combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The respective crude products were purified by recrystallization.

6-Methyl-6,7,8,13-tetrahydro-5*H*-dibenzo[*c*,*f*]azonine-5-carbonitrile (5a). Following the general procedure, tetrahydroisoquinolinium salt **3a** (788 mg, 1.91 mmol) was allowed to react with DBU (342 μL, 2.29 mmol) during 1 h to obtain azonine **5a** (435 mg, 1.66 mmol, 87%) as a colorless crystalline solid after recrystallization from methanol: mp 125.0−126.3 °C; R_f = 0.63 (cyclohexane/EtOAc, 3:2); IR (ATR) ν = 3060, 2945, 2798, 2226, 1487, 1450, 1039, 936, 808, 744, 619 cm^{-1}; ^{1}H NMR, COSY (400 MHz, C_6D_6, at 70 °C) δ = 7.48 (dd, J = 7.5, 1.3 Hz, 1H, H-4), 7.08 (dd, J = 7.6, 1.3 Hz, 1H, H-2), 7.04 (dd, J = 7.8, 1.6 Hz, 1H, H-12), 7.20−7.12 (m, 1H, H-1), 7.01−6.88 (m, 3H, H-3, H-10, H-11), 6.82 (dd, J = 7.3, 1.8 Hz, 1H, H-9), 4.73 (s, 1H, H-5), 4.16 (d, J = 14.0 Hz, 1H, H-13), 3.63 (d, J = 14.0 Hz, 1H, H-13), 2.77−2.57 (m, 2H, H-7, H-8), 2.59−2.42 (m, 1H, H-8), 2.31−2.26 (m, 1H, H-7), 1.92 (s, 3H, N−Me) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, C_6D_6, at 70 °C) δ = 141.4 (C13a), 139.2 (C12a), 138.7 (C8a), 133.8 (C4a), 131.7 (C1), 129.9 (C12), 129.8 (C9), 129.0 (C2), 127.8 (C4), 127.1 (C11), 127.0 (C10), 126.9 (C3), 115.4 (CN), 57.4 (C5), 55.9 (C7), 38.0 (N−Me), 37.8 (C13), 33.9 (C8) ppm; ESI-MS (m/z) 263.1 (100) $[M + H]^+$; ESI-HRMS calcd for $[C_{18}H_{19}N_2]^+$ 263.1548, found 263.1540.

2-Chloro-6-methyl-6,7,8,13-tetrahydro-5*H*-dibenzo[*c*,*f*]azonine-5-carbonitrile (5b). Following the general procedure, tetrahydroisoquinolinium salt **3b** (100 mg, 224 μmol) was allowed to react with DBU (40 μL, 269 μmol) during 40 min to obtain azonine **5b** (56 mg, 189 μmol, 84%) as a colorless crystalline solid after recrystallization from methanol: mp 165.4−166.2 °C; R_f = 0.63 (cyclohexane/EtOAc, 3:2); IR (ATR) ν = 3058, 3015, 2945, 2849, 2801, 2227, 1568, 1482, 1143, 1042, 911, 846, 773, 754 cm^{-1}; ^{1}H NMR, COSY (600 MHz, C_6D_6, at 70 °C) δ = 7.23 (d, J = 7.9 Hz, 2H, H-4), 7.22 (s, 1H, H-1), 6.97−6.91 (m, 2H, H-3, H-10), 6.90−6.86 (m, 2H, H-11, H-12), 6.78 (d, J = 7.5 Hz, 1H, H-9), 4.55 (s, 1H, H-5), 4.00 (br s, 1H, H-13), 3.42 (d, J = 14.1 Hz, 1H, H-13), 2.63−2.55 (m, 2H, H-7, H-8), 2.48−2.34 (m, 1H, H-8), 2.25−2.14 (m, 1H, H-7), 1.85 (s, 3H, N−Me).ppm; ^{13}C NMR, HMBC, HSQC (150.9 MHz, C_6D_6, at 70 °C) δ = 143.4 (C13a), 138.7 (C8a), 138.3 (C12a), 135.0 (C2), 132.5 (C4a), 131.9 (C1), 130.1 (C12), 129.9 (C9), 129.1 (C4), 127.4 (C3), 127.0 (C12), 126.9 (2C, C10, C11), 115.2 (CN), 56.9 (C5), 55.9 (C7), 38.1 (N−Me), 37.6 (C13), 34.0 (C8) ppm; ESI-MS (m/z) 297.1 (100) $[M + H]^+$; ESI-HRMS calcd for $[C_{18}H_{18}ClN_2]^+$ 297.1159, found 297.1159.

2-Fluoro-6-methyl-6,7,8,13-tetrahydro-5*H*-dibenzo[*c*,*f*]azonine-5-carbonitrile (5c). Following the general procedure, tetrahydroisoquinolinium salt **3c** (100 mg, 232 μmol) was allowed to react with DBU (41 μL, 278 μmol) during 40 min to obtain azonine **5c** (55 mg, 197 μmol, 85%) as a colorless crystalline solid after recrystallization from methanol: mp 164.6−165.3 °C; R_f = 0.61 (cyclohexane/EtOAc, 3:2); IR (ATR) ν = 3059, 3015, 2945, 2848, 2802, 2227, 1612, 1589, 1493, 1450, 1246, 1121, 1040, 965, 796, 756 cm^{-1}; ^{1}H NMR, COSY (600 MHz, C_6D_6, at 70 °C) δ = 7.28 (dd, J = 8.5, 5.6 Hz, 1H, H-4), 6.98−6.92 (m, 1H, H-10), 6.92−6.86 (m, 3H, H-1, H-11, H-12), 6.79 (d, J = 7.3 Hz, 1H, H-9), 6.61 (td, J = 8.3, 2.8 Hz, 1H, H-3), 4.58 (s, 1H, H-5), 4.01 (br s, 1H, H-13), 3.45 (d, J = 14.1 Hz, 1H, H-1), 2.71−2.53 (m, 2H, H-7, H-8), 2.51−2.36 (m, 1H, H-8), 2.30−2.12 (m, 1H, H-7), 1.86 (s, 3H, N−Me) ppm; ^{13}C NMR, HMBC, HSQC (150.9 MHz, C_6D_6, at 70 °C) δ = 163.2 (d, J = 247.4 Hz, C2), 143.4 (d, J = 7.2 Hz, C13a), 138.6 (C8a), 138.2 (C12a), 129.9(C12), 129.8 (C9), 129.6 (d, J = 3.0 Hz, C4a), 129.2 (d, J = 8.7 Hz, C4), 127.2 (C11), 127.1 (C10), 118.9 (d, J = 21.7 Hz, C1), 115.2 (CN), 113.0 (d, J = 21.1 Hz, C3), 56.9 (C5), 55.6 (C7), 37.9 (N−Me), 37.6 (C13), 33.8 (C8) ppm; ESI-MS (m/z) 297.1 (100) $[M + H]^+$; ESI-HRMS calcd for $[C_{18}H_{18}FN_2]^+$ 281.1454, found 281.1459.

6-Methyl-2-(trifluoromethyl)-6,7,8,13-tetrahydro-5*H*-dibenzo[*c*,*f*]azonine-5-carbonitrile (5d). Following the general procedure, tetrahydroisoquinolinium salt **3d** (100 mg, 208 μmol) was allowed to react with DBU (37 μL, 250 μmol) during 30 min to obtain azonine **5d** (61 mg, 185 μmol, 89%) as a colorless crystalline solid after recrystallization from methanol: mp 171.5−172.1 °C; R_f = 0.61 (cyclohexane/EtOAc, 3:2); IR (ATR) ν = 3061, 2947, 2853, 2804, 2228, 1618, 1491, 1465, 1451, 1365, 1218, 1162, 1043, 855, 800, 779 cm^{-1}; ^{1}H NMR, COSY (600 MHz, C_6D_6, at 70 °C) δ = 7.50 (s, 1H, H-1), 7.34 (d, J = 7.9 Hz, 1H, H-4), 7.17 (dd, J = 7.9, 1.7 Hz, 1H, H-3), 6.97−6.91 (m, 1H, H-10), 6.88−6.84 (m, 2H, H-11, H-12), 6.78 (d, J = 7.5 Hz, 1H, H-9), 4.59 (s, 1H, H-5), 4.07 (br s, 1H, H-13), 3.47 (d, J = 14.2 Hz, 1H, H-13), 2.65−2.55 (m, 2H, H-7, H-8), 2.45−2.35 (m, 1H, H-8), 2.24−2.14 (m, 1H, H-7), 1.82 (s, 3H, N−Me).ppm; ^{13}C NMR, HMBC, HSQC (150.9 MHz, C_6D_6, at 70 °C) δ = 142.4 (C13a), 138.5 (C8a), 137.8 (C12a), 137.4 (C4a), 131.3 (q, J = 32.2 Hz, C2), 129.9 (C12), 129.8 (C9), 128.3 (q, J = 3.6 Hz, C1), 128.1 (C4), 127.4 (C10), 127.4 (C11), 126.6 (q, J = 272.3 Hz, CF_3), 123.9 (q, J = 3.9 Hz, C1), 114.7 (CN), 57.0 (C5), 55.8 (C7), 37.9 (N−Me), 37.5 (C13), 33.9 (C8) ppm; ESI-MS (m/z) 331.2 (100) $[M + H]^+$; ESI-HRMS calcd for $[C_{19}H_{17}F_3N_2]^+$ 331.1422, found 331.1410.

2-Methoxy-6-methyl-6,7,8,13-tetrahydro-5*H*-dibenzo[*c*,*f*]azonine-5-carbonitrile (5e). Following the general procedure, tetrahydroisoquinolinium salt **3e** (100 mg, 226 μmol) was allowed to react with DBU (40 μL, 271 μmol) during 1 h and 30 min to obtain azonine **5e** (53 mg, 183 μmol, 81%) as a colorless crystalline solid after recrystallization from methanol: mp 129.6−130.5 °C; R_f = 0.61 (cyclohexane/EtOAc, 3:2); IR (ATR) ν = 3058, 3014, 2944, 2838, 2798, 2227, 1613, 1578, 1495, 1253, 1037, 756 cm^{-1}; ^{1}H NMR, COSY (600 MHz, C_6D_6, at 70 °C) δ = 7.42 (d, J = 8.3 Hz, 1H, H-4), 7.06 (dd, J = 7.5, 1.5 Hz, 1H, H-12), 6.99−6.93 (m, 2H, H-1, H-11), 6.91 (td, 1H, J = 7.5, 1.5 Hz, 1H, H-10), 6.82 (dd, J = 7.5, 1.6 Hz, 1H, H-9), 6.49 (dd, J = 8.35, 2.7 Hz, 1H, H-3), 4.58 (s, 1H, H-5), 4.15 (br s, 1H, H-13), 3.59 (d, J = 14.0 Hz, 1H, H-1), 337 (s, 3H, OMe-2), 2.74−2.58 (m, 2H, H-7, H-8), 2.55−2.41 (m, 1H, H-8), 2.30−2.24 (m, 1H, H-7), 1.96 (s, 3H, N−Me) ppm; ^{13}C NMR, HMBC, HSQC (150.9 MHz, C_6D_6, at 70 °C) δ = 160.7 (C2), 142.7 (C13a), 139.2 (C12a), 138.9 (C8a), 130.1 (C12), 129.8 (C9), 128.9 (C4), 127.2 (C10), 127.1 (C11), 126.3 (C4a), 119.2 (C1), 115.9 (CN), 57.0 (C5), 55.9 (C7), 55.2 (OMe-2), 38.1 (N−Me), 38.0 (C13), 34.1 (C8) ppm; ESI-MS (m/z) 293.1 (100) $[M + H]^+$; ESI-HRMS calcd for $[C_{19}H_{21}N_2O]^+$ 293.1654, found 293.1659.

1,2,3-Trimethoxy-6-methyl-6,7,8,13-tetrahydro-5*H*-dibenzo-[*c*,*f*]azonine-5-carbonitrile (5f). Following the general procedure, tetrahydroisoquinolinium salt **3f** (200 mg, 398 μmol) was allowed to react with DBU (71 μL, 478 μmol) during 3 h and 45 min to obtain azonine **5f** (115 mg, 326 μmol, 82%) as a colorless crystalline solid after recrystallization from diethyl ether: mp 122.4−122.9 °C; R_f = 0.54 (cyclohexane/EtOAc, 3:2); IR (ATR) ν = 2942, 2836, 2799, 2226, 1600, 1490, 1404, 1332, 1117, 1033, 757 cm^{-1}; ^{1}H NMR, COSY (600 MHz, C_6D_6, at 70 °C) δ = 7.51 (d, J = 7.1 Hz, 1H, H-12), 7.04−6.97 (m, 2H, H-10, H-11), 6.98 (s, 1H, H-4), 6.85 (dd, J = 7.1, 1.9 Hz, 1H, H-9), 4.83 (s, 1H, H-5), 4.31 (d, J = 14.1 Hz, 1H, H-1), 3.93−3.84 (m, 1H, H-1), 3.79 (s, 3H, OMe-1), 3.73 (s, 3H,

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OMe-2), 3.42 (s, 3H, OMe-3), 2.71 (dt, J = 13.0, 5.1 Hz, 1H, H-7), 2.67−2.55 (m, 2H, H-8), 2.29 (dt, J = 13.0, 6.4 Hz, 1H, H-7), 1.99 (s, 3H, N−Me) ppm; ^{13}C NMR, HMBC, HSQC (150.9 MHz, C_6D_6, at 70 °C) δ = 153.3 (C1), 152.2 (C2), 143.7 (C3), 140.5 (C12a), 138.7 (C8a), 130.5 (C12), 129.7 (C9), 129.3 (C13a), 127.6 (C4a), 127.2 (C4), 126.2 (C11), 115.8 (CN), 108.4 (C4), 60.9 (OMe-1), 60.5 (OMe-2), 57.3 (C5), 56.0 (2C, C7, OMe-3), 38.4 (N−Me), 33.5 (C8), 28.6 (C13).ppm; ESI-MS (m/z) 353.2 (100) $[M + H]^+$; ESI-HRMS calcd for $[C_{21}H_{25}N_2O_3]^+$ 353.1865, found 353.1864.

5-Methyl-5,6,7,12-tetrahydro-4*H*-benzo[*f*]thieno[2,3-*c*]-azonine-4-carbonitrile (5g). Following the general procedure, tetrahydroisoquinolinium salt **3g** (200 mg, 478 μmol) was allowed to react with DBU (86 μL, 573 μmol) during 1 h to obtain azonine **5g** (100 mg, 373 μmol, 78%) as a slightly violet crystalline solid after recrystallization from methanol: mp 134.4−135.2 °C; R_f = 0.54 (cyclohexane/EtOAc, 3:2); IR (ATR) ν = 3059, 2945, 2911, 2849, 2799, 2227, 1539, 1464, 1117, 1087, 754, 686, 659 cm^{-1}; ^{1}H NMR, COSY (400 MHz, C_6D_6) δ = 7.01−6.92 (m, 3H, H-9, H-10, H-11), 6.77−6.69 (m, 1H, H-8), 6.64 (d, J = 5.0 Hz, 1H, H-2), 6.61 (d, J = 5.0 Hz, 1H, H-1), 4.53 (s, 1H, H-4), 3.72 (d, J = 14.0 Hz, 1H), 3.66 (d, J = 14.2 Hz, 1H), 2.43 (dt, J = 12.6, 5.8 Hz, 1H, H-6), 2.36 (t, J = 5.5 Hz, 2H, H-7), 2.19 (dt, J = 12.6, 5.0 Hz, 1H, H-6), 2.08 (s, 3H, N−Me) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, C_6D_6) δ = 140.4 (C12a), 139.3 (C7a), 138.3 (C11a), 130.6 (C11), 130.4 (2C, C2, C7), 130.2 (C2a), 127.1 (C10), 127.0 (C9), 116.4 (CN), 54.8 (C6), 53.1 (C4), 39.2 (N−Me), 33.0 (C12), 32.0 (C7) ppm; ESI-MS (m/z) 260.1 (100) $[M - CN + H_2O]^+$; ESI-HRMS calcd for $[C_{15}H_{18}NOS]^+$ 260.1109, found 260.1099.

10,11-Dimethoxy-6-methyl-6,7,8,13-tetrahydro-5*H*-dibenzo[*c*,*f*]azonine-5-carbonitrile (5h). Following the general procedure, tetrahydroisoquinolinium salt **3h** (100 mg, 212 μmol) was allowed to react with DBU (38 μL, 254 μmol) during 1 h to obtain azonine **5h** (57 mg, 178 μmol, 84%) as a colorless crystalline solid after recrystallization from methanol: mp 173.9−174.5 °C; R_f = 0.33 (cyclohexane/EtOAc, 3:2); IR (ATR) ν = 2940, 2829, 2797, 2224, 1607, 1515, 1450, 1268, 1223, 1096, 743 cm^{-1}; ^{1}H NMR, COSY (600 MHz, C_6D_6, at 70 °C) δ = 7.53 (d, J = 7.5 Hz, 1H, H-4), 7.22−7.15 (m, 1H, H-1), 7.09 (td, J = 7.4, 1.4 Hz, 1H, H-2), 6.99 (td, J = 7.5, 1.5 Hz, 1H, H-3), 6.62 (s, 1H, H-12), 6.43 (s, 1H, H-9), 4.85 (s, 1H, H-5), 4.30 (d, J = 14.1 Hz, 1H, H-13), 3.63 (d, J = 14.1 Hz, 1H, H-13), 3.51 (s, 3H, OMe-11), 3.35 (s, 3H, OMe-10), 2.80−2.63 (m, 2H, H-7, H-8), 2.48−2.38 (m, 1H, H-8), 2.37−2.26 (m, 1H, H-7), 2.02 (s, 3H, N−Me) ppm; ^{13}C NMR, HMBC, HSQC (150.9 MHz, C_6D_6, at 70 °C) δ = 149.3 (C11), 149.2 (C10), 141.1 (C13a), 133.4 (C4a), 131.1 (C1), 130.9 (C12a), 130.7 (C8a), 128.4 (C2), 127.3 (C4), 126.4 (C3), 115.0 (CN), 114.8 (C12), 114.6 (C-9), 57.1 (C5), 56.0 (C7), 55.7 (OMe-11), 55.3 (OMe-10), 37.6 (C13), 37.5 (N−Me), 33.6 (C8) ppm; ESI-MS (m/z) 323.2 (100) $[M + H]^+$; ESI-HRMS calcd for $[C_{20}H_{23}N_2O_2]^+$ 323.1760, found 323.1765.

2,10,11-Trimethoxy-6-methyl-6,7,8,13-tetrahydro-5*H*-dibenzo[*c*,*f*]azonine-5-carbonitrile (5i). Following the general procedure, tetrahydroisoquinolinium salt **3i** (200 mg, 452 μmol) was allowed to react with DBU (81 μL, 542 μmol) during 2 h to obtain azonine **5i** (132 mg, 375 μmol, 83%) as a colorless crystalline solid after recrystallization from diethyl ether: mp 143.9−144.2 °C; R_f = 0.32 (cyclohexane/EtOAc, 3:2); IR (ATR) ν = 2939, 2836, 2225, 1610, 1578, 1515, 1464, 1268, 1095, 1037, 735 cm^{-1}; ^{1}H NMR, COSY (400 MHz, C_6D_6, at 70 °C) δ = 7.47 (d, J = 8.3 Hz, 1H, H-4), 6.97 (d, J = 2.6 Hz, 1H, H-1), 6.64 (s, 1H, H-12), 6.50 (dd, J = 8.4, 2.7 Hz, 1H, H-3), 6.42 (s, 1H, H-9), 4.82 (s, 1H, H-5), 4.31 (br s, 1H, H-13), 3.60 (d, J = 14.1 Hz, 1H, H-13), 3.49 (s, 3H, OMe-11), 3.37 (s, 3H, OMe-2), 3.31 (s, 3H, OMe-10), 2.82−2.62 (m, 2H, H-7, H-8), 2.48−2.38 (m, 1H, H-8), 2.37−2.29 (m, 1H, H-7), 2.07 (s, 3H, N−Me) ppm; ^{13}C NMR, HMBC, HSQC (150.9 MHz, C_6D_6, at 70 °C) δ = 160.6 (C2), 149.6 (C11), 149.5 (C10), 143.0 (C13a), 131.1 (C12a), 131.0 (C8a), 128.9 (C4), 126.3 (C4a), 119.1 (C1), 115.8 (CN), 115.0 (C12), 114.8 (C9), 110.5 (C3), 57.1 (C5), 56.3 (OMe-11), 56.0 (OMe-10), 55.6 (C7), 55.0 (OMe-2), 38.1 (C13), 38.0 (N−Me), 34.1 (C8) ppm; ESI-MS (m/z) 353.2 (100) $[M + H]^+$; ESI-HRMS calcd for $[C_{21}H_{25}N_2O_3]^+$ 353.1865, found 353.1850.

6-Butyl-2-methoxy-6,7,8,13-tetrahydro-5*H*-dibenzo[*c*,*f*]-azonine-5-carbonitrile (5j). Following the general procedure, tetrahydroisoquinolinium salt **3j** (100 mg, 206 μmol) was allowed to react with DBU (37 μL, 247 μmol) during 1 h and 30 min to obtain azonine **5j** (55 mg, 165 μmol, 80%) as a colorless crystalline solid after recrystallization from methanol: mp 101.2−101.8 °C; R_f = 0.69 (cyclohexane/EtOAc, 3:2); IR (ATR) ν = 3014, 2956, 2833, 2225, 1613, 1578, 1495, 1253, 1135, 1040, 754 cm^{-1}; ^{1}H NMR, COSY (600 MHz, C_6D_6, at 70 °C) δ = 7.47 (d, J = 8.3 Hz, 1H, H-4), 7.08 (dd, J = 7.2, 1.8 Hz, 1H, H-12), 7.00−6.88 (m, 3H, H-1, H-11, H-12), 6.81 (dd, J = 7.1, 1.9 Hz, 1H, H-10), 6.49 (dd, J = 8.3, 2.7 Hz, 1H, H-3), 4.72 (s, 1H, H-5), 4.11 (br s, 1H, H-13), 3.62 (d, J = 13.9 Hz, 1H, H-13), 3.35 (s, 3H, OMe-2), 2.67−2.55 (m, 3H, 2H-8, H-7), 2.52−2.42 (m, 1H, H-7), 2.41−2.31 (m, 2H,H-1′), 0.98−0.58 (m, 2H,H-2′), 0.61−0.42 (m, 2H,H-3′), 0.43 (t, J = 7.2 Hz, 3H,H-4′) ppm; ^{13}C NMR, HMBC, HSQC (150.9 MHz, C_6D_6, at 70 °C) δ = 160.6 (C2), 142.8 (C13a), 139.1 (C12a), 138.9 (C8a), 129.8 (C12), 129.7 (C9), 128.7 (C4), 126.4 (C4a), 119.0 (C1), 116.5 (CN), 110.5 (C3), 56.6 (C5), 55.0 (OMe-2), 52.2 (C7), 50.1 (C1′), 37.8 (C13), 33.9 (C8), 30.2 (C2′), 19.8 (C3′), 13.6 (C4′) ppm; ESI-MS (m/z) 335.2 (100) $[M + H]^+$; ESI-HRMS calcd for $[C_{22}H_{27}N_2O]^+$ 335.2123, found 335.2120.

4-(2,6-Dichlorophenyl)-3-methyl-2,3-dihydro-1*H*-benzo[*d*]-azepine (6). Following the same general procedure for the synthesis of dibenzo[*c*,*f*]azonines, tetrahydroisoquinolinium salt **3k** (200 mg, 415 μmol) was allowed to react with DBU (74 μL, 499 μmol) during 1.5 h to obtain benzazepine **6** (100 mg, 329 μmol, 79%) as a yellow oil after purification by flash column chromatography (Isolera Flash Purification System, cyclohexane/EtOAc, gradient 0−18%): R_f = 0.63 (cyclohexane/EtOAc, 10:1); IR (ATR) ν = 3012, 2926, 2795, 1608, 1558, 1487, 1438, 1222, 775, 747 cm^{-1}; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.37 (d, J = 8.0 Hz, 2H, H-3′, H-5′), 7.21 (dd, J = 8.6, 7.5 Hz, 1H, H-4′), 7.15−7.06 (m, 3H, H-6, H-7, H-8), 7.04−6.95 (m, 1H, H-9), 5.26 (s, 1H, H-1), 3.58−3.33 (m, 2H, H-4), 3.23−2.99 (m, 2H, H-5), 2.64 (s, 3H, N−Me) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 142.2 (C2), 138.9 (C5a), 138.3 (C9a), 137.3 (C1′), 135.7 (2C, C2′,6′), 129.7 (C6), 129.3 (C-4′), 128.9 (C7), 128.0 (2C, C3′,5′), 126.1 (C8), 123.4 (C9), 104.8 (C1), 54.3 (C4), 41.0 (N−Me), 37.2 (C5) ppm; ESI-MS (m/z) 304.1 (100) $[M + H]^+$; ESI-HRMS calcd for $[C_{17}H_{16}NCl_2]^+$ 304.0660, found 304.0667.

Reductive Decyanation: Synthesis of 6-Methyl-6,7,8,13-tetrahydro-5*H*-dibenzo[*c*,*f*]azonine (7). To a solution of azonine **5a** (50 mg, 190 μmol) in dry THF (3 mL) was added dropwise $LiAlH_4$ (THF solution 2M, 104 μL, 209 μmol) at 0 °C. After 10 min of stirring at this temperature, the mixture was allowed to reach room temperature and the stirring was continued overnight. The reaction was quenched with 10 mL of water and extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash column chromatography (cyclohexane/EtOAc 3:2) to obtain compound **7** as a slightly yellow oil (38 mg, 160 μmol, 84%): R_f = 0.17 (cyclohexane/EtOAc, 3:2); IR (ATR) ν = 3059, 3013, 2934, 2832, 2787, 1600, 1489, 1364, 1046, 741, 624 cm^{-1}; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.44 (d, J = 7.4 Hz, 1H, H-4), 7.31−7.21 (m, 2H, H-3, H-12), 7.19−7.02 (m, 5H, H-1, H-2, H-9, H-10, H-11), 4.26 (s, 2H, H-13), 3.50 (s, 1H, H-5), 3.07 (t, J = 5.7 Hz, 2H, C-8)), 2.73 (t, J = 5.7 Hz, 1H, H-7), 2.30 (s, 3H, N−Me) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 141.7 (C13a), 139.6 (2C, C8a, C12a) 137.3 (C4a), 130.7 (C4), 130.3 (C1), 129.9 (C12), 129.5 (C9), 127.7 (C13), 126.7 (C2), 126.5 (C11), 126.3 (C10), 58.1 (C5), 57.0 (C7), 44.3 (N−Me), 37.4 (C13), 32.6 (C8) ppm; ESI-MS (m/z) 238.2 (100) $[M + H]^+$; ESI-HRMS calcd for $[C_{17}H_{20}N]^+$ 238.1596, found 238.1593. The spectroscopic data are in accordance with those reported in the literature.[16]

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■ ASSOCIATED CONTENT

Supporting Information

NMR spectra of all synthesized compounds as well as the crystallographic data (.cif) for compounds **5a** and **5g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professor Hans-Ulrich Reissig on the occasion of his 65th birthday.

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