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A Strategy to Construct *cis*-Hydrocarbazole via Nickel/Lewis Acid Dual-Catalyzed Arylcyanation

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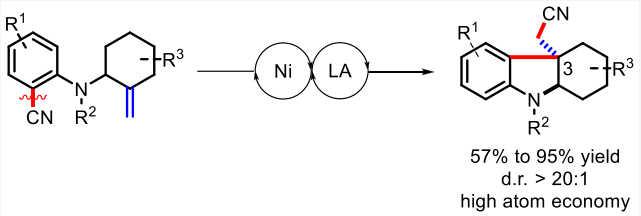
ABSTRACT: A strategy for the synthesis of *cis*-hydrocarbazole with a C3 quaternary carbon center has been developed through nickel/Lewis acid dual-catalyzed arylcyanation. A wide array of *cis*-hydrocarbazoles was accessed with high diastereoselectivities and atom economies in a good yield. The rich chemistry of the installed nitrile group was demonstrated in the preparation of tryptamine- and tryptophol-derived *cis*-hydrocarbazoles.



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The *cis*-hydrocarbazole unit bearing two vicinal chiral carbon centers at the C2 and C3 positions with C3 as the all-carbon quaternary center is a prevalent structural element of many terpene-indole alkaloids (Figure 1) with various

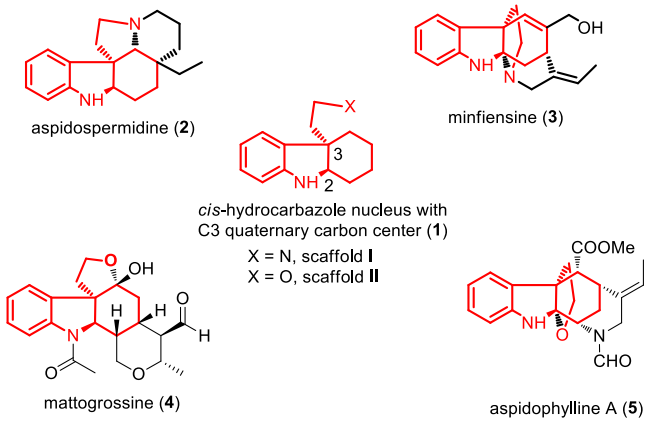

Figure 1. Selected members of hydrocarbazole alkaloids.

biological properties and high structural diversity.[1] For instance, aspidospermidine (**2**) and minfiensine (**3**) share the tryptamine-derived scaffold **I**,[2,10e] while mattogrossine (**4**) and aspidophylline A (**5**) share the tryptophol-derived scaffold **II**.[3] In addition, analogues of tryptamine-derived hydrocarbazole were recently reported to resensitize methicillin-resistant *Staphylococcus aureus* to *β*-lactam antibiotics.[4] Therefore, methods for constructing *cis*-hydrocarbazole in a highly diastereoselective manner would be of great significance.

Numerous synthetic strategies to *cis*-fused hydrocarbazole have been reported.[5] Among them, [4+2] cycloaddition[6] is the most common approach (Scheme 1a). In 2017, our group developed a novel [3+2]-annulation of *p*-quinamines and *in situ* generated arynes to provide an alternative approach to a variety of *cis*-hydrocarbazoles[10c] (Scheme 1b). Efficient strategies for the synthesis of *cis*-hydrocarbazoles, particularly those containing the C3 quaternary carbon center, are still highly desirable. Inspired by research works from Nakao, Hiyama, Ogoshi et al.,[7] and Jacobsen et al.[8] on nickel-catalyzed arylcyanation,[9] affording indanes or indolines, and with our continuing interests in synthesis of biologically active terpene-indole alkaloids,[10] herein we report a novel synthetic strategy for constructing *cis*-hydrocarbazoles containing C3 quaternary carbon, utilizing nickel and Lewis acid dual-catalyzed arylcyanation (Scheme 1c).

Our study was initiated with easily accessible benzonitrile **8b** as the model substrate to examine the feasibility of our proposed strategy (Table 1). All substrates **8b**−**19b** were achieved through a three-step sequence consisting of a substitution reaction between *α*-bromoketone **6** and aniline **7**, Wittig reaction, and alkylation of aniline **8a**−**19a** (Scheme 2). Thus, benzonitrile **8b** was treated with $Ni(cod)_2$ (5 mol %), $AlMe_2Cl$ (20 mol %), and DPPE (10 mol %) in toluene at 100 °C for 12 h. To our delight, the *cis*-hydrocarbazole product **8c** was obtained in 10% yield with high regioselectivity and diastereoselectivity (entry 1). The relative configuration of **8c** was established by NOE experiments (see the Supporting Information for details). After screening several ligands (entries 1−5) and Lewis acids (entries 5−7), the best set of conditions include the $Ni(cod)_2/PEt_3/AlMe_2Cl$ system with toluene as a solvent at 100 °C. As shown in Table 1, Lewis acids ($AlMe_2Cl$) could significantly promote the arylcyanation

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Scheme 1. Established Methods and Our Strategy for Constructing *cis*-Hydrocarbazole

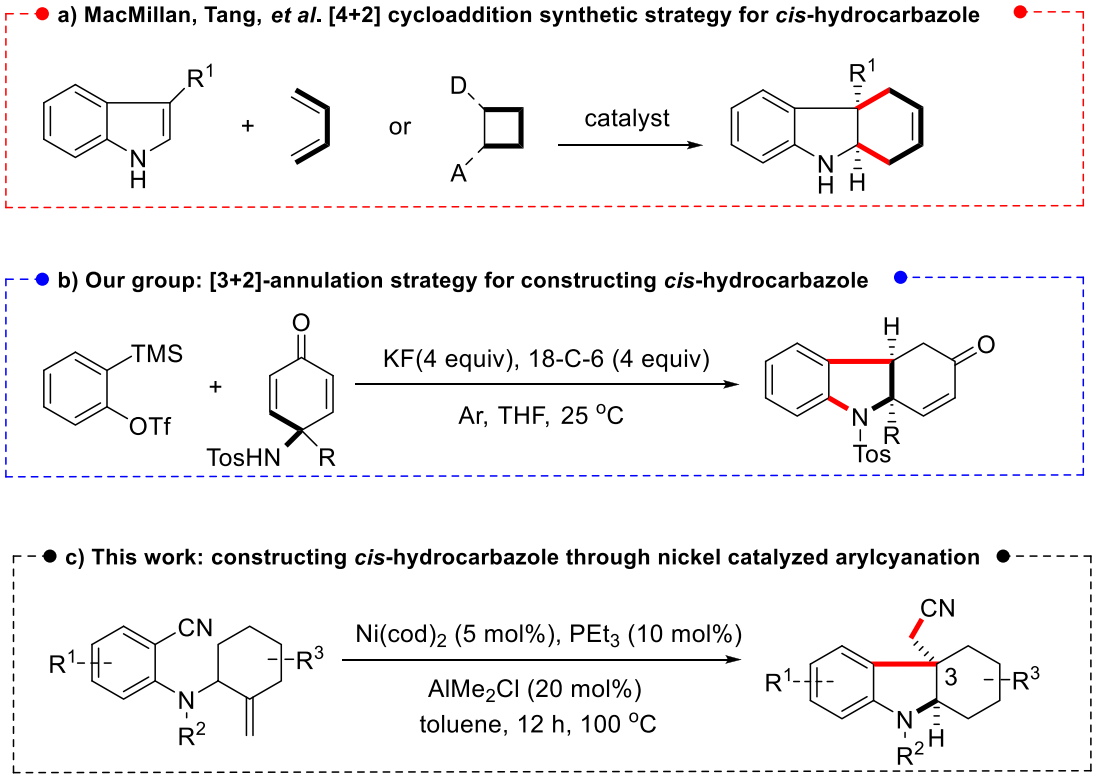
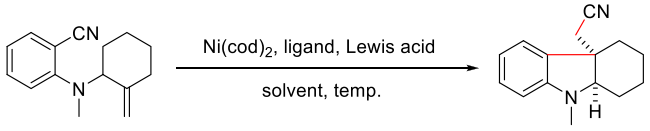


Table 1. Optimization of the Reaction Conditions[a]



8b **8c**

entry	ligand	solvent	Lewis acid	temp (°C)	time (h)	yield[b] (%)
1	DPPE[c]	toluene	$AlMe_2Cl$	100	12	10[e]
2	PPh_3	toluene	$AlMe_2Cl$	100	12	44[e]
3	TPFPP[d]	toluene	$AlMe_2Cl$	100	12	0
4	PMe_3	toluene	$AlMe_2Cl$	100	12	81[e]
5	PEt_3	toluene	$AlMe_2Cl$	100	12	83[e]
6	PEt_3	toluene	$AlMe_3$	100	12	0
7	PEt_3	toluene	$AlEtCl_2$	100	12	nr
8	PEt_3	CH_3CN	$AlMe_2Cl$	100	24	59[e]
9	PEt_3	DMF	$AlMe_2Cl$	100	12	74[e]
10	PEt_3	DMSO	$AlMe_2Cl$	100	12	nr
11	PEt_3	toluene	$AlMe_2Cl$	60	24	62[e]
12	PEt_3	toluene		100	12	nr
13		toluene	$AlMe_2Cl$	100	12	nr

[a]Reaction conditions: Substrate **8b** (0.2 mmol), $Ni(cod)_2$ (5 mol %), ligand (10 mol %), Lewis Acid (20 mol %), and degassed solvent (2 mL) under argon. [b]Isolated yields. [c]DPPE = 1,2-bis-(diphenylphosphino)ethane. [d]TPFPP = Tris(pentafluorophenyl)-phosphine. [e]Diastereomeric ratio, dr > 20:1.

of **8b**, presumably through coordination with the cyano group to further polarize the C−CN bond and accelerate the oxidative addition step. We then turned our attention to investigate the solvent effects for the arylcyanation and found that the use of polar solvents CH_3CN, DMF, and DMSO gave inferior results (entries 8−10). Blank experiments verified the importance of each reagent. In the absence of the Lewis acid (entry 12) or nickel/PEt_3 (entry 13), experiments failed to generate *cis*-hydrocarbazole product **8c**.

With the optimized conditions in hand, we set out to explore the scope of this strategy. As outlined in Table 2, several *cis*-hydrocarbazoles were accessed through intramolecular arylcyanation in moderate to high yields and with high diastereoselectivity. Both electron-withdrawing (**9c**) and electron-donating substituents (**10c**, **11c**) on the aryl ring were well-tolerated. Specifically, the electron-withdrawing group (F) and weak electron-donating group (methyl) at either the *meta*- or *para*-position yield *cis*-hydrocarbazoles in a comparable yield as that of the nonsubstituted substrate. Accordingly, the strong electron-donating group MeO (**12c**) shows a deleterious effect on the yield. The reactivity of a series of N-protected substrates was also examined. For instance, *N*-methyl (**8c**), -ethyl (**13b**), and -benzyl (**14b**) benzonitrile proceeded smoothly. N−H and N-propargyl substrates decomposed and failed to provide the desired products. The Al (III) would bond to the nitrogen atom of the secondary amine in the N−H substrate (**8a**), which would promote the oxidative addition of an electron-rich nickel catalyst to allylic aniline, resulting in the formation of an inactive π-allyl-nickel complex. A large-scale version of the reaction using substrate **14b** was carried out, and the desired hydrocarbazole **14c** was obtained in 73% yield on a 0.44 g scale. To further illustrate the power of this synthetic strategy, the influence of substituents on cyclohexene was also investigated. *gem*-Dimethyl (**15c**) and ketal protection (**16c**, **17c**) had no significant impact. It is worth noting that a ketal group convertible to various organic groups survived the present conditions.

Encouraged by the success of the intramolecular arylcyanation with substrates to deliver *cis*-hydrocarbazoles, we intended to apply this strategy to the rapid synthesis of other types of

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Scheme 2. Synthesis of Substrates 8b−19b

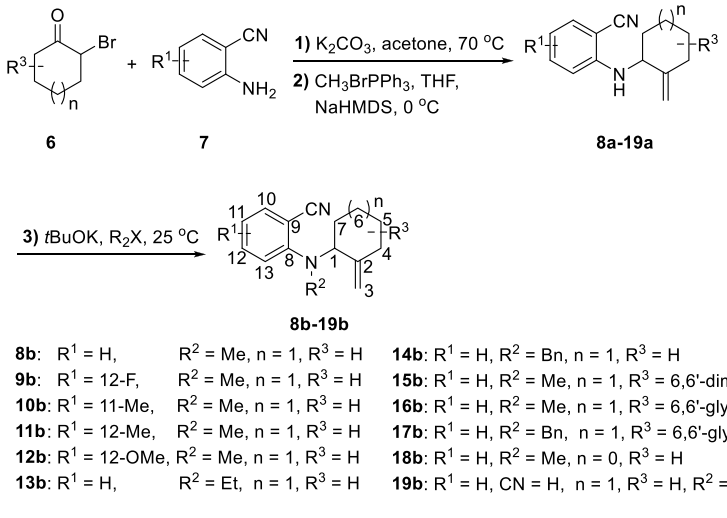
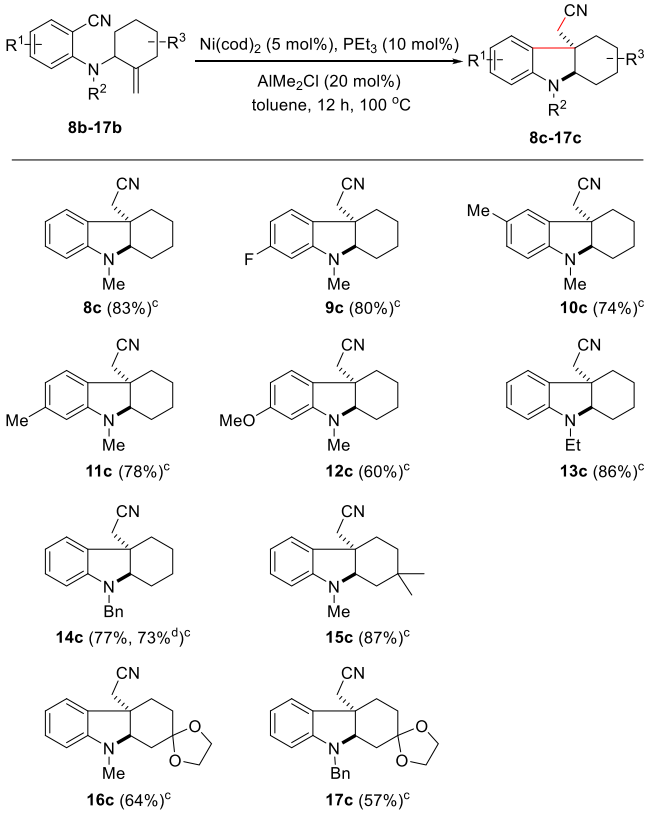


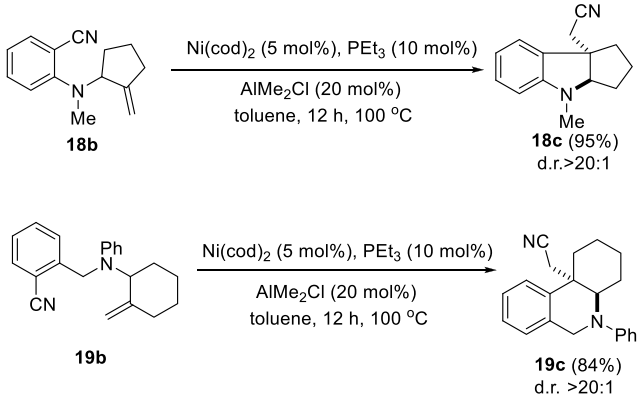
Table 2. Substrate Scope for the Synthesis of *cis*-Hydrocarbazole[a]



[a]Reaction conditions: substrate **8b−17b** (0.2 mmol), $Ni(cod)_2$ (5 mol %), PEt_3 (10 mol %), and $AlMe_2Cl$ (20 mol %) in degassed toluene (2 mL) at 100 °C under argon for 12 h. [b]All yields shown are isolated yields. [c]Diastereomeric ratio, dr > 20:1. [d]Substrate **14b** (2 mmol), $Ni(cod)_2$ (5 mol %), PEt_3 (10 mol %), and $AlMe_2Cl$ (20 mol %) in degassed toluene (20 mL) at 100 °C under argon for 12 h.

polycyclic cores, such as cyclopentane-fused indoline 6/5/5 and cyclohexane-fused tetrahydroisoquinoline 6/6/6 (Scheme 3). When cyclopentene substrate **18b** and *o*-nitrile benzylamine substrate **19b** were subjected to our optimized reaction conditions, **18c** and **19c** were obtained in up to 95% yields.

Scheme 3. Substrate Scope for the Synthesis of Other Polycyclic Systems



Compound **18c** possesses a 6/5/5 tricyclic skeleton of indole alkaloid spermacoceine.[11] Cyclohexane-fused tetrahydroisoquinoline **19c** is the privileged substructure of amaryllidaceae alkaloids, such as crinine.[12] The relative configuration of **18c** and **19c** was established by NOE experiments (see the Supporting Information for details).

The chemistry detailed above has demonstrated the substrate scope of the synthetic strategy. Some conversions were conducted using *cis*-hydrocarbazole **14c** to further assess that the hydrocarbazoles thus obtained could serve as versatile synthetic intermediates (Scheme 4). Upon treatment of **14c** with $LiAlH_4$, tryptamine-derived *cis*-hydrocarbazole **20** was obtained in an 88% yield. The tryptophol-derived *cis*-hydrocarbazol **21** was readily achieved from **14c** via two-step reduction. Aldehyde **22** could also be obtained via reduction of **14c** in an 82% yield.

A plausible mechanism for the synthesis of hydrocarbazole **8c** from **8b** via the nickel and Lewis acid dual-catalyzed intramolecular arylcyanation was proposed in Scheme 5. The arylcyanation is initiated by the coordination of a cyano group to nickel in **A** with the aid of $AlMe_2Cl$, followed by oxidation addition into the Aryl-CN bond.[7a,8] The Lewis acid ($AlMe_2Cl$) is suggested to coordinate with the cyano group to further polarize the aryl-CN bond and promote the oxidative addition step. Then, coordination and migratory insertion of intramolecular alkene into the resulting aryl-nickel bond **B** give

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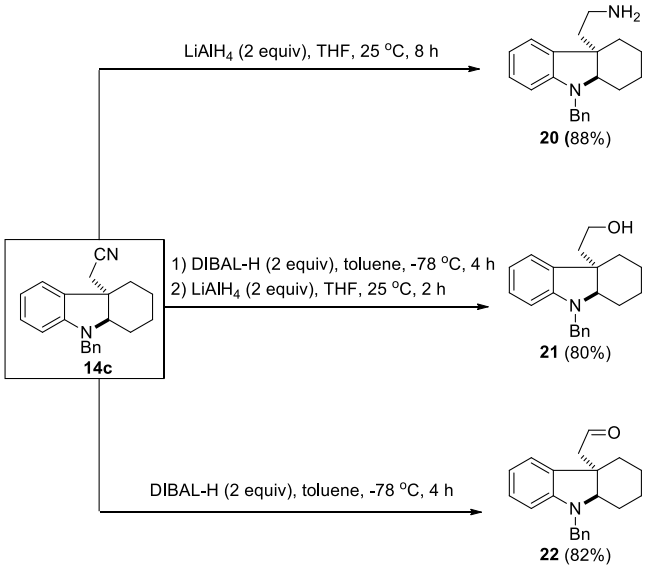
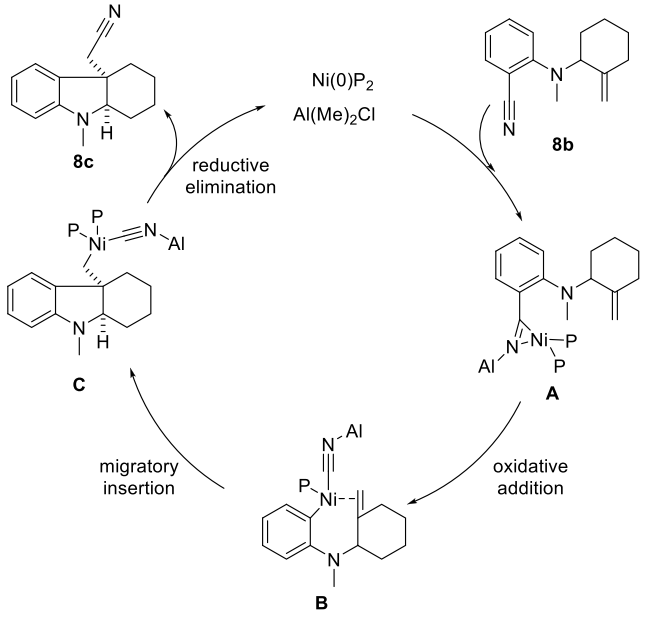
Scheme 4. Derivatization Studies of *cis*-Hydrocarbazole 14c



Scheme 5. Plausible Catalytic Cycle of the Formation of Compound 8c



complex **C**. Finally, reductive elimination of intermediate **C** will afford the desired hydrocarbazole **8c** and regenerate the catalyst.

In conclusion, we have developed the novel synthetic strategy for efficient construction of *cis*-hydrocarbazoles bearing a quaternary carbon center at the C3-position through nickel and Lewis acid dual-catalyzed arylcyanation. A series of synthetic conversions of the resulting *cis*-hydrocarbazoles have also been described for the preparation of tryptamine- and tryptophol-derived *cis*-hydrocarbazoles, the key core structures of many terpene-indole alkaloids. Moreover, the synthetic strategy could also be extended to enable access to complex 6/5/5 and 6/6/6 polycyclic systems with a benzylic quaternary carbon center, which are the common structures of indole alkaloids and amaryllidaceae alkaloids, respectively. Further synthetic applications of this synthetic strategy toward the total synthesis of relevant natural products are in progress.

EXPERIMENTAL SECTION

General Information. All commercially available reagents were used without further purification unless otherwise noted. Column chromatography was generally performed on silica gel (200−300 mesh), and reactions were monitored by thin-layer chromatography (TLC) using silica gel GF254 plates. NMR spectra were recorded on a 400 MHz (^{1}H, 400 MHz; ^{13}C, 100 MHz) spectrometer at 298 K. The chemical shifts (δ) are reported in ppm with a reference to the internal residual solvent [^{1}H NMR, $CDCl_3$ (7.26); ^{13}C NMR, $CDCl_3$ (77.0)]. Coupling constants (J) are reported in hertz (Hz). High-resolution mass spectra (HRMS) were recorded on a FT-ICR spectrometer using electrospray ionization (ESI).

General Procedure A: Synthesis of α-Amino Ketone. Under an argon atmosphere, potassium carbonate (15 mmol, 1.5 equiv), aniline **7** (10 mmol, 1.0 equiv), and acetone (0.5 M) were preheated at 70 °C and stirred for 1 h. Then the mixture was cooled down, and the solution of α-bromoketone **6** (10 mmol, 1.0 equiv) in DCM−acetone (1:3, v/v) was added to the above suspension slowly. Then the mixture was heated in an oil bath at 70 °C and stirred for 20 h. Then the mixture was cooled down and filtered. The filtrate was concentrated under the reduced pressure. The residue was purified by column chromatography (silica gel, PE/EA = 3:1) to give α-amino ketone.

General Procedure B: Wittig Olefination of α-Amino Ketone to Provide Allylic Anilines 8a−19a. To a suspension of methyltriphenylphosphonium bromide (11 mmol, 2.2 equiv) in dried THF (0.2 M) at 0 °C under Ar was added NaHMDS (2 M in THF, 11 mmol, 2.2 equiv), and the reaction mixture was stirred at 25 °C for 1 h. The suspension was cooled to 0 °C, and a solution of α-amino ketone (5.0 mmol, 1.0 equiv) in dried THF (10 mL) was added dropwise. The reaction mixture was warmed to 25 °C and stirred for 2 h. The reaction was quenched by the saturated aqueous NH_4Cl solution. The mixture was extracted with EA (3×). The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. The solution was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, PE/EA = 3:1) to give allylic anilines **8a−19a**.

General Procedure C: Alkylation of Allylic Aniline 8a−19a to Provide Precursors 8b−19b. To the solution of allylic anilines **8a−19a** (2.0 mmol, 1.0 equiv) in dried DMF (0.2 M) was added *t*BuOK (6.0 mmol, 3.0 equiv) at 0 °C under Ar. The reaction mixture was stirred at 25 °C for 30 min. Then, the alkyl iodide or benzyl bromide (10 mmol, 5.0 equiv) was added dropwise to the reaction. After the resulting mixture was stirred at 25 °C for 10 h, the reaction was quenched by the saturated aqueous NH_4Cl solution. The mixture was extracted with EA (3×). The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. The solution was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, PE/EA = 5:1) to give the precursors **8b−19b**.

General Procedure D: Nickel/Lewis Acid Catalyzed Intramolecular Arylcyanation of 8b−19b. To a dried sealable Schlenk tube was added $Ni(cod)_2$ (0.01 mmol, 0.05 equiv) under argon in a glovebox. The tube was sealed and taken out of the glovebox. The PEt_3 (0.02 mmol, 0.1 equiv) was added into the solution of $Ni(cod)_2$ in degassed toluene (0.1 M). The mixture was stirred at 25 °C for 10 min. Benzonitriles **8b−19b** (0.2 mmol, 1.0 equiv) and $AlMe_2Cl$ (1 M in hexane, 0.04 mmol, 0.2 equiv) were added sequentially into the reaction mixture. The vial was heated in an oil bath at 100 °C for 12 h. Then the mixture was cooled down and filtered through a silica gel pad. The filtrate was concentrated under the reduced pressure. The residue was purified by column chromatography (silica gel, PE/EA = 3:1) to give hexahydrocarbazoles **8c−19c**.

2-((2-Methylenecyclohexyl)amino)benzonitrile (8a). Compound **8a** was prepared by following general procedures A and B and was obtained as a colorless oil (1.29 g, 61%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 (dd, J = 7.7, 1.6 Hz, 1H), 7.32 (t, J = 7.9 Hz,

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1H), 6.64 (td, J = 7.7, 0.9 Hz, 1H), 6.56 (d, J = 8.6 Hz, 1H), 4.77 (d, J = 1.3 Hz, 1H), 4.73 (d, J = 0.9 Hz, 1H), 4.61 (d, J = 6.4 Hz, 1H), 3.85−3.70 (m, 1H), 2.44 (dd, J = 13.4, 1.5 Hz, 1H), 2.10 (dd, J = 11.8, 3.6 Hz, 2H), 1.98−1.71 (m, 2H), 1.69−1.33 ppm (m, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 149.6, 147.5, 134.0, 132.5, 118.0, 116.3, 111.7, 110.0, 106.8, 95.1, 56.1, 35.1, 34.2, 27.9, 25.2 ppm. HRMS (m/z): $[M + Na]^+$ calcd for $C_{14}H_{16}N_2Na^+$, 235.1206; found, 235.1208.

2-(Methyl(2-methylenecyclohexyl)amino)benzonitrile (8b). Compound **8b** was prepared by following general procedure C from intermediate **8a** and was obtained as a colorless oil (246 mg, 77%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.47 (dd, J = 7.8, 1.7 Hz, 1H), 7.34 (td, J = 7.9, 1.7 Hz, 1H), 6.87 (d, J = 8.6 Hz, 1H), 6.84−6.72 (m, 1H), 4.87 (d, J = 1.6 Hz, 1H), 4.69 (d, J = 1.5 Hz, 1H), 4.11−4.00 (m, 1H), 3.05 (s, 3H), 2.49 (d, J = 13.8 Hz, 1H), 2.24−2.07 (m, 1H), 1.89 (dt, J = 6.7, 3.2 Hz, 2H), 1.81−1.66 (m, 2H), 1.53−1.30 ppm (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 154.7, 146.1, 135.0, 133.1, 119.8, 118.4, 117.9, 107.7, 100.1, 65.0, 36.3, 34.4, 32.0, 27.4, 25.4 ppm. HRMS (m/z): $[M + Na]^+$ calcd for $C_{15}H_{18}N_2Na^+$, 249.1362; found, 249.1366.

2-(9-Methyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-4a-yl)-acetonitrile (8c). Compound **8c** was prepared by following general procedure D from **8b** and was obtained as a colorless oil (38 mg, 83% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.15 (td, J = 7.6, 1.2 Hz, 1H), 7.13 (d, J = 7.4 Hz, 1H), 6.74 (td, J = 7.4, 0.9 Hz, 1H), 6.51 (d, J = 7.8 Hz, 1H), 3.20 (dd, J = 6.8, 5.1 Hz, 1H), 2.73 (s, 3H), 2.65 (d, J = 16.7 Hz, 1H), 2.57 (d, J = 16.7 Hz, 1H), 2.06−1.94 (m, 1H), 1.82−1.70 (m, 2H), 1.63−1.40 (m, 3H), 1.36−1.27 ppm (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 150.8, 133.0, 128.6, 121.7, 118.18, 118.15, 108.1, 69.8, 44.7, 32.3, 31.5, 27.0, 24.0, 21.6, 21.0 ppm. HRMS (m/z): $[M + Na]^+$ calcd for $C_{15}H_{18}N_2Na^+$, 249.1362; found, 249.1363.

4-Fluoro-2-(methyl(2-methylenecyclohexyl)amino)-benzonitrile (9b). Compound **9b** was prepared by following general procedures A, B, and C and was obtained as a colorless oil (184 mg, 58%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.38−7.47 (m, 1H), 6.42−6.52 (m, 2H), 4.87 (d, J = 1.4 Hz, 1H), 4.61 (d, J = 1.4 Hz, 1H), 4.06 (d, J = 8.3 Hz, 1H), 3.08 (s, 3H), 2.49 (d, J = 13.7 Hz, 1H), 2.23−2.08 (m, 1H), 1.98−1.86 (m, 2H), 1.86−1.65 (m, 2H), 1.48 (dd, J = 9.3, 3.2 Hz, 1H), 1.32 ppm (d, J = 12.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 165.8 (d, J_{C-F} = 252.1 Hz), 163.6 (d, J_{C-F} = 18.5 Hz), 145.2, 137.2 (d, J_{C-F} = 11.7 Hz), 119.4, 111.1, 107.6, 105.9 (d, J_{C-F} = 23.4 Hz), 103.8 (d, J_{C-F} = 25.7 Hz), 65.0, 36.0, 34.5, 32.2, 27.2, 25.7 ppm. HRMS (m/z): $[M + Na]^+$ calcd for $C_{15}H_{17}FN_2Na^+$, 267.1268; found, 267.1270.

2-(7-Fluoro-9-methyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-4a-yl)acetonitrile (9c). Compound **9c** was prepared by following general procedure D from **9b** and was obtained as a colorless oil (39 mg, 80% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.02 (dd, J = 8.0, 5.5 Hz, 1H), 6.39 (ddd, J = 10.1, 8.1, 2.3 Hz, 1H), 6.19 (dd, J = 10.1, 2.2 Hz, 1H), 3.26 (dd, J = 7.1, 5.2 Hz, 1H), 2.73 (s, 3H), 2.67−2.46 (m, 2H), 2.00 (dd, J = 8.2, 5.5 Hz, 1H), 1.82−1.69 (m, 2H), 1.53 (ddd, J = 11.5, 9.7, 6.4 Hz, 2H), 1.47−1.35 (m, 1H), 1.33−1.26 ppm (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 164.2 (d, J_{C-F} = 242.4 Hz), 152.4 (d, J_{C-F} = 11.5 Hz), 128.2, 122.4 (d, J_{C-F} = 10.7 Hz), 118.0, 103.9 (d, J_{C-F} = 22.9 Hz), 96.1 (d, J_{C-F} = 26.9 Hz), 70.1, 44.4, 32.0, 31.4, 27.5, 24.3, 21.5, 21.0 ppm. HRMS (m/z): $[M + Na]^+$ calcd for $C_{15}H_{17}FN_2Na^+$, 267.1268; found, 267.1271.

5-Methyl-2-((2-methylenecyclohexyl)amino)benzonitrile (10a). Compound **10a** was prepared by following general procedures A and B and was obtained as a colorless oil (1.47 g, 65%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.18 (d, J = 2.0 Hz, 1H), 7.14 (dd, J = 8.6, 2.0 Hz, 1H), 6.48 (d, J = 8.6 Hz, 1H), 4.74 (d, J = 11.3 Hz, 2H), 4.47 (d, J = 6.2 Hz, 1H), 3.75 (s, 1H), 2.43 (dd, J = 11.1, 3.8 Hz, 1H), 2.19 (d, J = 5.3 Hz, 3H), 2.06 (dd, J = 16.3, 8.7 Hz, 2H), 1.95−1.73 (m, 2H), 1.67−1.37 ppm (m, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 147.8, 147.7, 135.0, 132.2, 125.5, 118.2, 111.9, 106.7, 95.0, 56.2, 35.2, 34.2, 28.0, 25.2, 19.9 ppm. HRMS (m/z): $[M + Na]^+$ calcd for $C_{15}H_{18}N_2Na^+$, 249.1362; found, 249.1365.

5-Methyl-2-(methyl(2-methylenecyclohexyl)amino)-benzonitrile (10b). Compound **10b** was prepared by following general procedure C from intermediate **10a** and was obtained as a colorless oil (252 mg, 79%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, J = 1.4 Hz, 1H), 7.17 (dd, J = 8.6, 1.9 Hz, 1H), 6.83 (d, J = 8.6 Hz, 1H), 4.86 (s, 1H), 4.72 (d, J = 1.0 Hz, 1H), 3.97 (dd, J = 9.4, 2.8 Hz, 1H), 2.97 (s, 3H), 2.56−2.40 (m, 1H), 2.24 (s, 3H), 2.14 (dd, J = 16.3, 8.3 Hz, 1H), 1.93−1.80 (m, 2H), 1.80−1.62 (m, 2H), 1.41 ppm (dd, J = 19.2, 10.2 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 152.8, 146.6, 134.3, 134.0, 128.5, 119.5, 118.6, 107.8, 101.2, 65.0, 36.8, 34.1, 31.7, 27.4, 24.9, 19.9 ppm. HRMS (m/z): $[M + Na]^+$ calcd for $C_{16}H_{20}N_2Na^+$, 263.1519; found, 263.1522.

2-(6,9-Dimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-4a-yl)acetonitrile (10c). Compound **10c** was prepared by following general procedure D from **10b** and was obtained as a colorless oil (36 mg, 74% yield). ^1H NMR (300 MHz, $CDCl_3$): δ 6.94−7.01 (m, 2H), 6.44 (d, J = 8.3 Hz, 1H), 3.21−3.10 (m, 1H), 2.75−2.51 (m, 5H), 2.29 (s, 3H), 1.97 (ddd, J = 11.0, 7.2, 3.4 Hz, 1H), 1.83−1.67 (m, 2H), 1.51 (ddd, J = 14.4, 13.0, 8.0 Hz, 3H), 1.35 ppm (dd, J = 13.2, 6.9 Hz, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 148.7, 133.4, 128.8, 127.5, 122.4, 118.3, 108.2, 69.9, 44.5, 32.7, 31.6, 26.6, 23.7, 21.6, 21.1, 20.9 ppm. HRMS (m/z): $[M + Na]^+$ calcd for $C_{16}H_{20}N_2Na^+$, 263.1519; found, 263.1521.

4-Methyl-2-((2-methylenecyclohexyl)amino)benzonitrile (11a). Compound **11a** was prepared by following general procedures A and B and was obtained as a colorless oil (1.43 g, 63%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, J = 7.88 Hz, 1H), 6.46 (d, J = 7,.92 Hz, 1H), 6.36 (s, 1H), 4.77 (s, 1H), 4.74 (s, 1H), 4.53 (d, J = 6.3 Hz, 1H), 3.85−3.72 (m, 1H), 2.44 (dd, J = 13.4, 1.4 Hz, 1H), 2.28 (s, 3H), 2.08 (dd, J = 11.9, 3.6 Hz, 2H), 1.89 (dd, J = 8.7, 4.8 Hz, 1H), 1.80 (dd, J = 8.7, 4.0 Hz, 1H), 1.64−1.56 (m, 1H), 1.52−1.39 ppm (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 149.7, 147.8, 145.0, 132.4, 118.4, 117.7, 112.1, 106.9, 92.6, 56.1, 35.3, 34.3, 28.0, 25.2, 22.4 ppm. HRMS (m/z): $[M + Na]^+$ calcd for $C_{15}H_{18}N_2Na^+$, 249.1362; found, 249.1361.

4-Methyl-2-(methyl(2-methylenecyclohexyl)amino)-benzonitrile (11b). Compound **11b** was prepared by following general procedure C from intermediate **11a** and was obtained as a colorless oil (261 mg, 82%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, J = 7.9 Hz, 1H), 6.67 (s, 1H), 6.61 (d, J = 7.9 Hz, 1H), 4.87 (d, J = 1.3 Hz, 1H), 4.71 (d, J = 1.4 Hz, 1H), 4.14−3.98 (m, 1H), 3.02 (s, 3H), 2.55−2.44 (m, 1H), 2.32 (d, J = 6.6 Hz, 3H), 2.16 (td, J = 13.2, 4.3 Hz, 1H), 1.96−1.82 (m, 2H), 1.81−1.64 (m, 2H), 1.52−1.31 ppm (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 154.7, 146.3, 143.9, 134.8, 120.0, 119.8, 118.3, 107.7, 97.5, 65.0, 36.2, 34.4, 32.0, 27.4, 25.4, 22.1 ppm. HRMS (m/z): $[M + Na]^+$ calcd for $C_{16}H_{20}N_2Na^+$, 263.1519; found, 263.1523.

2-(7,9-Dimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-4a-yl)acetonitrile (11c). Compound **11c** was prepared by following general procedure D from **11b** and was obtained as a colorless oil (38 mg, 78% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.04 (d, J = 7.4 Hz, 1H), 6.59 (d, J = 7.4 Hz, 1H), 6.37 (s, 1H), 3.21 (dd, J = 6.8, 5.2 Hz, 1H), 2.74 (s, 3H), 2.65 (d, J = 16.7 Hz, 1H), 2.56 (d, J = 16.7 Hz, 1H), 2.33 (s, 3H), 2.08−1.95 (m, 1H), 1.77 (ddd, J = 13.9, 7.7, 3.9 Hz, 2H), 1.63−1.42 (m, 3H), 1.41−1.28 ppm (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 150.8, 138.5, 130.3, 121.4, 118.9, 118.2, 109.2, 69.9, 44.4, 32.2, 31.5, 27.1, 24.0, 21.7, 21.5, 21.0 ppm. HRMS (m/z): $[M + Na]^+$ calcd for $C_{16}H_{20}N_2Na^+$, 263.1519; found, 263.1520.

4-Methoxy-2-((2-methylenecyclohexyl)amino)benzonitrile (12a). Compound **12a** was prepared by following general procedures A and B and was obtained as a colorless oil (1.65 g, 68%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, J = 8.6 Hz, 1H), 6.22 (dd, J = 8.6, 2.3 Hz, 1H), 6.05 (d, J = 2.3 Hz, 1H), 4.82−4.72 (m, 2H), 4.58 (d, J = 6.2 Hz, 1H), 3.77 (s, 4H), 2.47−2.35 (m, 1H), 2.12−2.01 (m, 2H), 1.93−1.84 (m, 1H), 1.81−1.74 (m, 1H), 1.61−1.56 (m, 1H), 1.55−1.50 (m, 1H), 1.46−1.38 ppm (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 164.4, 151.3, 147.5, 134.1, 118.5, 107.1, 103.0, 97.1, 88.3, 56.3, 55.3, 35.1, 34.1, 28.0, 25.0 ppm. HRMS (m/z): $[M + Na]^+$ calcd for $C_{15}H_{18}N_2ONa^+$, 265.1311; found, 265.1315.

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4-Methoxy-2-(methyl(2-methylenecyclohexyl)amino)-benzonitrile (12b). Compound **12b** was prepared by following general procedure C from intermediate **12a** and was obtained as a colorless oil (203 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, J = 8.5 Hz, 1H), 6.36 (dd, J = 8.6, 2.1 Hz, 1H), 6.34 (s, 1H), 4.87 (s, 1H), 4.69 (s, 1H), 4.08 (d, J = 10.3 Hz, 1H), 3.79 (s, 3H), 3.04 (s, 3H), 2.49 (d, J = 13.7 Hz, 1H), 2.14 (td, J = 13.2, 4.4 Hz, 1H), 1.89 (dd, J = 11.6, 2.5 Hz, 2H), 1.74 (ddd, J = 14.0, 9.5, 3.7 Hz, 2H), 1.52−1.29 ppm (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 163.5, 156.4, 146.1, 136.6, 120.2, 107.7, 104.9, 103.0, 92.6, 65.1, 55.3, 36.1, 34.5, 32.0, 27.4, 25.5 ppm. HRMS (m/z): [M + Na]$^+$ calcd for $C_{16}H_{20}N_2ONa^+$, 279.1468; found, 279.1466.

2-(7-Methoxy-9-methyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-4a-yl)acetonitrile (12c). Compound **12c** was prepared by following general procedure D from **12b** and was obtained as a colorless oil (31 mg, 60% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (d, J = 8.1 Hz, 1H), 6.26 (dd, J = 8.0, 2.1 Hz, 1H), 6.08 (d, J = 2.1 Hz, 1H), 3.78 (s, 3H), 3.21 (dd, J = 6.9, 5.4 Hz, 1H), 2.72 (s, 3H), 2.57 (q, J = 16.6 Hz, 2H), 2.08−1.95 (m, 1H), 1.74 (ddd, J = 14.0, 9.8, 3.9 Hz, 2H), 1.60−1.47 (m, 2H), 1.43−1.36 (m, 1H), 1.34−1.25 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 161.0, 152.2, 125.5, 122.2, 118.3, 101.9, 95.7, 70.1, 55.3, 44.3, 32.0, 31.5, 27.6, 24.3, 21.6, 21.2 ppm. HRMS (m/z): [M + Na]$^+$ calcd for $C_{16}H_{20}N_2ONa^+$, 279.1468; found, 279.1467.

2-(Ethyl(2-methylenecyclohexyl)amino)benzonitrile (13b). Compound **13b** was prepared by following general procedure C from intermediate **8a** and was obtained as a colorless oil (204, 60%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (dd, J = 7.7, 1.7 Hz, 1H), 7.43 (td, J = 7.9, 1.7 Hz 1H), 7.09 (d, J = 7.9 Hz, 1H), 6.96 (td, J = 7.6, 1.0 Hz, 1H), 4.88 (d, J = 8.5 Hz, 2H), 4.08 (t, J = 6.3 Hz, 1H), 3.31 (dd, J = 11.5, 7.1 Hz, 2H), 2.47 (d, J = 4.7 Hz, 1H), 2.16−2.06 (m, 1H), 1.88−1.79 (m, 1H), 1.72 (t, J = 5.7 Hz, 2H), 1.58 (s, 1H), 1.50 (d, J = 3.9 Hz, 1H), 1.37 (s, 1H), 1.03 ppm (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 153.1, 148.0, 134.5, 132.5, 122.2, 120.9, 118.8, 108.4, 106.7, 64.7, 43.0, 33.5, 31.0, 27.6, 23.7, 12.3 ppm. HRMS (m/z): [M + Na]$^+$ calcd for $C_{16}H_{20}N_2Na^+$, 263.1519; found, 263.1517.

2-(9-Ethyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-4a-yl)-acetonitrile (13c). Compound **13c** was prepared by following general procedure D from **13b** and was obtained as a colorless oil (41 mg, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10−7.16 (m, 2H), 6.71 (t, J = 7.4 Hz, 1H), 6.49 (d, J = 7.7 Hz, 1H), 3.40 (dd, J = 7.2, 5.0 Hz, 1H), 3.27 (dt, J = 14.5, 7.2 Hz, 1H), 3.03 (dq, J = 14.0, 7.1 Hz, 1H), 2.62 (d, J = 16.6 Hz, 1H), 2.54 (d, J = 16.6 Hz, 1H), 2.14−2.01 (m, 1H), 1.76 (ddd, J = 14.0, 10.1, 4.0 Hz, 2H), 1.63−1.48 (m, 2H), 1.41−1.23 (m, 3H), 1.24−1.14 ppm (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 149.7, 132.5, 128.5, 121.9, 118.2, 117.6, 107.7, 66.3, 44.7, 38.4, 31.0, 27.5, 24.2, 21.6, 21.3, 12.4 ppm. HRMS (m/z): [M + Na]+ calcd for $C_{16}H_{20}N_2Na^+$, 263.1519; found, 263.1521.

2-(Benzyl(2-methylenecyclohexyl)amino)benzonitrile (14b). Compound **14b** was prepared by following general procedure C from intermediate **8a** and was obtained as a colorless oil (355 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (dd, J = 7.7, 1.5 Hz, 1H), 7.30−7.11 (m, 6H), 6.90 (d, J = 8.5 Hz, 1H), 6.85 (t, J = 7.5 Hz, 1H), 4.99 (s, 1H), 4.92 (s, 1H), 4.52 (s, 2H), 4.38−4.27 (m, 1H), 2.59−2.43 (m, 1H), 2.21 (dd, J = 11.2, 7.6 Hz, 1H), 1.87 (dd, J = 7.9, 3.9 Hz, 2H), 1.74−1.60 (m, 2H), 1.42 ppm (t, J = 8.4 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 152.9, 147.8, 138.0, 134.8, 132.7, 128.2, 127.4, 126.7, 121.5, 120.7, 119.0, 108.1, 105.0, 65.8, 51.7, 34.2, 31.3, 27.4, 24.6 ppm. HRMS (m/z): [M + Na]$^+$ calcd for $C_{21}H_{22}N_2Na^+$, 325.1675; found, 325.1676.

2-(9-Benzyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-4a-yl)-acetonitrile (14c). Compound **14c** was prepared by following general procedure D from **14b** and was obtained as a colorless oil (47 mg, 77% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42−7.31 (m, 4H), 7.23−7.29 (m, 1H), 7.15 (dd, J = 7.3, 0.6 Hz, 1H), 7.08 (td, J = 7.7, 1.2 Hz, 1H), 6.75 (td, J = 7.5, 0.7 Hz, 1H), 6.43 (d, J = 7.8 Hz, 1H), 4.39 (d, J = 15.3 Hz, 1H), 4.16−4.04 (m, 1H), 3.32 (dd, J = 7.7, 5.3 Hz, 1H), 2.61 (s, 2H), 2.24−2.09 (m, 1H), 1.73 (ddd, J = 17.7, 9.4, 4.2 Hz, 2H), 1.62−1.48 (m, 2H), 1.43−1.15 ppm (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 149.9, 138.2, 132.4, 128.52, 128.50, 127.3, 127.1, 122.0, 118.3, 118.0, 108.4, 67.8, 49.3, 44.9, 31.0, 27.7, 24.4, 21.5, 21.4 ppm. HRMS (m/z): [M + Na]$^+$ calcd for $C_{21}H_{22}N_2Na^+$, 325.1675; found, 325.1677.

2-((5,5-Dimethyl-2-methylenecyclohexyl)amino)-benzonitrile (15a). Compound **15a** was prepared by following general procedures A and B and was obtained as a colorless oil (1.49 g, 62%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 (dd, J = 7.8, 1.2 Hz, 1H), 7.33 (td, J = 8.0, 1.0 Hz, 1H), 6.64 (t, J = 7.5 Hz, 1H), 6.55 (d, J = 8.6 Hz, 1H), 4.76 (s, 1H), 4.69 (s, 1H), 4.51 (d, J = 6.5 Hz, 1H), 3.99−3.76 (m, 1H), 2.42−2.14 (m, 2H), 1.89−1.75 (m, 1H), 1.54 (dd, J = 12.7, 2.6 Hz, 1H), 1.42−1.23 (m, 2H), 1.11 (s, 3H), 1.00 ppm (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 149.7, 147.7, 134.1, 132.6, 118.0, 116.3, 111.6, 106.3, 95.2, 52.8, 48.0, 40.5, 32.2, 32.1, 30.8, 24.9 ppm. HRMS (m/z): [M + Na]$^+$ calcd for $C_{16}H_{20}N_2Na^+$, 263.1519; found, 263.1521.

2-((5,5-Dimethyl-2-methylenecyclohexyl)(methyl)amino)-benzonitrile (15b). Compound **15b** was prepared by following general procedure C from intermediate **15a** and was obtained as a colorless oil (254 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (dd, J = 7.7, 1.7 Hz, 1H), 7.33 (td, J = 7.9, 1.7 Hz, 1H), 6.84 (d, J = 8.6 Hz, 1H), 6.75 (td, J = 7.5, 0.8 Hz, 1H), 4.89 (s, 1H), 4.65 (s, 1H), 4.37−4.20 (m, 1H), 3.07 (s, 3H), 2.35 (dd, J = 7.8, 3.1 Hz, 2H), 1.60 (dd, J = 13.0, 6.4 Hz, 2H), 1.47 (d, J = 13.0 Hz, 1H), 1.36−1.23 (m, 1H), 1.04 (s, 3H), 0.99 ppm (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 154.8, 145.5, 135.2, 133.2, 120.0, 117.9, 117.2, 107.4, 98.9, 61.3, 44.3, 39.7, 35.4, 32.6, 32.1, 30.7, 24.2 ppm. HRMS (m/z): [M + Na]$^+$ calcd for $C_{17}H_{22}N_2Na^+$, 277.1675; found, 277.1677.

2-(2,2,9-Trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-4a-yl)acetonitrile (15c). Compound **15c** was prepared by following general procedure D from **15b** and was obtained as a colorless oil (44 mg, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 (td, J = 7.6, 0.8 Hz, 1H), 7.11(d, J = 7.1 Hz, 1H), 6.74 (t, J = 7.4 Hz, 1H), 6.46 (d, J = 7.8 Hz, 1H), 3.49 (dd, J = 9.4, 5.6 Hz, 1H), 2.74 (s, 3H), 2.59 (d, J = 16.5 Hz, 1H), 2.44 (d, J = 16.5 Hz, 1H), 2.24−2.12 (m, 1H), 2.02−1.93 (m, 1H), 1.55 (ddd, J = 13.4, 5.5, 2.0 Hz, 1H), 1.37−1.27 (m, 1H), 1.23−1.13 (m, 1H), 1.06−0.99 (m, 1H), 0.97 (d, J = 5.1 Hz, 3H), 0.88 ppm (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 150.2, 131.7, 128.9, 122.0, 118.4, 117.8, 107.7, 68.2, 44.8, 36.6, 34.6, 31.6, 31.5, 29.5, 28.4, 26.8, 25.0 ppm. HRMS (m/z): [M + Na]$^+$ calcd for $C_{17}H_{22}N_2Na^+$, 277.1675; found, 277.1678.

2-((8-Methylene-1,4-dioxaspiro[4.5]decan-7-yl)amino)-benzonitrile (16a). Compound **16a** was prepared by following general procedures A and B from 7-bromo-1,4-dioxaspiro[4.5]decan-8-one, which was synthesized according to literature,[13] and was obtained as a colorless oil (1.40 g, 52%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (dd, J = 8.0, 1.6 Hz, H), 7.32 (td, J = 7.1, 1.5 Hz, 1H), 6.73−6.53 (m, 2H), 5.69 (d, J = 7.7 Hz, 1H), 4.90 (s, 2H), 4.27−3.85 (m, 5H), 2.47 (dd, J = 14.0, 6.2 Hz, 1H), 2.32−2.15 (m, 1H), 2.09 (dd, J = 13.0, 4.6 Hz, 1H), 1.90 (dd, J = 13.1, 7.2 Hz, 1H), 1.78 ppm (t, J = 6.5 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 149.4, 145.4, 133.8, 132.5, 117.8, 116.1, 111.5, 109.8, 108.3, 95.7, 64.6, 64.4, 53.9, 41.2, 36.2, 28.8 ppm. HRMS (m/z): [M + Na]$^+$ calcd for $C_{16}H_{18}N_2O_2Na^+$, 293.1260; found, 293.1262.

2-(Methyl(8-methylene-1,4-dioxaspiro[4.5]decan-7-yl)-amino)benzonitrile (16b). Compound **16b** was prepared by following general procedure C from intermediate **16a** and was obtained as a colorless oil (192 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (dd, J = 7.8, 1.6 Hz, 1H), 7.33 (td, J = 7.9, 1.7 Hz, 1H), 6.85 (d, J = 8.6 Hz, 1H), 6.78 (td, J = 7.5, 0.7 Hz, 1H), 4.97 (s, 1H), 4.76 (s, 1H), 4.41−4.25 (m, 1H), 4.05−3.89 (m, 4H), 3.10 (s, 3H), 2.43 (dd, J = 7.3, 3.2 Hz, 2H), 1.98 (d, J = 11.3 Hz, 2H), 1.88−1.78 (m, 1H), 1.71−1.56 ppm (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 154.7, 143.4, 135.0, 133.2, 119.8, 118.4, 117.6, 108.9, 108.7, 99.6, 64.6, 64.5, 61.9, 39.9, 35.6, 35.3, 30.2 ppm. HRMS (m/z): [M + Na]$^+$ calcd for $C_{17}H_{20}N_2O_2Na^+$, 307.1417; found, 307.1415.

2-(9-Methyl-1,3,4,4a,9,9a-hexahydrospiro[carbazole-2,2′-[1,3]dioxolan]-4a-yl)acetonitrile (16c). Compound **6c** was prepared by following general procedure D from **16b** and was obtained as a colorless oil (36 mg, 64% yield). ^{1}H NMR (400 MHz,

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$CDCl_3$): δ 7.14−7.20 (m, 2H), 6.76 (t, J = 7.4 Hz, 1H), 6.48 (d, J = 7.7 Hz, 1H), 4.03−3.82 (m, 4H), 3.50 (dd, J = 9.3, 5.8 Hz, 1H), 2.73 (s, 3H), 2.62 (d, J = 16.5 Hz, 1H), 2.51 (d, J = 16.5 Hz, 1H), 2.36 (dt, J = 14.1, 4.2 Hz, 1H), 2.14−1.99 (m, 1H), 1.93 (ddd, J = 13.3, 5.8, 2.3 Hz, 1H), 1.66 (ddd, J = 13.2, 6.6, 4.2 Hz, 1H), 1.52 (td, J = 13.0, 4.3 Hz, 1H), 1.41 ppm (dd, J = 13.3, 9.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 150.1, 130.7, 129.0, 122.2, 118.1, 117.9, 108.1, 107.7, 69.6, 64.4, 64.2, 44.6, 33.0, 31.6, 30.4, 28.2, 27.5 ppm. HRMS (*m*/*z*): $[M + Na]^+$ calcd for $C_{17}H_{20}N_2O_2Na^+$, 307.1417; found, 307.1417.

2-(Benzyl(8-methylene-1,4-dioxaspiro[4.5]decan-7-yl)amino)benzonitrile (17b). Compound **17b** was prepared by following general procedure C from intermediate **16a** and was obtained as a colorless oil (296 mg, 74%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.40 (dd, J = 7.7, 1.6 Hz, 1H), 7.10−7.20 (m, 5H), 7.05 (t, J = 7.0 Hz, 1H), 6.83 (d, J = 8.5 Hz, 1H), 6.73 (t, J = 7.5 Hz, 1H), 5.04 (s, 1H), 4.89 (s, 1H), 4.61−4.46 (m, 2H), 4.37 (d, J = 16.7 Hz, 1H), 3.91−3.70 (m, 4H), 2.43−2.25 (m, 2H), 2.00−1.89 (m, 1H), 1.83 (t, J = 12.3 Hz, 1H), 1.75−1.62 (m, 1H), 1.59−1.43 ppm (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 153.1, 145.1, 138.2, 135.1, 132.8, 128.4, 127.0, 126.8, 120.6, 120.5, 118.7, 108.9, 108.5, 104.7, 64.5, 64.34, 64.29, 50.0, 38.8, 35.0, 30.5 ppm. HRMS (*m*/*z*): $[M + Na]^+$ calcd for $C_{23}H_{24}N_2O_2Na^+$, 383.1730; found, 383.1733.

2-(9-Benzyl-1,3,4,4a,9,9a-hexahydrospiro[carbazole-2,2′-[1,3]dioxolan]-4a-yl)acetonitrile (17c). Compound **17c** was prepared by following general procedure D from **17b** and was obtained as a colorless oil (41 mg, 57% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.41−7.27 (m, 5H), 7.20 (d, J = 7.2 Hz, 1H), 7.12 (td, J = 7.7, 1.0 Hz, 1H), 6.78 (t, J = 7.4 Hz, 1H), 6.44 (d, J = 7.8 Hz, 1H), 4.39 (d, J = 14.9 Hz, 1H), 4.06 (d, J = 14.9 Hz, 1H), 3.88 (dd, J = 5.6, 1.7 Hz, 4H), 3.52 (dd, J = 9.7, 5.9 Hz, 1H), 2.73 (d, J = 16.4 Hz, 1H), 2.51 (d, J = 16.4 Hz, 1H), 2.43 (d, J = 14.1 Hz, 1H), 2.01 (d, J = 4.3 Hz, 1H), 1.91 (ddd, J = 13.2, 5.9, 2.4 Hz, 1H), 1.74−1.62 (m, 1H), 1.60−1.41 ppm (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 149.4, 137.8, 130.6, 129.1, 128.7, 127.6, 127.4, 122.6, 118.6, 117.9, 108.7, 107.7, 67.6, 64.4, 64.2, 48.9, 44.6, 33.4, 30.4, 28.5, 27.4 ppm. HRMS (*m*/*z*): $[M + Na]^+$ calcd for $C_{23}H_{24}N_2O_2Na^+$, 383.1730; found, 383.1736.

2-((2-Methylenecyclopentyl)amino)benzonitrile (18a). Compound **18a** was prepared by following general procedures A and B and was obtained as a colorless oil (1.29 g, 65%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.34−7.39 (m, 2H), 6.72 (d, J = 8.7 Hz, 1H), 6.65 (t, J = 7.5 Hz, 1H), 5.11 (dd, J = 4.5, 2.2 Hz, 1H), 5.06 (dd, J = 4.1, 2.2 Hz, 1H), 4.60 (d, J = 6.3 Hz, 1H), 4.20 (d, J = 7.2 Hz, 1H), 2.45 (ddd, J = 9.8, 5.0, 2.9 Hz, 2H), 2.19 (td, J = 11.7, 6.6 Hz, 1H), 1.81 (ddd, J = 12.3, 8.8, 3.6 Hz, 1H), 1.74−1.60 (m, 1H), 1.53 ppm (ddd, J = 16.4, 12.2, 7.8 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 152.4, 149.9, 134.1, 132.7, 117.8, 116.2, 111.1, 107.8, 95.6, 56.9, 33.5, 31.0, 22.2 ppm. HRMS (*m*/*z*): $[M + Na]^+$ calcd for $C_{13}H_{14}N_2Na^+$, 221.1049; found, 221.1049.

2-(Methyl(2-methylenecyclopentyl)amino)benzonitrile (18b). Compound **18b** was prepared by following general procedure C from intermediate **18a** and was obtained as a colorless oil (263 mg, 82%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (dd, J = 7.7, 1.6 Hz, 1H), 7.38 (td, J = 7.9, 1.6 Hz, 1H), 6.98 (d, J = 8.5 Hz, 1H), 6.82 (t, J = 7.5 Hz, 1H), 5.12 (d, J = 1.9 Hz, 1H), 4.96 (d, J = 2.2 Hz, 1H), 4.72−4.59 (m, 1H), 2.84 (s, 3H), 2.51−2.29 (m, 2H), 2.08−1.98 (m, 1H), 1.89−1.71 (m, 2H), 1.64−1.52 ppm (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 155.5, 148.9, 134.9, 133.3, 119.4, 119.0, 118.1, 108.0, 101.5, 67.2, 33.6, 31.8, 29.0, 22.5 ppm. HRMS (*m*/*z*): $[M + Na]^+$ calcd for $C_{14}H_{16}N_2Na^+$, 235.1206; found, 235.1206.

2-(4-Methyl-1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indol-8b-yl)acetonitrile (18c). Compound **18c** was prepared by following general procedure D from and was obtained as a colorless oil (40 mg, 95% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.13 (t, J = 7.6 Hz, 1H), 7.10 (d, J = 7.8 Hz, 1H), 6.66 (t, J = 7.4 Hz, 1H), 6.37 (d, J = 7.8 Hz, 1H), 3.79 (d, J = 3.7 Hz, 1H), 2.83 (s, 3H), 2.74 (d, J = 16.7 Hz, 1H), 2.66 (d, J = 16.7 Hz, 1H), 2.15−2.02 (m, 1H), 2.02−1.87 (m, 2H), 1.81 (tt, J = 12.8, 4.8 Hz, 2H), 1.66−1.52 ppm (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 151.6, 132.6, 128.7, 122.5, 118.0, 116.8, 105.6, 75.9, 53.2, 39.6, 32.6, 31.8, 28.6, 24.9 ppm. HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{14}H_{17}N_2^+$, 213.1386; found, 213.1383.

***N*-(2-Methylenecyclohexyl)aniline (19a).** Compound **19a** was prepared by following general procedures A and B and was obtained as a colorless oil (1.35 g, 72%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.15 (td, J = 8.0, 1.2 Hz, 2H), 6.66 (tt, J = 7.3, 1.1 Hz, 1H), 6.62−6.50 (m, 2H), 4.81 (s, 1H), 4.75 (s, 1H), 3.70 (dd, J = 10.6, 4.1 Hz, 2H), 2.50−2.33 (m, 1H), 2.08 (dd, J = 21.5, 9.4 Hz, 2H), 1.81 (dd, J = 11.0, 8.4 Hz, 2H), 1.57 (d, J = 13.0 Hz, 1H), 1.46−1.31 ppm (m, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 149.3, 147.6, 129.1, 116.9, 113.0, 106.4, 56.5, 35.6, 34.4, 28.2, 25.4 ppm. HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{13}H_{18}N^+$, 188.1434; found, 188.1434.

2-(((2-Methylenecyclohexyl)(phenyl)amino)methyl)benzonitrile (19b). Compound **19b** was prepared by following general procedure C from intermediate **19a** and obtained as a colorless oil (266 mg, 55%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 7.6 Hz, 1H), 7.45−7.54 (m, 2H), 7.33 (td, J = 7.2, 1.1 Hz, 1H), 7.18 (d, J = 7.6 Hz, 2H), 6.72 (t, J = 7.2 Hz, 1H), 6.58 (d, J = 8.4 Hz, 2H), 4.83 (d, J = 12.5 Hz, 2H), 4.66 (d, J = 18.8 Hz, 1H), 4.52 (s, 1H), 4.27 (d, J = 8.1 Hz, 1H), 2.52 (d, J = 13.6 Hz, 1H), 2.17 (dd, J = 13.2, 3.8 Hz, 1H), 1.93−1.73 (m, 3H), 1.57−1.39 (m, 2H), 1.32 ppm (dd, J = 8.4, 4.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 148.9, 144.8, 144.6, 132.84, 132.78, 129.0, 127.7, 127.0, 117.1, 112.7, 109.5, 107.6, 61.6, 50.0, 34.9, 32.9, 27.3, 26.3 ppm. HRMS (*m*/*z*): $[M + Na]^+$ calcd for $C_{21}H_{22}N_2Na^+$, 325.1675; found, 325.1674.

2-(5-Phenyl-1,2,3,4,4a,5,6,10b-octahydrophenanthridin-10b-yl)acetonitrile (19c). Compound **19c** was prepared by following general procedure D from **19b** and was obtained as a colorless oil (51 mg, 84% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.49−7.38 (m, 1H), 7.37−7.24 (m, 5H), 7.02 (d, J = 8.1 Hz, 2H), 6.84 (t, J = 7.3 Hz, 1H), 4.47 (d, J = 16.2 Hz, 1H), 4.33 (d, J = 16.2 Hz, 1H), 3.96 (dd, J = 11.5, 3.6 Hz, 1H), 2.83 (d, J = 16.7 Hz, 1H), 2.68 (dd, J = 14.1, 2.1 Hz, 1H), 2.62 (d, J = 16.7 Hz, 1H), 1.86−1.76 (m, 1H), 1.71−1.55 (m, 3H), 1.39−1.15 ppm (m, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 148.7, 135.5, 133.7, 129.4, 127.2, 127.1, 125.7, 118.5, 118.1, 114.4, 59.8, 46.6, 41.7, 33.6, 31.9, 25.2, 23.3, 21.5 ppm. HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{21}H_{23}N_2^+$, 303.1856; found, 303.1856.

2-(9-Benzyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-4a-yl)ethanamine (20). A solution of compound **14c** (24 mg, 0.08 mmol) in THF (1 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (12 mg, 0.32 mmol) in THF (3 mL). The solution was then stirred at 25 °C for 8 h. To the mixture was added slowly H_2O and 10% NaOH at 0 °C. The mixture was stirred at 25 °C for an additional 0.5 h. The mixture was filtered through a pad of silica gel and washed with Et_2O. The solution was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH = 10:1) to give pure compound **20** (22 mg, 88% yield) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.27−7.40 (m, 5H), 7.03−7.09 (m, 2H), 6.73 (t, J = 7.3 Hz, 1H), 6.41 (d, J = 8.0 Hz, 1H), 4.40 (d, J = 15.7 Hz, 1H), 4.12 (dd, J = 15.0, 9.3 Hz, 1H), 3.72 (s, 2H), 3.51 (t, J = 5.5 Hz, 1H), 1.93−1.83 (m, 1H), 1.73 (ddd, J = 14.3, 8.9, 4.1 Hz, 1H), 1.63−1.52 (m, 4H), 1.50−1.42 (m, 2H), 1.35 (ddd, J = 12.4, 7.9, 3.8 Hz, 1H), 1.28−1.23 (m, 2H), 0.91−0.80 ppm (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 151.6, 138.9, 133.1, 128.5, 128.0, 127.3, 126.9, 122.0, 117.8, 108.0, 67.4, 65.1, 50.0, 48.6, 34.5, 30.1, 24.3, 21.5, 21.2 ppm. HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{21}H_{27}N_2^+$, 307.2169; found, 307.2170.

2-(9-Benzyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-4a-yl)ethanol (21). A solution of compound **22** (41 mg, 0.134 mmol) in THF (1 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (10 mg, 0.27 mmol) in THF (3 mL). The solution was then stirred at 25 °C for 2 h. To the mixture were added slowly H_2O and 10% NaOH at 0 °C. The mixture was stirred at 25 °C for an additional 0.5 h. The mixture was filtered through a pad of silica gel and washed with Et_2O. The solution was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, PE/EA = 2:1) to give pure compound **21** (40 mg, 97% yield) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.41−7.26 (m, 5H), 7.05 (td, J = 7.7, 1.2 Hz, 1H), 7.02 (d, J = 7.2 Hz,1 H), 6.73 (t, J = 7.3 Hz, 1H), 6.45 (d, J = 7.8

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Hz, 1H), 4.40 (d, J = 15.5 Hz, 1H), 4.10 (d, J = 15.5 Hz, 1H), 3.70−3.60 (m, 1H), 3.58−3.47 (m, 1H), 3.32 (t, J = 5.3 Hz, 1H), 2.15 (dt, J = 14.3, 7.2 Hz, 1H), 1.91−1.76 (m, 3H), 1.69 (dt, J = 14.4, 4.8 Hz, 1H), 1.59−1.44 (m, 4H), 1.36−1.23 ppm (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 151.1, 138.7, 135.6, 128.5, 127.53, 127.46, 127.0, 121.9, 118.1, 108.5, 67.9, 59.9, 50.2, 45.3, 40.7, 34.7, 24.2, 21.7, 21.3 ppm. HRMS (m/z): $[M + Na]^+$ calcd for $C_{21}H_{25}NONa^+$, 330.1828; found, 330.1825.

2-(9-Benzyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-4a-yl)-acetaldehyde (22). To a solution of **14c** (50 mg, 0.16 mmol) in toluene (5 mL) was added dropwise DIBAL-H (1 M in toluene, 0.33 mL, 0.33 mmol) at −78 °C under Ar. The solution was then stirred at −78 °C for 4 h. The reaction was quenched with saturated sodium potassium tartrate. The mixture was stirred at 25 °C for 1 h. The mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. The solution was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, PE/EA = 10:1) to give **22** (41 mg, 82%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 9.56 (dd, J = 4.0, 2.4 Hz, 1H), 7.39−7.31 (m, 4H), 7.31−7.26 (m, 1H), 7.11 (d, J = 7.2 Hz, 1H), 7.09 (td, J = 7.6, 1.2 Hz, 1H), 6.77 (td, J = 7.5, 0.8 Hz, 1H), 6.46 (d, J = 7.8 Hz, 1H), 4.40 (d, J = 15.2 Hz, 1H), 4.09 (d, J = 15.2 Hz, 1H), 3.28 (dd, J = 7.3, 5.1 Hz, 1H), 2.70 (dd, J = 14.8, 4.0 Hz, 1H), 2.52 (dd, J = 14.8, 2.4 Hz, 1H), 2.06 (ddd, J = 13.7, 7.2, 3.9 Hz, 1H), 1.79−1.66 (m, 1H), 1.64−1.38 (m, 4H), 1.38−1.14 ppm (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 202.8, 150.7, 138.3, 133.8, 128.5, 128.0, 127.7, 127.1, 122.0, 118.3, 108.5, 68.1, 52.0, 49.8, 45.4, 33.5, 24.2, 21.6, 21.5 ppm. HRMS (m/z): $[M + Na]^+$ calcd for $C_{21}H_{23}NONa^+$, 328.1672; found, 328.1672.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.9b03243.

Full spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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