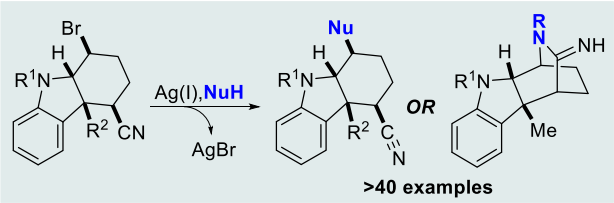
Diversification of Nucleophile-Intercepted Beckmann Fragmentation (NuBFr) Products and Related DFT Studies

Leah L. Lowder,[a] Fengyue Zhao,[b] Mathes M. Vaughan,[a] K. N. Houk,*[c] Fang Liu,*[b] and Jimmy Wu*[a]

[a]Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755, United States, Email: jimmy.wu@dartmouth.edu

[b]College of Sciences, Nanjing Agricultural University, Nanjing, 210095 CHINA, Email: acialiu@njau.edu.cn

[c]Department of Chemistry and Biochemistry, University of California, Los Angeles, CA 90095, United States, Email: houk@chem.ucla.edu

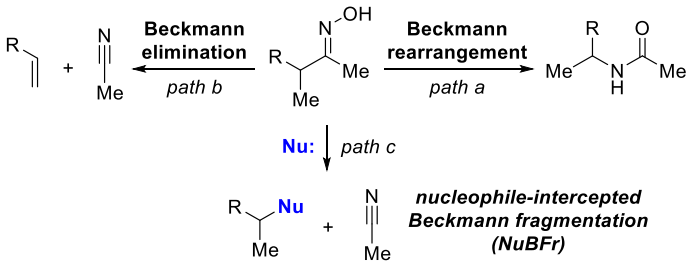


Abstract: The nucleophile-intercepted Beckmann fragmentation (NuBFr) has the potential to be broadly applicable to the synthesis of indoline alkaloid based natural products. However, the reaction has not been widely adopted, in part, because of limitations associated with the availability of appropriate promoter–Nu reagents. We have devised a stereospecific Ag(I)-promoted reaction for functionalizing NuBFr products to give novel compositions-of-matter that may be useful in synthesis and medicinal chemistry. With unhindered amine nucleophiles, structurally unique [2.2.2]-bicycloamidines are generated. We also disclose for the first time detailed density functional theory (DFT) studies which shed light on the mechanism of the NuBFr and Ag-promoted substitution reaction that supports an unusual aziridinium ion as a key intermediate.

INTRODUCTION

The Beckmann rearrangement depicted in Scheme 1 (path a) has been a mainstay of synthetic chemists for many years. While in most instances, amides are produced as the target compounds, the presence of beta hydrogens adjacent to the oxime can lead to elimination products (path b).[1] In contrast,

the related fragmentation reaction that is accompanied by nucleophilic trapping has not been broadly adopted (path c). The reason for its limited use is likely related to the scarcity of examples of these transformations, which we will herein refer to as the nucleophile-intercepted Beckmann fragmentation reaction (NuBFr).



Scheme 1. Variations of the Beckmann Rearrangement

The earliest instance of a NuBFr of which we are aware was described by Hassner and Nash in which they converted ketoxime **1** to chloride **2** with ejection of acetonitrile (Figure 1, eq 1).[2] Notably, there are no beta protons available, so elimination pathways were not possible. Kirihara reported the Beckmann fragmentation of **3** with fluoride nucleophiles to give nitrile **4** (eq 2).[3] And in the synthesis of biotin, Confalone et al. reported that treating oxime **5** with thionyl chloride resulted in the unexpected formation of aziridine **7** (eq 3).[4,5] The authors postulated that the reaction proceeds through episulfonium intermediate **6** formed by neighboring group participation of sulfur. Other instances of NuBFr reactions are similarly comprised of examples in which NuBFr products are generated where Beckmann rearrangement products are desired. There are also a few reports

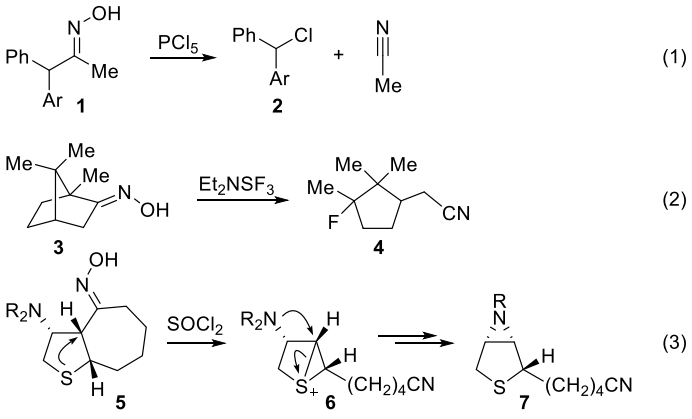


Figure 1. Previous examples of the nucleophilic Beckmann fragmentation.

of photochemically-initiated single-electron transfer (SET) processes for inducing fragmentation of oximes to give NuBFr-type products.[6,7]

Recognizing the potential utility of the title reaction in synthesis, we recently reported that indole oximes **8** undergo NuBFr to give products **10** (Figure 2).[8] The oximes are prepared by the dearomative (3+2) annulation of 3-substituted indoles,[9,10] also reported by us, followed by treatment with hydroxylamine·HCl. At the time, we had proposed that upon activation of the oxime by a promoter–**Nu** reagent, the indole nitrogen lone pair initiates fragmentation to generate the aziridinium intermediate **9**, analogous to episulfonium **6** proposed by Confalone.[4,5] Nucleophilic attack of **9** by the anionic species released from the promoter furnishes the observed product **10**. Double inversion at the carbon bearing the nucleophile results in net retention at that stereocenter. Guided by this mechanistic hypothesis, we showed in that paper that a wide range of promoters such as MsCl, MsBr, diphenylphosphoryl azide (i.e. DPPA, Shiori's reagent), Ms_2O, TFAA, and $PhNTf_2$ were amenable to the reaction and could serve as precursors for the various nucleophiles examined. Although the scope of the reaction with respect to the indoline component is broad, in its current form, the NuBFr is limited to promoter—**Nu** combinations that are either commercially available or readily prepared.

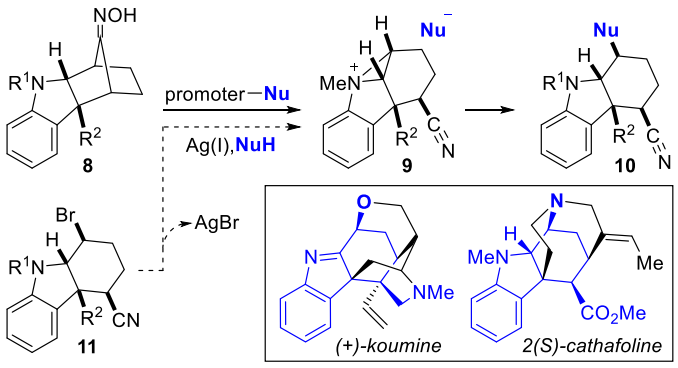


Figure 2. Our previous findings on the NuBFr reaction, proposed strategy for this work, and natural product targets.

Thus, we envisioned that treating the NuBFr product bromide **11** in Figure 2 with silver salts would result in halide abstraction and recapitulation of the aziridinium intermediate **9** which may in turn be trapped by a wider range of nucleophiles than previously reported. We anticipated that this process would also proceed by double stereoinversion to give the predicted stereochemical outcome shown. Such products

may be useful intermediates en route to the synthesis of members of the akuammiline[11–13] and koumine[14–17] alkaloids (Figure 2). Moreover, this method would provide an efficient means to access a collection of novel compositions-of-matter with structural similarities to these natural products, which are reported to possess inhibitory properties against the sodium-glucose co-transporters 1 and 2 (SGLT1 and SGLT2)[18] and have the ability to stabilize calcium levels in the endoplasmic reticulum (ER).[19] Small molecules that induce these phenotypes may be useful in targeting type 1 and 2 diabetes or diseases and disorders resulting from ER dysregulation.

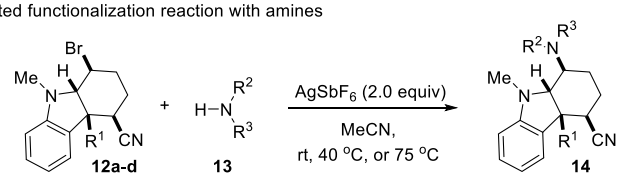
In the present study, we report: 1) full experimental results for the Ag(I)-mediated substitution reaction with amines and other nucleophiles, 2) unexpected formation of [2.2.2]-amidine products, 3) synthesis of intermediates that possess the ABCE rings corresponding to the *aspidosperma* and *strychnos* alkaloids, and 4) detailed DFT studies to support the proposed mechanism of the NuBFr and Ag(I)-promoted reactions.

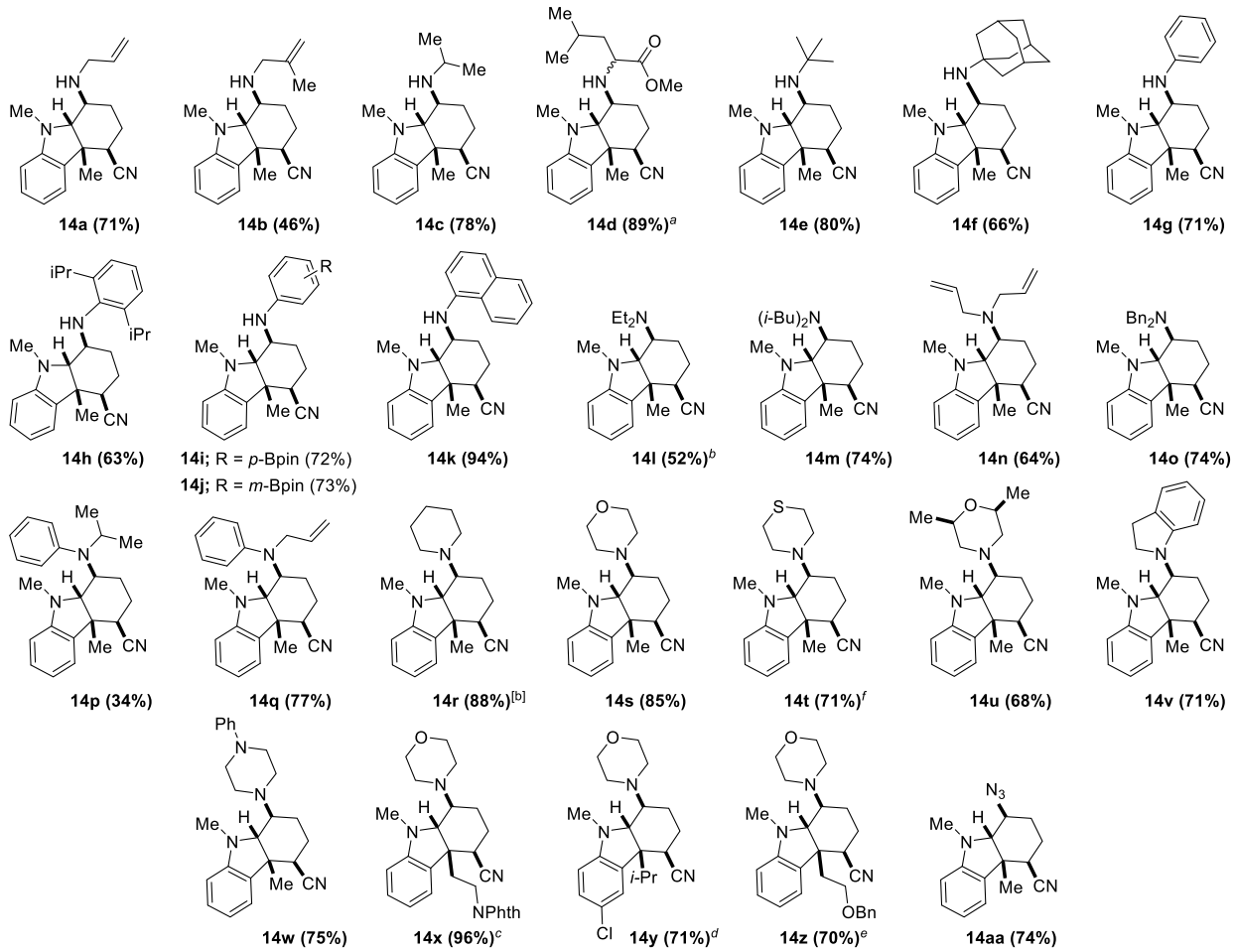
RESULTS AND DISCUSSION

$AgSbF_6$-Promoted Substitution Reactions

We began our studies by surveying the use of both AgOTf and $AgSbF_6$ in various solvents to regenerate the key aziridinium ion. After extensive optimization, we discovered that for secondary amines the addition of $AgSbF_6$ (2 equiv) to a mixture of indolinyl bromide **12** and an amine nucleophile **13** (3–4 equiv) in acetonitrile at 75 °C resulted in formation of the expected product **14** in overall good to excellent yields (Table 1). As predicted, the relative stereochemical configuration of the carbon bearing the amine was confirmed to be that shown. When unhindered primary amines were used, it was necessary to carry out the reactions at either room temperature or with only slight heating (40 °C) in order to avoid the formation of amidine products (*vide infra*). A broad range of nitrogen nucleophiles were amenable to the reaction. These include primary and secondary amines that are allylic, alkyl, benzyl, aryl, indolinyl, morpholine, thiomorpholine, *N*-phenylpiperazine, and azide. The use of *meta*- and *para*-aminophenylboronic pinacol ester gave compounds **14i** and **14j** which can be further functionalized by

Table 1. Scope of the silver-promoted functionalization reaction with amines





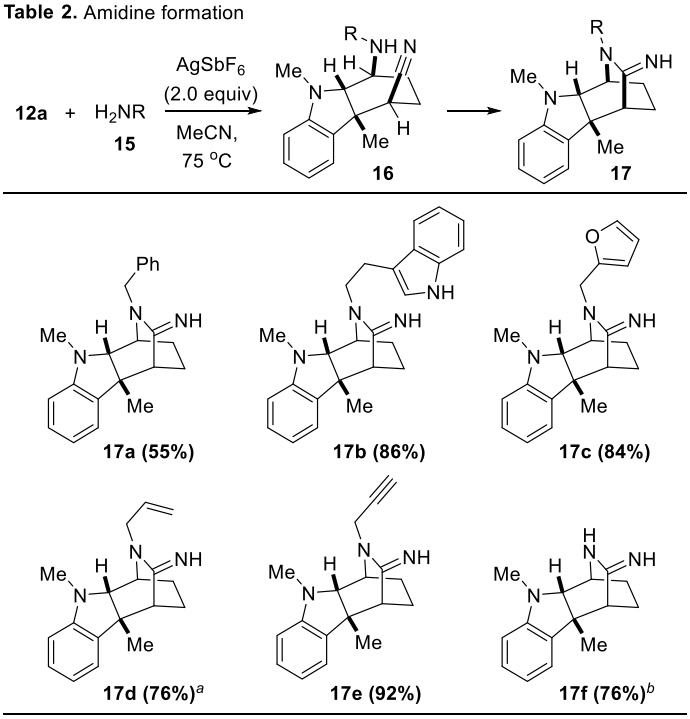
Reaction conditions: Indoline **12a** (1 equiv), $AgSbF_6$ (2 equiv), **13** (4 equiv), [0.3] M. [a]1:1 separable mixture of diastereomers. [b]AgOTf (2 equiv) in place of $AgSbF_6$. [c]Used indoline **12b**. [d]Used indoline **12c**. [e]Used indoline **12d**. [f]Conducted on 1.0 mmol scale.

means of transition metal-catalyzed cross-coupling reactions. With L-leucine, we obtained an approximately equal mixture of diastereomers that were separable by silica gel chromatography. The fact that highly sterically hindered amines such as *t*-butylamine and adamantylamine (**14e** and **14f**) are competent nucleophiles is consistent with conclusions gleaned from our DFT studies that indicate the formation of the key aziridinium intermediate by halide abstraction is rate-limiting. The substituents at C3 of the indoline could also be varied and we were able to utilize indole starting materials derived from tryptamine, *N*-methyl-3-isopropylindole, and tryptophol (**14x, y, z**). The use of NaN_3 as a nucleophile also

worked well to give **14aa**. It should be noted that starting with the corresponding indolinyl chloride resulted in longer reaction times and reduced yields, which is also consistent with halide abstraction being the rate-limiting step in the reaction.

With primary amine nucleophiles, the silver-promoted substitution reaction of bromide **12** at 75 °C gave the unexpected amidine product **17** at shown in Table 2. We believe that this reaction proceeds through the prototypical substitution product **16**. But because of the smaller steric size of primary amines and the *cis* stereochemical relationship of the relevant functional groups, nitrogen is appropriately positioned for nucleophilic attack of the nearby nitrile to give the observed amidines. Notably, the parent amidine **17f** was made using hexamethyldisilazane (HMDS) as the nucleophile. Loss of both TMS groups during the reaction resulted in formation of **17f**. These unusual [2.2.2]-bicyclo-indolinyl amidines have not previously been described in the literature. In a survey of the entire CAS registry, Lipkus discovered that the majority of the structures are represented by only a small subset of frameworks.[20] In a related study, Ijzerman found that the NCI database of >250,000 compounds contained frequent fragment

Table 2. Amidine formation

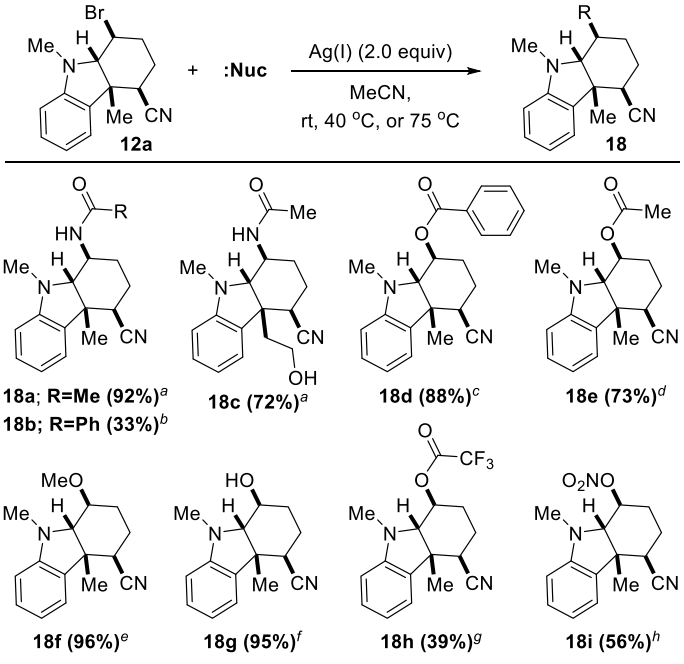


Reaction conditions: **12a** (1 equiv), $AgSbF_6$ (2 equiv), amine nucleophile **15** (4 equiv), [0.3] M. [a]Used AgOTf (2 equiv) in place of $AgSbF_6$. [b]Used HMDS as nucleophile.

co-occurrences to which they refer as "chemical clichés".[21] Thus, the ability to rapidly and efficiently access novel compositions-of- matter such as **17** is of high intrinsic value.

The title reaction is also amenable to the use of non-amine nucleophiles (Table 3). For instance, carrying out the reaction in the absence of an amine resulted in the solvent, acetonitrile (for **18a, c**) or benzonitrile (for **18b**), adding to the aziridinium intermediate in a Ritter-like transformation. Presumably, hydration of the putative nitrilium ion intermediate leads to the formation of the observed products. The use of potassium acetate, methanol, and water as nucleophiles resulted in the formation of compounds **18e**–**g**. Replacing $AgSbF_6$ with silver benzoate, silver trifluoroacetate, or silver nitrate as promoters led to the formation of **18d**, **18h**, and nitrate ester **18i**.[22]

Table 3. Scope of the nucleophiles

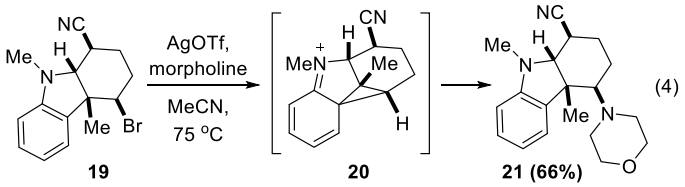


18a; **R=Me (92%)**[a]
18b; R=Ph (33%)[b]
18c (72%)[a]
18d (88%)[c]
18e (73%)[d]
18f (96%)[e]
18g (95%)[f]
18h (39%)[g]
18i (56%)[h]

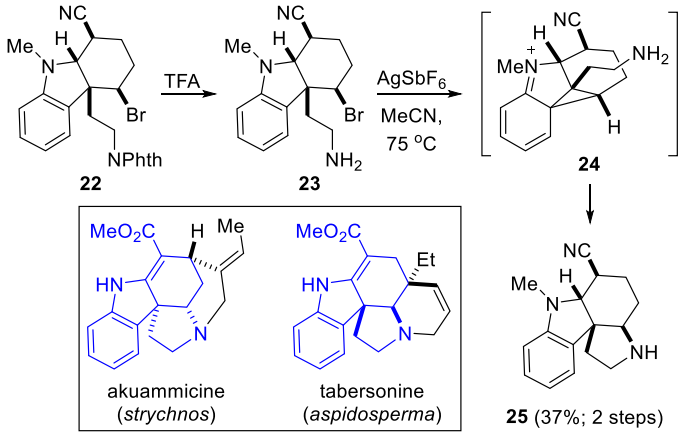
Reaction conditions: **12a** (1 equiv), $AgSbF_6$ (2 equiv), Nuc (4 equiv), [0.3] M. [a]No added nucleophile. [b]Used benzonitrile in place of MeCN as solvent. [c]Used Ag(I)-benzoate. [d]Used KOAc as nucleophile. [e]Used MeOH as nucleophile. [f]Used DI water as nucleophile. [g]Used Ag(I)-trifluoroacetate. [h]Used $AgNO_2$.

We also showed that subjecting the minor regioisomeric product **19** (made during the NuBFr) to the optimized reaction conditions results in stereoretentive substitution of bromide with the amine nucleophile (eq 4). The success of this reaction is consistent with the proposed phenonium ion **20** being a

key intermediate in the formation of the minor regioisomeric product during the NuBFr reaction (*vide infra*).



We then examined the intramolecular variant of the silver-promoted substitution reaction using **23** (Scheme 2). This compound was made by phthalimide deprotection of **22**, which was in turn produced as the minor regioisomeric component of the corresponding NuBFr reaction. Thus, we hypothesize that treatment of **23** with $AgSbF_6$ would generate the phenonium **24** which may be trapped intramolecularly by the pendant amine nucleophile. Product **25** was obtained in 37% yield over two steps and maps on well to the structures of both the *strychnos* and *aspidosperma* monoterpenoid indoline alkaloids.[23–25] We are currently working on strategies to reverse the inherent regioselectivity of the NuBFr, which would offer the opportunity for employing this method to prepare members of these two classes of natural products as well as analogues for exploring their biology.



Scheme 2. Synthesis of intermediate **25** related tot he *Strychnos* and *Aspidosperma* alkaloids

DFT Studies

The mechanisms of the NuBFr reaction and following substitution were studied by DFT computations within the Gaussian 16 program.[26] Of particular interest were the selectivities for reaction

occurring proximal to the indole nitrogen and the stereoselectivity of nucleophilic attack. All structures were optimized with the B3LYP-D3[27–29] density functional with the 6-31G(d,p) basis set in solution using the CPCM[30,31] solvent model of dichloromethane. The reactant and transition state conformations were located by first performing conformational searches for the reactants using Macromodel and the MMFF force field, followed by re-optimization of low (<3kcal/mol) energy conformers with B3LYP-D3. The vibrational frequency analyses were performed at the same level of theory to verify that minima have no imaginary frequencies and each transition state has only one imaginary frequency, and to evaluate its zero-point vibrational energy (ZPVE) and thermal corrections at 298 K. Single point energies were calculated on these geometries with the M06-2X[32,33] functional with larger basis set of 6-311+G(d,p) and the CPCM solvation model for dichloromethane. The formation of the major product **29** from the ***E*-26** and the formation of the minor product **27** from the ***Z*-26** were studied (Figure 3). The rate-determining steps for these two pathways are the formation of the aziridinium intermediate **28** from ***E*-26** and the phenonium intermediate **20** from ***Z*-26**. Calculations show that the former transformation requires a somewhat smaller

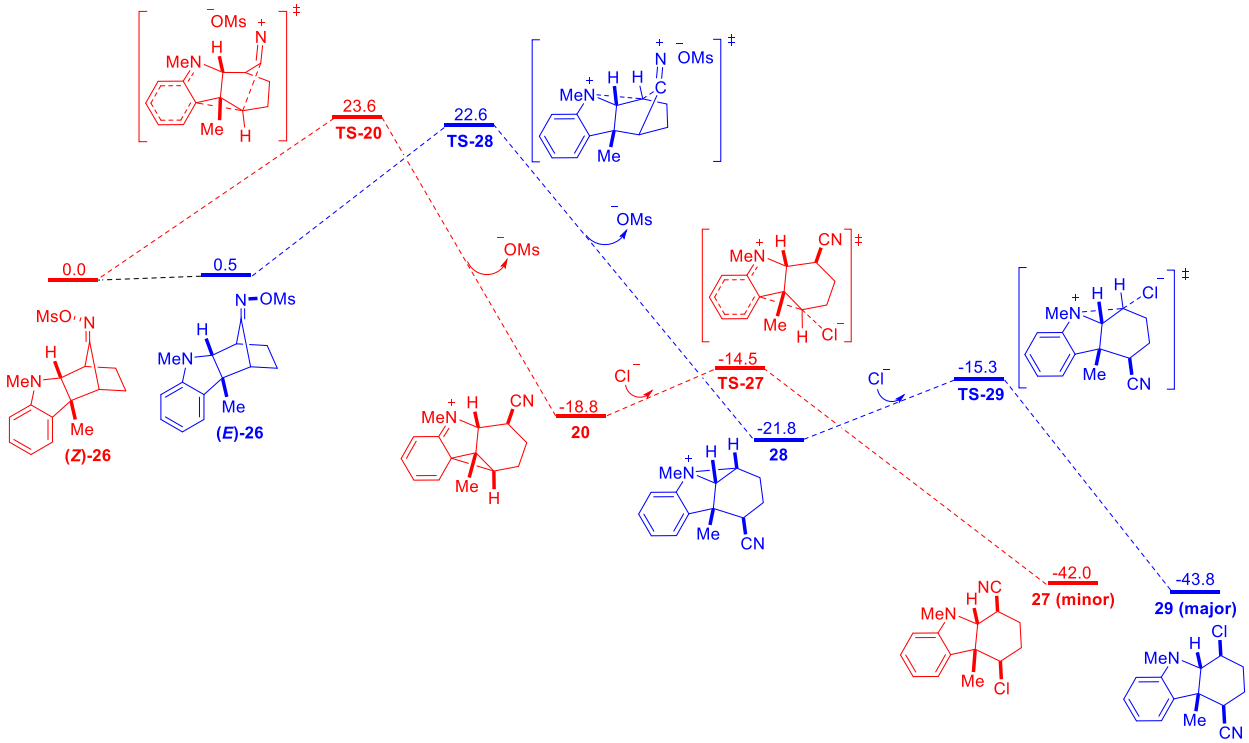


Figure 3. Nucleophile-intercepted Beckmann fragmentation surface. Free energies in kcal/mol, calculated from M06-2X/6-311+G(d,p)//B3LYP-D3/6-31G(d,p), CPCM (dichloromethane).

activation barrier (22.6 kcal/mol vs. 23.6 kcal/mol) and leads to a thermodynamically more stable intermediate and final product, as observed experimentally.

We tested the energetics of these transformations with a variety of functionals, and the difference in energy between **TS-28** and **TS-20** ranges from 0.9 to 2.1 kcal/mol with different methods (see SI–Table 1). The reactants are relatively rigid with conformational variability mainly in the leaving group. The M06-2X geometries and relative energies of the low-energy conformers are shown in the SI–Figure 1. The location of the transition states began from the reactant conformer with lowest energy.

We also studied the silver-promoted amine substitution starting from cyano bromide **12** (R^1 = Me) formed by the NuBFr. The silver ion promotes ionization of the halide and formation of the aziridinium **28** (Figure 4). We studied the reactions of both an aliphatic and an aromatic amine to give products **14a** and **14g**, respectively. Both react readily with the aziridinium intermediate **28**, and the stereochemistry of nucleophilic attack explains the fact that relative stereochemical configuration of halide carbon is retained in the amination.

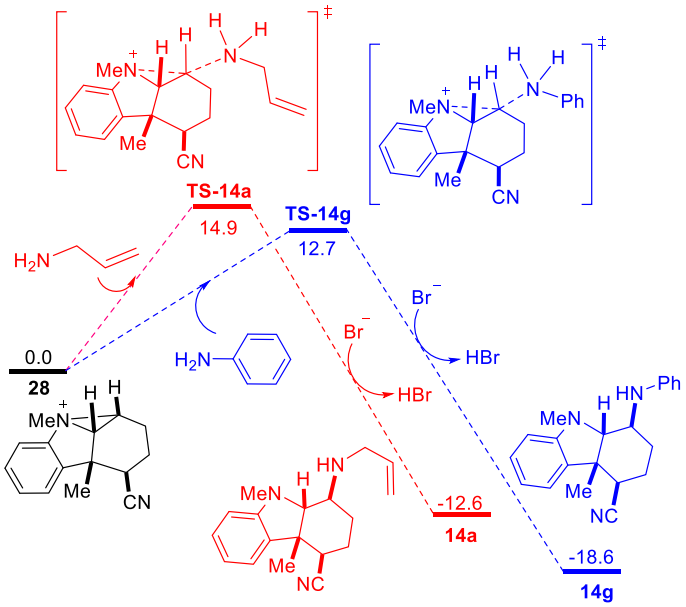


Figure 4. Amine attack on aziridinium with ring opening. Free energies in kcal/mol, calculated from M06-2X/6-311+G(d,p)//B3LYP-D3/6-31G(d,p), CPCM (dichloromethane).

CONCLUSIONS

In summary, we have reported a method for the stereo-retentive, silver-promoted nucleophilic substitution of indoline cyano bromides obtained from the NuBFr reaction. We provide numerous examples utilizing a wide range of nitrogen- and oxygen-based nucleophiles. Mechanistic insights gleaned from in-depth DFT studies of the both the NuBFr and silver-promoted reactions reveal the key role that aziridinium and phenonium intermediates play in the transformation. With sterically unhindered primary amines, the substitution products spontaneously proceed to the corresponding bicyclic amidines. We believe that the NuBFr and subsequent silver-promoted substitution reactions are a powerful combination that may find utility in the synthesis of the akuammiline, koumine, aspidosperma, and strychnos families of monoterpenoid indoline alkaloids.

EXPERIMENTAL SECTION

General Information

^{1}H-NMR data were recorded on a Bruker Avance III 500 MHz spectrometer (TBI probe) and a Bruker Avance III 600 MHz spectrometer (BBFO probe) with calibration of spectra to $CDCl_3$ (7.26 ppm). ^{13}C-NMR data were recorded at 150 MHz on a Bruker Avance III 600 MHz spectrometer (BBFO probe) at ambient temperature (unless otherwise stated) and are expressed in ppm using solvent as the internal standard ($CDCl_3$ at 77.16 ppm). Two-dimensional NMR spectra, including COSY, HSQC, HMBC and NOESY were recorded on a Bruker Avance III 600 MHz spectrometer (BBFO probe). Infrared spectra were recorded on a JASCO FT/IRM4100 Fourier Transform Infrared Spectrometer. Electronic Paramagnetic Resonance spectra was recorded on an Elexsys E500 CW-EPR spectrometer. Chemical shift values (δ) are expressed in ppm downfield relative to internal standard (tetramethylsilane at 0 ppm). Multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br s (broad singlet). Coupling constants are reported in Hertz (Hz). Analytical thin layer chromatography (TLC) was performed on SILICYCLE pre-coated TLC plates (silica gel 60 F254, 0.25 mm). Visualization was

accomplished with UV light and/or with ceric ammonium molybdate (CAM) or KMnO4 staining solutions. Flash column chromatography was performed using a Biotage® Isolera System on Biotage® SNAP Ultra columns (part No. FSUL-0442-0010 and FSUL-0442-0025). High resolution mass spectra were acquired from the Mass Spectrometry Laboratory of University of Illinois (Urbana-Champaign, IL).

Reagents were used as received without purification unless stated otherwise. Tetrahydrofuran, methylene chloride and dimethylformamide were dried and purified by solvent system using the Glass Contour Solvent Purification System® (from Pure Process Technology, LLC) by passing the solvents through two drying columns. The room temperature in the laboratory was measured at 20.0 °C.

General Procedure A – synthesis of 12a–d, 19, and 22: To a solution of oxime (1.0 equiv) in 1,2-dichloroethane (0.20 M) was added 4-dimethylaminopyridine (0.05 equiv) and triethylamine (5.0 equiv) and the reaction was cooled to 0 °C before phosphoryl bromide (1.0 equiv) was added. The reaction mixture was warmed to room temperature and stirred until judged complete by thin layer chromatographic analysis (hexanes/EtOAc). The reaction mixture was extracted three times with methylene chloride. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. The crude material was concentrated and purified by silica gel flash column chromatography (hexanes/EtOAc) to afford the desired products.

(1S,4R,4aR,9aS)-1-bromo-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole-4-carbonitrile (**12a**) and *(1S,4R,4aR,9aR)-4-bromo-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole-1-carbonitrile* (**19**) – Following General Procedure A, a mixture of the corresponding oxime *(1S,4R,4aR,9aR,E)-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-1,4-methanocarbazol-10-one oxime* (0.080 g, 0.330 mmol, 1 equiv), 4-dimethylaminopyridine (0.002 g, 0.016 mmol, 0.05 equiv), triethylamine (0.230 mL, 1.650 mmol, 5 equiv), and mesyl bromide (0.080 mL, 0.990 mmol, 3 equiv) in 1,2-dichloroethane (2.0 mL, 0.20 M) afforded a mixture of major and minor reqioisomers (total yield 71%). The major product **12a** was purified *via* silica gel flash column chromatography (4:1 hexanes/EtOAc) as a pale yellow solid (0.047 g, 47% yield). R_f = 0.38 in 7:3 hexanes/EtOAc. NMR data matches previously reported characterization data.[8] The minor

product **19** was purified *via* silica gel flash column chromatography (4:1 hexanes/EtOAc) as a pale yellow solid (0.0245 g, 24% yield). R_f = 0.29 in 7:3 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.27 – 7.25 (1H, m), 7.21 (1H, td, *J* = 7.7, 1.3 Hz), 6.86 (1H, td, *J* = 7.5, 0.9 Hz), 6.64 (1H, d, *J* = 7.9 Hz), 4.00 (1H, dd, *J* = 12.3, 3.8 Hz), 3.34 – 3.30 (1H, m), 3.29 – 3.25 (1H, m), 2.71 (3H, s), 2.37 (1H, dtd, *J* = 13.6, 12.1, 4.1 Hz), 2.17 (1H, dq, *J* = 13.8, 3.8 Hz), 2.09 – 1.98 (2H, m), 1.73 (3H, s). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 150.4, 135.4, 128.7, 123.7, 120.7, 119.9, 109.8, 74.9, 59.6, 47.7, 34.6, 29.7, 25.9, 25.3, 20.2. **IR** (film, cm^{-1}): 2943, 2835, 2235, 1640, 1477, 1376. **HRMS (ESI)** calcd. for $C_{15}H_{18}BrN_2$ (*m/z* M+H+): 305.0653, found: 305.0651.

(1S,4R,4aR,9aS)-1-bromo-4a-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-9-methyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole-4-carbonitrile (**12b**) and *(1S,4R,4aR,9aR)-4-bromo-4a-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-9-methyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole-1-carbonitrile* (**22**) – Following General Procedure A, a mixture of the corresponding oxime *2-(2-((1S,4aR,9aR,E)-10-(hydroxyimino)-9-methyl-1,2,3,4,9,9a-hexahydro-4aH-1,4-methanocarbazol-4a-yl)ethyl)isoindoline-1,3-dione*[8] (0.435 g, 1.084 mmol, 1 equiv), 4-dimethylaminopyridine (0.006 g, 0.054 mmol, 0.05 equiv), triethylamine (0.755 mL, 5.422 mmol, 5 equiv), and phosphoryl bromide (0.310 g, 1.084 mmol, 1 equiv) in 1,2-dichloroethane (5.4 mL, 0.20 M) afforded a mixture of major and minor reqioisomers. The major product **12b** was purified *via* silica gel flash column chromatography (4:1 hexanes/EtOAc) as a yellow solid (0.267 g, 53% yield). R_f = 0.30 in 7:3 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.73 (2H, dd, *J* = 5.4, 3.1 Hz), 7.66 (2H, dd, *J* = 5.5, 3.0 Hz), 7.33 – 7.30 (1H, m), 7.04 (1H, td, *J* = 7.7, 1.2 Hz), 6.65 (1H, td, *J* = 7.4, 1.0 Hz), 6.56 (1H, d, *J* = 7.9 Hz), 4.79 – 4.72 (1H, m), 3.94 – 3.85 (2H, m), 3.85 – 3.77 (1H, m), 2.81 (3H, s), 2.77 (2H, t, *J* = 7.3 Hz), 2.64 – 2.58 (1H, m), 2.31 – 2.23 (2H, m), 2.21 – 2.14 (1H, m), 1.85 (1H, d, *J* = 10.2 Hz). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 168.2, 133.9, 132.2, 129.1, 123.4, 123.2, 122.4, 120.5, 119.9, 109.8, 71.0, 46.0, 45.9, 38.6, 35.3, 34.7, 29.6, 28.4, 20.7. **IR** (film, cm^{-1}): 2948, 2871, 2236, 1773, 1710, 1481, 1397, 1375; **HRMS (ESI)** calcd. for $C_{24}H_{23}BrO_2N_3$ (*m/z* M+H^+): 464.0974, found: 464.0968. The minor product **22** was purified *via* silica gel flash column chromatography (4:1 hexanes/EtOAc) as a pale yellow solid (0.044 g,

9% yield). R_f = 0.24 in 7:3 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.71 (2H, dd, *J* = 5.4, 3.1 Hz), 7.64 (2H, dd, *J* = 5.5, 3.0 Hz), 7.18 (1H, dd, *J* = 7.5, 1.3 Hz), 7.00 (1H, td, *J* = 7.7, 1.3 Hz), 6.56 – 6.51 (2H, m), 4.16 (1H, dd, *J* = 11.1, 3.5 Hz), 3.87 (1H, d, *J* = 3.5 Hz), 3.80 (2H, ddd, *J* = 7.9, 6.0, 3.9 Hz), 3.16 (1H, d, *J* = 4.2 Hz), 2.95 – 2.88 (1H, m), 2.81 (3H, s), 2.40 – 2.30 (2H, m), 2.10 (1H, dq, *J* = 13.3, 4.1 Hz), 2.04 (2H, h, *J* = 4.4 Hz). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 168.3, 134.1, 133.8, 132.2, 131.3, 128.7, 123.7, 123.1, 120.7, 119.4, 109.7, 69.3, 59.6, 34.6, 34.4, 29.6, 26.3, 24.9. **IR** (film, cm^{-1}): 2947, 2857, 2253, 1709, 1400, 1398. **HRMS (ESI)** calcd. for $C_{24}H_{23}BrO_2N_3$ (*m/z* M+H+): 464.0974, found: 464.0974

(1S,4R,4aR,9aS)-1-bromo-6-chloro-4a-isopropyl-9-methyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole-4-carbonitrile (**12c**) – Following General Procedure A, a mixture of the corresponding oxime *(4R,4aR,9aR,Z)-6-chloro-4a-isopropyl-9-methyl-2,3,4,4a,9,9a-hexahydro-1H-1,4-methanocarbazol-10-one oxime* (0.702 g, 2.304 mmol, 1 equiv), 4-dimethylaminopyridine (0.014 g, 0.115 mmol, 0.05 equiv), triethylamine (1.606 mL, 1.116 mmol, 5 equiv), and phosphoryl bromide (0.661 g, 2.304 mmol, 1 equiv) in 1,2-dichloroethane (11.5 mL, 0.20 M) afforded a mixture of major and minor reqioisomers. The major product **12c** was purified *via* silica gel flash column chromatography (9:1 hexanes/EtOAc) as a yellow solid (0.224 g, 27% yield). R_f = 0.33 in 4:1 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$) δ ^{1}H NMR δ 7.10 (1H, dd, *J* = 8.3, 2.1 Hz), 6.82 (1H, d, *J* = 2.1 Hz), 6.28 (1H, d, *J* = 8.3 Hz), 3.90 (1H, ddd, *J* = 11.1, 6.8, 5.4 Hz), 3.71 (1H, d, *J* = 6.8 Hz), 3.32 (1H, t, *J* = 4.5 Hz), 3.02 (3H, s), 2.34 – 2.25 (1H, m), 2.25 – 2.12 (2H, m), 2.10 – 1.99 (2H, m), 1.68 – 1.58 (1H, m), 0.91 (3H, d, *J* = 6.8 Hz), 0.81 (3H, d, *J* = 6.8 Hz); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 149.0, 129.2, 128.6, 123.3, 121.7, 120.6, 107.1, 75.3, 52.8, 37.3, 33.7, 33.0, 30.7, 25.6, 18.3, 17.3. **IR** (film, cm^{-1}): 2962, 2937, 2871, 2234, 1601, 1491, 1273, 1175; **HRMS (ESI)** calcd. for $C_{17}H_{21}BrClN_2$ (*m/z* M+H^+): 367.0577, found: 367.0575.

(1S,4R,4aR,9aS)-4a-(2-(benzyloxy)ethyl)-1-bromo-9-methyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole-4-carbonitrile (**12d**) – Following General Procedure A, a mixture of the corresponding oxime *(4R,4aR,9aR,E)-4a-(2-(benzyloxy)ethyl)-9-methyl-2,3,4,4a,9,9a-hexahydro-1H-1,4-methanocarbazol-10-one oxime*[8] (0.423 g, 1.168 mmol, 1 equiv), 4-dimethylaminopyridine (0.007 g, 0.058 mmol, 0.05 equiv),

triethylamine (0.814 mL, 5.843 mmol, 5 equiv), and phosphoryl bromide (0.335 g, 1.168 mmol, 1 equiv) in 1,2-dichloroethane (6.0 mL, 0.20 M) afforded a mixture of major and minor reqioisomers. The major product **12d** was purified *via* silica gel flash column chromatography (9:1 hexanes/EtOAc) as a white solid (0.175 g, 35% yield). R_f = 0.34 in 4:1 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.33 – 7.28 (2H, m), 7.27 – 7.23 (6H, m), 7.20 (1H, td, *J* = 7.7, 1.3 Hz), 6.86 (1H, dd, *J* = 7.4, 1.0 Hz), 6.60 (1H, d, *J* = 7.9 Hz), 4.61 (1H, d, *J* = 3.2 Hz), 4.46 (2H, d, *J* = 2.4 Hz), 3.66 (1H, td, *J* = 9.3, 5.9 Hz), 3.52 – 3.42 (2H, m), 2.81 – 2.75 (2H, m), 2.75 (3H, s), 2.74 – 2.69 (1H, m), 2.63 (1H, ddd, *J* = 14.3, 9.3, 5.3 Hz), 2.26 (2H, ddd, *J* = 11.1, 6.2, 2.5 Hz), 2.18 (1H, dt, *J* = 7.5, 4.4 Hz), 1.87 – 1.79 (1H, m). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 149.9, 138.5, 132.4, 129.1, 128.5, 127.6, 127.6, 122.7, 120.3, 120.2, 109.6, 73.0, 72.5, 67.1, 46.5, 46.4, 38.0, 35.2, 30.2, 29.9, 21.1. **IR** (film, cm^{-1}): 2961, 2865, 2360, 2336, 2253, 1481, 1096. **HRMS (ESI)** calcd. for $C_{23}H_{26}BrON_2$ (*m/z* M+H+): 425.1229, found: 425.1219

General Procedure B – silver-promoted reactions: To a solution of bromide (1.0 equiv) in acetonitrile (0.30 M) was added nucleophile (4.0 equiv) and $AgSbF_6$ (2.0 equiv), and then heated to the temperature indicated using a modular heating block. The reaction mixture stirred until judged complete by thin layer chromatographic analysis (hexanes/EtOAc). The crude reaction mixture was then concentrated and purified by silica gel flash column chromatography (hexanes/EtOAc) to afford the desired products.

(1S,4R,4aR,9aS)-1-(allylamino)-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole-4-carbonitrile (**14a**) – Following General Procedure B, a mixture of bromide **12a** (0.0101 g, 0.030 mmol, 1.0 equiv), allyl amine (15 μL, 0.098 mM, 4 equiv), and $AgSbF_6$ (22.5 mg, 0.065 mmol, 2 equiv), in acetonitrile (0.3 mL, 0.10 M) was stirred at room temperature and afforded **14a** (6.5 mg, 71% yield) as a white solid. R_f = 0.29 in 1:1 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$): δ, ppm 7.28 (1H, dd, *J* = 7.4, 1.3 Hz), 7.18 (1H, td, *J* = 7.7, 1.3 Hz), 6.86 – 6.79 (1H, m), 6.61 (1H, d, *J* = 7.8 Hz), 5.91 (1H, ddt, *J* = 16.4, 10.2, 5.8 Hz), 5.24 – 5.17 (1H, m), 5.13 (1H, dt, *J* = 10.3, 1.5 Hz), 3.37 – 3.29 (1H, m), 3.29 – 3.21 (2H, m), 2.84 (1H, d, *J* = 1.9 Hz), 2.71 (3H, s), 2.53 (1H, dd, *J* = 12.9, 3.4 Hz), 2.10 (1H, qd, *J* = 12.7, 4.1

Hz), 1.79 – 1.66 (6H, m), 1.34 (1H, dd, *J*=7.8, 4.9 Hz); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ, ppm 151.2, 137.1, 136.3, 128.6, 122.3, 121.3, 119.6, 116.1, 109.3, 76.2, 50.5, 50.5, 43.1, 37.7, 34.8, 25.5, 20.0, 19.5. **IR** (film, cm^{-1}): 2955, 2922, 2805, 2233, 1604, 1481, 1455; **HRMS (ESI)** calcd. for $C_{18}H_{24}N_3$ (*m/z* $M+H^+$): 282.1970, found: 282.1960.

(1S,4R,4aR,9aS)-4a,9-dimethyl-1-((2-methylallyl)amino)-2,3,4,4a,9,9a-hexahydro-1H-carbazole-4-carbonitrile (**14b**) – Following General Procedure B, a mixture of bromide **12a** (0.0100 g, 0.033 mmol, 1.0 equiv), 2-methylallylamine (12 μL, 0.131 mmol, 4 equiv), and AgOTf (0.0168 g, 0.065 mmol, 2 equiv), in acetonitrile (0.1 mL, 0.3 M) was stirred at room temperature and afforded **14b** (0.0044 g, 46% yield) as a white solid. R_f = 0.26 in 1:1 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.29 (1H, dd, *J* = 7.4, 1.3 Hz), 7.18 (1H, td, *J* = 7.7, 1.3 Hz), 6.83 (1H, td, *J* = 7.4, 1.0 Hz), 6.61 (1H, d, *J* = 7.8 Hz), 4.94 – 4.82 (2H, m), 3.27 – 3.13 (3H, m), 2.87 – 2.80 (1H, m), 2.71 (3H, s), 2.53 (1H, dd, *J* = 12.9, 3.4 Hz), 2.16 – 2.07 (1H, m), 1.80 – 1.71 (8H, m), 1.71 – 1.64 (1H, m). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 151.2, 144.3, 136.3, 128.6, 122.3, 121.4, 119.6, 111.3, 109.3, 76.3, 54.1, 50.4, 43.1, 37.7, 34.8, 25.6, 20.9, 20.0, 19.5. **IR** (film, cm^{-1}): 2959, 2918, 2234, 1605, 1460; **HRMS (ESI)** calcd. for $C_{19}H_{26}N_3$ (*m/z* $M+H^+$): 296.2127, found: 296.2122.

(1S,4R,4aR,9aS)-1-(isopropylamino)-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole-4-carbonitrile (**14c**) – Following General Procedure B, a mixture of bromide **12a** (0.0535 g, 0.175 mmol, 1.0 equiv), isopropylamine (60 μL, 0.701 mmol, 4 equiv), and $AgSbF_6$ (0.1200 g, 0.350 mmol, 2 equiv), in acetonitrile (0.5 mL, 0.3 M) was heated to 75 °C and afforded **14c** (0.0384 g, 78% yield) as a pale yellow oil. R_f = 0.16 in 4:1 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.28 (1H, dd, *J* = 7.4, 1.3 Hz), 7.18 (1H, td, *J* = 7.7, 1.3 Hz), 6.82 (1H, td, *J* = 7.4, 1.0 Hz), 6.60 (1H, d, *J* = 7.8 Hz), 3.33 (1H, q, *J* = 2.9 Hz), 2.93 – 2.85 (1H, m), 2.85 – 2.78 (1H, m), 2.73 (3H, s), 2.52 (1H, dd, *J* = 12.9, 3.4 Hz), 2.06 (1H, dd, *J* = 12.9, 3.5 Hz), 1.79 – 1.66 (6H, m), 1.08 (6H, dd, *J* = 20.2, 6.3 Hz); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 151.2, 136.3, 128.6, 122.2, 121.4, 119.5, 109.2, 76.4, 47.9, 46.1, 43.0, 37.6, 34.8, 26.2, 23.9, 23.1, 20.0, 19.6. **IR** (film, cm^{-1}):

2959, 2857, 2360, 2236, 1604, 1481,1381, 1297; **HRMS (ESI)** calcd. for $C_{18}H_{26}N_3$ (*m/z* $M+H^+$): 284.2127, found: 284.2120.

methyl ((1S,4R,4aR,9aS)-4-cyano-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-carbazol-1-yl)leucinate (**14d**) – Following General Procedure B, a mixture of bromide **12a** (0.0503 g, 0.164 mmol, 1.0 equiv), L-leucine (0.0787 g, 0.494 mmol, 3 equiv), and $AgSbF_6$ (0.1130 g, 0.329 mmol, 2 equiv), in acetonitrile (0.5 mL, 0.3 M) was heated to 40 °C and afforded a mixture of two diastereomers (resulting in an 89% overall yield of both diastereomers) in a 1:1 ratio as determined by ^{1}H NMR spectroscopy of the unpurified residue. **14d** (*less polar diastereomer*) (R_f = 0.26 in 4:1 hexanes/EtOAc) was purified *via* silica gel flash column chromatography as a white solid (0.0270 g, 44% yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.28 (1H, dd, *J* = 7.4, 1.3 Hz), 7.17 (1H, dd, *J* = 7.7, 1.3 Hz), 6.83 (1H, td, *J* = 7.4, 1.0 Hz), 6.60 (1H, d, *J* = 7.9 Hz), 3.73 (3H, s), 3.40 (1H, t, *J* = 7.3 Hz), 3.15 (1H, q, *J* = 2.6 Hz), 2.72 (1H, t, *J* = 1.6 Hz), 2.68 (3H, s), 2.51 (1H, dd, *J* = 13.0, 3.3 Hz), 2.11 (1H, dd, *J* = 13.1, 2.9 Hz), 1.88 (1H, dt, *J* = 13.5, 6.8 Hz), 1.77 – 1.72 (1H, m), 1.71 (3H, s), 1.67 – 1.53 (2H, m), 1.46 (2H, dd, *J* = 7.8, 6.5 Hz), 0.95 (6H, dd, *J* = 14.6, 6.6 Hz); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 176.7, 151.1, 136.1, 128.7, 122.2, 121.3, 119.7, 109.4, 78.3, 57.1, 51.9, 49.2, 43.1, 43.0, 38.0, 34.9, 25.1, 24.1, 23.4, 21.7, 19.7, 19.5. **IR** (film, cm^{-1}): 2951, 2864, 2362, 2234, 1732, 1604, 1481,1302, 1263; **HRMS (ESI)** calcd. for $C_{22}H_{31}N_3O_2$ (*m/z* $M+H^+$): 370.2495, found: 370.2493. **14d** (*more polar diastereomer*) (R_f = 0.16 in 4:1 hexanes/EtOAc) was purified *via* silica gel flash column chromatography as a clear oil (0.0262 g, 43% yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.29 (1H, dd, *J* = 7.4, 1.3 Hz), 7.18 (1H, td, *J* = 7.7, 1.3 Hz), 6.83 (1H, td, *J* = 7.4, 1.0 Hz), 6.60 (1H, d, *J* = 7.9 Hz), 3.74 (3H, s), 3.40 (1H, t, *J* = 7.2 Hz), 3.04 (1H, dt, *J* = 4.1, 2.4 Hz), 2.90 (1H, t, *J* = 1.5 Hz), 2.65 (3H, s), 2.51 (1H, dd, *J* = 12.9, 3.3 Hz), 2.12 – 2.04 (1H, m), 1.88 (1H, ddd, *J* = 14.1, 10.3, 3.7 Hz), 1.80 (1H, dt, *J* = 13.4, 6.7 Hz), 1.74 (3H, s), 1.73 – 1.66 (2H, m), 1.29 – 1.22 (2H, m), 0.91 (6H, dd, *J* = 19.5, 6.6 Hz); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 177.0, 151.3, 136.3, 128.6, 122.3, 121.2, 119.7, 109.4, 73.7, 58.1, 51.9, 49.6, 43.3, 43.0, 37.5, 34.7, 28.1, 24.7, 23.1, 22.1, 20.3, 19.4. **IR** (film, cm^{-1}): 2955, 2868, 2360, 2236, 1732, 1604, 1481,1381, 1261; **HRMS (ESI)** calcd. for $C_{22}H_{31}N_3O_2$ (*m/z* $M+H^+$): 370.2495, found: 370.2492.

(1S,4R,4aR,9aS)-1-(tert-butylamino)-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole-4-carbonitrile (**14e**) – Following General Procedure B, a mixture of bromide **12a** (0.0522 g, 0.171 mmol, 1.0 equiv), *tert*-butylamine (72 μL, 0.684 mmol, 4 equiv), and $AgSbF_6$ (0.1172 g, 0.342 mmol, 2 equiv), in acetonitrile (0.5 mL, 0.3 M) was heated to 75 °C and afforded **14e** (0.0408 g, 80% yield) as a clear oil. R_f = 0.16 in 4:1 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.29 – 7.27 (1H, m), 7.17 (1H, td, *J* = 7.7, 1.3 Hz), 6.82 (1H, td, *J* = 7.4, 1.0 Hz), 6.60 (1H, d, *J* = 7.9 Hz), 3.30 (1H, d, *J* = 3.0 Hz), 2.83 (1H, t, *J* = 1.7 Hz), 2.76 (3H, s), 2.48 (1H, dd, *J* = 12.9, 3.4 Hz), 1.99 (1H, dd, *J* = 13.2, 2.9 Hz), 1.86 – 1.79 (1H, m), 1.72 (1H, dd, *J* = 13.2, 3.5 Hz), 1.70 (3H, s), 1.60 (1H, ddd, *J* = 13.7, 3.4, 1.2 Hz), 1.10 (9H, s); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 151.2, 136.4, 128.6, 122.2, 121.4, 119.5, 109.1, 78.5, 51.7, 44.7, 43.1, 37.3, 34.5, 29.8, 28.6, 20.3, 19.2. **IR** (film, cm^{-1}): 2962, 2857, 2358, 2237, 1601, 1481, 1378, 1263; **HRMS (ESI)** calcd. for $C_{19}H_{28}N_3$ (*m/z* $M+H^+$): 298.2283, found: 298.2278.

(1S,4R,4aR,9aS)-1-(((3R,5R,7R)-adamantan-1-yl)amino)-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole-4-carbonitrile (**14f**) – Following General Procedure B, a mixture of bromide **12a** (0.0549 g, 0.179 mmol, 1.0 equiv), adamantylamine (0.1088 g, 0.719 mmol, 4 equiv), and $AgSbF_6$ (0.1236 g, 0.361 mmol, 2 equiv), in acetonitrile (0.5 mL, 0.3 M) was heated to 75 °C and afforded **14f** (0.0446 g, 66% yield) as a white solid. R_f = 0.19 in 4:1 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.28 (1H, d, *J* = 1.3 Hz), 7.17 (1H, td, *J* = 7.7, 1.3 Hz), 6.81 (1H, td, *J* = 7.4, 1.0 Hz), 6.59 (1H, d, *J* = 7.9 Hz), 3.44 (1H, q, *J* = 3.0 Hz), 2.81 (1H, t, *J* = 1.6 Hz), 2.76 (3H, s), 2.48 (1H, dd, *J* = 12.9, 3.4 Hz), 2.06 (3H, p, *J* = 3.3 Hz), 2.01 (1H, dd, *J* = 13.3, 2.9 Hz), 1.85 – 1.77 (1H, m), 1.71 (4H, s), 1.69 – 1.54 (13H, m); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 151.2, 136.4, 128.6, 122.1, 121.4, 119.4, 109.0, 78.8, 51.7, 43.8, 43.0, 42.5, 37.3, 36.8, 34.6, 29.9, 29.7, 29.0, 20.3, 19.3. **IR** (film, cm^{-1}): 2900, 2849, 2234, 1605, 1481, 1448; **HRMS (ESI)** calcd. for $C_{25}H_{34}N_3$ (*m/z* $M+H^+$): 376.2753, found: 376.2748.

(1S,4R,4aR,9aS)-4a,9-dimethyl-1-(phenylamino)-2,3,4,4a,9,9a-hexahydro-1H-carbazole-4-carbonitrile (**14g**) – Following General Procedure B, a mixture of bromide **12a** (0.0530 g, 0.173 mmol, 1.0 equiv),

aniline (65 μL, 0.694 mmol, 4 equiv), and $AgSbF_6$ (0.1190 g, 0.347 mmol, 2 equiv), in acetonitrile (0.5 mL, 0.3 M) was heated to 75 °C and afforded **14g** (0.0391 g, 71% yield) as a white solid. R_f = 0.22 in 4:1 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.28 (1H, dd, *J* = 7.4, 1.3 Hz), 7.24 – 7.17 (3H, m), 6.85 (1H, td, *J* = 7.5, 1.0 Hz), 6.75 (1H, tt, *J* = 7.2, 1.1 Hz), 6.67 – 6.62 (3H, m), 4.02 (1H, q, *J* = 3.0 Hz), 3.72 (1H, s), 3.13 (1H, d, *J* = 2.3 Hz), 2.86 (3H, s), 2.64 (1H, dd, *J* = 11.5, 3.8 Hz), 2.05 – 1.91 (3H, m), 1.86 (1H, dt, *J* = 13.2, 4.2 Hz), 1.70 (3H, s); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 150.9, 146.6, 135.4, 129.7, 128.9, 122.2, 120.9, 119.8, 118.3, 113.3, 109.4, 74.7, 47.0, 43.2, 36.9, 34.6, 25.4, 20.4, 19.6. **IR** (film, cm^{-1}): 3402, 2959, 2234, 1602, 1841; **HRMS (ESI)** calcd. for $C_{21}H_{24}N_3$ (*m/z* $M+H^+$): 318.1970, found: 318.1963.

(1S,4R,4aR,9aS)-1-((2,6-diisopropylphenyl)amino)-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole-4-carbonitrile (**14h**) – Following General Procedure B, a mixture of bromide **12a** (0.0524 g, 0.172 mmol, 1.0 equiv), 2,6-diisopropylaniline (0.129 mL, 0.683 mmol, 4 equiv), and $AgSbF_6$ (0.1177 g, 0.343 mmol, 2 equiv), in acetonitrile (0.5 mL, 0.3 M) was heated to 75 °C and afforded **14h** (0.0382 g, 63% yield) as a white solid. R_f = 0.21 in 4:1 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.33 (1H, dd, *J* = 7.4, 1.2 Hz), 7.22 (1H, td, *J* = 7.7, 1.3 Hz), 7.14 – 7.07 (3H, m), 6.86 (1H, td, *J* = 7.4, 1.0 Hz), 6.64 (1H, d, *J* = 7.8 Hz), 3.38 (1H, q, *J* = 3.2 Hz), 3.29 – 3.25 (1H, m), 3.22 (2H, q, *J* = 6.8 Hz), 2.79 (3H, s), 2.64 (1H, dd, *J* = 12.6, 3.5 Hz), 2.10 (1H, dd, *J* = 13.4, 3.8 Hz), 1.92 – 1.84 (1H, m), 1.79 (3H, s), 1.71 – 1.57 (2H, m), 1.25 (12H, dd, *J* = 6.8, 5.7 Hz); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 150.9, 142.8, 142.3, 135.6, 128.9, 124.3, 123.9, 122.2, 121.2, 119.7, 109.3, 78.3, 54.7, 43.3, 36.8, 34.5, 28.3, 24.5, 24.3, 24.2, 20.8, 19.3. **IR** (film, cm^{-1}): 2959, 2865, 2234, 1605, 1481, 1456; **HRMS (ESI)** calcd. for $C_{27}H_{36}N_3$ (*m/z* $M+H^+$): 402.2909, found: 402.2899.

(1S,4R,4aR,9aS)-4a,9-dimethyl-1-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-2,3,4,4a,9,9a-hexahydro-1H-carbazole-4-carbonitrile (**14i**) – Following General Procedure B, a mixture of bromide **12a** (0.0541 g, 0.177 mmol, 1.0 equiv), 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolane-2-yl)aniline

(0.1554, 0.709 mmol, 4 equiv), and $AgSbF_6$ (0.1218 g, 0.355 mmol, 2 equiv), in acetonitrile (0.5 mL, 0.3 M) was heated to 75 °C and afforded **14i** (0.0566 g, 72% yield) as a white solid. R_f = 0.31 in 4:1 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.68 – 7.64 (2H, m), 7.27 (1H, d, *J* = 1.3 Hz), 7.20 (1H, td, *J* = 7.7, 1.3 Hz), 6.84 (1H, td, *J* = 7.4, 1.0 Hz), 6.65 – 6.59 (3H, m), 4.05 (1H, s), 3.95 – 3.84 (1H, m), 3.10 (1H, d, *J* = 2.3 Hz), 2.85 (3H, s), 2.68 – 2.59 (1H, m), 1.95 (3H, t, *J* = 2.2 Hz), 1.90 – 1.81 (1H, m), 1.67 (3H, s), 1.32 (12H, s); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 150.9, 149.0, 136.7, 135.2, 128.9, 122.2, 120.8, 119.8, 112.3, 109.4, 83.5, 74.7, 46.6, 43.3, 36.9, 34.6, 25.3, 25.0, 20.4, 19.7. **IR** (film, cm^{-1}): 3396, 2966, 2864, 2360, 1601, 1477, 1356, 1261; **HRMS (ESI)** calcd. for $C_{27}H_{35}BN_3O_2$ (*m/z* M+H$^+$): 444.2822, found: 444.2821.

(1S,4R,4aR,9aS)-4a,9-dimethyl-1-((3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-2,3,4,4a,9,9a-hexahydro-1H-carbazole-4-carbonitrile (**14j**) – Following General Procedure B, a mixture of bromide **12a** (0.0540 g, 0.177 mmol, 1.0 equiv), 3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolane-2-yl)aniline (0.1550, 0.709 mmol, 4 equiv), and $AgSbF_6$ (0.1212 g, 0.355 mmol, 2 equiv), in acetonitrile (0.5 mL, 0.3 M) was heated to 75 °C and afforded **14j** (0.0569 g, 73% yield) as a white solid. R_f = 0.42 in 4:1 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.28 (1H, dd, *J* = 7.5, 1.3 Hz), 7.25 – 7.18 (3H, m), 7.11 (1H, d, *J* = 2.6 Hz), 6.84 (1H, td, *J* = 7.4, 0.9 Hz), 6.74 (1H, ddd, *J* = 7.8, 2.7, 1.4 Hz), 6.65 (1H, d, *J* = 7.9 Hz), 4.04 (1H, d, *J* = 2.8 Hz), 3.84 – 3.57 (1H, m), 3.13 (1H, d, *J* = 2.2 Hz), 2.88 (3H, s), 2.66 – 2.59 (1H, m), 2.01 – 1.92 (3H, m), 1.88 – 1.81 (1H, m), 1.69 (3H, s), 1.34 (13H, s); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 151.0, 146.0, 135.4, 129.1, 128.9, 124.6, 122.2, 120.9, 119.9, 119.7, 115.6, 109.4, 83.9, 74.8, 46.9, 43.2, 37.0, 34.6, 25.5, 25.0, 25.0, 20.4, 19.6. **IR** (film, cm^{-1}): 3396, 2977, 2864, 2358, 1604, 1481, 1357, 1266; **HRMS (ESI)** calcd. for $C_{27}H_{35}BN_3O_2$ (*m/z* M+H$^+$): 444.2822, found: 444.2822.

(1S,4R,4aR,9aS)-4a,9-dimethyl-1-(naphthalen-1-ylamino)-2,3,4,4a,9,9a-hexahydro-1H-carbazole-4-carbonitrile (**14k**) – Following General Procedure B, a mixture of bromide **12a** (0.0487 g, 0.159 mmol, 1.0 equiv), 1-napthylamine (0.0914, 0.638 mmol, 4 equiv), and $AgSbF_6$ (0.1094 g, 0.319 mmol, 2 equiv), in

acetonitrile (0.5 mL, 0.3 M) was heated to 75 °C and afforded **14k** (0.0552 g, 94% yield) as a white solid. R_f = 0.43 in 4:1 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.85 – 7.78 (2H, m), 7.54 – 7.47 (2H, m), 7.35 (1H, t, *J* = 7.8 Hz), 7.33 – 7.28 (2H, m), 7.22 (1H, td, *J* = 7.7, 1.3 Hz), 6.86 (1H, td, *J* = 7.4, 1.0 Hz), 6.68 (2H, dd, *J* = 7.7, 4.1 Hz), 4.32 (1H, s), 4.24 (1H, s), 3.25 (1H, t, *J* = 1.6 Hz), 2.92 (3H, s), 2.70 (1H, dd, *J* = 12.5, 3.5 Hz), 2.20 – 2.07 (2H, m), 2.07 – 1.97 (1H, m), 1.90 (1H, dd, *J* = 13.5, 3.6 Hz), 1.80 (3H, s); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 150.9, 141.5, 135.4, 134.7, 129.1, 128.9, 126.4, 126.2, 125.4, 124.0, 122.2, 120.9, 119.9, 119.7, 118.5, 109.5, 104.9, 75.0, 46.7, 43.2, 37.2, 34.7, 25.2, 20.7, 19.7. **IR** (film, cm^{-1}): 2959, 2926, 2853,1579,1481,1409; **HRMS (ESI)** calcd. for $C_{25}H_{26}N_3$ (*m/z* M+H$^+$): 368.2127, found: 368.2117.

(1S,4R,4aR,9aS)-1-(diethylamino)-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole-4-carbonitrile (**14l**) – Following General Procedure B, a mixture of bromide **12a** (10 mg, 0.030 mmol, 1.0 equiv), diethylamine (16.9 μL, 0.163 mM, 5 equiv), and AgOTf (0.0168 g, 0.065 mmol, 2 equiv), in acetonitrile (0.3 mL, 0.10 M) was heated to 75 °C and afforded **14l** (0.0051 g, 52% yield) as a white solid. R_f = 0.29 in 4:1 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.15 (2H, t, *J* = 7.1 Hz), 6.73 (1H, dd, *J* = 7.9, 6.9 Hz), 6.51 – 6.48 (1H, m), 3.17 (1H, d, *J* = 5.7 Hz), 2.91 (3H, s), 2.83 (2H, ddt, *J* = 8.2, 5.6, 3.2 Hz), 2.69 (2H, dq, *J* = 14.3, 7.3 Hz), 2.50 (2H, dq, *J* = 13.8, 7.0 Hz), 2.03 – 1.94 (1H, m), 1.79 – 1.69 (3H, m), 1.58 (3H, s), 1.02 (6H, t, *J* = 7.1 Hz); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 151.3, 134.6, 128.7, 122.0, 121.5, 118.2, 107.8, 72.7, 57.5, 44.9, 43.3, 35.2, 34.9, 23.0, 22.5, 19.4, 13.0. **IR** (film, cm^{-1}): 2965, 2926, 2871, 2234, 1604, 1488, 1452, 1382, 1255; **HRMS (ESI)** calcd. for $C_{19}H_{28}N_3$ (*m/z* M+H$^+$): 298.2283, found: 298.2276.

(1S,4R,4aR,9aS)-1-(diisobutylamino)-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole-4-carbonitrile (**14m**) – Following General Procedure B, a mixture of bromide **12a** (0.0490 g, 0.160 mmol, 1.0 equiv), diisobutylamine (0.112 mL, 0.642 mmol, 4 equiv), and $AgSbF_6$ (0.1160 g, 0.329 mmol, 2 equiv), in acetonitrile (0.3 mL, 0.5 M) was heated to 75 °C and afforded **14m** (0.0419 g, 74% yield) as a white solid. R_f = 0.44 in 9:1 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.17 – 7.12 (2H, m), 6.72 (1H, td, *J*

= 7.4, 1.0 Hz), 6.47 – 6.43 (1H, m), 3.19 (1H, d, *J* = 7.1 Hz), 3.04 (3H, s), 2.90 (1H, dd, *J* = 9.2, 6.8 Hz), 2.78 (1H, ddd, *J* = 12.4, 7.1, 4.1 Hz), 2.24 (2H, dd, *J* = 13.0, 4.2 Hz), 2.13 (2H, dd, *J* = 13.0, 9.5 Hz), 2.07 – 2.00 (1H, m), 1.92 – 1.85 (1H, m), 1.85 – 1.80 (1H, m), 1.74 – 1.68 (2H, m), 1.68 – 1.61 (1H, m), 1.54 (3H, s), 0.96 (6H, d, *J* = 6.5 Hz), 0.87 (6H, d, *J* = 6.7 Hz); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 151.7, 133.6, 128.9, 122.5, 121.7, 118.0, 107.3, 72.9, 61.5, 60.5, 45.8, 35.6, 32.5, 27.1, 24.0, 23.2, 21.6, 21.6, 15.7. **IR** (film, cm^{-1}): 2955, 2816, 2237, 1670, 1597, 1481, 1364; **HRMS (ESI)** calcd. for $C_{23}H_{35}N_3$ (*m/z* $M+H^+$): 354.2909, found: 354.2899.

(1S,4R,4aR,9aS)-1-(diallylamino)-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole-4-carbonitrile (**14n**) – Following General Procedure B, a mixture of bromide **12a** (0.0570 g, 0.186 mmol, 1.0 equiv), diallylamine (95 μL, 0.746 mmol, 4 equiv), and $AgSbF_6$ (0.1240 g, 0.362 mmol, 2 equiv), in acetonitrile (0.3 mL, 0.5 M) was heated to 75 °C and afforded **14n** (0.0354 g, 64% yield) as a white solid. R_f = 0.46 in 4:1 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.19 – 7.11 (2H, m), 6.75 (1H, td, *J* = 7.4, 1.0 Hz), 6.51 (1H, d, *J* = 7.8 Hz), 5.85 (2H, dddd, *J* = 17.2, 10.2, 7.0, 5.8 Hz), 5.21 – 5.10 (4H, m), 3.39 – 3.30 (2H, m), 3.23 (1H, d, *J* = 5.5 Hz), 3.10 (2H, dd, *J* = 14.7, 7.0 Hz), 2.96 (1H, dt, *J* = 7.4, 5.4 Hz), 2.89 (3H, s), 2.84 – 2.78 (1H, m), 2.00 (1H, ddd, *J* = 10.7, 7.5, 6.1 Hz), 1.81 – 1.71 (3H, m), 1.60 (3H, s); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 151.3, 135.8, 134.5, 128.7, 122.0, 121.4, 118.4, 117.5, 108.0, 72.4, 56.9, 52.8, 44.9, 35.3, 34.9, 22.7, 22.2, 19.4. **IR** (film, cm^{-1}): 3076, 2966, 2814, 2234, 1604, 1484; **HRMS (ESI)** calcd. for $C_{21}H_{28}N_3$ (*m/z* $M+H^+$): 322.2283, found: 322.2280.

(1S,4R,4aR,9aS)-1-(dibenzylamino)-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole-4-carbonitrile (**14o**) – Following General Procedure B, a mixture of bromide **12a** (0.0494 g, 0.162 mmol, 1.0 equiv), dibenzylamine (0.124 mL, 0.647 mmol, 4 equiv), and $AgSbF_6$ (0.1109 g, 0.323 mmol, 2 equiv), in acetonitrile (0.3 mL, 0.5 M) was heated to 75 °C and afforded **14o** (0.0502 g, 74% yield) as a white solid. R_f = 0.29 in 9:1 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.32 (8H, m), 7.28 – 7.26 (2H, m), 7.15 – 7.08 (2H, m), 6.70 (1H, td, *J* = 7.4, 1.0 Hz), 6.36 (1H, d, *J* = 7.9 Hz), 3.87 (2H, d, *J* = 13.7 Hz), 3.53 (2H,

d, J = 13.7 Hz), 3.32 (1H, d, J = 6.5 Hz), 3.03 – 2.97 (1H, m), 2.84 (3H, s), 2.81 (1H, dd, J = 9.4, 5.9 Hz), 2.01 (1H, ddd, J = 9.7, 7.5, 4.2 Hz), 1.93 – 1.86 (1H, m), 1.86 – 1.78 (2H, m), 1.56 (3H, s); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 151.4, 139.2, 133.6, 129.3, 128.8, 128.5, 127.3, 122.3, 121.5, 118.1, 107.4, 72.9, 58.4, 54.6, 45.5, 35.1, 33.0, 23.6, 22.8, 17.1. **IR** (film, cm^{-1}): 2959, 2853, 2236, 1604, 1481, 1119; **HRMS (ESI)** calcd. for $C_{29}H_{32}N_3$ (*m/z* M+H$^+$): 422.2596, found: 422.2588.

(1S,4R,4aR,9aS)-1-(isopropyl(phenyl)amino)-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole-4-carbonitrile (**14p**) – Following General Procedure B, a mixture of bromide **12a** (0.0465 g, 0.152 mmol, 1.0 equiv), *N*-isopropylaniline (88 μL, 0.609 mmol, 4 equiv), and $AgSbF_6$ (0.1047 g, 0.305 mmol, 2 equiv), in acetonitrile (0.5 mL, 0.3 M) was heated to 40 °C and afforded **14p** (0.0186 g, 34% yield) as a white solid. R_f = 0.51 in 95:5 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.27 (2H, d, J = 8.0 Hz), 7.21 (1H, dd, J = 7.3, 1.3 Hz), 7.16 – 7.08 (4H, m), 6.76 (1H, td, J = 7.4, 1.0 Hz), 6.53 (1H, d, J = 7.9 Hz), 3.92 (1H, q, J = 3.5 Hz), 3.64 – 3.56 (1H, m), 3.04 (1H, d, J = 2.7 Hz), 2.66 (3H, s), 2.63 (1H, dd, J = 11.9, 3.8 Hz), 2.13 – 2.02 (2H, m), 1.87 – 1.79 (1H, m), 1.73 (3H, s), 1.71 – 1.66 (1H, m), 1.05 (3H, d, J = 6.7 Hz), 0.94 (3H, d, J = 6.5 Hz); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 151.2, 145.5, 135.9, 129.0, 128.5, 128.3, 124.7, 122.0, 121.4, 119.3, 109.1, 72.4, 52.3, 47.5, 43.7, 37.4, 34.7, 23.8, 22.1, 20.6, 20.1, 17.2. **IR** (film, cm^{-1}): 2959, 2923, 2860, 2233, 1604, 1481; **HRMS (ESI)** calcd. for $C_{24}H_{30}N_3$ (*m/z* M+H$^+$): 360.2440, found: 360.2431.

(1S,4R,4aR,9aS)-1-(isopropyl(phenyl)amino)-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole-4-carbonitrile (**14q**) – Following General Procedure B, a mixture of bromide **12a** (0.0517 g, 0.169 mmol, 1.0 equiv), *N*-allylaniline (97 μL, 0.677 mmol, 4 equiv), and $AgSbF_6$ (0.1183 g, 0.345 mmol, 2 equiv), in acetonitrile (0.5 mL, 0.3 M) was heated to 40 °C and afforded **14q** (0.0466 g, 77% yield) as a white solid. R_f = 0.15 in 95:5 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.24 – 7.19 (2H, m), 7.17 (1H, td, J = 7.7, 1.3 Hz), 7.09 (1H, dd, J = 7.4, 1.2 Hz), 6.80 (3H, dd, J = 12.2, 7.5 Hz), 6.74 (1H, td, J = 7.4, 1.0 Hz), 6.47 (1H, d, J = 7.8 Hz), 5.87 (1H, ddd, J = 11.8, 10.4, 5.2 Hz), 5.26 – 5.16 (2H, m), 3.98 – 3.88 (2H, m), 3.81 (1H, ddd, J = 11.3, 7.1, 4.3 Hz), 3.44 (1H, d, J = 7.1 Hz), 3.09 (1H, dd, J = 7.5, 5.0 Hz), 2.81 (3H, s),

2.09 – 2.00 (1H, m), 2.00 – 1.90 (1H, m), 1.90 – 1.79 (1H, m), 1.76 – 1.65 (1H, m), 1.55 (3H, s); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 150.5, 148.4, 135.4, 133.3, 129.2, 129.0, 121.6, 121.2, 119.0, 118.1, 117.3, 116.9, 107.6, 71.9, 58.4, 49.7, 46.3, 34.4, 33.9, 25.2, 23.3, 22.5. **IR** (film, cm^{-1}): 2959, 2920, 2850, 2236, 1597, 1502; **HRMS (ESI)** calcd. for $C_{24}H_{28}N_3$ (*m/z* $M+H^+$): 358.2283, found: 358.2272.

(1S,4R,4aR,9aS)-4a,9-dimethyl-1-(piperidin-1-yl)-2,3,4,4a,9,9a-hexahydro-1H-carbazole-4-carbonitrile (**14r**) – Following General Procedure B, a mixture of bromide **12a** (0.0505 g, 0.165 mmol, 1.0 equiv), piperidine (50 μL, 0.474 mmol, 3 equiv), and AgOTf (0.0812 g, 0.316 mmol, 2 equiv), in acetonitrile (0.3 mL, 0.5 M) was heated to 40 °C and afforded **14r** (0.0452 g, 88% yield) as a white solid. R_f = 0.47 in 4:1 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.21 – 7.12 (2H, m), 6.76 (1H, td, *J* = 7.4, 1.0 Hz), 6.53 (1H, d, *J* = 7.8 Hz), 3.19 (1H, d, *J* = 4.7 Hz), 2.83 (3H, s), 2.76 (1H, dd, *J* = 10.4, 4.4 Hz), 2.59 – 2.48 (3H, m), 2.44 (2H, s), 2.00 – 1.88 (1H, m), 1.88 – 1.78 (1H, m), 1.75 – 1.66 (2H, m), 1.63 (3H, s), 1.61 – 1.50 (4H, m), 1.46 (2H, q, *J* = 5.9 Hz); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 151.3, 135.2, 128.6, 121.9, 121.5, 118.6, 108.4, 72.3, 60.4, 51.4, 44.4, 35.8, 34.8, 26.7, 25.0, 21.9, 21.9, 20.1. **IR** (film, cm^{-1}): 2930, 2849, 2234, 1604, 1484, 1452; **HRMS (ESI)** calcd. for $C_{20}H_{28}N_3$ (*m/z* $M+H^+$): 310.2283, found: 310.2276.

(1S,4R,4aR,9aS)-4a,9-dimethyl-1-morpholino-2,3,4,4a,9,9a-hexahydro-1H-carbazole-4-carbonitrile (**14s**) – Following General Procedure B, a mixture of bromide **12a** (0.0507 g, 0.166 mmol, 1.0 equiv), morpholine (44 μL, 0.496 mmol, 3 equiv), and $AgSbF_6$ (0.1146 g, 0.334 mmol, 2 equiv), in acetonitrile (0.3 mL, 0.5 M) was heated to 75 °C and afforded **14s** (0.0439 g, 85% yield) as a white solid. R_f = 0.17 in 9:1 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.23 (1H, dd, *J* = 7.3, 1.3 Hz), 7.18 (1H, td, *J* = 7.7, 1.3 Hz), 6.80 (1H, td, *J* = 7.4, 1.0 Hz), 6.58 (1H, d, *J* = 7.8 Hz), 3.78 – 3.70 (4H, m), 3.17 (1H, d, *J* = 3.5 Hz), 2.77 (3H, s), 2.69 (1H, dd, *J* = 11.4, 4.1 Hz), 2.60 (1H, dt, *J* = 5.2, 3.5 Hz), 2.57 (4H, d, *J* = 4.8 Hz), 1.96 – 1.88 (2H, m), 1.76 (1H, dd, *J* = 11.1, 3.5 Hz), 1.69 (4H, s); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 151.1, 135.6, 128.7, 122.0, 121.2, 119.3, 109.0, 71.7, 67.4, 59.1, 51.2, 44.0, 36.7, 34.9, 21.1, 21.1, 20.5. **IR** (film,

cm^{-1}): 2959, 2853, 2806, 2236, 1604, 1481, 1120; **HRMS (ESI)** calcd. for $C_{19}H_{25}N_3O$ (*m/z* $M+H^+$): 312.2076, found: 312.2072.

(1S,4R,4aR,9aS)-4a,9-dimethyl-1-thiomorpholino-2,3,4,4a,9,9a-hexahydro-1H-carbazole-4-carbonitrile (**14t**) – Following General Procedure B, a mixture of bromide **12a** (0.3078 g, 1.009 mmol, 1.0 equiv), thiomorpholine (0.301 mL, 3.025 mmol, 3 equiv), and $AgSbF_6$ (0.693 g, 2.017 mmol, 2 equiv), in acetonitrile (2.0 mL, 0.5 M) was heated to 75 °C and afforded **14t** (0.234 g, 71% yield) as a white solid. R_f = 0.18 in 95:5 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.15 (1H, td, *J* = 7.6, 1.3 Hz), 7.10 (1H, dd, *J* = 7.5, 1.2 Hz), 6.73 (1H, td, *J* = 7.4, 1.0 Hz), 6.49 (1H, d, *J* = 7.8 Hz), 3.17 (1H, d, *J* = 6.3 Hz), 2.98 (2H, ddd, *J* = 11.9, 7.2, 2.8 Hz), 2.90 (4H, s), 2.78 – 2.71 (3H, m), 2.71 – 2.61 (4H, m), 2.56 – 2.50 (1H, m), 1.97 – 1.89 (1H, m), 1.78 – 1.69 (3H, m), 1.54 (3H, s); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 150.9, 134.0, 128.8, 121.7, 121.2, 118.3, 107.9, 71.9, 63.1, 52.2, 45.2, 35.1, 34.5, 29.9, 28.6, 24.0, 22.6, 18.8. **IR** (film, cm^{-1}): 2948, 2810, 2234, 1604, 1485, 1118; **HRMS (ESI)** calcd. for $C_{19}H_{25}N_3S$ (*m/z* $M+H^+$): 328.1847, found: 328.1837.

(1S,4R,4aR,9aS)-1-((2S,6R)-2,6-dimethylmorpholino)-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole-4-carbonitrile (**14u**) – Following General Procedure B, a mixture of bromide **12a** (0.0475 g, 0.155 mmol, 1.0 equiv), cis-2,6-dimethylmorpholine (58 μL, 0.466 mmol, 3 equiv), and $AgSbF_6$ (0.1070 g, 0.312 mmol, 2 equiv), in acetonitrile (0.5 mL, 0.3 M) was heated to 75 °C and afforded **14u** (0.0360 g, 68% yield) as a white solid. R_f = 0.15 in 95:5 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.20 (1H, dd, *J* = 7.4, 1.3 Hz), 7.17 (1H, td, *J* = 7.7, 1.3 Hz), 6.79 (1H, td, *J* = 7.4, 1.0 Hz), 6.57 (1H, d, *J* = 7.8 Hz), 3.71 – 3.61 (2H, m), 3.20 (1H, d, *J* = 3.8 Hz), 2.87 (1H, dt, *J* = 11.2, 2.2 Hz), 2.82 (1H, dt, *J* = 10.9, 2.2 Hz), 2.78 (3H, s), 2.71 (1H, dd, *J* = 11.0, 4.1 Hz), 2.55 (1H, dt, *J* = 5.6, 3.6 Hz), 1.98 – 1.81 (3H, m), 1.80 – 1.68 (3H, m), 1.66 (3H, s), 1.21 (3H, d, *J* = 6.3 Hz), 1.15 (3H, d, *J* = 6.3 Hz); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 151.2, 135.5, 128.7, 121.9, 121.2, 119.1, 108.8, 72.2, 71.8, 71.8, 59.1, 58.5, 55.1, 44.1, 36.5,

34.9, 21.4, 20.9, 20.8, 19.5, 19.4. **IR** (film, cm^{-1}): 2966, 2930, 2857, 2817, 2236, 1673, 1604, 1481, 1451, 1375; **HRMS (ESI)** calcd. for $C_{21}H_{30}N_3O$ (*m/z* $M+H^+$): 340.2389, found: 340.2381.

(1S,4R,4aR,9aS)-1-(indolin-1-yl)-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole-4-carbonitrile (**14v**) – Following General Procedure B, a mixture of bromide **12a** (0.0529 g, 0.173 mmol, 1.0 equiv), indoline (81 μL, 0.746 mmol, 4 equiv), and $AgSbF_6$ (0.1188 g, 0.347 mmol, 2 equiv), in acetonitrile (0.5 mL, 0.3 M) was heated to 75 °C and afforded **14v** (0.0419 g, 71% yield) as a white solid. R_f = 0.42 in 85:15 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.18 (1H, td, *J* = 7.7, 1.3 Hz), 7.08 (2H, ddd, *J* = 7.5, 5.0, 1.3 Hz), 7.05 – 6.99 (1H, m), 6.75 (1H, td, *J* = 7.4, 1.0 Hz), 6.63 (1H, td, *J* = 7.3, 0.9 Hz), 6.49 (1H, d, *J* = 7.8 Hz), 6.34 (1H, d, *J* = 7.9 Hz), 3.65 (1H, td, *J* = 8.4, 5.0 Hz), 3.55 – 3.46 (2H, m), 3.42 (1H, ddd, *J* = 10.6, 9.6, 8.3 Hz), 3.14 (1H, dd, *J* = 7.1, 4.8 Hz), 3.04 – 2.97 (2H, m), 2.91 (3H, s), 2.05 (1H, dtd, *J* = 9.4, 7.0, 4.6 Hz), 1.98 – 1.84 (2H, m), 1.69 – 1.59 (1H, m), 1.55 (4H, d, *J* = 2.2 Hz); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 150.5, 133.1, 130.2, 129.0, 127.4, 124.7, 121.5, 121.2, 118.1, 117.6, 107.7, 106.6, 71.6, 55.3, 47.7, 46.0, 33.9, 33.8, 28.5, 25.4, 23.6, 19.5. **IR** (film, cm^{-1}): 2933, 2861, 2234, 1604, 1485, 1255; **HRMS (ESI)** calcd. for $C_{23}H_{26}N_3$ (*m/z* $M+H^+$): 344.2127, found: 344.2116.

(1S,4R,4aR,9aS)-4a,9-dimethyl-1-(4-phenylpiperazin-1-yl)-2,3,4,4a,9,9a-hexahydro-1H-carbazole-4-carbonitrile (**14w**) – Following General Procedure B, a mixture of bromide **12a** (0.0490 g, 0.160 mmol, 1.0 equiv), *N*-phenylpiperazine (74 μL, 0.481 mmol, 3 equiv), and $AgSbF_6$ (0.1103 g, 0.321 mmol, 2 equiv), in acetonitrile (0.5 mL, 0.3 M) was heated to 40 °C and afforded **14w** (0.0448 g, 75% yield) as a white solid. R_f = 0.23 in 95:5 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.28 (2H, dd, *J* = 8.7, 7.2 Hz), 7.23 (1H, dd, *J* = 7.3, 1.3 Hz), 7.19 (1H, td, *J* = 7.7, 1.3 Hz), 6.97 – 6.92 (2H, m), 6.88 (1H, tt, *J* = 7.3, 1.1 Hz), 6.81 (1H, td, *J* = 7.4, 1.0 Hz), 6.59 (1H, d, *J* = 7.8 Hz), 3.22 (5H, dtd, *J* = 17.9, 11.2, 3.5 Hz), 2.81 (3H, s), 2.74 (5H, dddd, *J* = 13.2, 9.8, 6.7, 4.5 Hz), 2.67 (1H, dt, *J* = 5.7, 3.7 Hz), 2.03 – 1.91 (2H, m), 1.80 (1H, td, *J* = 10.7, 5.4 Hz), 1.77 – 1.70 (1H, m), 1.69 (3H, s); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 151.3, 151.2, 135.5, 129.3, 128.7, 122.0, 121.2, 120.0, 119.1, 116.1, 108.8, 72.1, 59.0, 50.4, 49.6, 44.1, 36.5, 34.9, 21.4,

21.0. **IR** (film, cm^{-1}): 2963, 2820, 2236, 1602, 1481, 1236; **HRMS (ESI)** calcd. for $C_{25}H_{30}N_4$ (*m/z* $M+H^+$): 387.2549, found: 387.2537.

(1S,4R,4aR,9aS)-4a-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-9-methyl-1-morpholino-2,3,4,4a,9,9a-hexahydro-1H-carbazole-4-carbonitrile (**14x**) – Following General Procedure B, a mixture of bromide **12b** (0.0537 g, 0.115 mmol, 1.0 equiv), morpholine (40 μL, 0.462 mmol, 4 equiv), and $AgSbF_6$ (0.0792 g, 0.230 mmol, 2 equiv), in acetonitrile (0.3 mL, 0.3 M) was heated to 75 °C and afforded **14x** (0.0382 g, 96% yield) as a white solid. R_f = 0.11 in 4:1 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.29 (1H, dd, *J* = 7.4, 1.2 Hz), 7.19 (1H, td, *J* = 7.7, 1.3 Hz), 6.84 (1H, td, *J* = 7.4, 0.9 Hz), 6.61 (1H, d, *J* = 7.8 Hz), 4.36 (1H, d, *J* = 3.0 Hz), 2.97 (1H, d, *J* = 2.5 Hz), 2.73 (3H, s), 2.55 (1H, dd, *J* = 12.8, 3.4 Hz), 2.19 – 2.09 (1H, m), 1.90 – 1.81 (2H, m), 1.75 (1H, dt, *J* = 13.3, 3.6 Hz), 1.71 (3H, s); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 151.0, 135.9, 128.7, 122.3, 121.1, 119.8, 109.3, 76.8, 64.8, 43.2, 37.2, 35.0, 28.3, 19.6, 19.2. **IR** (film, cm^{-1}): 3419, 2086, 1699, 1641, 1371, 1240, 1093; **HRMS (ESI)** calcd. for $C_{15}H_{19}N_2O$ (*m/z* $M+H^+$): 243.1497, found: 243.1492.

(1S,4R,4aR,9aS)-4a-isopropyl-9-methyl-1-morpholino-2,3,4,4a,9,9a-hexahydro-1H-carbazole-4-carbonitrile (**14y**) – Following General Procedure B, a mixture of bromide **12c** (0.0423 g, 0.115 mmol, 1.0 equiv), morpholine (40 μL, 0.435 mmol, 4 equiv), and $AgSbF_6$ (0.0745 g, 0.217 mmol, 2 equiv), in acetonitrile (0.3 mL, 0.4 M) was heated to 75 °C and afforded **14y** (0.0304 g, 71% yield) as a white solid. R_f = 0.21 in 4:1 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.07 (1H, dd, *J* = 8.3, 2.1 Hz), 6.75 (1H, d, *J* = 2.1 Hz), 6.20 (1H, d, *J* = 8.3 Hz), 3.79 – 3.64 (4H, m), 3.34 – 3.25 (2H, m), 2.96 (3H, s), 2.73 (2H, ddd, *J* = 11.8, 6.2, 3.2 Hz), 2.50 – 2.43 (2H, m), 2.29 (1H, dt, *J* = 9.1, 7.4 Hz), 2.19 (1H, p, *J* = 6.7 Hz), 2.00 (1H, dq, *J* = 13.7, 4.1 Hz), 1.69 – 1.62 (2H, m), 1.54 – 1.44 (1H, m), 0.90 (3H, d, *J* = 6.7 Hz), 0.76 (3H, d, *J* = 6.8 Hz).**^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 149.7, 128.9, 128.6, 123.3, 121.2, 120.4, 106.2, 68.9, 67.6, 66.7, 52.6, 49.5, 37.7, 33.2, 33.0, 24.1, 18.1, 17.0, 16.9. **IR** (film, cm^{-1}): 2959, 2937, 2882, 2853,

2813, 2234, 1714, 1601, 1495, 1386; **HRMS (ESI)** calcd. for $C_{21}H_{29}ClN_3O$ (*m/z* $M+H^+$): 374.1999, found: 374.1990.

(1S,4R,4aR,9aS)-4a-(2-(benzyloxy)ethyl)-9-methyl-1-morpholino-2,3,4,4a,9,9a-hexahydro-1H-carbazole-4-carbonitrile (**14z**) Following General Procedure B, a mixture of bromide **12d** (0.0402 g, 0.095 mmol, 1.0 equiv), morpholine (36 μL, 0.409 mmol, 4 equiv), and $AgSbF_6$ (0.0728 g, 0.212 mmol, 2 equiv), in acetonitrile (0.3 mL, 0.4 M) was heated to 75 °C and afforded **14z** (0.0284 g, 70% yield) as a white solid. R_f = 0.15 in 4:1 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.36 – 7.30 (2H, m), 7.30 – 7.26 (3H, m), 7.16 (1H, td, *J* = 7.7, 1.3 Hz), 7.03 (1H, dd, *J* = 7.3, 1.2 Hz), 6.72 (1H, td, *J* = 7.4, 1.0 Hz), 6.51 (1H, d, *J* = 7.8 Hz), 4.40 (2H, d, *J* = 1.9 Hz), 3.68 – 3.57 (4H, m), 3.43 (2H, t, *J* = 6.5 Hz), 3.33 (1H, d, *J* = 5.6 Hz), 3.07 (1H, dd, *J* = 8.9, 4.3 Hz), 2.87 (3H, s), 2.64 – 2.54 (2H, m), 2.52 – 2.42 (5H, m), 1.96 – 1.88 (1H, m), 1.81 (1H, dtd, *J* = 17.4, 8.5, 3.6 Hz), 1.75 – 1.63 (2H, m); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 151.2, 138.4, 131.0, 128.8, 128.5, 127.8, 127.7, 122.9, 121.3, 118.2, 108.3, 73.3, 68.9, 67.5, 67.4, 61.6, 50.4, 48.1, 35.5, 34.9, 32.7, 22.3, 19.2. **IR** (film, cm^{-1}): 2951, 2922, 2853, 2809, 2234, 1673, 1601, 1477, 1455, 1401, 1364, 1273, 1117; **HRMS (ESI)** calcd. for $C_{27}H_{34}N_3O_2$ (*m/z* $M+H^+$): 432.2651, found: 432.2643.

(1S,4R,4aR,9aS)-1-azido-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole-4-carbonitrile (**14aa**) – Following General Procedure B, a mixture of bromide **12a** (0.0503 g, 0.165 mmol, 1.0 equiv), sodium azide (0.0439 g, 0.675 mmol, 4 equiv), and $AgSbF_6$ (0.1157 g, 0.337 mmol, 2 equiv), in acetonitrile (0.3 mL, 0.50 M) was heated to 40 °C and afforded **14aa** (0.0325 g, 74% yield) as a white solid. R_f = 0.29 in 3:1 hexanes/EtOAc. NMR spectra matches previously reported characterization data.[8]

(1S,4R,4aR,9aS)-11-benzyl-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-1,4-(epiminomethano)carbazol-10-imine (**17a**) – Following General Procedure B, a mixture of bromide **12a** (0.0620 g, 0.203 mmol, 1.0 equiv), benzylamine (88 μL, 0.806 mmol, 4 equiv), and $AgSbF_6$ (0.1410 g, 0.412 mmol, 2 equiv), in acetonitrile (0.5 mL, 0.3 M) was heated to 75 °C and afforded **17a** (0.0367 g, 55% yield) as a white solid. R_f = 0.16 in EtOAc. Note, that two amidine protons appear in the 1H NMR spectrum at 8.93 and 8.58 ppm

due to protonation. One of them disappears upon washing with aqueous 1M NaOH solution. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.93 (1H, s), 8.58 (1H, s), 7.45 – 7.34 (6H, m), 7.10 (1H, td, *J* = 7.7, 1.2 Hz), 7.02 (1H, dd, *J* = 7.3, 1.2 Hz), 6.70 – 6.64 (1H, m), 6.32 (1H, d, *J* = 7.8 Hz), 4.90 (1H, d, *J* = 15.0 Hz), 4.69 (1H, d, *J* = 15.0 Hz), 3.77 (1H, d, *J* = 4.2 Hz), 3.44 (1H, t, *J* = 2.8 Hz), 3.05 (1H, s), 2.68 (3H, s), 1.75 – 1.64 (1H, m), 1.64 – 1.43 (3H, m), 1.32 (3H, s); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 169.7, 151.0, 133.0, 130.5, 129.5, 129.4, 129.3, 129.0, 124.0, 118.3, 106.0, 73.4, 56.4, 52.4, 47.8, 44.2, 33.2, 29.1, 20.8, 19.5. **IR** (film, cm^{-1}): 3405, 3036, 2959, 1671, 1619, 1604, 1491, 1451; **HRMS (ESI)** calcd. for $C_{22}H_{26}N_3$ (*m/z* $M+H^+$): 332.2127, found: 332.2121.

(1S,4R,4aR,9aS)-11-(2-(1H-indol-3-yl)ethyl)-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-1,4-(epiminomethano)carbazol-10-imine (**17b**) – Following General Procedure B, a mixture of bromide **12a** (0.0561 g, 0.183 mmol, 1.0 equiv), tryptamine (0.1178 g, 0.735 mmol, 4 equiv), and $AgSbF_6$ (0.1260 g, 0.367 mmol, 2 equiv), in acetonitrile (0.5 mL, 0.3 M) was heated to 75 °C and afforded **17b** (0.0609 g, 86% yield) as a white solid. R_f = 0.16 in EtOAc. Note, that two amidine protons appear in the 1H NMR spectrum at 8.58 and 8.33 ppm due to protonation. One of them disappears upon washing with aqueous 1M NaOH solution. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.58 (1H, s), 8.33 (1H, s), 8.19 (1H, s), 7.62 – 7.57 (1H, m), 7.39 (1H, dt, *J* = 8.1, 1.0 Hz), 7.23 – 7.18 (2H, m), 7.15 (1H, ddd, *J* = 8.1, 7.1, 1.1 Hz), 7.05 (1H, ddd, *J* = 7.8, 6.3, 1.3 Hz), 6.92 (1H, dd, *J* = 7.4, 1.3 Hz), 6.62 (1H, td, *J* = 7.4, 0.9 Hz), 6.23 (1H, d, *J* = 7.9 Hz), 4.20 (1H, dt, *J* = 14.6, 6.0 Hz), 3.91 (1H, dt, *J* = 14.6, 6.9 Hz), 3.47 (1H, d, *J* = 4.2 Hz), 3.31 – 3.19 (3H, m), 2.51 (1H, dd, *J* = 4.1, 1.3 Hz), 2.33 (3H, s), 1.44 (1H, t, *J* = 12.4 Hz), 1.37 – 1.22 (3H, m), 1.10 (3H, s); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 169.3, 151.1, 136.5, 130.8, 129.1, 127.0, 124.0, 123.7, 122.3, 119.7, 118.2, 117.7, 112.0, 110.8, 105.7, 72.8, 58.0, 49.4, 47.1, 44.3, 32.8, 29.8, 28.9, 23.4, 20.6, 19.5. **IR** (film, cm^{-1}): 3419, 3019, 2399, 1644, 1520, 1215; **HRMS (ESI)** calcd. for $C_{25}H_{29}N_4$ (*m/z* $M+H^+$): 385.2381, found: 385.2392.

(1S,4R,4aR,9aS)-11-(furan-2-ylmethyl)-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-1,4-(epiminomethano)carbazol-10-imine (**17c**) – Following General Procedure B, a mixture of bromide **12a** (0.0581 g, 0.190 mmol, 1.0 equiv), furfurylamine (67 μL, 0.758 mmol, 4 equiv), and $AgSbF_6$ (0.1305 g, 0.380 mmol, 2 equiv), in acetonitrile (0.5 mL, 0.3 M) was heated to 75 °C and afforded **17c** (0.0511 g, 84% yield) as a white solid. R_f = 0.18 in EtOAc. Note, that two amidate protons appear in the 1H NMR spectrum at 9.95 and 9.55 ppm due to protonation. One of them disappears upon washing with aqueous 1M NaOH solution. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 9.95 (1H, s), 9.55 (1H, s), 7.39 (1H, dd, *J* = 1.9, 0.8 Hz), 7.10 (1H, td, *J* = 7.7, 1.2 Hz), 7.02 (1H, dd, *J* = 7.4, 1.2 Hz), 6.81 (1H, d, *J* = 3.3 Hz), 6.64 (1H, td, *J* = 7.4, 0.9 Hz), 6.42 – 6.29 (2H, m), 5.23 (1H, d, *J* = 16.0 Hz), 4.84 (1H, d, *J* = 16.0 Hz), 3.94 (1H, d, *J* = 3.6 Hz), 3.51 (1H, d, *J* = 3.0 Hz), 3.23 – 3.16 (1H, m), 2.79 (3H, s), 1.73 (1H, s), 1.47 (3H, t, *J* = 12.0 Hz), 1.27 (3H, s); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 169.0, 151.2, 147.3, 143.3, 130.8, 129.1, 124.0, 117.9, 111.6, 111.2, 105.8, 73.3, 57.3, 47.6, 45.6, 43.8, 33.2, 29.2, 20.5, 19.4. **IR** (film, cm^{-1}): 3373, 1685, 1626, 1278, 1164, 1034; **HRMS (ESI)** calcd. for $C_{20}H_{23}N_3O$ (*m/z* $M+H^+$): 322.1919, found: 322.1915.

(1S,4R,4aR,9aS)-11-allyl-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-1,4-(epiminomethano)carbazol-10-imine (**17d**) – Following General Procedure B, a mixture of bromide **12a** (0.0620 g, 0.203 mmol, 1.0 equiv), allylamine (39 μL, 0.515 mmol, 4 equiv), and AgOTf (0.0884 g, 0.344 mmol, 2 equiv), in acetonitrile (0.5 mL, 0.3 M) was heated to 75 °C and afforded **17d** (0.0367 g, 76% yield) as a white solid. R_f = 0.15 in EtOAc. Note, that two amidate protons appear in the 1H NMR spectrum at 8.82 and 8.26 ppm due to protonation. One of them disappears upon washing with aqueous 1M NaOH solution. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.82 (1H, s), 8.26 (1H, s), 7.13 (1H, td, *J* = 7.7, 1.3 Hz), 7.04 (1H, dd, *J* = 7.4, 1.3 Hz), 6.69 (1H, td, *J* = 7.4, 1.0 Hz), 6.37 (1H, d, *J* = 7.9 Hz), 5.84 (1H, ddt, *J* = 16.7, 10.1, 6.4 Hz), 5.48 (1H, dq, *J* = 17.0, 1.3 Hz), 5.41 (1H, dq, *J* = 10.1, 1.1 Hz), 4.30 (1H, ddt, *J* = 15.7, 6.4, 1.3 Hz), 4.21 (1H, ddt, *J* = 15.7, 6.6, 1.3 Hz), 3.84 (1H, td, *J* = 3.8, 1.7 Hz), 3.47 – 3.37 (2H, m), 2.84 (3H, s), 1.86 – 1.79 (1H, m), 1.58 (1H, ddd, *J* = 12.3, 7.4, 2.7 Hz), 1.53 – 1.44 (2H, m), 1.36 (3H, s); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 169.7, 151.1, 130.4, 129.3, 128.8, 124.0, 121.7, 118.3, 106.0, 73.5, 57.2, 51.6, 47.7, 43.8, 33.3, 29.1, 20.6, 19.7.

IR (film, cm^{-1}): 3323, 3188, 1685, 1496, 1383, 1030; **HRMS (ESI)** calcd. for $C_{18}H_{24}N_3$ (*m/z* $M+H^+$): 282.1970, found: 282.1967.

(1S,4R,4aR,9aS)-4a,9-dimethyl-11-(prop-2-yn-1-yl)-2,3,4,4a,9,9a-hexahydro-1H-1,4-(epiminomethano)carbazol-10-imine (**17e**) – Following General Procedure B, a mixture of bromide **12a** (0.0561 g, 0.183 mmol, 1.0 equiv), propargyl amine (47 μL, 0.733 mmol, 4 equiv), and $AgSbF_6$ (0.1260 g, 0.367 mmol, 2 equiv), in acetonitrile (0.5 mL, 0.3 M) was heated to 75 °C and afforded **17e** (0.0474 g, 92% yield) as a white solid. R_f = 0.16 in EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.11 (1H, td, *J* = 7.7, 1.3 Hz), 7.05 (1H, dd, *J* = 7.3, 1.2 Hz), 6.64 (1H, td, *J* = 7.4, 0.9 Hz), 6.35 (1H, d, *J* = 7.9 Hz), 4.70 (1H, dd, *J* = 18.3, 2.5 Hz), 4.51 (1H, dd, *J* = 18.3, 2.5 Hz), 4.09 (1H, td, *J* = 3.9, 1.7 Hz), 3.53 (1H, dd, *J* = 4.2, 1.4 Hz), 3.36 (1H, t, *J* = 2.9 Hz), 2.85 (3H, s), 2.47 (1H, t, *J* = 2.5 Hz), 1.78 (1H, ddd, *J* = 14.3, 10.8, 7.5 Hz), 1.69 – 1.57 (1H, m), 1.53 (2H, ddd, *J* = 9.7, 5.9, 2.9 Hz), 1.36 (3H, s); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 169.6, 151.2, 130.6, 129.2, 124.0, 118.0, 105.9, 75.5, 75.1, 73.3, 57.6, 47.8, 44.6, 38.6, 33.2, 29.1, 20.7, 19.5. **IR** (film, cm^{-1}): 3449, 2959, 2852, 1685, 1627, 1265, 1167, 1032; **HRMS (ESI)** calcd. for $C_{18}H_{22}N_3$ (*m/z* $M+H^+$): 280.1814, found: 280.1815.

(1S,4R,4aR,9aS)-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-1,4-(epiminomethano)carbazol-10-imine (**17f**) – Following General Procedure B, a mixture of bromide **12a** (0.0499 g, 0.163 mmol, 1.0 equiv), hexamethyldisilazane (0.136 mL, 0.654 mmol, 4 equiv), and $AgSbF_6$ (0.1120 g, 0.326 mmol, 2 equiv), in acetonitrile (0.5 mL, 0.3 M) was heated to 75 °C and afforded **17f** (0.0301 g, 76% yield) as a white solid. R_f = 0.10 in EtOAc. Note, that two amidate protons appear in the 1H NMR spectrum at 9.34 and 8.29 ppm due to protonation. One of them disappears upon washing with aqueous 1M NaOH solution. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 9.34 (1H, s), 8.29 (1H, s), 7.86 (1H, s), 7.15 (1H, t, *J* = 7.8 Hz), 6.96 (1H, d, *J* = 7.3 Hz), 6.69 (1H, t, *J* = 7.4 Hz), 6.39 (1H, d, *J* = 7.9 Hz), 4.02 (1H, d, *J* = 4.8 Hz), 3.51 – 3.39 (1H, m), 3.02 (1H, q, *J* = 2.5 Hz), 2.85 (3H, s), 1.88 – 1.76 (1H, m), 1.66 – 1.59 (2H, m), 1.56 – 1.42 (2H, m), 1.36 (3H, s); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 172.6, 151.3, 129.9, 129.6, 123.5, 117.9, 106.1, 73.6, 49.7, 47.5, 43.3,

33.0, 29.2, 20.5, 19.7. **IR** (film, cm^{-1}): 3325, 3188, 3017, 2954, 2867, 1685, 1494, 1363, 1035; **HRMS (ESI)** calcd. for $C_{15}H_{19}N_3$ (*m/z* $M+H^+$): 242.1657, found: 242.1656.

N-((1S,4R,4aR,9aS)-4-cyano-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-carbazol-1-yl)acetamide (**18a**) – Following General Procedure B, a mixture of bromide **12a** (10 mg, 0.03 mmol, 1.0 equiv), $AgSbF_6$ (22.5 mg, 0.065 mmol, 2 equiv), in acetonitrile (0.3 mL, 0.10 M) was heated to 75 °C and afforded **18a** (8.5 mg, 92% yield) as a white solid. R_f 0.30 in 1:1 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$): δ, ppm 7.25 (1H, d, *J* = 1.2 Hz), 7.19 (1H, dd, *J* = 7.7, 1.3 Hz), 6.84 (1H, td, *J* = 7.4, 0.9 Hz), 6.62 (1H, d, *J* = 7.9 Hz), 5.58 (1H, d, *J* = 7.5 Hz), 4.55 – 4.45 (1H, m), 3.04 – 2.96 (1H, m), 2.81 (3H, s), 2.60 (1H, dd, *J* = 12.3, 3.5 Hz), 2.04 (3H, s), 1.95 – 1.86 (2H, m), 1.85 – 1.77 (2H, m), 1.64 (3H, s); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ, ppm 169.5, 150.9, 134.8, 129.1, 122.0, 120.7, 119.7, 109.5, 75.1, 43.6, 43.0, 36.8, 34.7, 25.2, 23.7, 20.8, 19.8. **IR** (film, cm^{-1}): 3419, 2940, 2252, 1652, 1546, 1477, 1372, 1255, 1233; **HRMS (ESI)** calcd. for $C_{17}H_{22}N_3O$ (*m/z* $M+H^+$): 284.1756, found: 284.1763.

N-((1S,4R,4aR,9aS)-4-cyano-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-carbazol-1-yl)benzamide (**18b**) – Following General Procedure B, a mixture of bromide **12a** (0.0502 g, 0.164 mmol, 1.0 equiv), $AgSbF_6$ (0.0214 g, 0.062 mmol, 2 equiv), in benzonitrile (0.30 mL, 0.50 M) was heated to 75 °C and afforded **18b** (0.0173 g, 33% yield) as a yellow solid. R_f 0.30 in 1:1 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$): δ, ppm 7.77 (2H, dd, *J* = 7.5, 1.4 Hz), 7.55 (1H, t, *J* = 7.4 Hz), 7.48 (2H, dt, *J* = 8.3, 7.0 Hz), 7.28 (1H, dd, *J* = 7.4, 1.2 Hz), 7.21 (1H, td, *J* = 7.7, 1.3 Hz), 6.85 (1H, td, *J* = 7.4, 0.9 Hz), 6.65 (1H, d, *J* = 7.9 Hz), 6.27 (1H, d, *J* = 7.1 Hz), 4.75 – 4.67 (1H, m), 3.15 (1H, d, *J* = 2.3 Hz), 2.88 (3H, s), 2.67 (1H, dd, *J* =12.0, 3.4 Hz), 2.04 – 1.98 (1H, m), 1.98 – 1.86 (3H, m), 1.71 (3H, s); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ, ppm 167.0, 151.0, 134.8, 134.3, 132.1, 129.1, 129.0, 126.9, 122.1, 120.7, 119.8, 109.6, 75.1, 44.0, 43.1, 36.8, 34.7, 25.2, 20.9, 19.9. **IR** (film, cm^{-1}): 3420, 2944, 2250, 1634, 1579, 1477, 1261; **HRMS (ESI)** calcd. for $C_{22}H_{24}N_3O$ (*m/z* $M+H^+$): 346.1919, found: 346.1919.

N-((1S,4R,4aR,9aS)-4-cyano-4a-(2-hydroxyethyl)-9-methyl-2,3,4,4a,9,9a-hexahydro-1H-carbazol-1-yl)acetamide (**18c**) – A mixture of bromide **12d** (0.0200 g, 0.047 mmol, 1.0 equiv) in ethanol (0.5 mL, 0.10 M) and 10% palladium on carbon (0.0005 g) was stirred under a balloon of H_2 gas at atmospheric pressure until the reaction was judged complete by thin layer chromatographic analysis (hexanes/EtOAc). The crude mixture was then filtered over Celite, concentrated, and used without further purification. Following General Procedure B, a mixture of the debenzylated intermediate (0.0245 g, 0.071 mmol, 1.0 equiv), $AgSbF_6$ (0.0500 g, 0.146 mmol, 2 equiv), in acetonitrile (0.20 mL, 0.30 M) was heated to 75 °C and afforded **18c** (0.0164 g, 72% yield) as a white solid. R_f = 0.21 in 4:1 EtOAc/hexanes. **^{1}H NMR** (600 MHz, $CDCl_3$): δ, ppm 7.40 (1H, s), 7.24 – 7.18 (1H, m), 7.12 (1H, d, *J* = 7.4 Hz), 6.84 (1H, t, *J* = 7.4 Hz), 6.65 (1H, d, *J* = 7.9 Hz), 5.12 (1H, s), 4.31 (1H, s), 4.05 – 3.95 (1H, m), 3.78 (1H, t, *J* = 10.0 Hz), 3.34 (2H, d, *J* = 9.8 Hz), 2.76 (3H, s), 2.71 – 2.62 (2H, m), 2.35 – 2.20 (2H, m), 1.98 (3H, s), 1.89 (2H, qd, *J* = 13.3, 3.1 Hz), 1.80 – 1.68 (2H, m); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ, ppm 170.8, 151.6, 132.2, 129.2, 122.1, 120.7, 119.8, 109.8, 70.8, 58.8, 46.4, 44.7, 37.5, 34.7, 31.0, 24.3, 23.5, 20.4. **IR** (film, cm^{-1}): 3280, 2963, 2930, 2864, 2813, 2236, 1652, 1601, 1550, 1481, 1455, 1371; **HRMS (ESI)** calcd. for $C_{18}H_{24}N_3O_2$ (*m/z* $M+H^+$): 314.1869, found: 314.1862.

(1S,4R,4aR,9aS)-4-cyano-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-carbazol-1-yl benzoate (**18d**) – Following General Procedure B, a mixture of bromide **12a** (0.0351 g, 0.115 mmol, 1.0 equiv), silver benzoate (0.1053 g, 0.459 mmol, 4 equiv) in acetonitrile (0.5 mL, 0.3 M) was heated to 75 °C and afforded **18d** (0.0350 g, 88% yield) as a white solid. R_f = 0.25 in 9:1 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.11 – 8.03 (2H, m), 7.65 – 7.58 (1H, m), 7.54 – 7.47 (2H, m), 7.33 (1H, dd, *J* = 7.4, 1.2 Hz), 7.22 (1H, td, *J* = 7.7, 1.3 Hz), 6.87 (1H, td, *J* = 7.4, 1.0 Hz), 6.66 (1H, d, *J* = 7.9 Hz), 5.66 (1H, d, *J* = 2.8 Hz), 3.14 – 3.08 (1H, m), 2.84 (3H, s), 2.64 (1H, dd, *J* = 12.9, 3.4 Hz), 2.19 – 2.05 (2H, m), 2.02 – 1.84 (2H, m), 1.75 (3H, s); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 165.7, 151.0, 135.4, 133.6, 130.0, 129.7, 129.0, 128.8, 122.4, 120.8, 120.1, 109.7, 74.3, 67.4, 43.2, 37.2, 35.1, 25.6, 20.5, 19.0.**IR** (film, cm^{-1}): 3057, 2969, 2813, 2358,

2237, 1717, 1604, 1481, 1273, 1109; **HRMS (ESI)** calcd. for $C_{22}H_{23}N_2O_2$ (*m/z* $M+H^+$): 347.1760, found: 347.1748.

(1S,4R,4aR,9aS)-4-cyano-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-carbazol-1-yl acetate (**18e**) – Following General Procedure B, a mixture of bromide **12a** (0.0399 g, 0.130 mmol, 1.0 equiv), potassium acetate (0.0513, 0.522 mmol, 4 equiv), and AgOTf (0.0896 g, 0.261 mmol, 2 equiv), in acetonitrile (0.5 mL, 0.3 M) was heated to 75 °C and afforded **18e** (0.0271 g, 73% yield) as a white solid. R_f = 0.25 in 9:1 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.29 (1H, dd, *J* = 7.3, 1.2 Hz), 7.20 (1H, td, *J* = 7.7, 1.2 Hz), 6.86 (1H, td, *J* = 7.5, 1.0 Hz), 6.63 (1H, d, *J* = 7.9 Hz), 5.39 (1H, q, *J* = 2.9 Hz), 2.97 – 2.90 (1H, m), 2.77 (3H, d, *J* = 0.9 Hz), 2.56 (1H, dd, *J* = 12.9, 3.3 Hz), 2.12 (3H, d, *J* = 0.9 Hz), 2.07 – 1.90 (2H, m), 1.90 – 1.77 (2H, m), 1.65 (3H, s); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 170.1, 150.9, 135.5, 128.9, 122.3, 120.8, 120.0, 110.1, 109.6, 74.1, 66.8, 43.2, 37.0, 35.0, 25.4, 21.4, 20.3, 18.7. **IR** (film, cm^{-1}): 2966, 2809, 2360, 2339, 1736, 1481, 1240; **HRMS (ESI)** calcd. for $C_{17}H_{21}N_2O_2$ (*m/z* $M+H^+$): 285.1603, found: 285.1602.

(1S,4R,4aR,9aS)-1-methoxy-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole-4-carbonitrile (**18f**) – Following General Procedure B, a mixture of bromide **12a** (0.0300 g, 0.098 mmol, 1.0 equiv) and $AgSbF_6$ (0.0510 g, 0.198 mmol, 2 equiv) in methanol (0.98 mL, 0.1 M) was heated to 75 °C and afforded **18f** (0.0242 g, 96% yield) as a white solid. R_f = 0.46 in 4:1 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.28 (1H, dd, *J* = 7.4, 1.3 Hz), 7.19 (1H, td, *J* = 7.7, 1.3 Hz), 6.84 (1H, td, *J* = 7.4, 1.0 Hz), 6.61 (1H, d, *J* = 7.9 Hz), 3.72 (1H, q, *J* = 2.8 Hz), 3.39 (3H, s), 3.03 (1H, dd, *J* = 2.7, 1.3 Hz), 2.72 (3H, s), 2.53 (1H, dd, *J* = 12.8, 3.4 Hz), 2.07 – 1.94 (2H, m), 1.72 – 1.65 (2H, m), 1.64 (3H, s); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 151.2, 136.1, 128.7, 122.3, 121.2, 119.8, 109.3, 74.3, 73.8, 57.0, 43.3, 37.3, 34.9, 24.2, 19.9, 18.7. **IR** (film, cm^{-1}): 2940, 2879, 2813, 2239, 1604, 1481, 1455, 1385, 1261, 1099. **HRMS (ESI)** calcd. for $C_{16}H_{21}N_2O$ (*m/z* $M+H^+$): 257.1654, found: 257.1649.

(1S,4R,4aR,9aS)-1-hydroxy-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole-4-carbonitrile (**18g**) – Following General Procedure B, a mixture of bromide **12a** (0.0506 g, 0.165 mmol, 1.0 equiv), de-ionized

water (12 μL, 0.667 mmol, 4 equiv), and $AgSbF_6$ (0.1137 g, 0.331 mmol, 2 equiv), in acetonitrile (0.3 mL, 0.30 M) was heated to 75 °C and afforded **18g** (0.0382 g, 95% yield) as a white solid. R_f = 0.11 in 4:1 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.29 (1H, dd, *J* = 7.4, 1.2 Hz), 7.19 (1H, td, *J* = 7.7, 1.3 Hz), 6.84 (1H, td, *J* = 7.4, 0.9 Hz), 6.61 (1H, d, *J* = 7.8 Hz), 4.36 (1H, d, *J* = 3.0 Hz), 2.97 (1H, d, *J* = 2.5 Hz), 2.73 (3H, s), 2.55 (1H, dd, *J* = 12.8, 3.4 Hz), 2.19 – 2.09 (1H, m), 1.90 – 1.81 (2H, m), 1.75 (1H, dt, *J* = 13.3, 3.6 Hz), 1.71 (3H, s); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 151.0, 135.9, 128.7, 122.3, 121.1, 119.8, 109.3, 76.8, 64.8, 43.2, 37.2, 35.0, 28.3, 19.6, 19.2. **IR** (film, cm^{-1}): 3419, 2086, 1699, 1641, 1371, 1240, 1093; **HRMS (ESI)** calcd. for $C_{15}H_{19}N_2O$ (*m/z* $M+H^+$): 243.1497, found: 243.1492.

(1S,4R,4aR,9aS)-4-cyano-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-carbazol-1-yl 2,2,2-trifluoroacetate (**18h**) – Following General Procedure B, a mixture of bromide **12a** (0.0327 g, 0.107 mmol, 1.0 equiv) and silver trifluoroacetate (0.0947 g, 0.428 mmol, 4 equiv), in acetonitrile (0.3 mL, 0.3 M) was heated to 75 °C and afforded **18h** (0.0141 g, 39% yield) as a white solid. R_f = 0.19 in 4:1 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$): δ, ppm 7.31 (1H, d, *J* = 7.2 Hz), 7.23 (1H, d, *J* = 7.7 Hz), 6.89 (1H, t, *J* = 7.5 Hz), 6.66 (1H, d, *J* = 8.2 Hz), 5.58 - 5.53 (1H, m), 3.02 - 2.99 (1H, m), 2.80 (3H, s), 2.61 (1H, dd, *J* = 3.5, 12.3 Hz), 2.09 - 1.97 (3H, m), 1.93 - 1.86 (1H, m), 1.66 (3H, s); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ, ppm 156.7 (q, *J* = 42.3 Hz), 150.5, 135.0, 129.2, 122.4, 120.6, 120.2, 114.6 (q, *J* = 285 Hz), 109.9, 73.6, 71.8, 43.3, 36.9, 35.2, 25.1, 20.0, 18.4. NMR data matches previously reported characterization data.[4]

(1S,4R,4aR,9aS)-4-cyano-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-carbazol-1-yl nitrate (**18i**) – Following General Procedure B, a mixture of bromide **12a** (0.0353 g, 0.115 mmol, 1.0 equiv) and silver nitrate (0.0786 g, 0.462 mmol, 4 equiv) in acetonitrile (0.3 mL, 0.30 M) was heated to 75 °C and afforded **18i** (0.0187 g, 56% yield) as a white solid. R_f = 0.25 in 3:1 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.31 (1H, d, *J* = 7.4 Hz), 7.23 (1H, td, *J* = 7.8, 1.4 Hz), 6.89 (1H, t, *J* = 7.5 Hz), 6.66 (1H, d, *J* = 7.9 Hz), 5.50 (1H, d, *J* = 2.7 Hz), 3.07 (1H, d, *J* = 2.5 Hz), 2.81 (3H, s), 2.62 – 2.54 (1H, m), 2.16 – 2.08 (1H, m), 2.02 – 1.93 (2H, m), 1.87 (1H, dt, *J* = 7.0, 3.8 Hz), 1.66 (3H, s); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 150.5,

135.0, 129.2, 122.5, 120.6, 120.2, 110.0, 76.1, 72.8, 43.2, 36.9, 35.2, 24.4, 20.2, 18.5. **IR** (film, cm^{-1}): 2955, 2922, 1626, 1481, 1279; **HRMS (ESI)** calcd. for $C_{15}H_{18}N_3O_3$ (*m/z* $M+H^+$): 288.1348, found: 288.1342.

(1S,4R,4aS,9aR)-4a,9-dimethyl-4-morpholino-2,3,4,4a,9,9a-hexahydro-1H-carbazole-1-carbonitrile (**21**) – Following General Procedure B, a mixture of bromide **19** (0.1103 g, 0.361 mmol, 1.0 equiv), morpholine (0.124 mL, 1.44 mmol, 4 equiv), and AgOTf (0.1850 g, 0.720 mmol, 4 equiv) in acetonitrile (2.0 mL, 0.20 M) was heated to 75 °C and afforded **21** (0.0743 g, 66% yield) as a white solid. R_f = 0.15 in 4:1 hexanes/EtOAc. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.38 (1H, dd, *J* = 7.3, 1.3 Hz), 7.15 (1H, td, *J* = 7.7, 1.4 Hz), 6.80 (1H, td, *J* = 7.4, 1.0 Hz), 6.61 (1H, d, *J* = 7.8 Hz), 3.72 – 3.59 (4H, m), 3.26 – 3.20 (1H, m), 3.15 (1H, t, *J* = 1.7 Hz), 2.67 (5H, s), 2.20 (3H, dt, *J* = 14.8, 7.4 Hz), 2.12 – 2.07 (1H, m), 2.01 – 1.94 (1H, m), 1.88 – 1.78 (2H, m), 1.57 (3H, s). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 150.2, 137.4, 127.8, 123.6, 121.3, 119.4, 109.2, 75.6, 67.7, 67.4, 48.2, 34.8, 26.0, 25.0, 18.5, 18.1. **IR** (film, cm^{-1}): 2955, 2930, 2857, 2809, 2241, 2190, 1717, 1667, 1481; **HRMS (ESI)** calcd. for $C_{19}H_{26}N_3O$ (*m/z* $M+H^+$): 312.2076, found: 312.2071.

(3aR,6S,6aR,11bS)-7-methyl-2,3,3a,4,5,6,6a,7-octahydro-1H-pyrrolo[2,3-d]carbazole-6-carbonitrile (**25**) – To a solution of bromide **22** (0.0650 g, 0.140 mmol, 1.0 equiv) in ethanol (0.7 mL, 0.20 M) was added hydrazine hydrate (14.9 μL, 0.307 mmol, 2.2 equiv). The reaction was heated to 50 °C and stirred until judged complete by thin layer chromatographic analysis (EtOAc/MeOH). The reaction mixture was cooled to room temperature, concentrated, and diluted with aqueous 1M NaOH and extracted with EtOAc. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. The crude material *(1S,4R,4aR,9aR)-4a-(2-aminoethyl)-4-bromo-9-methyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole-1-carbonitrile* (**23**) was used in the next reaction without any further purification. Following General Procedure B, a mixture of bromide **23** (0.0350 g, 0.105 mmol, 1.0 equiv) and silver(I) hexafluoroantimonate (0.0720 g, 0.210 mmol, 2 equiv), in acetonitrile (0.3 mL, 0.30 M) was heated to 75 °C and afforded **25** (0.0097 g, 37% yield) as a white solid. R_f = 0.29 in 3:1 EtOAc/hexanes. **^{1}H NMR** (600 MHz, $CDCl_3$): δ

7.16 (1H, td, J = 7.7, 1.3 Hz), 6.99 (1H, dd, J = 7.3, 1.3 Hz), 6.78 (1H, td, J = 7.4, 1.0 Hz), 6.55 (1H, d, J = 7.8 Hz), 3.56 (1H, d, J = 5.1 Hz), 3.31 – 3.25 (2H, m), 3.16 (1H, dd, J = 8.2, 4.7 Hz), 2.88 (3H, s), 2.86 – 2.83 (1H, m), 2.45 (1H, ddd, J = 14.0, 8.1, 6.3 Hz), 2.03 – 1.96 (2H, m), 1.85 (1H, ddt, J = 13.2, 9.3, 3.5 Hz), 1.82 – 1.74 (2H, m), 1.68 – 1.63 (1H, m); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 150.1, 128.5, 121.8, 121.4, 119.3, 108.3, 70.6, 60.9, 43.8, 36.9, 34.3, 29.9, 27.5, 24.8, 21.9. **IR** (film, cm^{-1}): 3312, 2951, 2922, 2853, 2820, 2237, 1667, 1604, 1554, 1484, 1448, 1375, 1298, 1214, 1153; **HRMS (ESI)** calcd. for $C_{16}H_{20}N_3$ (*m/z* M+H$^+$): 254.1657, found: 254.1648.

ASSOCIATED CONTENT

Supporting Information

The supporting Information is available free of charge on the ACS Publications website at DOI:

Supporting Information: NMR spectra including ^{1}H, ^{13}C, 2D-NOESY, COSY, HMBC, HSQC and optimized coordinates for all DFT structures.

AUTHOR INFORMATION

Corresponding Authors

Jimmy Wu – *Dartmouth College, Hanover, New Hampshire, USA; orcid.org/0000-0002-0938-8019;* Email: jimmy.wu@dartmouth.edu

K. N. Houk – *University of California, Los Angeles, California, USA; orcid.org/0000-0002-8387-5261;* Email: houk@chem.ucla.edu

Fang Liu – *College of Sciences, Nanjing Agricultural University, Nanjing, China*; *orcid.org/0000-0002-0046-8434;* Email: acialiu@njau.edu.cn

Other Authors

Leah L. Lowder – *Dartmouth College, Hanover, New Hampshire, USA; orcid.org/0000-0002-0504-9685;* Email: Leah.L.Lowder.Gr@dartmouth.edu

Mathes M. Vaughan – *Dartmouth College, Hanover, New Hampshire, USA; orcid.org/0000-0002-0467-207X;* Email: Mathes.M.Vaughan.22@dartmouth.edu

Fengyue Zhao – *College of Sciences, Nanjing Agricultural University, Nanjing, China; orcid.org/0000-0001-8186-2611;* Email: zhfyue@126.com

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGEMENTS

JW acknowledges the generous support of the NIH NIGMS (R01GM111638) and the National Science Foundation (CHE-1856273). KH acknowledges the generous support of National Science Foundation (CHE-1764328). FL acknowledges the generous support of the Jiangsu Science Foundation (BK20190505).

REFERENCES

(1) Gawley, R. E. The Beckmann Reactions: Rearrangements, Eliminations-Additions, Fragmentations, and Rearrangement-Cyclizations. In *Organic Reactions*; Kende, A. S., Ed.; John Wiley & Sons, Inc., 1988; Vol. 35.

(2) Hassner, A.; Nash, E. G. The Beckmann Cleavage of 1,1diaryl-2-Propanone Oximes. *Tetrahedron Lett.* **1965**, *6* (9), 525–529. https://doi.org/10.1016/S0040-4039(00)89991-8.

(3) Kirihara, M.; Niimi, K.; Okumura, M.; Momose, T. Fluorinative Beckmann Fragmentation: Fluorinative a-Cleavage of Cyclic Ketoximes by Diethylaminosulfur Trifluoride. *Chem. Pharm. Bull. (Tokyo)* **2000**, *48* (2), 220–222.

(4) Confalone, P. N.; Lollar, E. D.; Pizzolato, G.; Uskokovic, M. R. Use of Intramolecular [3 + 2] Cycloaddition Reactions in the Synthesis of Natural Products. A Stereospecific Synthesis of (+-)-

Biotin from Cycloheptene. *J. Am. Chem. Soc.* **1978**, *100* (19), 6291–6292. https://doi.org/10.1021/ja00487a086.

(5) Confalone, P. N.; Pizzolato, G.; Lollar-Confalone, D.; Uskokovic, M. R. Olefinic Nitrone and Nitrile Oxide [3 + 2] Cycloadditions. A Short Stereospecific Synthesis of Biotin from Cycloheptene. *J. Am. Chem. Soc.* **1980**, *102* (6), 1954–1960. https://doi.org/10.1021/ja00526a033.

(6) Dauncey, E. M.; Morcillo, S. P.; Douglas, J. J.; Sheikh, N. S.; Leonori, D. Photoinduced Remote Functionalisations by Iminyl Radical Promoted C−C and C−H Bond Cleavage Cascades. *Angew. Chem. Int. Ed.* **2018**, *57* (3), 744–748. https://doi.org/10.1002/anie.201710790.

(7) Ai, W.; Liu, Y.; Wang, Q.; Lu, Z.; Liu, Q. Cu-Catalyzed Redox-Neutral Ring Cleavage of Cycloketone *O*-Acyl Oximes: Chemodivergent Access to Distal Oxygenated Nitriles. *Org. Lett.* **2018**, *20* (2), 409–412. https://doi.org/10.1021/acs.orglett.7b03707.

(8) Touchette, S. J.; Dunkley, E. M.; Lowder, L. L.; Wu, J. Nucleophile-Intercepted Beckmann Fragmentation Reactions. *Chem. Sci.* **2019**, *10* (33), 7812–7815. https://doi.org/10.1039/C9SC00926D.

(9) Li, H.; Hughes, R. P.; Wu, J. Dearomative Indole (3 + 2) Cycloaddition Reactions. *J. Am. Chem. Soc.* **2014**, *136* (17), 6288–6296. https://doi.org/10.1021/ja412435b.

(10) Li, H.; Wu, J. (3+2)-Cycloaddition Reactions of Oxyallyl Cations. *Synthesis* **2014**, *47* (01), 22–33. https://doi.org/10.1055/s-0034-1378918.

(11) Ramirez, A.; García-Rubio, S. Current Progress in the Chemistry and Pharmacology of Akuammiline Alkaloids. *Curr. Med. Chem.* **2003**, *10* (18), 1891–1915.

(12) Eckermann, R.; Gaich, T. The Akuammiline Alkaloids; Origin and Synthesis. *Synthesis* **2013**, *45* (20), 2813–2823.

(13) Smith, J. M.; Moreno, J.; Boal, B. W.; Garg, N. K. Cascade Reactions: A Driving Force in Akuammiline Alkaloid Total Synthesis. *Angew. Chem. Int. Ed.* **2015**, *54*, 400–412. https://doi.org/10.1002/anie.201406866.

(14) Magnus, P.; Mugrage, B.; DeLuca, M.; Cain, G. A. Total Synthesis of (+)-Koumine, (+)-Taberpsychine, and (+)-Koumidine. *J. Am. Chem. Soc.* **1989**, *111* (2), 786–789. https://doi.org/10.1021/ja00184a086.

(15) Magnus, P.; Mugrage, B.; DeLuca, M. R.; Cain, G. A. Studies on Gelsemium Alkaloids. Total Synthesis of (+)-Koumine, (+)-Taberpsychine, and (+)-Koumidine. *J. Am. Chem. Soc.* **1990**, *112* (13), 5220–5230. https://doi.org/10.1021/ja00169a033.

(16) Xu, Y.-K.; Yang, L.; Liao, S.-G.; Cao, P.; Wu, B.; Hu, H.-B.; Guo, J.; Zhang, P. Koumine, Humantenine, and Yohimbane Alkaloids from *Gelsemium Elegans*. *J. Nat. Prod.* **2015**, *78* (7), 1511–1517. https://doi.org/10.1021/np5009619.

(17) Kerkovius, J. K.; Kerr, M. A. Total Synthesis of Isodihydrokoumine, (19*Z*)-Taberpsychine, and (4*R*)-Isodihydroukoumine N_4-Oxide. *J. Am. Chem. Soc.* **2018**, *140* (27), 8415–8419. https://doi.org/10.1021/jacs.8b05095.

(18) Arai, H.; Hirasawa, Y.; Rahman, A.; Kusumawati, I.; Zaini, N. C.; Sato, S.; Aoyama, C.; Takeo, J.; Morita, H. Alstiphyllanines E–H, Picraline and Ajmaline-Type Alkaloids from Alstonia Macrophylla Inhibiting Sodium Glucose Cotransporter. *Bioorg. Med. Chem.* **2010**, *18* (6), 2152–2158. https://doi.org/10.1016/j.bmc.2010.01.077.

(19) Kearney, S. E.; Zahoránszky-Kőhalmi, G.; Brimacombe, K. R.; Henderson, M. J.; Lynch, C.; Zhao, T.; Wan, K. K.; Itkin, Z.; Dillon, C.; Shen, M.; Cheff, D. M.; Lee, T. D.; Bougie, D.; Cheng, K.; Coussens, N. P.; Dorjsuren, D.; Eastman, R. T.; Huang, R.; Iannotti, M. J.; Karavadhi, S.; Klumpp-Thomas, C.; Roth, J. S.; Sakamuru, S.; Sun, W.; Titus, S. A.; Yasgar, A.; Zhang, Y.-Q.; Zhao, J.; Andrade, R. B.; Brown, M. K.; Burns, N. Z.; Cha, J. K.; Mevers, E. E.; Clardy, J.; Clement, J. A.; Crooks, P. A.; Cuny, G. D.; Ganor, J.; Moreno, J.; Morrill, L. A.; Picazo, E.; Susick, R. B.; Garg, N. K.; Goess, B. C.; Grossman, R. B.; Hughes, C. C.; Johnston, J. N.; Joullie, M. M.; Kinghorn, A. D.; Kingston, D. G. I.; Krische, M. J.; Kwon, O.; Maimone, T. J.; Majumdar, S.; Maloney, K. N.; Mohamed, E.; Murphy, B. T.; Nagorny, P.; Olson, D. E.; Overman, L. E.; Brown, L. E.; Snyder, J. K.; Porco, J. A.; Rivas, F.; Ross, S. A.; Sarpong, R.; Sharma, I.; Shaw, J. T.; Xu, Z.; Shen, B.; Shi,

W.; Stephenson, C. R. J.; Verano, A. L.; Tan, D. S.; Tang, Y.; Taylor, R. E.; Thomson, R. J.; Vosburg, D. A.; Wu, J.; Wuest, W. M.; Zakarian, A.; Zhang, Y.; Ren, T.; Zuo, Z.; Inglese, J.; Michael, S.; Simeonov, A.; Zheng, W.; Shinn, P.; Jadhav, A.; Boxer, M. B.; Hall, M. D.; Xia, M.; Guha, R.; Rohde, J. M. Canvass: A Crowd-Sourced, Natural-Product Screening Library for Exploring Biological Space. *ACS Cent. Sci.* **2018**, *4* (12), 1727–1741. https://doi.org/10.1021/acscentsci.8b00747.

(20) Lipkus, A. H.; Yuan, Q.; Lucas, K. A.; Funk, S. A.; Bartelt, W. F.; Schenck, R. J.; Trippe, A. J. Structural Diversity of Organic Chemistry. A Scaffold Analysis of the CAS Registry. *J. Org. Chem.* **2008**, *73* (12), 4443–4451. https://doi.org/10.1021/jo8001276.

(21) Lameijer, E.-W.; Kok, J. N.; Bäck, T.; IJzerman, A. P. Mining a Chemical Database for Fragment Co-Occurrence: Discovery of "Chemical Clichés." *J. Chem. Inf. Model.* **2006**, *46* (2), 553–562. https://doi.org/10.1021/ci050370c.

(22) Boschan, R.; Merrow, R. T.; van Dolah, R. W. The Chemistry of Nitrate Esters. *Chem. Rev.* **1955**, *55* (3), 485–510. https://doi.org/10.1021/cr50003a001.

(23) O'Connor, S. E.; Maresh, J. J. Chemistry and Biology of Monoterpene Indole Alkaloid Biosynthesis. *Nat. Prod. Rep.* **2006**, *23* (4), 532–547. https://doi.org/10.1039/b512615k.

(24) de Almeida, V. L.; Silva, C. G.; Silva, A. F.; Campana, P. R. V.; Foubert, K.; Lopes, J. C. D.; Pieters, L. Aspidosperma Species: A Review of Their Chemistry and Biological Activities. *J. Ethnopharmacol.* **2019**, *231*, 125–140. https://doi.org/10.1016/j.jep.2018.10.039.

(25) Saya, J. M.; Ruijter, E.; Orru, R. V. A. Total Synthesis of *Aspidosperma* and *Strychnos* Alkaloids through Indole Dearomatization. *Chem. – Eur. J.* **2019**, *25* (38), 8916–8935. https://doi.org/10.1002/chem.201901130.

(26) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.;

Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. *Gaussian 16 Rev. C.01*; Wallingford, CT, 2016.

(27) Becke, A. D. Density-functional Thermochemistry. III. The Role of Exact Exchange. *J. Chem. Phys.* **1993**, *98* (7), 5648–5652. https://doi.org/10.1063/1.464913.

(28) Lee, C.; Yang, W.; Parr, R. G. Development of the Colle-Salvetti Correlation-Energy Formula into a Functional of the Electron Density. *Phys. Rev. B* **1988**, *37* (2), 785–789. https://doi.org/10.1103/PhysRevB.37.785.

(29) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. A Consistent and Accurate *Ab Initio* Parametrization of Density Functional Dispersion Correction (DFT-D) for the 94 Elements H-Pu. *J. Chem. Phys.* **2010**, *132* (15), 154104. https://doi.org/10.1063/1.3382344.

(30) Barone, V.; Cossi, M. Quantum Calculation of Molecular Energies and Energy Gradients in Solution by a Conductor Solvent Model. *J. Phys. Chem. A* **1998**, *102* (11), 1995–2001. https://doi.org/10.1021/jp9716997.

(31) Cossi, M.; Rega, N.; Scalmani, G.; Barone, V. Energies, Structures, and Electronic Properties of Molecules in Solution with the C-PCM Solvation Model. *J. Comput. Chem.* **2003**, *24* (6), 669–681. https://doi.org/10.1002/jcc.10189.

(32) Zhao, Y.; Truhlar, D. G. The M06 Suite of Density Functionals for Main Group Thermochemistry, Thermochemical Kinetics, Noncovalent Interactions, Excited States, and Transition Elements: Two New Functionals and Systematic Testing of Four M06-Class Functionals and 12 Other Functionals. *Theor. Chem. Acc.* **2008**, *120* (1–3), 215–241. https://doi.org/10.1007/s00214-007-0310-x.

(33) Zhao, Y.; Truhlar, D. G. Density Functionals with Broad Applicability in Chemistry. *Acc. Chem. Res.* **2008**, *41* (2), 157–167. https://doi.org/10.1021/ar700111a.