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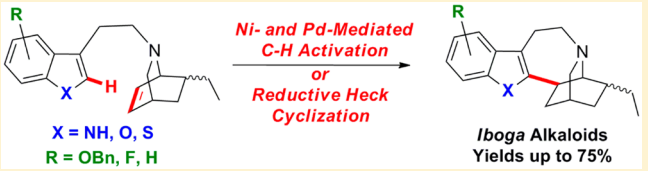
Constructing *Iboga* Alkaloids via C−H Bond Functionalization: Examination of the Direct and Catalytic Union of Heteroarenes and Isoquinuclidine Alkenes

Andrew C. Kruegel, Souvik Rakshit, Xiaoguang Li, and Dalibor Sames*

Department of Chemistry, Columbia University, New York, New York 10027, United States

Supporting Information

ABSTRACT: The *iboga* alkaloids have attracted considerable attention in both the scientific community and popular media due to their reported ability to reverse or markedly diminish cravings for, and self-administration of, the major drugs of abuse. We have developed three new intramolecular C−H functionalization procedures leading to the core seven-membered ring of the *iboga* skeleton, a cyclization that proved to be highly challenging. The electrophilic palladium salt $Pd(CH_3CN)_4(BF_4)_2$ was effective for the cyclization of diverse *N*-(2-arylethyl)isoquinuclidines with yields of 10−35%. A two-step, bromination-reductive Heck reaction protocol was also effective for the synthesis of ibogamine in 42% yield. Finally, a direct Ni(0)-catalyzed C−H functionalization provided the benzofuran analogues of ibogamine (74%) and *epi*-ibogamine (38%). Although each approach suffers from significant shortcomings, in combination, the methods described provide practical routes to diverse ibogamine analogues.



INTRODUCTION

***Iboga* Alkaloids: Background and Pharmacology.** The *iboga* alkaloids, represented by ibogamine and ibogaine (Figure 1A), are a class of natural products isolated from *Tabernanthe iboga*, a plant used in folk and ritualistic medicine in west Africa.

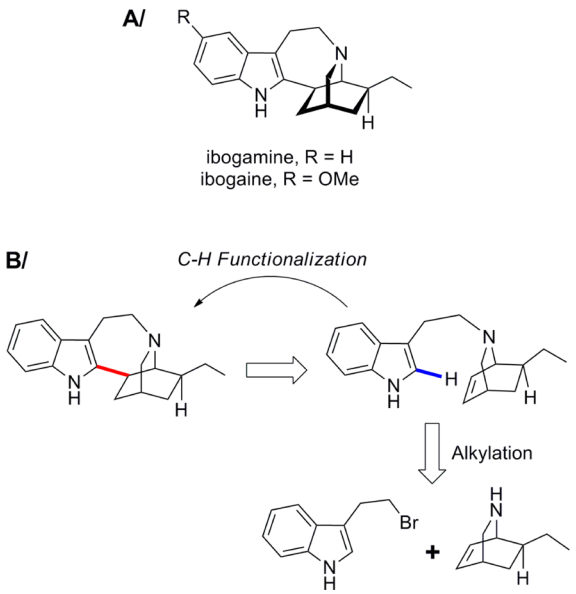


Figure 1. (A) Structure of *iboga* alkaloids. (B) The indicated disconnection unlocks a rapid and modular approach to ibogamine analogues. The key C−H functionalization is however highly challenging as described in this report.

Ibogaine has historically received significant attention in both the scientific community and popular media due to widespread anecdotal reports of its remarkable ability to reverse or markedly attenuate drug addiction and dependence in humans.[1,2] These claims have largely been recapitulated in rodents, where ibogaine reduces self-administration and reinstatement of major drugs of abuse, including cocaine, morphine, alcohol, and nicotine.[1] Despite this substantial evidence for ibogaine's efficacy in animal models, the mechanism of action responsible for its antiaddictive effects is not clear. The pharmacological activity of ibogaine has been extensively studied, and it is known to bind to a variety of CNS receptors with micromolar potency.[1,3] The complexity of ibogaine's pharmacological profile is further complicated by the high doses typically used in treatment and thus the high brain concentrations achieved.[4] Therefore, even targets of low binding affinity (>10 μM) may be of significant importance in mediating its effects. A particularly compelling hypothesis is that ibogaine is capable of increasing expression of glial cell line-derived neurotrophic factor in the ventral tegmental area of the brain and that this modulation is responsible for its antiaddictive properties.[5] However, ibogaine has also shown binding affinity and/or functional activity at a variety of other CNS targets, including the *N*-methyl-D-aspartate receptor, the dopamine and serotonin transporters, mu-opioid receptor, sigma 2 receptor, 5-HT2a, acetylcholine receptors, and others, so the overall interactions and effects of its complex pharmacology remain unclear.[1,3,6]

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Synthesis of *Iboga* Alkaloids via C−H Functionalization. In light of their interesting pharmacological and clinical properties, the *iboga* alkaloids have attracted considerable interest from the synthetic community, with several total syntheses of the desmethoxy analogue ibogamine (Figure 1A) reported in the literature.[7] In the context of a research program studying the pharmacology and cell signaling biology of *iboga* alkaloids, we required a modular and robust synthesis for the preparation of ibogamine and unnatural analogues. Finding existing synthetic strategies poorly suited to this task, we endeavored to develop new synthetic methods providing access to the *iboga* skeleton.

For many years, we have been advancing "C−H bond functionalization" as a general concept in chemical synthesis to provide new strategic opportunities in the construction of complex molecular skeletons.[8] In the context of *iboga* alkaloid synthesis, we were interested in rapid construction of the polycyclic core structure by formation of the seven-membered ring, via C−H bond/alkene coupling, as the key strategic step (Figure 1B). This is a powerful disconnection that would enable modular and convergent synthesis of ibogamine analogues from a diverse set of readily available isoquinuclidines and bromoethylheteroarenes.

This approach was employed by Trost in the synthesis of ibogamine and related systems.[9−11] Unfortunately, the original conditions reported by Trost for this cyclization suffer from several significant disadvantages. First, stoichiometric quantities of both palladium and silver are required, making the transformation quite costly. More importantly, we found this procedure inconsistent and low yielding, and yields over 15% were never obtained despite extensive variation of the reaction conditions. Our results are in agreement with those of Hodgson, reported independently.[12] Therefore, we set out to systematically examine this powerful, but challenging, C−H functionalization step for cyclization of the *iboga* skeleton, with the main goal of developing new catalytic procedures to provide ibogamine analogues for our chemical biology project.

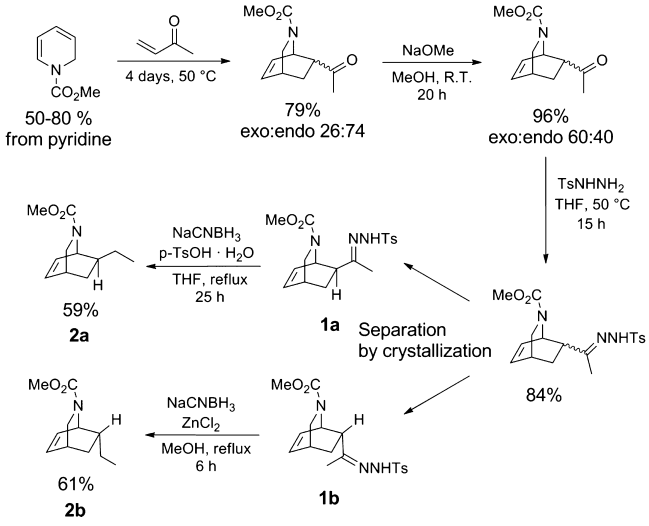
RESULTS AND DISCUSSION

Synthesis of Starting Materials. A collection of cyclization substrates was first prepared via a modular route. To prepare the isoquinuclidine fragment, *exo*- and *endo*-tosylhydrazones **1a** and **1b** were prepared according to the method of Krow (Scheme 1).[13] It should be noted that the stereochemistry of these products was incorrectly assigned in this original report, as noted and corrected by Hodgson based on crystallographic results.[12] We have independently confirmed the corrected stereochemistry of both hydrazones based on NMR experiments. Finding the reported reduction procedures of the hydrazones to be low yielding, we developed alternative conditions. Interestingly, the two isomers required different reduction conditions, with the *exo* isomer **1a** being much more resistant to reduction. By our modified conditions, both *exo*- and *endo*-7-ethylisoquinuclidines **2a** and **2b** were successfully obtained (Scheme 1).

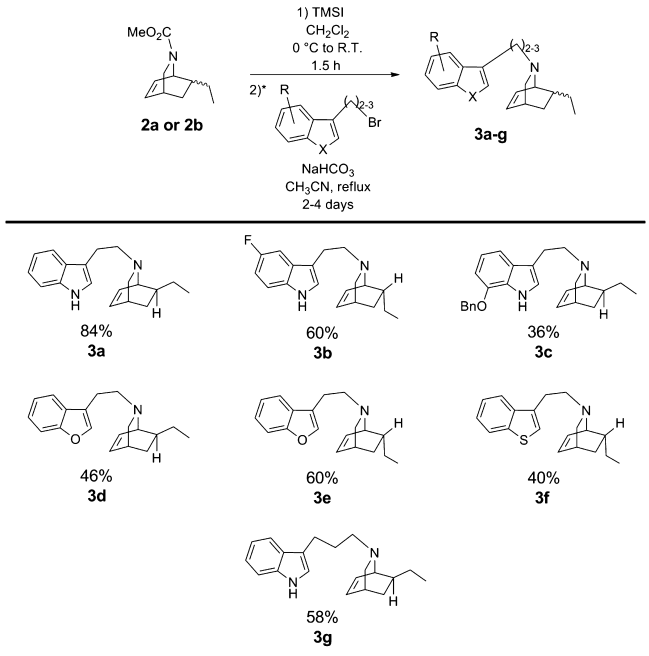
These were then deprotected and the resulting amine hydroiodide salts alkylated with various bromoalkylheteroarenes **S2a−e** (for synthesis, see Experimental Section and Supporting Information, Scheme S1) to obtain a collection of *N*-(heteroarylalkyl)isoquinuclidines **3a−g** (Scheme 2).

Indole C−H Bond Functionalization: Electrophilic Approach. Initially, it was hoped that a catalytic electrophilic activation strategy could be developed under acidic conditions.

Scheme 1. Synthesis of Isoquinuclidine Building Blocks via Diels−Alder Reaction



Scheme 2. Synthesis of *N*-(Heteroarylalkyl)isoquinuclidines by Alkylation



*For synthesis of bromoalkylheteroarenes, see Experimental Section (compounds **S2a−e**) and Supporting Information (Scheme S1)

Electrophilic palladium(II) species are known to activate arenes for addition to olefins in oxidative couplings (effectively stoichiometric Heck reactions).[14,15] Likewise, Trost[9−11] and others[16] have shown that the intermediate alkyl-palladium species in these reactions can be reduced to afford a reductive coupling process. Therefore, it was hoped that in the *iboga* system, where oxidative cyclization is not feasible due to strain considerations, the intermediate alkyl-palladium species would be susceptible to protonolysis. In such a reaction, an electrophilic palladium (or other metal) species would activate the system either through direct metalation of indole or through coordination to the olefin. Following C−C bond

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formation, protonative removal of the metal could regenerate the electrophilic catalyst (Figure 2).

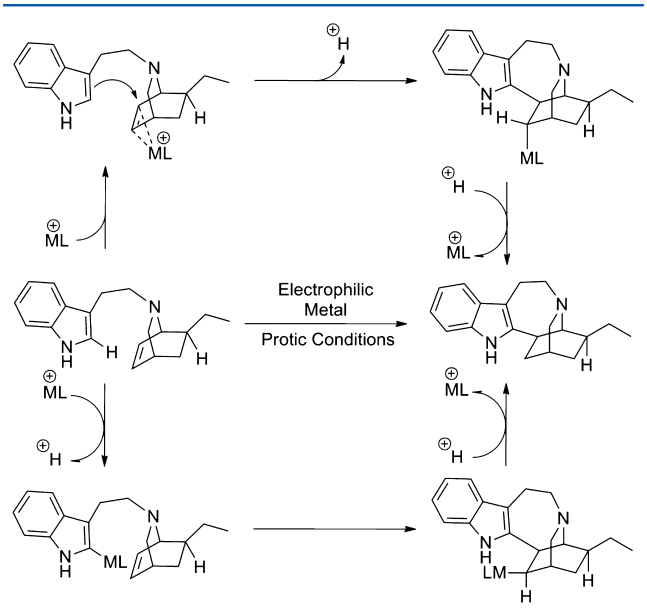
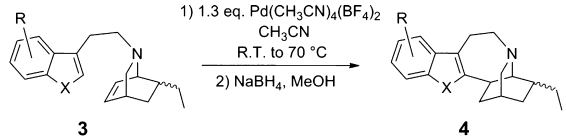


Figure 2. Proposed mechanistic rationale for an electrophilic cyclization. ML represents the metal (M) attached to one or more ligands (L).

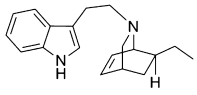
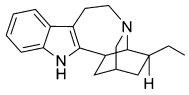
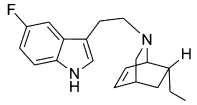
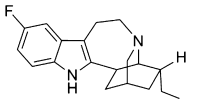
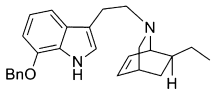
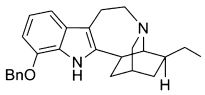
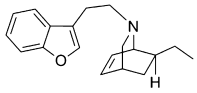
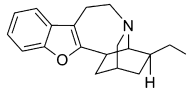
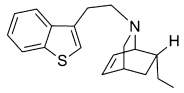
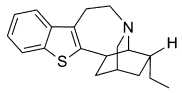
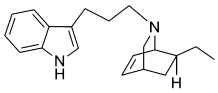
Unfortunately, a variety of Pd(II) salts under protic/acidic conditions failed to effect cyclization (see Supporting Information, Table S1). We also examined a large variety of other electrophilic transition metal conditions (see Supporting Information, Table S2), including platinum and ruthenium catalysts effective for intramolecular indole−alkene hydroarylation reactions.[17,18] Several gold-catalyzed conditions reported for indole−alkene coupling were also attempted, as well as the nonmetallic electrophilic reagent *N*-phenylselenophthalimide.[19−21] However, in all cases, none or only a trace of the desired product was detected. A frequent problem in many trials was the rapid reduction and precipitation of the electrophilic metal species as the corresponding neutral metal (e.g., palladium black). We suspect that reduction by the tertiary amine of the substrate is a primary driver of these difficulties. Furthermore, addition of a variety of oxidants did not successfully prevent reduction and precipitation of the metal in the case of palladium.

In contrast to these disappointing results, it was found that the original conditions[9−11] could be improved by a simple modification. When the preformed palladium tetrafluoroborate salt $Pd(CH_3CN)_4(BF_4)_2$ was used in place of a mixture of $PdCl_2(CH_3CN)_2$ and $AgBF_4$, modest, but consistent, yields of ibogamine were obtained following sodium borohydride reduction of the resulting organopalladium intermediate (Table 1, entry 1). This result indicates that silver is not directly involved in electrophilic activation of the substrate and serves only to exchange chloride for noncoordinating tetrafluoroborate, thus generating a more active electrophile. Indeed, a reagent system consisting of equimolar amounts of $Pd(CH_3CN)_4(BF_4)_2$ and $AgBF_4$ provided an identical yield to the palladium salt alone, thus confirming the likely role of silver as a simple halide scavenger. Our modified conditions were applied with success to a variety of substrates (Table 1, entries 2−5). As expected, lower yields were obtained when the

Table 1. Preparation of Ibogamine Analogues via Electrophilic Palladation−Cyclization[a]



3 4

Entry	Substrate	Result[b]
1	 3a	 29% (33%) 4a
2	 3b	 11% (16%) 4b
3[c]	 3c	 23% (27%) 4c
4	 3d	 (11%) 4d
5[d]	 3f	 34% (35%) 4f
6[d]	 3g	No Product

[a]Reactions run at 0.250 mmol scale. [b]Isolated yields from representative examples of two or more independent trials, NMR yields in parentheses, trial-to-trial variation typically <5%. [c]Run at 0.100 mmol scale. [d]Run at 0.060 mmol scale.

heteroarene was more electron-poor, with both the fluoroindole **3b** and benzofuran **3d** providing significantly reduced yields. However, these conditions were not effective for the formation of the eight-membered ring analogue when applied to **3g** (Table 1, entry 6). In all cases, the primary side products were the hydrogenated starting materials (olefin reduced), which were often observed in comparable yields to the desired products. Presumably, these side products result from residual starting material that is hydrogenated by liberated hydrogen during the sodium borohydride quench. Accordingly, it was found that extended reaction times reduced the amount of hydrogenated byproduct but, surprisingly, did not increase yields of the cyclized product. Using these conditions, an attempt was also made to probe the viability of a protic demetalation catalytic cycle (Figure 2). After treatment of **3a** with $Pd(CH_3CN)_4(BF_4)_2$ in the usual manner, tetrafluoroboric acid diethyl ether complex was added in place of the normal

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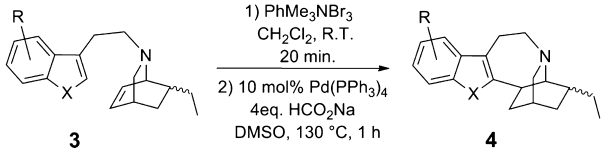
$NaBH_4$ treatment. Unfortunately, no conversion of the intermediate organopalladium species to the product was observed under these conditions, either at room temperature or upon heating. Therefore, a strategy based on protonolysis to regenerate an active Pd(II) catalytic species does not appear to be feasible, and thus, we were unable to overcome the need for stoichiometric palladium using this strategy.

Indole C−H Bond Functionalization: Bromination and Reductive Heck Coupling. Encountering such difficulties with the electrophilic activation approach and still desiring a catalytic route to the *iboga* skeleton, an alternative strategy was pursued employing traditional palladium chemistry. It was found that substrate **3a** could be selectively brominated at the indole 2-position using trimethylphenylammonium tribromide in ∼65% yield. This aryl bromide intermediate was then cyclized by a reductive Heck reaction[22] employing $Pd(PPh_3)_4$ as catalyst, with sodium formate as the hydride source (Table 2, entry 1). Although initial trials with this reaction were low yielding, some optimization identified DMSO as the ideal solvent for this transformation, and with the optimized conditions, yields of ∼65% were obtained with only trace quantities of **3a** observed (resulting from competing aryl bromide reduction). Reduced catalyst loadings achieved complete conversion but provided lower yields of product. Likewise, alternative formates (potassium and ammonium) resulted in significantly reduced yields. Furthermore, it was found that purification of the intermediate bromide was not required. The crude bromination mixture could simply be washed with aqueous ammonia *in situ*, concentrated, and used directly in the cyclization step. This protocol provided an overall yield of 42% over two steps, in agreement with the yields obtained when the two steps were run independently. The total synthesis of ibogamine was thus accomplished in seven steps from pyridine (6.4% overall yield).

Table 2. Preparation of Ibogamine Analogues via Reductive Heck Reaction



entry	substrate	result
1	**3a**	**4a**, 42%[a]
2	**3b**	**4b**, 3%
3	**3c**	bromination at 4-position
4	**3d**	no bromination
5	**3f**	no bromination
6	**3g**	no cyclization

[a]∼65% yield for each individual step.

Pleased with the success of the reductive Heck reaction for the efficient total synthesis of ibogamine, we attempted to apply the same procedure to related substrates (Table 2, entries 2−6). Unfortunately, these efforts met with poor results. With electron-poor indole substrate **3b**, only a very small quantity of the desired product could be isolated, and the product mixture was very complex, hindering purification. Further examination revealed that both the bromination step and the cyclization step (with pure bromide) were independently low yielding (<25%). Difficulty was also encountered with electron-rich substrate **3c**, as bromination was selective for the indole 4-position, *para* to the benzyloxy group. When benzofuran (**3d**) and benzothiophene (**3f**) substrates were used, no bromination was observed. Finally, substrate **3g** was successfully brominated, but no cyclization occurred, only reduction of the aryl bromide back to the starting material **3g**. Therefore, although effective for the synthesis of ibogamine itself, the reductive Heck procedure did not provide a general solution for the synthesis of ibogamine analogues varied at the aryl moiety.

Indole C−H Bond Functionalization: Low-Valent Metal Insertion Approach. At this time, we became interested in an alternative strategy employing a direct C−H insertion mechanism. It was envisioned that oxidative addition of a low-valent transition metal into the 2-position heteroaryl C−H bond might provide a metal hydride species that could then add directly to the olefin, followed by reductive elimination to provide the cyclized product and regenerate the catalyst (Figure 3). In particular, we were interested by a recent report of intermolecular hydroheteroarylation of styrenes employing a nickel(0)/*N*-heterocyclic carbene (NHC) catalyst system.[23] The substrate scope of this work included both electron-poor indoles (electron-withdrawing group at the 3-position) and benzofuran, as well as a single example demonstrating hydroheteroarylation of an aliphatic olefin. Therefore, it was hoped that this Ni(0) catalyst system might be employed intramolecularly to afford cyclization of the *iboga* skeleton. Applying 20 mol % $Ni(COD)_2$ and 24 mol % IMes (1,3-bis(2,4,6-trimethylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene) in toluene at 130 °C to benzofuran substrate **3d**, good yields of the cyclized product **4d** could be obtained. After some optimization, it was found that heptane was a slightly superior solvent for this transformation (Table 3, entry 1). Interestingly, yields with the *endo*-epimer substrate **3e** were not as high (Table 3, entry 2). This disparity may result from a difference in steric shielding of the tertiary amine by the ethyl group between **3d** and **3e**, allowing for greater interference with the catalytic species by the amine in *endo*-substrate **3e**. Alternatively, the steric bulk of the *exo*-ethyl group in **3d** may act to enrich the *N*-atom configuration in which the heteroarylethyl substituent is constrained on the olefin side and thus appropriately aligned for cyclization. Yields for these transformations could not be further improved. Alternative sources of Ni(0) or the use of phosphine ligands in place of IMes strongly inhibited product formation. Likewise, use of the alternative NHC ligand IPr did provide the desired products, but in lower yield, while other NHCs provided only traces of

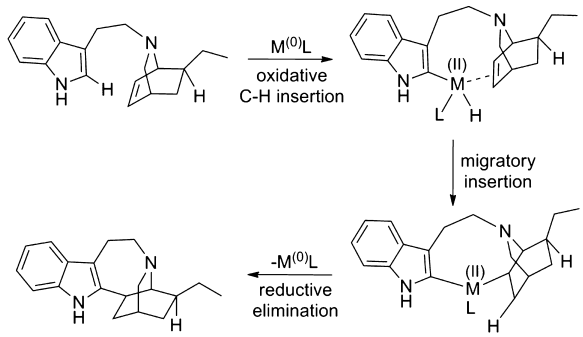


Figure 3. Alternative strategy for *iboga* cyclization relying on direct C−H insertion of a low-valent metal. ML represents the metal (M) attached to one or more ligands (L).

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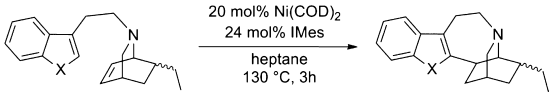
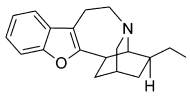
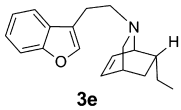
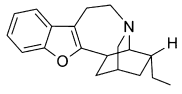
Table 3. Preparation of Ibogamine Analogues via Ni-Catalyzed C−H Activation[a]



Entry	Substrate	Result[b]
1	3d	 74% (86%) 4d
2	 3e	 38% (42%) 4e
3[c]	3a	No Conversion
4[d]	3f	No Conversion

[a]Reactions run at 0.500 mmol scale. [b]Isolated yields from representative examples of two or more independent trials, NMR yields in parentheses, trial-to-trial variation typically <5%. [c]Run at 0.250 mmol scale with 10 mol % $Ni(COD)_2$ and 10 mol % IMes in toluene. [d]Run at 0.250 mmol scale in toluene.

product (see Supporting Information, Table S3). Furthermore, reduction of the catalyst loading to 10 mol % resulted in incomplete conversion. Other low-valent metals were also completely ineffective for this transformation, with $(COD)_2Ir(BF_4)$ and $(COD)_2Rh(BF_4)$ showing no conversion of starting material, both with and without IMes. Finally, the analogous intermolecular reaction between **2b** and 3-methylbenzofuran was ineffective under these conditions, indicating that this reaction benefits from intramolecular entropic enhancement.

Building on these results, application of similar conditions to indole and benzothiophene substrates was attempted. Unfortunately, no conversion was observed in either case (Table 3, entries 3 and 4). In the case of the indole substrate, it was presumed that the reaction might be inhibited by competing insertion into the more acidic N−H bond or by the higher electron density of the heteroarene (compared to benzofuran). Therefore, we felt that protection of the indole nitrogen could remedy both of these potential difficulties by removing the problematic N−H bond while decreasing the electron richness of the heteroarene (with electron-withdrawing protecting groups). Unfortunately, analogues of **3a** protected at nitrogen with a tosyl, triflyl, acetyl, or [2-(trimethylsilyl)ethoxy]methyl group[24] also failed in the cyclization. Similarly, an attempt to use a pyridin-2-ylsulfonyl group on the indole nitrogen to provide a directing effect also met with failure. Therefore, the remarkable Ni-mediated transformation appears to be limited to benzofuran substrates. A variety of alternative low-valent metal catalyst systems were also screened on **3a** and its *N*-protected analogues, but no further effective conditions were identified (see Supporting Information, Table S3).

CONCLUSION

In closing, we examined the modular synthesis of the *iboga* alkaloid core centered on a direct intramolecular cyclization. This key C−H bond functionalization step proved unexpectedly difficult. Although there are a number of catalytic systems that effect hydroarylation of unactivated alkenes, most of them failed in the specific context of this cyclization. We propose that the following structural features contribute to the difficulty of this transformation: (1) the substitution of the indole in the 3-position with an electron-donating group (that sterically hinders indole metalation); (2) the isoquinuclidine's basic amine (that deactivates and reduces transition metal catalysts); (3) the bicyclic nature of the isoquinuclidine (that prevents oxidative cyclization); and (4) formation of a medium-sized ring. Nevertheless, we have found a direct nickel-catalyzed cyclization for the furan substrates that provides novel oxaibogamine analogues and two palladium-based systems for the formation of the seven-membered ring in *iboga* alkaloids. Unfortunately, all three procedures suffer from significant shortcomings, most notably low yields, high or stoichiometric catalyst loading, and/or poor substrate scope. However, in combination, the methods described do indeed provide practical routes to several novel ibogamine analogues and permit rapid access to a larger analogue library for a molecular scaffold of high pharmacological interest. The difficulties encountered in this work serve to highlight the challenges of C−H bond functionalization methodology development within the context of a complex substrate class and the shortcomings of existing methodologies when applied to substrates with interfering functional groups and multiple structural features.

EXPERIMENTAL SECTION

General Considerations. Reagents and solvents (including anhydrous solvents) were obtained from commercial sources and were used without further purification unless otherwise stated. All reactions were performed in flame-dried glassware under argon atmosphere unless otherwise stated and monitored by TLC using solvent mixtures appropriate to each reaction. Column chromatography was performed on silica gel (40−63 μm). Nuclear magnetic resonance spectra were recorded on 300, 400, or 500 MHz instruments as indicated. Chemical shifts are reported as δ values in parts per million referenced to $CDCl_3$ (^{1}H NMR = 7.26 and ^{13}C NMR = 77.16). Multiplicity is indicated as follows: s (singlet); d (doublet); t (triplet); q (quartet); p (pentet); h (heptet); dd (doublet of doublets); ddd (doublet of doublet of doublets); dt (doublet of triplets); td (triplet of doublets); m (multiplet); br (broad). For those described compounds containing a carbamate group, complex spectra with split peaks are observed. This effect can be ascribed to the presence of conformers about the carbamate group. As a result of these effects, multiple peaks may correspond to the same proton group or carbon atom. When possible, this is indicated by an "and" joining two peaks or spectral regions. Furthermore, compounds containing fluorine are subject to C−F coupling, resulting in splitting of some carbon peaks. In these cases, peaks are listed as doublets, and the associated coupling constants are indicated. Alternatively, certain carbon peaks overlap and thus represent two carbons (indicated by (2C) designation). In all cases the assignments of these complex peaks were determined by COSY, HSQC, and/or DEPT-135 experiments. All carbon peaks are rounded to one decimal place unless such rounding would cause two close peaks to become identical. In these cases, two decimal places are retained. High-resolution mass spectra (HRMS) were acquired on a high-resolution sector-type double-focusing mass spectrometer (ionization mode: FAB+). In calculated masses, the mass difference for loss of one electron has been taken into account for positive ions.

2-(5-Fluoro-1*H*-indol-3-yl)ethanol (S1a). Compound **S1a** was prepared using the modified Fischer indole synthesis protocol

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described by Campos.[25] 4-Fluorophenylhydrazine hydrochloride (8.13 g, 50.0 mmol) was dissolved in a mixture of DMAc (70 mL) and 4% m/m aqueous H_2SO_4 (70 mL) and heated to 100 °C. 2,3-Dihydrofuran (3.78 mL, 50.0 mmol) was then added dropwise over 2 min, and the brown solution was stirred for 3 h at 100 °C. After cooling to room temperature, the mixture was extracted with EtOAc (3 × 50 mL, then 25 mL), and the combined organics were washed with H_2O (3 × 50 mL), dried over Na_2SO_4, and concentrated to give a yellow-orange oil. This was purified by column chromatography (1:1 hexanes:EtOAc) to yield alcohol **S1a** as an orange-red oil (5.57 g, 62%). Spectral and physical properties were in agreement with those previously reported.[26]

2-(7-(Benzyloxy)-1*H*-indol-3-yl)ethanol (S1b). Glyoxylate ester **S3** (5.64 g, 18.2 mmol, see below for preparation) was carefully added to a suspension of $LiAlH_4$ (2.08 g, 54.7 mmol) in anhydrous THF (90 mL) at room temperature, and the resulting yellowish-gray mixture was refluxed for 5 h. After cooling in ice, the reaction was quenched by the successive addition of H_2O (2.1 mL), 15% aqueous NaOH (2.1 mL), and H_2O again (6.3 mL). The resulting mixture was stirred vigorously until the aluminum salts were white and loose and then filtered, washing the filter cake with Et_2O (3 × 50 mL). The combined filtrate and washings were concentrated to afford alcohol **S1b** as a cloudy pale-brown oil that slowly crystallized to an off-white solid (4.86 g, 100%). Mp 70−72 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (br s, 1H), 7.49 (dd, J = 7.7, 1.1 Hz, 2H), 7.45−7.35 (m, 3H), 7.26 (d, J = 8.0 Hz, 1H), 7.05 (t, J = 7.9 Hz, 1H), 7.02 (d, J = 2.3 Hz, 1H), 6.75 (d, J = 7.7 Hz, 1H), 5.21 (s, 2H), 3.89 (br s, 2H), 3.02 (t, J = 6.4 Hz, 2H), 1.59 (br s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.6, 137.2, 129.1, 128.8, 128.3, 128.0, 127.8, 122.3, 120.0, 112.8, 112.0, 103.4, 70.4, 62.8, 29.0; HRMS (FAB+) m/z $[M]^+$ calcd for $C_{17}H_{18}NO_2^+$ 268.1332, found 268.1334.

2-(Benzofuran-3-yl)ethanol (S1c). A solution of ester **S4** (6.21 g, 30.4 mmol, see below for preparation) in anhydrous THF (25 mL) was added dropwise to a suspension of $LiAlH_4$ (3.00 g, 79.0 mmol) in anhydrous THF (80 mL) over 10 min, and the resulting mixture was then refluxed for 1 h. After cooling to room temperature the reaction was quenched by the successive addition of H_2O (3 mL), 15% aqueous NaOH (3 mL), and H_2O again (9 mL). The resulting mixture was stirred vigorously until the aluminum salts were white and loose and then filtered, washing the filter cake with Et_2O (2 × 30 mL, then 2 × 50 mL). The combined filtrate and washings were concentrated to yield the pure alcohol **S1c** as a yellow oil (4.81 g, 98%). Spectral and physical properties were in agreement with those previously reported.[27]

2-(Benzo[*b*]thiophen-3-yl)ethanol (S1d). Compound **S1d** was prepared via $LiAlH_4$ reduction of benzo[*b*]thiophene-3-acetic acid as previously described.[28] The crude product was obtained as an orange oil of sufficient purity for the next step (895 mg, 97%). Spectral and physical properties were in agreement with those previously reported.[29]

3-(2-Bromoethyl)-5-fluoro-1*H*-indole (S2a). To a solution of alcohol **S1a** (5.51 g, 30.75 mmol) and carbon tetrabromide (14.28 g, 43.05 mmol) in anhydrous CH_3CN (160 mL) at 0 °C was added triphenylphosphine (10.49 g, 39.98 mmol) in five equal portions over 10 min, and the resulting mixture was stirred for 20 min at 0 °C. At this time, the reaction mixture was concentrated, and the resulting dark-orange oil was dissolved in CH_2Cl_2 and washed through a silica plug, washing with CH_2Cl_2 until all product had passed through. The eluate was then concentrated and washed through a second silica plug, starting with 2:1 hexanes/CH_2Cl_2 until most of the upper bromoform impurity had been eluted and then with CH_2Cl_2 to finish elution of the product. The collected eluate-containing product was again concentrated and purified by column chromatography (6:1 hexanes:EtOAc) to yield pure bromide **S2a** as a yellow oil which slowly solidified to a waxy yellow-brown solid (4.97 g, 67%). Spectral and physical properties were in agreement with those previously reported.[30]

7-(Benzyloxy)-3-(2-bromoethyl)-1*H*-indole (S2b). To a solution of alcohol **S1b** (4.81 g, 18.0 mmol) and carbon tetrabromide (8.95 g, 27.0 mmol) in anhydrous CH_2Cl_2 (36 mL) at room temperature was carefully added triphenylphosphine (7.08 g, 27.0 mmol), and the resulting mixture was stirred for 1 h. At this time, the reaction mixture was filtered through a silica plug, washing the plug with additional CH_2Cl_2 (225 mL). The filtrate was concentrated to afford a yellow oil that was further purified by column chromatography (hexanes, two column volumes → 8:2 hexanes:Et_2O, three column volumes) to yield the pure bromide **S2b** as a pale-yellow oil that slowly crystallized to an off-white solid (3.78 g, 64%). Mp 65−67 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (br s, 1H), 7.48 (d, J = 7.1 Hz, 2H), 7.44−7.39 (m, 2H), 7.39−7.34 (m, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.08−7.02 (m, 2H), 6.74 (d, J = 7.7 Hz, 1H), 5.21 (s, 2H), 3.64 (t, J = 7.7 Hz, 2H), 3.33 (t, J = 7.7 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.6, 137.1, 128.8, 128.6, 128.3, 128.0, 127.0, 122.0, 120.2, 114.1, 111.6, 103.4, 70.4, 33.1, 29.7; HRMS (FAB+) m/z $[M]^+$ calcd for $C_{17}H_{17}NO^{79}Br^+$ 330.0488, found 330.0483.

3-(2-Bromoethyl)benzofuran (S2c). To a solution of alcohol **S1c** (4.76 g, 29.35 mmol) and carbon tetrabromide (14.60 g, 44.03 mmol) in anhydrous CH_2Cl_2 (60 mL) at room temperature was carefully added triphenylphosphine (11.55 g, 44.03 mmol), and the resulting dark orange-brown mixture was left to stir for 30 min. At this time, the reaction mixture was filtered through a silica plug, washing the plug with additional CH_2Cl_2 (150 mL). The filtrate was concentrated to afford a yellow oil which was redissolved in CH_2Cl_2 (50 mL) and washed through a second silica plug, again washing the plug with additional CH_2Cl_2 (150 mL). The yellow oil obtained on concentration of the filtrate was then purified by column chromatography (hexanes, two column volumes → 20:1 hexanes:Et_2O, three column volumes) to yield pure bromide **S2c** as a pale-yellow oil (6.35 g, 96%). Spectral and physical properties were in agreement with those previously reported.[27]

3-(2-Bromoethyl)benzo[*b*]thiophene (S2d). To a solution of alcohol **S1d** (895 mg, 5.02 mmol) and carbon tetrabromide (2.50 g, 7.53 mmol) in anhydrous CH_2Cl_2 (10 mL) at room temperature was carefully added triphenylphosphine (1.98 g, 7.53 mmol), and the resulting dark red-brown mixture was stirred for 15 min. The reaction mixture was then concentrated and purified directly by column chromatography (6:1 hexanes:EtOAc) to yield pure bromide **S2d** as an orange oil after thorough drying under high vacuum to remove bromoform impurity (1.14 g, 94%). Spectral and physical properties were in agreement with those previously reported.[31]

3-(3-Bromopropyl)-1*H*-indole (S2e). Alcohol **S1e** (3-(1*H*-indol-3-yl)propan-1-ol) was prepared starting from phenylhydrazine hydrochloride (2.17 g, 15.0 mmol) using a modified Fischer indole synthesis protocol as previously described.[25] The crude alcohol was obtained as an orange oil containing solvent and other impurities (2.44 g). The whole of this material was dissolved in anhydrous CH_2Cl_2 (30 mL) along with carbon tetrabromide (6.93 g, 20.90 mmol), and triphenylphosphine (5.82 g, 20.90 mmol) was carefully added at room temperature. After stirring for 30 min, the reaction mixture was concentrated and purified directly by column chromatography (6:1 hexanes:EtOAc) to yield pure bromide **S2e** as a pale-yellow oil (1.81 g, 51% for two steps). Spectral and physical properties were in agreement with those previously reported.[32]

Methyl 2-(7-(Benzyloxy)-1*H*-indol-3-yl)-2-oxoacetate (S3). To a solution of 7-benzyloxyindole (4.91 g, 22.0 mmol) in anhydrous THF (65 mL) at 0 °C was added oxalyl chloride (2.49 mL, 28.6 mmol) dropwise over 5 min, and the resulting yellow-orange solution was stirred at 0 °C for 4 h. The reaction mixture was then concentrated *in vacuo* to yield the crude acyl chloride intermediate as a yellow-brown solid. To this material was added anhydrous MeOH (40 mL); the mixture was cooled in ice; and one neck of the flask was opened under a strong flow of argon to remove any evolved HCl gas as Et_3N (3.99 mL, 28.6 mmol) was added dropwise over 3 min. The yellow mixture was then sealed again and refluxed for 2 h and then cooled to 0 °C, and the solids were collected by filtration, washing at the filter with several small portions of ice-cold MeOH. Glyoxylate ester **S3** was thus obtained as yellow ochre crystals (5.67 g, 83%). Mp 175−178 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (br s, 1H), 8.41 (d, J = 3.3 Hz, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.49−7.44 (m, 2H), 7.44−7.34 (m, 3H), 7.25 (t, J = 8.0 Hz, 1H), 6.86 (d, J = 7.7 Hz, 1H), 5.21 (s, 2H), 3.94 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.9, 163.3,

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145.4, 136.6, 135.7, 128.9, 128.6, 128.1, 127.8, 126.8, 124.4, 115.4, 115.0, 106.0, 70.7, 52.9; HRMS (FAB+) m/z [M + H]$^+$ calcd for $C_{18}H_{16}NO_4^+$ 310.1074, found 310.1079.

Ethyl 2-(Benzofuran-3-yl)acetate (S4). Compound **S4** was prepared by a slight modification of the literature procedure.[33] A solution of benzofuran-3(2*H*)-one (5.00 g, 37.3 mmol) and (carbethoxymethylene)triphenylphosphorane (14.28 g, 41.0 mmol) in anhydrous toluene (125 mL) was refluxed for 87 h and then concentrated *in vacuo*. On standing, copious crystals formed in the dark-brown liquid. The mixture was diluted with 10:1 hexanes:EtOAc and the crystalline mass crushed thoroughly. The supernatant was then decanted, leaving behind as much of the solids as possible. The residual crystalline solids were washed 3× with 10:1 hexanes:EtOAc, removing and saving the supernatant each time. The combined washes were then purified directly by column chromatography (10:1 hexanes:EtOAc, large fractions collected) to yield the pure ester **S4** as an orange oil (6.30 g, 83%). Spectral and physical properties were in agreement with those previously reported.[34]

***exo*-Methyl 7-(1-(2-Tosylhydrazono)ethyl)-2-azabicyclo-[2.2.2]oct-5-ene-2-carboxylate (1a) and *endo*-Methyl 7-(1-(2-Tosylhydrazono)ethyl)-2-azabicyclo[2.2.2]oct-5-ene-2-carboxylate (1b).** *Exo*-tosylhydrazone **1a** and *endo*-tosylhydrazone **1b** were prepared by the method of Krow.[13] However, in contrast to the previous report, crystalline products were obtained for both stereoisomers. Further, the stereochemistry of **1a** and **1b** has been revised from the initial report[13] as confirmed by 2D NMR experiments and by the reduction of **1a** to *exo* product **2a**, the structure of which has been previously assigned by Hodgson using X-ray crystallography.[12] Also, isoquinuclidine **2a** was converted to ibogamine, further confirming the *exo* stereochemistry of the 7-ethyl group. For clarification, the preparation of **1a** and **1b** is described as follows. A mixture of *exo*/*endo*-methyl 7-acetyl-2-azabicyclo[2.2.2]oct-5-ene-2-carboxylate[35] (60:40 *exo*:*endo* ratio, 34.93 g, 167 mmol) and *p*-toluenesulfonhydrazide (31.10 g, 167 mmol) in anhydrous THF (136 mL) was heated at 50 °C for 15 h, at which time a white precipitate had formed. The reaction mixture was cooled to room temperature, and the white precipitate was collected by filtration, washing 3× at the filter with ice-cold MeOH, to provide pure *endo*-tosylhydrazone **1b** as a fine white powder (19.55 g, 31%). The filtrate and washings were combined and concentrated to a tan solid, which was recrystallized from MeOH to obtain the pure *exo*-tosylhydrazone **1a** as white plates (33.14 g, 53%).

1a. The *exo*-tosylhydrazone was prepared by separation of the *exo*/*endo* mixture as described above. The spectral data were in agreement with the epimer incorrectly assigned to the *endo* configuration by Krow.[13] Mp 162−166 °C (inaccurate due to trapped MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) (spectrum complicated by conformers) δ 7.85 and 7.79 (d, J = 8.3 Hz, 2H), 7.35−7.28 (m, 3H), 6.46−6.37 (m, 2H), 4.74−4.68 and 4.61−4.57 (m, 1H), 3.52 and 3.34 (s, 3H), 3.02 and 2.94 (dd, J = 9.8, 2.2 Hz, 1H), 2.87 and 2.78 (dt, J = 9.8, 2.6 Hz, 1H), 2.73−2.67 (m, 1H), 2.48−2.37 (m, 1H), 2.44 (s, 3H), 2.30 and 2.09 (ddd, J = 13.1, 4.4, 2.4 Hz, 1H), 1.89 and 1.80 (s, 3H), 1.42−1.26 (m, 1H).

1b. The *endo*-tosylhydrazone was prepared by separation of the *exo*/*endo* mixture as described above. The spectral data were in agreement with the epimer incorrectly assigned to the *exo* configuration by Krow.[13] Mp 181−184 °C; ^{1}H NMR (400 MHz, $CDCl_3$) (spectrum complicated by conformers) δ 7.81 (t, J = 7.4 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.12 (s, 1H), 6.19 (q, J = 7.5 Hz, 1H), 6.02 (dd, J = 12.0, 5.6 Hz, 1H), 4.87 and 4.77 (d, J = 4.3 Hz, 1H), 3.69 and 3.66 (s, 3H), 3.23 (d, J = 10.1 Hz, 1H), 3.01−2.85 (m, 2H), 2.74 (br s, 1H), 2.45 and 2.44 (s, 3H), 1.87−1.66 (m, 1H), 1.71 and 1.69 (s, 3H), 1.59−1.47 (m, 1H).

***exo*-Methyl 7-Ethyl-2-azabicyclo[2.2.2]oct-5-ene-2-carboxylate (2a).** *exo*-Tosylhydrazone **1a** (33.02 g, 87.5 mmol), sodium cyanoborohydride (21.99 g, 350 mmol), and *p*-toluenesulfonic acid monohydrate (1.40 g, 7.36 mmol) were combined in anhydrous THF (250 mL) and refluxed for 21 h. At this time, additional *p*-TsOH·H_2O (0.35 g, 1.84 mmol) was added, and reflux was continued for an additional 4 h. The reaction mixture was then diluted with H_2O (250 mL) and extracted with cyclohexane (3 × 100 mL). The combined organics were washed with H_2O (250 mL), saturated aqueous $NaHCO_3$ (250 mL), and H_2O again (50 mL), dried over Na_2SO_4, and concentrated to provide a cloudy, pale-yellow oil. This was washed through a short silica column with 7:3 hexanes:EtOAc, and the eluate was concentrated to yield pure *exo*-isoquinuclidine **2a** as a pale-yellow oil (10.12 g, 59%). The spectral data were in agreement with the epimer incorrectly assigned to the *endo* configuration by Krow and in agreement with the data reported by Hodgson.[12,13]

***endo*-Methyl 7-Ethyl-2-azabicyclo[2.2.2]oct-5-ene-2-carboxylate (2b).** To a suspension of *endo*-tosylhydrazone **2b** (3.50 g, 9.27 mmol) in MeOH (41 mL) was added a solution of sodium cyanoborohydride (833 mg, 13.26 mmol) and $ZnCl_2$ (904 mg, 6.63 mmol) in MeOH (28 mL), and the resulting mixture was refluxed for 3 h. The reaction was then quenched with 1% aqueous NaOH (200 mL) and extracted with cyclohexane (3 × 50 mL). The combined organics were washed with H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated to provide a clear, colorless oil. This was washed through a short silica column with 1:1 hexanes:EtOAc, and the eluate was concentrated to yield pure *endo*-isoquinuclidine **2b** as a colorless oil (1.11 g, 61%). The spectral data were in agreement with the epimer incorrectly assigned to the *exo* configuration by Krow.[13]

General Procedure for Preparation of *N*-Arylalkylisoquinuclidines (3a−g). To a solution of *exo*- or *endo*-isoquinuclidine **2a** or **2b** (1 equiv) in anhydrous CH_2Cl_2 (0.125 M, based on **2**) at 0 °C was added iodotrimethylsilane (4 equiv), and the resulting mixture was stirred for 10 min at 0 °C and then at room temperature until TLC indicated that no **2** remained (typically ∼1 h). The reaction mixture was then concentrated to yield the deprotected isoquinuclidine hydroiodide salt in quantitative yield. To this material was added the appropriate bromoalkylheteroarene **S2a−e** (1 equiv) and $NaHCO_3$ (4 equiv), followed by anhydrous CH_3CN (0.208 M, based on **2**), and the resulting mixture was refluxed until TLC indicated the disappearance of the bromide (typically 2−4 days). The reaction was then diluted with H_2O, made strongly basic with aqueous NaOH, and extracted with $CHCl_3$ (3×). The combined organics were washed with H_2O, dried over Na_2SO_4, and concentrated to provide the crude product, which was purified by column chromatography with an appropriate solvent mixture (as described below for each compound).

***exo*-2-(2-(1*H*-Indol-3-yl)ethyl)-7-ethyl-2-azabicyclo[2.2.2]-oct-5-ene (3a).** The product **3a** was prepared using commercially available 3-(2-bromoethyl)-1*H*-indole and purified by column chromatography (8:2 hexanes:EtOAc + 2% Et_3N). It was obtained as a viscous yellow oil (4.82 g, 84%). Spectral and physical properties were in agreement with those previously reported.[12]

***endo*-7-Ethyl-2-(2-(5-fluoro-1*H*-indol-3-yl)ethyl)-2-azabicyclo[2.2.2]oct-5-ene (3b).** The product **3b** was purified by column chromatography (1:1 hexanes:EtOAc + 2% Et_3N) and obtained as a tan solid (450 mg, 60%). Mp 140−143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (br s, 1H), 7.26−7.20 (m, 2H), 7.05 (d, J = 2.2 Hz, 1H), 6.92 (td, J = 9.0, 2.5 Hz, 1H), 6.38 (t, J = 6.9 Hz, 1H), 6.18−6.11 (m, 1H), 3.41−3.36 (m, 1H), 3.03 (dd, J = 9.7, 1.8 Hz, 1H), 2.95−2.76 (m, 3H), 2.61−2.46 (m, 2H), 2.10 (dt, J = 9.7, 2.7 Hz, 1H), 2.07−1.98 (m, 1H), 1.79 (ddd, J = 12.1, 9.2, 2.8 Hz, 1H), 1.24−1.11 (m, 1H), 1.07−0.94 (m, 1H), 0.86 (t, J = 7.3 Hz, 3H), 0.82−0.74 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) (spectrum complicated by C−F coupling) δ 157.8 (d, J_{C-F} = 235 Hz), 133.8, 132.9, 130.2, 128.1 (d, J_{C-F} = 9.1 Hz), 123.5, 115.1 (d, J_{C-F} = 5.1 Hz), 111.7 (d, J_{C-F} = 10.1 Hz), 110.3 (d, J_{C-F} = 26.2 Hz), 103.9 (d, J_{C-F} = 20.2 Hz), 58.9, 57.3, 54.5, 40.6, 31.6, 30.8, 28.8, 24.6, 11.7; HRMS (FAB+) m/z [M + H]$^+$ calcd for $C_{19}H_{24}FN_2^+$ 299.1919; found 299.1928.

***exo*-2-(2-(7-(Benzyloxy)-1*H*-indol-3-yl)ethyl)-7-ethyl-2-azabicyclo[2.2.2]oct-5-ene (3c).** The product **3c** was purified by column chromatography (9:1 hexanes:EtOAc, three column volumes → 9:1 hexanes:EtOAc + 2% Et_3N, five column volumes) and obtained as a viscous yellow oil (70.3 mg, 36%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (br s, 1H), 7.48 (d, J = 7.1 Hz, 2H), 7.44−7.38 (m, 2H), 7.38−7.33 (m, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.04−6.98 (m, 2H), 6.71 (d, J = 7.7 Hz, 1H), 6.38−6.28 (m, 2H), 5.20 (s, 2H), 3.28 (s, 1H), 3.12 (d, J = 8.3 Hz, 1H), 2.93−2.75 (m, 3H), 2.58−2.48 (m, 1H), 2.45 (s, 1H),

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1.98 (d, J = 9.1 Hz, 1H), 1.69−1.53 (m, 2H), 1.53−1.45 (m, 1H), 1.35−1.28 (m, 1H), 0.98−0.94 (m, 1H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.5, 137.4, 132.9 (2C), 129.3, 128.7, 128.2, 127.9, 126.9, 121.2, 119.5, 115.7, 112.2, 103.1, 70.3, 59.2, 56.4, 56.1, 41.3, 31.8, 29.9, 27.3, 24.7, 12.7; HRMS (FAB+) m/z [M + H]$^+$ calcd for $C_{26}H_{31}N_2O^+$ 387.2431, found 387.2439.

***exo*-2-(2-(Benzofuran-3-yl)ethyl)-7-ethyl-2-azabicyclo[2.2.2]-oct-5-ene (3d).** The product **3d** was purified by column chromatography (19:1 hexanes:EtOAc) and obtained as an orange-brown oil (940 mg, 46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 7.3 Hz, 1H), 7.49 (s, 1H), 7.47−7.41 (m, 1H), 7.30−7.25 (m, 1H), 7.22 (td, J = 7.4, 1.1 Hz, 1H), 6.38−6.27 (m, 2H), 3.22 (d, J = 5.1 Hz, 1H), 3.09 (dd, J = 9.1, 2.1 Hz, 1H), 2.87−2.66 (m, 3H), 2.57−2.48 (m, 1H), 2.44 (br s, 1H), 1.94 (dt, J = 9.0, 2.4 Hz, 1H), 1.64−1.42 (m, 3H), 1.35−1.24 (m, 1H), 0.95−0.90 (m, 1H), 0.87 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.3, 141.7, 133.1, 132.8, 128.6, 124.1, 122.2, 119.7, 119.1, 111.5, 57.9, 56.3, 56.2, 41.3, 31.8, 29.9, 27.4, 23.0, 12.6; HRMS (FAB+) m/z [M + H]$^+$ calcd for $C_{19}H_{24}NO^+$ 282.1853; found 282.1862.

***endo*-2-(2-(Benzofuran-3-yl)ethyl)-7-ethyl-2-azabicyclo-[2.2.2]oct-5-ene (3e).** The product **3e** was purified by column chromatography (15:1 hexanes:EtOAc + 2% Et_3N, three column volumes → 9:1 hexanes:EtOAc + 2% Et_3N, three column volumes) and obtained as a pale-yellow oil (422 mg, 60%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, J = 7.3 Hz, 1H), 7.45 (s, 1H), 7.45 (d, J = 5.8 Hz, 1H), 7.30−7.25 (m, 1H), 7.25−7.20 (m, 1H), 6.39 (t, J = 7.3 Hz, 1H), 6.17−6.11 (m, 1H), 3.41−3.34 (m, 1H), 3.03 (dd, J = 9.6, 1.8 Hz, 1H), 2.91−2.74 (m, 3H), 2.59−2.53 (m, 1H), 2.53−2.47 (m, 1H), 2.07 (dt, J = 9.6, 2.7 Hz, 1H), 2.05−1.98 (m, 1H), 1.78 (ddd, J = 12.1, 9.2, 2.8 Hz, 1H), 1.23−1.13 (m, 1H), 1.06−0.96 (m, 1H), 0.86 (t, J = 7.4 Hz, 3H), 0.82−0.76 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 141.5, 133.7, 130.2, 128.5, 124.2, 122.3, 119.8, 118.9, 111.5, 57.9, 57.4, 54.5, 40.9, 31.6, 30.7, 28.8, 23.2, 11.8; HRMS (FAB+) m/z [M + H]$^+$ calcd for $C_{19}H_{24}NO^+$ 282.1853, found 282.1864.

***endo*-2-(2-(Benzo[*b*]thiophen-3-yl)ethyl)-7-ethyl-2-azabicyclo[2.2.2]oct-5-ene (3f).** The product **3f** was purified by column chromatography (9:1 hexanes:EtOAc, three column volumes → 9:1 hexanes:EtOAc + 2% Et_3N, three column volumes) and obtained as a yellow oil (150 mg, 40%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, J = 7.8 Hz, 1H), 7.77 (d, J = 7.7 Hz, 1H), 7.41−7.36 (m, 1H), 7.36−7.30 (m, 1H), 7.13 (s, 1H), 6.40 (t, J = 7.2 Hz, 1H), 6.17−6.12 (m, 1H), 3.44−3.39 (m, 1H), 3.08−2.97 (m, 3H), 2.97−2.88 (m, 1H), 2.66−2.57 (m, 1H), 2.55−2.49 (m, 1H), 2.11 (dt, J = 9.7, 2.7 Hz, 1H), 2.09−2.01 (m, 1H), 1.80 (ddd, J = 12.1, 9.2, 2.8 Hz, 1H), 1.24−1.14 (m, 1H), 1.07−0.96 (m, 1H), 0.86 (t, J = 7.4 Hz, 3H), 0.83−0.77 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.5, 139.2, 135.1, 133.8, 130.2, 124.2, 124.0, 123.0, 121.8, 121.7, 58.0, 57.5, 54.4, 40.6, 31.6, 30.7, 28.8, 27.9, 11.7; HRMS (FAB+) m/z [M + H]$^+$ calcd for $C_{19}H_{24}NS^+$ 298.1624, found 298.1625.

***exo*-2-(3-(1*H*-Indol-3-yl)propyl)-7-ethyl-2-azabicyclo[2.2.2]-oct-5-ene (3g).** The product **3g** was purified by column chromatography (15% EtOAc in hexanes + 2% Et_3N, three column volumes → 20% EtOAc in hexanes + 2% Et_3N) and obtained as a viscous pale-yellow oil (86 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (bs s, 1H), 7.62 (d, J = 7.9 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.21−7.15 (m, 1H), 7.13−7.08 (m, 1H), 6.99−6.96 (m, 1H), 6.34−6.23 (m, 2H), 3.19−3.16 (m, 1H), 3.05 (dd, J = 9.1, 2.3 Hz, 1H), 2.88−2.71 (m, 2H), 2.51 (dt, J = 11.8, 7.4 Hz, 1H), 2.43−2.37 (m, 1H), 2.30−2.21 (m, 1H), 1.87−1.69 (m, 3H), 1.68−1.53 (m, 2H), 1.51−1.42 (m, 1H), 1.34−1.24 (m, 1H), 0.96−0.88 (m, 1H), 0.92 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.5, 132.9 (2C), 127.8, 121.9, 121.3, 119.20, 119.16, 117.2, 111.1, 58.1, 56.4, 55.9, 41.5, 31.8, 30.0, 29.0, 27.4, 22.8, 12.7. HRMS (FAB+) m/z [M + H]$^+$ calcd for $C_{20}H_{27}N_2^+$ 295.2169, found 295.2182.

General Procedure for Preparation of *Iboga* Alkaloids by $Pd(CH_3CN)_4(BF_4)_2$-Mediated Cyclization of *N*-Arylalkylisoquinuclidines (4a−f). In a glovebox, a Schlenk flask was charged with $Pd(CH_3CN)_4(BF_4)_2$ (144 mg, 0.325 mmol). It was then sealed and removed from the glovebox, and anhydrous CH_3CN (3.5 mL) was added to form a yellow solution. To this solution was added a solution of the substrate **3a−g** (0.250 mmol) in anhydrous CH_3CN (9.0 mL) resulting in a color change (ranging from orange to deep-red depending on the substrate). The reaction mixture was stirred for 2 h at room temperature and then warmed to 70 °C and stirred for a further 16 h. At this time, the reaction was cooled to 0 °C, and anhydrous MeOH (2.25 mL) was added followed by $NaBH_4$ (30.3 mg, 0.800 mmol), causing the immediate precipitation of palladium black. The resulting black mixture was stirred for 20 min at 0 °C, then diluted with Et_2O (50 mL), and filtered through Celite, and the filter cake was washed with additional Et_2O (4 × 10 mL). The combined filtrate and washings were concentrated to afford the crude product. The NMR yield was then determined using mesitylene (10 μL) as an internal standard, and the product was purified by column chromatography with an appropriate solvent mixture (as described below for each compound).

***rac*-Ibogamine (4a).** The product **4a** was purified by column chromatography (9:1 hexanes:EtOAc + 2% Et_3N) and obtained as a colorless oil that slowly crystallized to a waxy white solid (20.3 mg, 29%). Spectral and physical properties were in agreement with those previously reported.[12] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (br s, 1H), 7.51−7.46 (m, 1H), 7.28−7.24 (m, 1H), 7.15−7.07 (m, 2H), 3.44−3.33 (m, 2H), 3.21−3.12 (m, 1H), 3.09 (dt, J = 9.2, 2.0 Hz, 1H), 3.00 (d, J = 9.1 Hz, 1H), 2.93 (ddd, J = 11.6, 4.0, 1.7 Hz, 1H), 2.88 (s, 1H), 2.75−2.64 (m, 1H), 2.11−2.01 (m, 1H), 1.89−1.78 (m, 2H), 1.66 (ddd, J = 13.2, 6.7, 3.5 Hz, 1H), 1.61−1.53 (m, 2H), 1.53−1.44 (m, 1H), 1.27−1.17 (m, 1H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.0, 134.8, 129.9, 121.1, 119.3, 118.1, 110.2, 109.4, 57.7, 54.3, 50.1, 42.1, 41.6, 34.3, 32.3, 28.0, 26.7, 20.8, 12.1.

***rac*-12-Fluoro-4-*epi*-ibogamine (4b).** The product **4b** was purified by column chromatography (7:3 hexanes:EtOAc + 2% Et_3N) and obtained as an amorphous off-white solid (8.3 mg, 11%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (br s, 1H), 7.15 (dd, J = 8.7, 4.4 Hz, 1H), 7.10 (dd, J = 9.8, 2.4 Hz, 1H), 6.84 (td, J = 9.1, 2.5 Hz, 1H), 3.44−3.23 (m, 3H), 3.20−3.09 (m, 2H), 3.05 (dd, J = 11.6, 5.3 Hz, 1H), 2.89 (s, 1H), 2.63−2.51 (m, 1H), 2.09−1.94 (m, 3H), 1.90 (s, 1H), 1.70−1.61 (m, 1H), 1.38 (p, J = 7.2 Hz, 2H), 1.13−1.03 (m, 1H), 0.93 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) (spectrum complicated by C−F coupling) δ 158.1 (d, J_{C-F} = 235 Hz), 144.0, 130.9, 130.2 (d, J_{C-F} = 10.1 Hz), 110.9 (d, J_{C-F} = 10.1 Hz), 110.5 (d, J_{C-F} = 5.1 Hz), 109.2 (d, J_{C-F} = 26.3 Hz), 103.0 (d, J_{C-F} = 24.2 Hz), 57.3, 54.7, 49.7, 42.0, 35.1, 34.4, 31.7, 28.5, 26.3, 20.3, 12.2; HRMS (FAB+) m/z [M + H]$^+$ calcd for $C_{19}H_{24}FN_2^+$ 299.1919, found 299.1924.

***rac*-14-(Benzyloxy)ibogamine (4c).** The reaction was run on a 0.100 mmol scale. The product **4c** was purified by column chromatography (20:1 hexanes:EtOAc + 2% Et_3N) and obtained as a pale-yellow glass (8.8 mg, 23%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (br s, 1H), 7.51−7.45 (m, 2H), 7.44−7.33 (m, 3H), 7.11 (d, J = 7.9 Hz, 1H), 6.99 (t, J = 7.8 Hz, 1H), 6.67 (d, J = 7.7 Hz, 1H), 5.19 (s, 2H), 3.42−3.31 (m, 2H), 3.20−3.05 (m, 2H), 3.01−2.88 (m, 2H), 2.85 (s, 1H), 2.69−2.60 (m, 1H), 2.03 (t, J = 12.4 Hz, 1H), 1.87−1.75 (m, 2H), 1.65 (dd, J = 13.1, 3.1 Hz, 1H), 1.60−1.39 (m, 3H), 1.25−1.17 (m, 1H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9, 141.8, 137.4, 131.3, 128.7, 128.2, 128.0, 125.0, 119.6, 111.3, 109.9, 102.7, 70.4, 57.7, 54.4, 50.2, 42.1, 41.6, 34.4, 32.3, 28.0, 26.7, 21.0, 12.1; HRMS (FAB+) m/z [M + H]$^+$ calcd for $C_{26}H_{31}N_2O^+$ 387.2431, found 387.2438.

***rac*-16-Oxaibogamine (4d).** The product was not isolated due to low yield. NMR yield was calculated as 11% in two independent trials. For spectral data, see the Ni-catalyzed preparation below.

***rac*-16-Thia-4-*epi*-ibogamine (4f).** The reaction was run on a 0.060 mmol scale. The product **4f** was purified by column chromatography (9:1 hexanes:EtOAc + 2% Et_3N, 4 column volumes → 8:2 hexanes:EtOAc + 2% Et_3N, 2 column volumes) and obtained as a pale-yellow oil (6.0 mg, 34%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J = 7.9 Hz, 1H), 7.62 (d, J = 8.1 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.26 (t, J = 7.6 Hz, 1H), 3.46−3.30 (m, 3H), 3.28−3.18 (m, 1H), 3.18−3.09 (m, 2H), 2.92 (s, 1H), 2.82 (d, J = 14.7 Hz, 1H), 2.13 (t, J = 12.5 Hz, 1H), 2.02−1.90 (m, 3H), 1.75 (dd, J = 13.4, 6.6 Hz, 1H), 1.46−1.36 (m, 2H), 1.11−1.00 (m, 1H), 0.94 (t, J = 7.4 Hz, 3H); ^{13}C

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NMR (126 MHz, $CDCl_3$) δ 145.3, 141.6, 138.2, 131.0, 124.0, 123.5, 122.2, 120.9, 57.7, 54.6, 50.7, 42.2, 35.6, 35.2, 31.6, 28.0, 26.5, 23.5, 12.2; HRMS (FAB+) m/z $[M + H]^+$ calcd for $C_{19}H_{24}NS^+$ 298.1624, found 298.1620.

General Procedure for the Preparation of Iboga Alkaloids by Reductive Heck Reaction (4a,b). To a solution of the substrate (**3a** or **3b**) (0.100 mmol) in anhydrous CH_2Cl_2 (0.90 mL) was added a solution of trimethylphenylammonium tribromide (41.4 mg, 0.110 mmol) in anhydrous CH_2Cl_2 (0.50 mL) dropwise at room temperature over 20 min. The resulting dark-red solution was stirred until TLC showed no starting material (~10 min) and then quenched with H_2O (2.0 mL) and basified with saturated NH_4OH (0.25 mL), and the aqueous layer was removed. The remaining organic layer was then washed with H_2O (1.0 mL) and concentrated *in vacuo* to provide the crude bromide as a viscous brown oil (Note: If desired, the bromide intermediate may be purified by column chromatography: 9:1 hexanes:EtOAc + 2% Et_3N for bromide from **3a**; 8:2 hexanes:EtOAc + 2% Et_3N for bromide from **3b**). To the crude bromide was added tetrakis(triphenylphosphine)palladium(0) (11.6 mg, 0.010 mmol) and sodium formate (27.2 mg, 0.400 mmol, powdered and dried with gentle heating under vacuum before use), followed by anhydrous DMSO (0.40 mL), and the resulting mixture was heated to 130 °C for 1 h (gas evolution occurs). The reaction was then diluted with H_2O (1 mL) and extracted with CH_2Cl_2 (3 × 1 mL) (Note: On a larger scale, the use of Et_2O is recommended to avoid excessive DMSO in the organic extracts). The combined organics were dried over Na_2SO_4 and concentrated to afford the crude product. The NMR yield was then determined using mesitylene (10 μL) as an internal standard, and the product was purified by column chromatography with an appropriate solvent mixture (as described below for each compound).

***rac*-Ibogamine (4a).** The reaction was run on a 0.100 mmol scale. The product **4a** was purified by column chromatography (9:1 hexanes:EtOAc + 2% Et_3N) and obtained as a colorless oil that slowly crystallized to a waxy white solid (11.9 mg, 42%). Spectral and physical properties were in agreement with those previously reported[12] and with those of the material obtained from the electrophilic Pd procedure (see above).

***rac*-12-Fluoro-4-*epi*-ibogamine (4b).** The reaction was run on a 0.500 mmol scale. The product **4b** was purified by repeated column chromatography on both silica (8:2 hexanes:EtOAc + 2% Et_3N, two column volumes → 7:3 hexanes:EtOAc + 2% Et_3N, two column volumes → 6:4 hexanes:EtOAc + 2% Et_3N, until product eluted) and ethyltrichlorosilane-treated silica (see below for preparation) (column 1 = 20:1 → 10:1 → 5:1 CH_2Cl_2:MeOH; column 2 = 20:1 CH_2Cl_2:MeOH, three column volumes → 20:1 CH_2Cl_2:MeOH + 2% Et_3N) and obtained as an amorphous off-white solid (5.1 mg, 3%). Spectral and physical properties were in agreement with those of the material obtained from the electrophilic Pd procedure (see above).

General Procedure for Preparation of Oxaibogamine Analogues by Ni(0) C–H Insertion (4d,e). In a glovebox, a vial was charged with $Ni(COD)_2$ (27.5 mg, 0.100 mmol) and 1,3-bis(2,4,6-trimethylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene (IMes, 36.5 mg, 0.120 mmol) followed by anhydrous heptane (1.0 mL), and the resulting black solution was stirred at room temperature for 15 min. To this mixture was then added a solution of the benzofuran substrate (**3d** or **3e**) (141 mg, 0.500 mmol) in anhydorus heptane (1.5 mL), and the reaction vessel was sealed, removed from the glovebox, and heated at 130 °C for 3 h. After cooling to room temperature the reaction mixture was purified directly by a combination of column chromatography and preparative TLC as described below for each substrate.

***rac*-16-Oxaibogamine (4d).** The crude reaction mixture was purified directly by column chromatography (40:1 hexanes:EtOAc + 2% Et_3N) to yield several fractions as viscous, pale-yellow oils. The central fractions provided pure product (20.3 mg), while the early (96.1 mg) and later (26.1 mg) fractions were contaminated with coeluting impurities. The later fractions were purified on a second chromatography column (hexanes + 4% Et_3N) to provide a colorless oil (14.2 mg). This material was combined with the early fractions from the first column, and the whole was purified by preparative TLC (20 × 20 cm plate, 1 mm silica layer, 80:1 hexanes:EtOAc + 2% Et_3N) to provide a second portion of pure product as a viscous, nearly colorless oil (83.8 mg). The overall yield of pure product **4d** was 104 mg (74%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.43–7.39 (m, 1H), 7.39–7.35 (m, 1H), 7.24–7.18 (m, 2H), 3.47–3.39 (m, 1H), 3.28–3.13 (m, 3H), 3.02–2.92 (m, 2H), 2.82 (s, 1H), 2.54 (d, J = 15.7 Hz, 1H), 2.05 (t, J = 12.4 Hz, 1H), 1.90–1.77 (m, 2H), 1.66 (ddd, J = 13.3, 6.4, 3.1 Hz, 1H), 1.62–1.43 (m, 3H), 1.25–1.17 (m, 1H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.0, 153.7, 130.9, 123.3, 122.1, 118.7, 111.6, 110.6, 57.3, 53.3, 49.7, 41.5, 41.1, 33.0, 32.3, 27.5, 26.5, 19.5, 11.9; HRMS (FAB+) m/z $[M]^+$ calcd for $C_{19}H_{23}NO^+$ 281.1775, found 281.1772.

***rac*-16-Oxa-4-*epi*-ibogamine (4e).** The crude reaction mixture was purified directly by column chromatography (9:1 hexanes:EtOAc + 2% Et_3N) to yield a viscous, orange-brown oil contaminated with a coeluting impurity. The NMR yield of product contained in this material (42%) was determined using mesitylene (10 μL) as an internal standard, and it was then further purified by preparative TLC (20 × 20 cm plate, 1 mm silica layer, Et_2O + 1% Et_3N) to provide the pure product **4e** as a viscous, pale-yellow oil (53.3 mg, 38%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.43–7.39 (m, 1H), 7.38–7.34 (m, 1H), 7.24–7.18 (m, 2H), 3.44 (ddd, J = 13.8, 4.7, 2.3 Hz, 1H), 3.38–3.29 (m, 2H), 3.25 (ddd, J = 17.0, 12.3, 4.7 Hz, 1H), 3.12–3.02 (m, 2H), 2.88 (s, 1H), 2.57–2.49 (m, 1H), 2.09–1.94 (m, 3H), 1.92–1.85 (m, 1H), 1.62 (ddd, J = 13.3, 6.0, 3.7 Hz, 1H), 1.47–1.34 (m, 2H), 1.18–1.09 (m, 1H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.7, 153.4, 130.7, 123.3, 122.2, 118.6, 112.1, 110.7, 56.5, 53.5, 49.1, 41.9, 34.3, 34.1, 31.6, 28.5, 26.4, 18.9, 12.3; HRMS (FAB+) m/z $[M + H]^+$ calcd for $C_{19}H_{24}NO^+$ 282.1853, found 282.1859.

Ethyltrichlorosilane-Treated Silica Gel. Deactivated silica was prepared as follows. To a suspension of silica gel (40–63 μm, 50 g) in CH_2Cl_2 (200 mL) was added ethyltrichlorosilane (4.0 mL) (gas evolution occurs), and the resulting mixture was stirred for 15 min. At this time the treated silica was collected by filtration, washed with CH_2Cl_2 (2 × 100 mL) and MeOH (3 × 100 mL), and dried *in vacuo* with gentle warming. Treated TLC plates were prepared in the same manner. However, these were UV opaque and thus were developed in an iodine chamber.

■ ASSOCIATED CONTENT

Supporting Information

Supplemental schemes outlining the synthesis of starting materials, tables of attempted cyclization conditions, ^1H NMR for all compounds, and ^{13}C NMR for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: sames@chem.columbia.edu.

Notes

The authors declare no competing financial interest.

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