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Effect of Terminal Alkylation of Aryl and Heteroaryl Hydrazines in the Fischer Indole Synthesis

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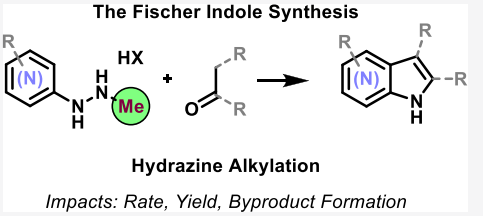
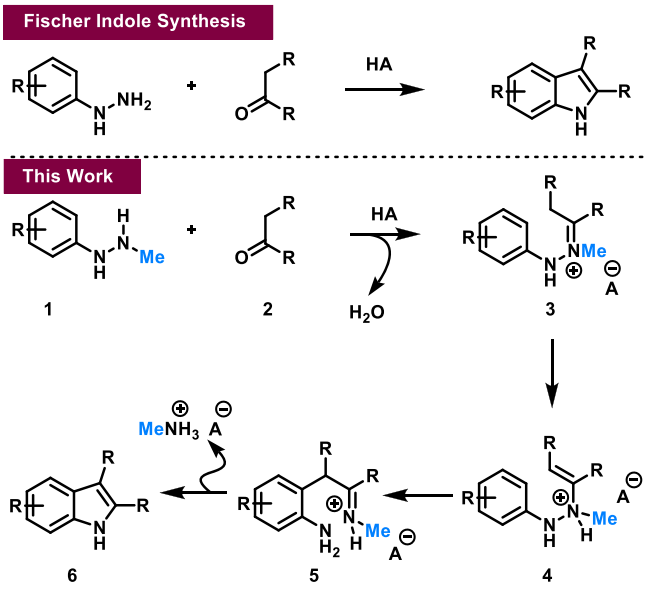
ABSTRACT: The effect of alkylation on the terminal position of aryl and heteroaryl hydrazines in the Fischer indole synthesis was examined. Compared to their unalkylated counterparts, reactions using alkylated hydrazines provided indole products with higher yields and faster rates. The reactions can be conducted at lower temperatures and are compatible with acid-sensitive functionality. The terminally alkylated hydrazines were readily prepared by a new two-step sequence and held as stable hydrazinium salts. The mild formation of the salts along with the favorable Fischer indole reaction conditions highlights the potential of this approach in later-stage synthetic use.



INTRODUCTION

The Fischer indole synthesis is an enduringly popular method for the construction of a wide range of indoles.[1] Since its initial report ~140 years ago,[2] a tremendous amount of research has elucidated many idiosyncratic features of the reaction.[1,3] In practice, this reaction is limited to relatively simple substrates because of the harsh conditions commonly used (excess acid/Lewis acid, elevated temperatures). We considered terminal alkylation of the arylhydrazine starting material **1** (Scheme 1) as a way to reduce the severity of the reaction conditions. We hypothesized that terminal alkylation of the arylhydrazine can facilitate key aspects of the transformation. For example, an *N*-alkylated hydrazine is expected to be more nucleophilic and would not be capable of forming a stable hydrazone intermediate. More subtle benefits were also considered. They include a more favorable tautomerization from **3** to **4**,[4] easier access to the reactive conformer (i.e., **4**), and a greater stability of the [3,3] sigmatropic rearrangement product **5**.[5] This modification would be traceless, as the alkyl group would depart with the amine in the final stage of the reaction (i.e., **5** to **6**) without the need for further processing of the indole. Such an approach has scarcely any precedent and no systematic or synthetic study, being used only as a mechanistic probe in the study of the Fischer indole synthesis.[6] In this work, we describe our investigation of this strategy. First, we report the synthesis of a range of terminal *N*-alkyl hydrazines and then test their reactivity in Fischer indole reactions.

Scheme 1. Fischer Indole Reaction (Top); Methylated Hydrazine Shown with Mechanistic Details (Bottom, This Work)



RESULTS AND DISCUSSION

Synthesis of the *N*-Alkylhydrazine Salts. We explored a two-step approach that yielded the *N*-alkyl hydrazine substrates as HCl or HBF_4 salts (Figure 1). The copper or palladium cross-coupling reaction of aryl or heteroaryl bromides with commercially available 1-methyl-1-Boc hydrazine (**7**) provided *N*′-Boc-*N*′-methyl-*N*-arylhydrazine products. The copper conditions recently reported by Singer et al.[7] (CuI, **L1**, K_2CO_3,

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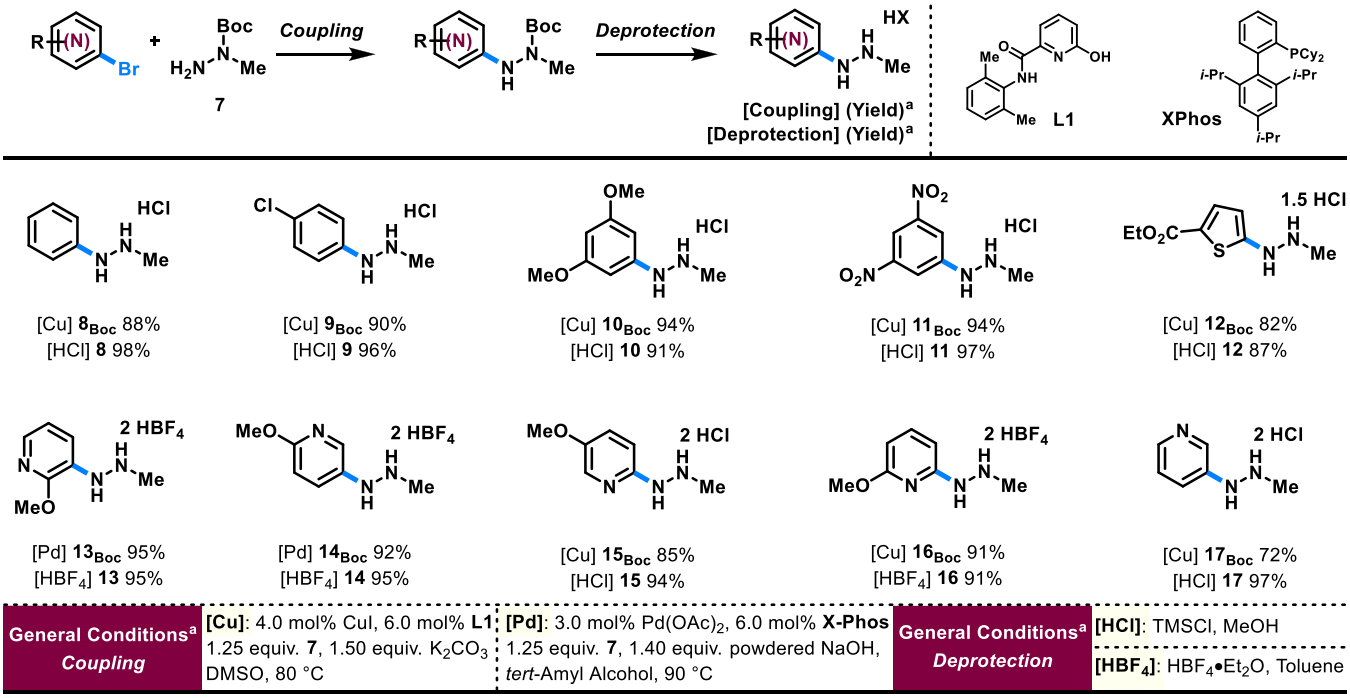


Figure 1. Preparation of the terminally methylated hydrazine salts.

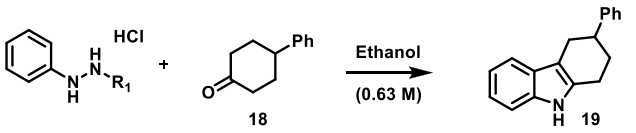
DMSO) worked well for unencumbered substrates (Figure 1). For more challenging substrates, the palladium-catalyzed conditions developed by Mauger and Mignani[8] ($Pd(OAc)_2$, X-Phos, NaOH, *tert*-amyl alcohol) for the formation of *N*-aryl benzophenone hydrazones proved successful. Even these conditions fared poorly though, with 1-bromo-2,6-dichlorobenzene (18% isolated yield after 16 h), so for this particular substrate **44** (*vide infra*), we prepared it via terminal formylation of 2,6-dichlorophenylhydrazine, methylation, and deprotection/salt formation in a similar way to the reported conditions.[6a] The Boc groups in compounds $\mathbf{8}_{Boc}$–$\mathbf{17}_{Boc}$ were removed with concomitant salt formation under the action of either TMSCl in methanol or $HBF_4{\cdot}OEt_2$ in toluene. The salts studied herein were stable, free-flowing, easily filterable solids.[9]

While methyl-substituted hydrazine **7** is readily available, we prepared others in the series[10] to examine the effect of the alkyl chain in the Fischer indole reaction. These variants were coupled to bromobenzene and deprotected affording salts in an analogous manner: Et $\mathbf{8}_{Et}$ (52% overall), *i*-Pr $\mathbf{8}_{i\text{-}Pr}$ (42% overall), Bn $\mathbf{8}_{Bn}$ (48% overall), please see the Experimental Section for more details.

Alkylated Hydrazines in the Fischer Indole Reaction. We examined the Fischer indole transformation using the alkylated analogues of phenylhydrazine (i.e., **8**) (Table 1). To simplify our studies, the reactions were carried out without additional acids or Lewis acids. We used 4-phenylcyclohexanone (**18**) as a representative carbonyl compound. A reaction using an equimolar amount of **8** and **18** in ethanol (0.63 M) provided indole **19** in 96% yield after 20 min at 50 °C. At 23 °C, the reaction took 24 h to reach completion (99%). The expected byproduct, methylamine hydrochloride, was detected by ^1H NMR spectroscopy of the crude reaction mixture.[9] We did not observe any intermediates (i.e., **3** or **4**) by LC-MS, and the reaction was homogeneous. This was in stark contrast to the reaction of the desmethylated phenylhydrazine $\mathbf{8}_H$ with **18** (Table 1, entry 2). We observed rapid precipitation of the intermediate hydrazone by LC-MS. This precipitation may be a contributing factor in the 12-fold increased reaction time (240 min) needed to form **19**. The higher alkyl groups ($\mathbf{8}_{Et}$, $\mathbf{8}_{i\text{-}Pr}$, $\mathbf{8}_{Bn}$) were compared to **8** Table 1, entries 3–6), and a striking sensitivity of the reaction rate was observed.[9] Gratifying, the most accessible salt, **8**, was highly effective (99% solution yield) over $\mathbf{8}_{Et}$ (89% solution yield) or $\mathbf{8}_{i\text{-}Pr}$ (27% solution yield). The benzyl analogue $\mathbf{8}_{Bn}$ also proceeded well (99% solution yield), similar to **8**. The performance of $\mathbf{8}_{Bn}$ may be attributed to subtle effects on the pK_a of the intermediates. Ethanol was the preferred solvent over MeCN, DMF, DCM, and THF, affording the highest yield of **19** in the shortest reaction times.[9]

It is noteworthy that the Boc-protected methylhydrazine precursor $\mathbf{8}_{Boc}$ (Table 1, entry 7) could be used directly in the Fischer indole reaction under acidic conditions (0.45 M ethanol, 1.00 equiv of $\mathbf{8}_{Boc}$, 1.50 equiv of TMSCl, 50 °C, 1 h), affording

Table 1. Effect of Different Terminal Substitution on the Fischer Indole Reaction



entry	salt	temp/time	isolated yield or (solution yield)[b]
1	R_1 = Me **8**	50 °C/20 min	96%
2	R_1 = H $\mathbf{8}_H$	50 °C/240 min	93%
3	R_1 = Me **8**	23 °C/24 h	(99%)
4	R_1 = Et $\mathbf{8}_{Et}$	23 °C/24 h	(89%)
5	R_1 = i-Pr $\mathbf{8}_{i\text{-}Pr}$	23 °C/24 h	(27%)
6	R_1 = Bn $\mathbf{8}_{Bn}$	23 °C/24 h	(99%)
7	$\mathbf{8}_{Boc}$	50 °C/1 h[a]	90%

[a]1.50 equiv of TMSCl was added, and the reaction was run at 0.45 M. [b]Solution yield refers to the yield at the end of the reaction as determined by calibrated HPLC analysis.

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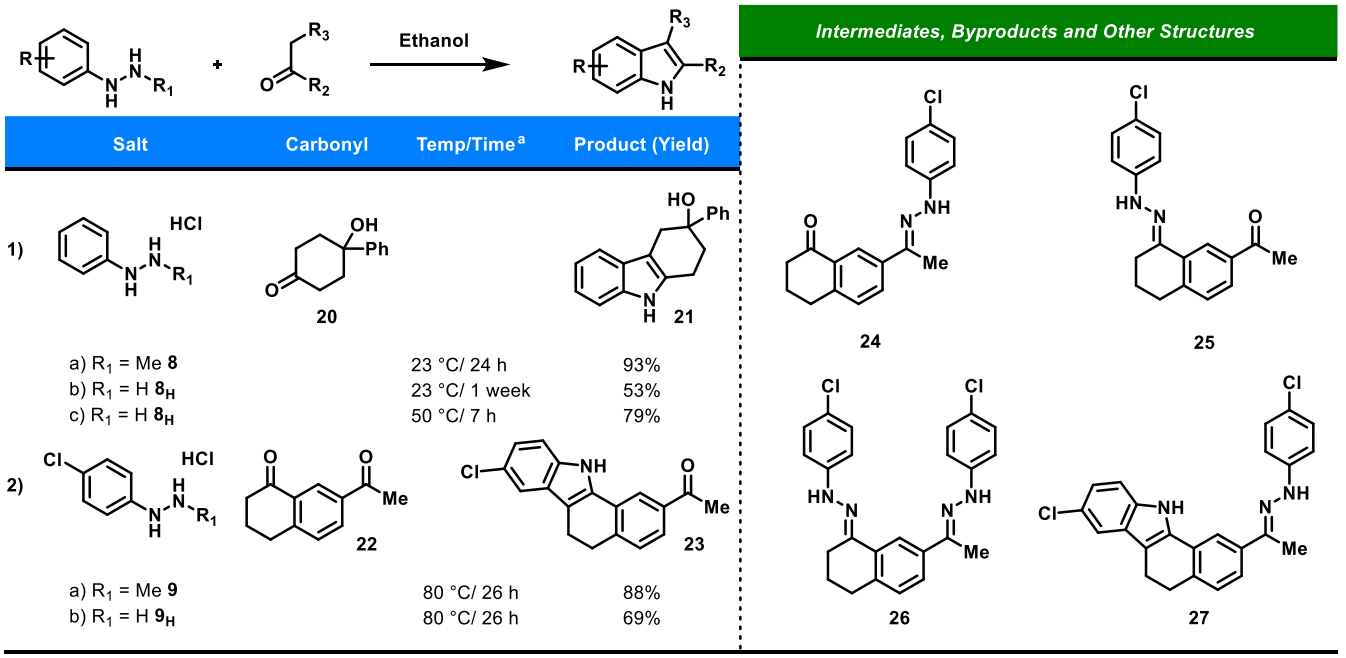
Table 2. Fischer Indole Reaction of Sensitive Ketone 20 and Diketone 22



[a]Please see the Experimental Section for exact conditions.

19 in 90% isolated yield. This single-step option may be useful if isolation of the salt is problematic.

Scope and Limitations. The effect of the hydrazine alkylation on the Fischer indole reaction was evaluated by directly comparing against the parent desmethylated aryl- or heteroaryl- hydrazine. As before, an equimolar ratio of hydrazine salt and carbonyl compound was used, no additional acids or Lewis acids were added, and identical concentration and temperatures were used unless noted.

The reaction of **8** with acid-sensitive 4-hydroxy-4-phenylcyclohexanone (**20**) proceeded efficiently to provide indole **21** in 93% yield after 24 h at 23 °C (Table 2, entry 1a). With the desmethyl salt $\mathbf{8_H}$, we observed rapid precipitation of the hydrazone (identified by LC-MS) and a slow conversion to **21**, affording only 53% after 1 week with an incomplete reaction (Table 2, entry 1b). At 50 °C, the reaction with $\mathbf{8_H}$ was homogeneous and faster (7 h), though only a 79% yield of **21** was obtained (Table 2, entry 2c). Despite the improved kinetics, multiple impurities were observed. These impurities are likely formed by oligomerization stemming from the tertiary benzylic alcohol in **20** or **21**.

We examined subtle effects on the carbonyl group with 7-acetyl-1-tetralone **22** (Table 2, entry 2a).[11] Salt **9** reacted cleanly with diketone **22** over 26 h at 80 °C affording exclusively the indole **23** in 88% yield. Using desmethyl salt $\mathbf{9_H}$, indole **23** was formed in 69% yield, though the reaction was far more complex (Table 2, entry 2b).[9] ^{1}H NMR spectroscopy and LC-MS analysis of the reaction after 5 min revealed four products in addition to the starting materials and the desired product. Two products were identified as the isomeric monohydrazones (**24** and **25** 2:1 molar ratio, respectively). The remaining two minor products were bishydrazone **26** and the hydrazone of the indole product **27**. We conclude that $\mathbf{9_H}$ can reversibly react with the unique carbonyl groups of **22** and selectively forms product **23**.

An electronically differentiated ketone **28** was prepared[12] to examine the relationship between the ease of tautomerization (i.e., Scheme 1, **3** to **4**) and the indole product distribution (Table 3, entry 1). As a control experiment, we heated **28** for 24 h at 50 °C in deuterated ethanol, and ^{1}H NMR spectroscopy was used to monitor deuterium incorporation. The methylene adjacent to the *p*-nitrophenyl group incorporated deuterium (74.5%) over the methylene adjacent to the *p*-methoxyphenyl group (~1%), indicating enolization of the carbon adjacent to the *p*-nitrophenyl group (Table 3, $\mathbf{28_D}$) was facile. The electron-rich arylhydrazine salt **10** reacted with **28** to provide indole **29** in 83% yield over 22 h at 80 °C (Table 3, entry 1a). Other indole isomers were not detected by LC-MS. Two-dimensional NMR spectroscopy confirmed the structure, suggesting that the product arises out of an enehydrazine in conjugation with the *p*-methoxyphenyl group. A reaction under a Curtin−Hammett scenario could explain this result (Table 3). The corresponding parent desmethyl salt $\mathbf{10_H}$ afforded the indole product **29**, exclusively, in 69% yield, though the rate was significantly faster (1.5 h versus 22 h), possibly due to reduced steric interactions throughout the reaction (Table 3, entry 1c).[13]

To investigate a Curtin−Hammett scenario, the reaction of **10** and **28** was run in deuterated ethanol, and we obtained indole **29** with 71% deuterium incorporation at the methylene position. A control experiment reveals **29** does not incorporate deuterium under the reaction conditions. In addition, salt **10** was reacted with truncated 1-aryl-2-propanones **31** and **32**. As expected, the reaction of **10** with **31** (Table 2, entry 2) was rapid and clean, forming product **33** in 30 min (78%), while reaction with **32** (Table 3, entry 3) was slower, necessitating 4 h to form product **34** (85%).

Conversely to **10**, the reaction of electron-poor arylhydrazine salt **11** with **28** at 80 °C for 4 h consumed all of **11** and led to multiple products (Table 3, entry 1b). Only Neber-like product **30** could be identified in 6% yield.[14] Under identical conditions, the parent desmethyl salt $\mathbf{11_H}$ was very sluggish to react with **28**, and after 24 h, both starting materials mostly remained (Table 3, entry 1d).

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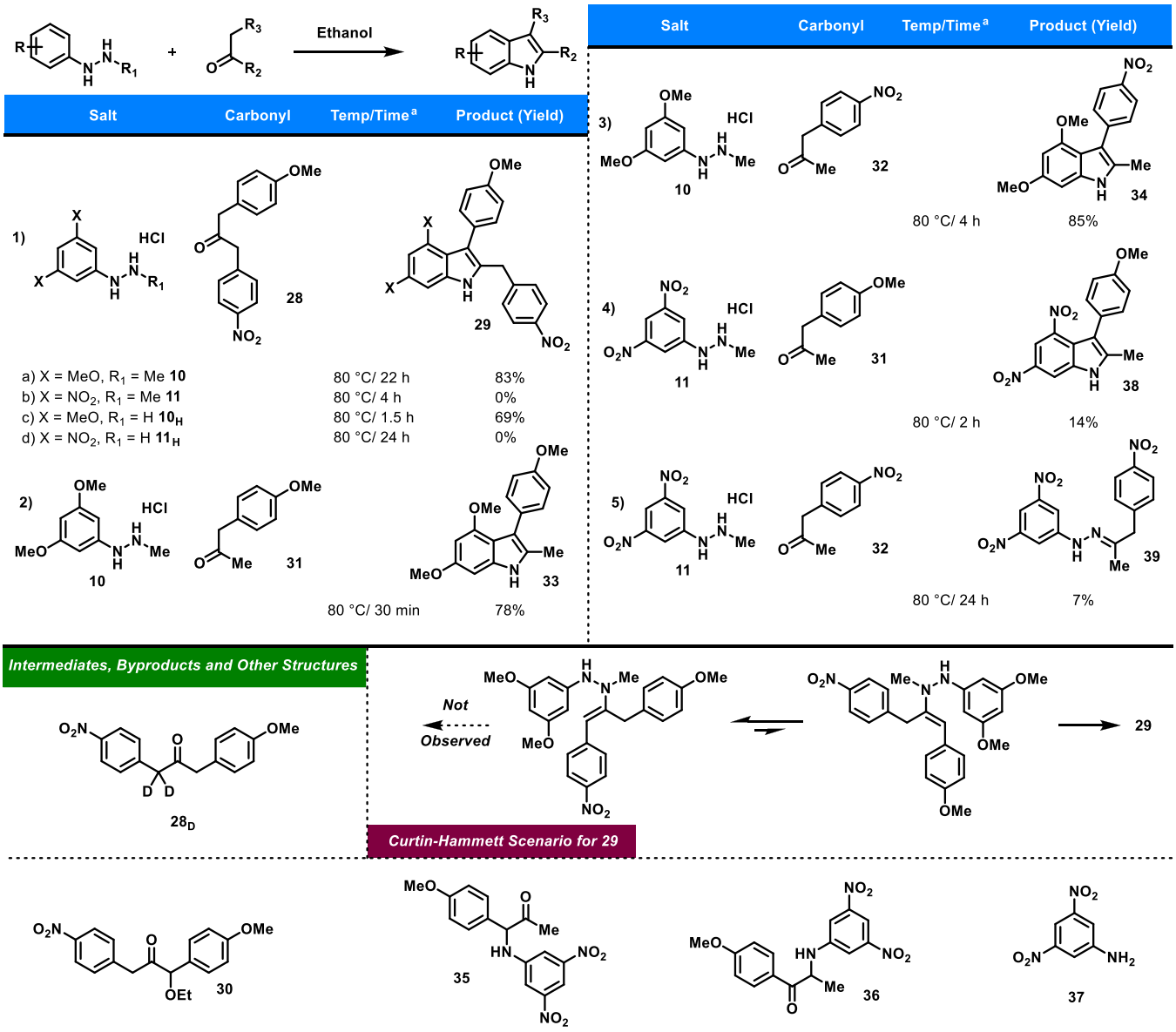
Table 3. Fischer Indole Studies on an Electronically Differentiated Ketone 22



[a]Please see the Experimental Section for exact conditions.

Dinitro salt **11** was also reacted with **31** and **32**. In the case of **31** (Table 3, entry 4), four products were isolated. Two products were an inseparable mixture of ketones **35** and **36** (54:46 ratio, respectively, 15% combined yield), another was 3,5-dinitroaniline (**37**, 61%), and the final product was the desired indole **38** (14%). The reaction of **11** with **32** (Table 3, entry 5) was slow at 80 °C, and multiple products were observed. A major byproduct was **37** and a yellow solid identified as the hydrazone **39** (7%), indicating *N*-demethylation took place. The difficulty of electron-deficient arylhydrazines to engage in the Fischer indole synthesis is known[3a] and was observed with methylated hydrazines; the major pathway being the dissociative fragmentation of the *N*-*N* bond to an aniline and an oxidized carbonyl compound.

2-Hydrazinothiophenes are an interesting class of non-benzenoid heterocycles capable of engaging carbonyl compounds in a Fischer-like reaction.[15] The reaction of thiophene salt **12** with ketone **40** (94:6 er, Table 4, entry 1a)[16] was initially performed in ethanol at 75 °C, though transesterification of the isopropyl ester with the solvent could be observed by LC-MS (~5−10%). The addition of 0.5 equiv of pyridine was found to suppress transesterification while maintaining the desired reaction. By switching the solvent to 1-butanol and performing the reaction at 90 °C, complete consumption of **12** was observed. Analysis of the reaction by LC-MS indicated that **12** is consumed faster than ketone **40**. It was found that salt **12** is not stable under the reaction conditions and is degraded to multiple products. A major byproduct was identified as tricycle **42** (2% isolated yield).[9] The yield of indole **41** was improved by adding an additional 1.00 equiv **12** and 0.50 equiv pyridine after 10 h. This protocol provided indole **41** in 54% yield and with no erosion of enantiopurity (94:6 er). The reaction of $\mathbf{12}_{\mathbf{H}}$ with **40** in 1-butanol at 90 °C led down a drastically different pathway, rapidly (2 h) forming the lactam **43** as the major product (50%), with only trace amounts of the desired product (Table 4, entry 1b).

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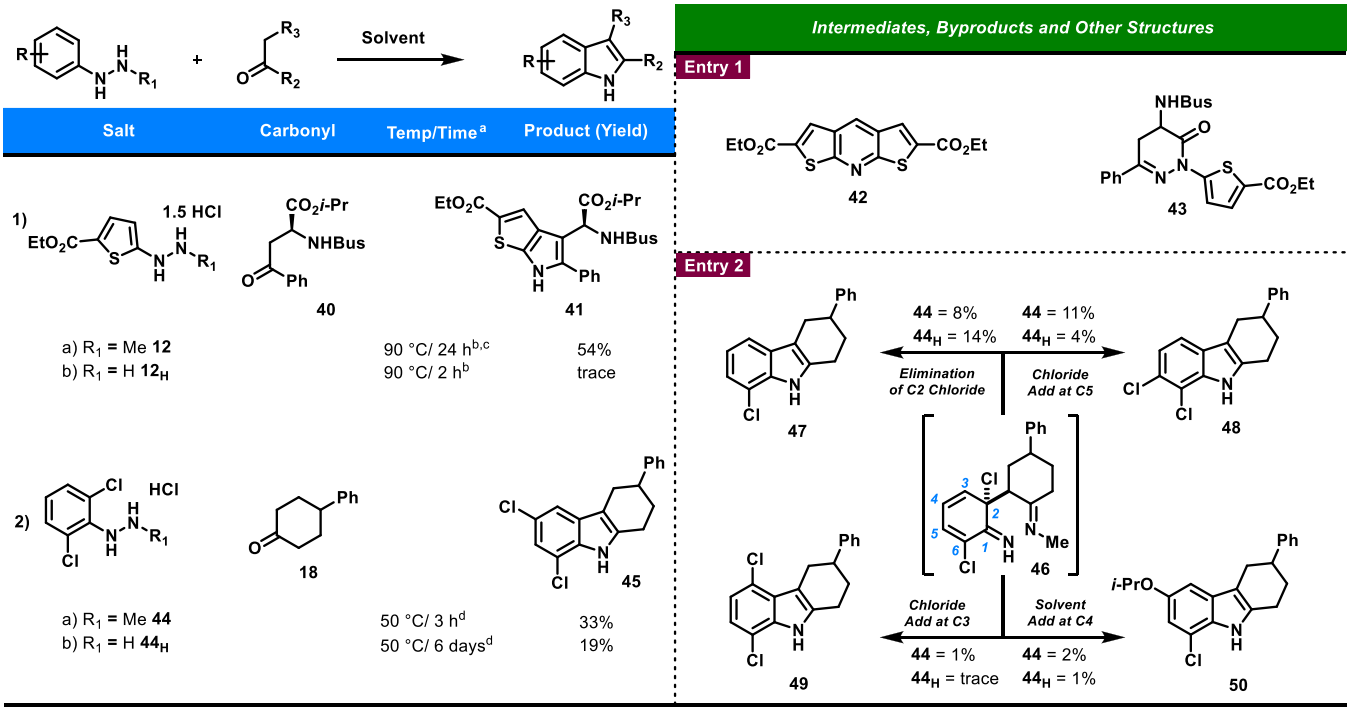
Table 4. Fischer Indole Studies of Nonstandard Hydrazine Salts



[a]Please see the Experimental Section for exact conditions. [b]1-Butanol was used as the solvent. [c]1.00 equiv of salt **12** and 0.50 equiv of pyridine were used, and this charge was repeated after 10 h. [d]Isopropanol was used as the solvent.

2,6-Dichlorophenyl hydrazine salt **44**, as a free base, can be used in a Fischer indole synthesis with cyclohexanone in benzene at room temperature.[6a] A complex mixture of products is formed, due to the chlorine atom inhibiting facile rearomatization post [3,3] sigmatropic rearrangement (see Table 4, **46** C2-chlorine).[1a,6a] Substrate **44** was examined under our conditions. (Table 4, entry 2a). The reaction of **44** with **18** in ethanol at 50 °C by LC-MS revealed a complicated mixture of products from the incorporation of the solvent. By switching to isopropanol, we could identify **45** as the major component (33%), monochloro **47** (8%), and **48** (11%). Indoles **49** and **50** were observed in 1% and 2%, respectively. We hypothesized that the prevalence of dichloro products arises from the exogenous chloride brought in as the HCl salt. The free chloride can attack intermediate **46** at the 3, 4, or 5 positions (Table 4, **46**), leading to products **49**, **45**, or **48**, respectively.[17] The desmethylated salt $\mathbf{44_H}$, as expected, rapidly (<30 min) formed the hydrazone, though converted very slowly over 6 days to indole products (Table 4, entry 2b). The distribution of products was similar to **44** (19%, **45**;14% ,**47**; 4%, **48**; trace, **49**; 1%, **50**), though the yield of product **45** was lower.

Azaindoles are an important class of pharmaceutically relevant heterocycles, and the electron-rich subset is accessible via the Fischer indole synthesis.[18] The initial reaction of 1-(2-methoxy-3-pyridyl)-2-methylhydrazine bishydrochloride ($\mathbf{13_{2HCl}}$) with hexanal (**51**, 1.10 equiv) for 2 h at 50 °C afforded a mixture with four major products (Figure 2, entry a). The desired 6-azaindole **52** (47%) was identified along with desmethyl azaindole **53** (8%). Two other unexpected products were the *N*-methyl azaindole product **54** (9%) and the ethoxylated 4-azaindole isomer **55** (11%).[17,19]

We expected desmethyl product **53** to be formed by demethylation via chloride ion. Treatment of **52** with TMSCl in ethanol at 50 °C revealed that **53** was formed. We, therefore,

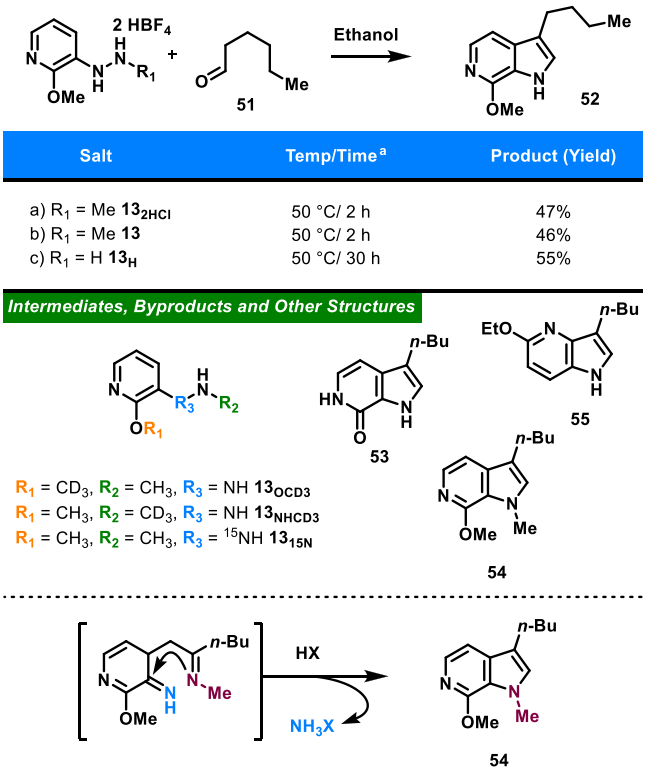


Figure 2. Fischer indole reaction of **13** and **51** (top). Proposed formation of **54** (below).

prepared the tetrafluoroborate salt form **13**, and any subsequent substrate with a 2-methoxypyridine structure was also prepared as a tetrafluoroborate salt (Figure 1, **13**, **14**, and **16**). The reaction of **13** with **51** for 2 h at 50 °C afforded product **52** in

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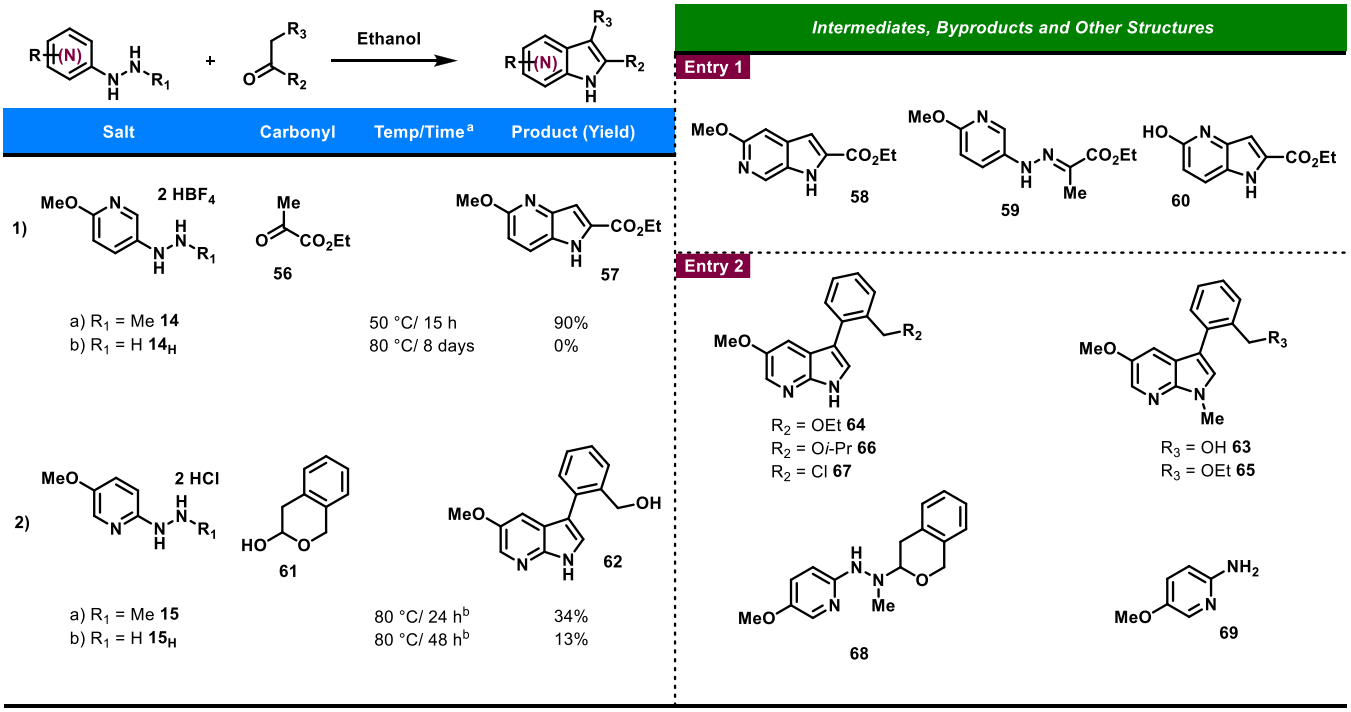
Table 5. Fischer Indole Reactions of Salts 14 and 15



[a]Please see the Experimental Section for exact conditions. [b]1-Butanol was used as the solvent.

46% yield, along with **54** (11%) and **55** (15%) (Figure 2, entry b). Product **53** was eliminated. Intrigued by the formation of *N*-methyl azaindole **54**, we prepared two deuterium-labeled salts, $\mathbf{13}_{\mathbf{OCD3}}$[20] and $\mathbf{13}_{\mathbf{NHCD3}}$.[21] These two substrates clearly showed that the methyl on the indole nitrogen of **54** comes from the terminal methyl group of the initial hydrazine salt.[9] Intermolecular exchange of methylamine was ruled out by spiking a reaction of $\mathbf{13}_{\mathbf{NHCD3}}$ with unlabeled methylammonium tetrafluoroborate. The **54** product of this reaction contained only the indole *N*-CD_3 label. A final experiment using ^{15}N-labeled salt $\mathbf{13}_{\mathbf{15N}}$ was performed,[22] and the **54** product was found to be unlabeled. The sum of these results point toward an intramolecular transfer of the methylamine group and would be an example of a Fischer indole reaction where, subsequent to the [3,3] rearrangement, the core heteroaryl nitrogen is lost, rather than the side chain nitrogen.[23] The reaction with the parent desmethyl hydrazine salt $\mathbf{13}_{\mathbf{H}}$, under identical conditions, took 30 h to reach completion, affording **52** in 55% yield along with **55** (16%) (Figure 2, entry c). The inability to form **54** is likely responsible for the higher yield.

The reaction of salt **14** with ethyl pyruvate (**56**, 1.10 equiv) was very efficient, forming azaindole **57** in 90% yield after 15 h at 50 °C (Table 5, entry 1a). The isomeric azaindole **58** was obtained in a 1% yield. While the remainder of the mass balance was multiple unidentified products, one major byproduct was hydrazone **59** in ∼5% yield. Interestingly, in this example, we did not observe any *N*-methylated indole products. In stark contrast, the desmethyl hydrazine $\mathbf{14}_{\mathbf{H}}$, under identical conditions, stalls at the hydrazone **59** and does not convert to the product over 1 week of reaction time. Increasing the temperature to 80 °C for 8 days does not lead to product **57**, hydrazone **59** was recovered in 62% yield, and the only observed indole product was the desmethylated product **60** in 8% yield (Table 5, entry 1b).

Functional aldehyde equivalents such as lactols can be used in the Fischer indole reaction. The reaction of salt **15** with isochroman-3-ol[24] (**61**) at 80 °C for 24 h afforded the desired product **62** (30%) (Table 5, entry 2a). The *N*-methylated product **63** was also isolated (4%). We observed ethyl benzyl ethers **64** and **65** by LC-MS; therefore, we changed the solvent to *tert*-amyl alcohol, expecting to eliminate these ethers. We noted that the reaction appeared to boil and build pressure at 80 °C. We speculate that the conditions cause the dehydration of the solvent to form amylene (bp 35−38 °C). We identified one major intermediate, the hemiaminal **68** by LCMS and ^{1}H NMR spectroscopy, though the majority of the mass balance was multiple unidentified byproducts. Performing the reaction in isopropanol reduced the number of ether impurities, and we obtained **62** in 34% yield and **63** in 2% yield. Besides a small amount of the isopropyl ether **66** (4% yield), we also identified benzyl chloride **67** (4% yield) and the aniline **69** (13% yield) byproducts. The parent desmethyl salt $\mathbf{15}_{\mathbf{H}}$ was reacted with **61** for 48 h at 80 °C (Table 5, entry 2b). A complex mixture of multiple, low quantity products were observed. The expected hydrazone intermediate was identified by LC-MS analysis as the major species and converted inefficiently to product **62** (13%).

Encouraged by the heightened reactivity offered by methylation, we examined pyridylhydrazines that are considered challenging substrates for the synthesis of azaindoles (Table 6).[18a,b] We screened the reaction of salt **16** with three different carbonyl compounds, 1-hexanal (**51**), ethyl pyruvate (**56**), and 4-*tert*-butylcyclohexanone (**70**). Only in the case of **70** did we observe any indole products. We observed nondescript decomposition with ethyl pyruvate and aldol-like dimerization products with hexanal. The reaction of salt **16** with **70** after 8 h at 90 °C in 1-butanol led to product **71** in 97% yield (Table 6, entry 1a). We did not observe any indole *N*-methylated byproducts.

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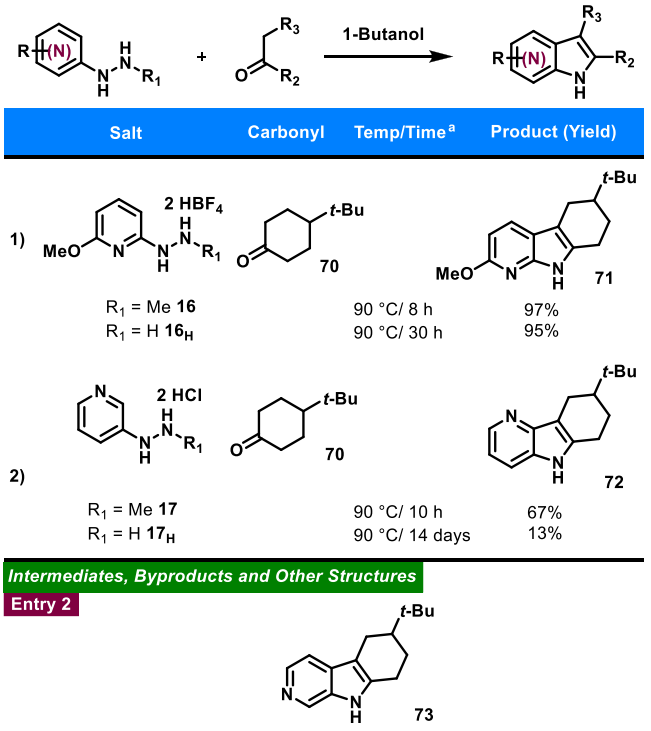
Table 6. Challenging Hydrazine Substrates



[a]Please see the Experimental Section for exact conditions.

The desmethyl salt $\mathbf{16_H}$ took 30 h to reach full conversion, though the yield was similar (95%) (Table 6, entry 1b).

Unsubstituted 3-pyridyl methylhydrazine salt **17** was likewise screened with **51**, **54**, and **70**. Similarly to the reaction with **16**, only **70** afforded an indole product. The reaction of **17** with **70** after 10 h at 90 °C in 1-butanol afforded the expected 4-azaindole product **72** in 67% yield The 6-azaindole isomer **73** was isolated in 6% yield (Table 6, entry 2a). We did observe a trace amount of a methylated product in the course of the reaction by LC-MS analysis. The desmethyl analogue $\mathbf{17_H}$ was reacted under identical conditions, and while hydrazone formation was rapid (<1 h by LC-MS analysis), the conversion to the azaindole products was extremely slow, necessitating 2 weeks for complete conversion of the hydrazone (Table 6, entry 2b). Unlike the reaction with **17**, the reaction with $\mathbf{17_H}$ and **70** produced many products, along with a significant amount of an insoluble material. The azaindole **72** was isolated in a 13% yield. The isomer **73** was detected in trace amounts

We explored the possibility of terminally methylated hydrazines forming unsubstituted (i.e., C2,C3 = H) indoles (Figure 3). Screening **8** with either acetaldehyde, acetaldehyde diethyl acetal, or *n*-butyl vinyl ether in ethanol (10 mg/mL **8**) at 80 °C for 24 h afforded the same major product in all cases, which was identified as 2-methylquinoline (**74**). Product **74** may arise via a variant of the Skraup–Döbner–von Miller reaction,

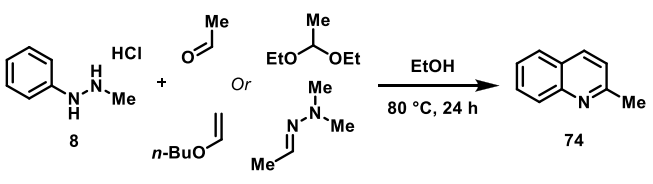


Figure 3. Attempt to form parent indole.

no indole was observed. We scaled the reaction with 2.00 equiv of acetaldehyde diethyl acetal, but after 29 h, only a 16% yield of **74** was obtained. The use of a less electrophilic *N*,*N*-dimethylhydrazone of acetaldehyde led to decomposition; no indole or **74** was observed.

CONCLUSIONS

There are key advantages to using methylated hydrazines for a Fischer indole reaction. The reactions can proceed at lower temperatures and are often higher yielding with fewer byproducts. For the reactions described herein, no additional acid or Lewis acid was needed, and the substrate salt alone was sufficiently reactive for the Fischer indole reaction to proceed by warming in alcohol. These results allow for more sensitive functionality to survive and bode well for the implementation of a Fischer indole reaction in late-stage synthetic sequences. In addition, the reactions were more likely to be homogeneous due to the inability to form insoluble hydrazones. This aids in mass transfer and improves the reaction rate. As a consequence of the cleaner reaction profiles, product isolation is more straightforward.

The alkylated salts were readily prepared using a two-step strategy. First, a flexible C–N cross-coupling reaction formed an *N*-Boc-*N*-methyl arylhydrazine, which can be deprotected, and the salt isolated in a direct-drop process. Additionally, the Boc-intermediate can also be used directly in the Fischer indole reaction without detriment, offering flexibility in the strategy.

EXPERIMENTAL SECTION

General Remarks. All reactions were performed in round-bottom flasks or vials, and stainless steel syringes were used to transfer liquids (unless noted otherwise). To heat reactions, where noted, the flasks or vials were inserted into appropriate aluminum reaction blocks (Chemglass Optitherm blocks for flasks, Chemglass reactor pie-blocks for vials). Flash column chromatography was performed on a Teledyne ISCO CombiFlash R_f using silica gel (20–40 μm, Gold grade silica, Teledyne ISCO). Organic solutions were concentrated on a Büchi Rotavapor R-143 at ~20 Torr at 25–35 °C.

Commercial reagents and solvents were used as received. All quantities expressed in the individual experiments are corrected for purity as specified by the vendor. Arylhydrazine hydrochloride salts $\mathbf{8_H}$, $\mathbf{9_H}$, $\mathbf{17_H}$, and $\mathbf{44_H}$ are commercially available. Salt $\mathbf{10_H}$ was prepared by the method of Yu et al.;[25] herein, we report the ^{1}H NMR spectra. Compounds **37**, **58**, **69**, and **74** were confirmed by comparison of ^{1}H NMR spectra against purchased standards.

Reactions were monitored using a Shimadzu Nexera X2 UPLC system equipped with a Shimadzu LCMS-2020 mass spectrometer. A general method was used [Sample preparation: 20 μL reaction sample diluted to 1.5 mL with 10 mM ammonium acetate in MeCN/water (95:5 v/v%). Column: Agilent Poroshell EC-C18, 1.7 μm, 2.1 mm × 50 mm. Oven temperature: 40 °C. Injection volume: 1.0 μL. Flow rate: 1.0 mL/min. Detector wavelength: 220 nm. Mobile phase "A": 10 mM ammonium acetate in MeCN/water (5:95 v/v%). Mobile phase "B": 10 mM ammonium acetate in MeCN/water (95:5 v/v%). Gradient, 0% "B" ramp to 100% "B" over 4 min, then hold for 0.5 min]. Water content was measured by coulometric titration (Karl Fischer titration) with a Mitsubishi Chemical Analytech CA-310 Moisture meter. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a Bruker DPX 400 spectrometer and are recorded in parts per million from internal tetramethylsilane on the δ scale and are referenced from the residual protium in the NMR solvent ($CHCl_3$, δ 7.27; C_2D_5HSO, δ 2.50; C_2D_3HO, δ 3.56, 1.11; CD_2HOD, δ 3.31; C_6D_5H, δ 7.16). Data is reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant(s) in hertz, integration]. Carbon nuclear magnetic resonance ($^{13}C\{^1H\}$ NMR) spectra were recorded with a Bruker DPX 400 spectrometer and are

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recorded in parts per million from internal tetramethylsilane on the δ scale and are referenced from the carbon resonances in the NMR solvent ($CDCl_3$, δ 77.00; DMSO-d_6, δ 39.51; MeOD-d_4; δ 49.15; C_6D_6, δ 128.39). Data is reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant(s) in hertz]. Infrared data (FTIR) were obtained with an Agilent Cary 630 FTIR spectrometer and are reported as follows: [frequency of absorption (cm^{-1}), intensity of absorption (a = apparent, s = strong, m = medium, w = weak, br = broad). Melting points were determined with a Thomas-Hoover capillary melting point apparatus. High-resolution mass spectrometry (HRMS) was collected on an Aglient Technologies 6230 series TOF LC/MS instrument or a Themo LTQ-Orbitrap Discovery instrument. Optical rotations were measured on a Reichert Polar3 Polarimeter. DSC measurements[26] were performed in a TA Instruments Q2000 DSC instrument, and data was obtained as follows. Approximately 3−5 mg, recorded to 2 decimal places, were accurately weighed into M20 gold-plated crucibles (TÜV SÜD Schweiz AG) rated to 217 bar. The crucibles were sealed under air with the appropriate press (Schmidt Technologies Manual Press). After equilibrating at 25 °C, the samples were heated at a rate of 4.0 °C per min to a maximum temperature of 350 °C. Mass loss after completion of the measurements was <1.0%. Data analysis was conducted using TA Instruments Universal Analysis software version 4.5.0.5. Data is reported as follows: (solvent system of isolation), T_{onset} corresponding to the left-limit onset, T_{peak}, (ΔH_D: kJ/mol) of the major exo- or endotherms.

Note! Many hydrazine salts exhibit proton NMR spectra with extremely broadened resonances for the heteroatom-bonded protons often leading to spectra with different than the theoretical amount of protons. The data presented herein is reported as observed.

Caution! The carbon−nitrogen cross-coupling reactions are sensitive toward air, especially so at their operating temperatures. To monitor these reactions, they are first cooled to room temperature and then sampled strictly under nitrogen with a nitrogen-purged stainless steel needle and syringe. Sampling at elevated temperatures raises the risk of prematurely terminating the reaction.

Synthesis of *N*-Alkylated Hydrazine Salts. *2-Methyl-1-phenylhydrazine Hydrochloride (**8**).* To a dried flask equipped with a thermocouple were added copper(I) iodide (480 mg, 2.52 mmol, 0.040 equiv), ligand **L1** (917 mg, 3.78 mmol, 0.060 equiv), and potassium carbonate (13.07 g, 94.58 mmol, 1.50 equiv). The vessel was flushed and then maintained under a nitrogen atmosphere. Bromobenzene (6.67 mL, 63.05 mmol, 1.00 equiv) was added, followed by hydrazine **7** (12.1 mL, 78.8 mmol, 1.25 equiv) and then dimethyl sulfoxide (63 mL, deoxygenated by nitrogen sparging for 30 min, water content 396 ppm by Karl Fisher titration). The mixture was heated to an internal temperature of 75 °C and stirred for 8 h. After cooling to room temperature, the reaction mixture was filtered over a pad of Celite (4.5 cm diameter, 1 cm height), and the pad was washed with isopropyl acetate (2 × 50 mL). The mixture was poured into a 1.0 M aqueous solution of a pH 7 sodium phosphate buffer (100 mL), forming a triphasic mixture (dark brown top layer, green middle layer, blue bottom layer). The bottom two layers (green and blue) were separated and extracted with isopropyl acetate (100 mL). The combined organic extracts were washed with water (100 mL) and a saturated, aqueous solution of brine (100 mL) and then dried over anhydrous sodium sulfate. The drying agent was removed by filtration, and the solution was concentrated *in vacuo* to afford a brown oil. The oil was purified by flash column chromatography over silica gel (0−15% ethyl acetate in hexanes gradient) to afford product $\mathbf{8}_{Boc}$ as a white solid (12.34 g, 88%). R_f (10% ethyl acetate in hexanes): 0.31 (UV). Mp (ethyl acetate/hexanes): 76−78 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.87 (br s, 1H), 7.16 (t, J = 7.9 Hz, 2H), 6.72 (t, J = 7.3 Hz, 1H), 6.58 (d, J = 7.7 Hz, 2H), 3.06 (s, 3H), 1.33 (br s, 9H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 155.4, 148.1, 128.8, 118.6, 111.7, 79.3, 37.1 (br), 27.8. IR (solid) (cm^{-1}): 3288 (m), 1674 (s), 1364 (s), 1155 (s) 752 (s). HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{12}H_{18}N_2NaO_2$, 245.1261; found, 245.1263.

The Boc hydrazine $\mathbf{8}_{Boc}$ (10.00 g, 44.99 mmol, 1.00 equiv) dissolved in methanol (20 mL) after stirring for 15 min. The solution was cooled to an internal temperature of 4 °C with an ice−water bath, and a light purge of nitrogen was applied to the headspace, venting to the back of the hood. Chlorotrimethylsilane (8.75 mL, 67.48 mmol, 1.50 equiv) was added dropwise at a rate such that the internal temperature did not exceed 6.0 °C (10 min). The reaction mixture was warmed to room temperature and stirred for 3 h. A crystalline slurry formed during the process. The stirring was suspended, toluene (20 mL) was added, and the meniscus was marked. Additional toluene (40 mL) was added, and the slurry was concentrated *in vacuo* to the marked line. The slurry was cooled to an internal temperature of 4 °C with an ice−water bath and held for 30 min. The crystals were collected by filtration, washed with toluene (2 × 20 mL), and then dried at an ambient temperature under reduced pressure until a constant weight was achieved. Salt **8** was obtained as white crystals (7.00 g, 98%) and was stored under nitrogen at −20 °C. DSC (methanol/toluene), T_{onset} 125.98 °C, T_{peak} 197.44 °C (ΔH_D 150.5 kJ/mol). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.40 (br s, 2H), 8.48 (br s, 1H), 7.29 (app t, J = 7.8 Hz, 2H), 7.15 (d, J = 8.2 Hz, 2H), 6.98 (t, J = 7.3 Hz, 1H), 2.75 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 143.6, 129.1, 122.3, 115.9, 33.8. IR (solid) (cm^{-1}): 2672 (br m), 1457 (m), 1383 (m), 768 (s), 690 (s). HRMS (ESI): m/z [M + H]$^+$ calcd for $C_7H_{11}N_2$, 123.0917; found, 123.0915.

The higher alkyl derivatives $\mathbf{8}_{Et}$, $\mathbf{8}_{i\text{-}Pr}$, and $\mathbf{8}_{Bn}$ were prepared analogously, though the procedure was not optimized.

*2-Ethyl-1-phenylhydrazine Hydrochloride (**8**$_{Et}$):* 3.17 mmol scale. 60% yield for the CN coupling and 87% yield for the HCl salt formation. White solid (286 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.11−11.21 (br m, 2H), 8.32−8.35 (br m, 1H), 7.31 (app t, J = 7.0 Hz, 2H), 7.11−7.15 (m, J = 8.2 Hz, 2H), 6.99 (t, J = 7.3 Hz, 1H), 3.16 (q, J = 7.2 HZ, 2H), 1.27 (t, J = 7.3 HZ, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 143.6, 129.1, 122.1, 115.9, 42.9, 9.4. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_8H_{13}N_2$, 137.1073; found, 137.1070.

*2-Isopropyl-1-phenylhydrazine Hydrochloride (**8**$_{i\text{-}Pr}$):* 4.23 mmol scale. 47% yield for the CN coupling and 90% yield for the HCl salt formation. White solid (337 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.13 (br s, 2H), 8.30 (br s, 1H), 7.29 (app t, J = 7.1 Hz, 2H), 7.18 (d, J = 8.1 Hz, 2H), 6.97 (t, J = 7.1 Hz, 1H), 3.53 (septet, J = 6.5 Hz, 1H), 1.32 (d, J = 6.5 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 143.6, 129.0, 121.1, 116.0, 50.6, 17.3. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_9H_{15}N_2$, 151.1230; found, 151.1227.

*2-Benzyl-1-phenylhydrazine Hydrochloride (**8**$_{Bn}$):* 4.08 mmol scale. 62% yield for the CN coupling and 77% yield for the HCl salt formation. White solid (396 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.55 (br s, 2H), 8.49 (br s, 1H), 7.56−7.58 (m, 2H), 7.40−7.43 (m, 3H), 7.31 (app t, J = 7.9 Hz, 2H), 7.15 (d, J = 7.8 Hz, 2H), 6.98 (t, J = 7.3 Hz, 1H), 4.31 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 143.6, 130.9, 130.5, 129.1, 129.0, 128.4, 122.0, 116.0, 51.4. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{13}H_{15}N_2$, 199.1230; found, 199.1226.

*2-Methyl-1-(4-chlorophenyl)hydrazine Hydrochloride (**9**).* To a dried flask equipped with a thermocouple were added copper(I) iodide (591 mg, 3.10 mmol, 0.040 equiv), ligand **L1** (1.13 g, 4.65 mmol, 0.060 equiv), and potassium carbonate (16.1 g, 116 mmol, 1.50 equiv). The vessel was flushed and then maintained under a nitrogen atmosphere. 1-Bromo-4-chlorobenzene (15.0 g, 77.6 mmol, 1.00 equiv) was added, followed by hydrazine **7** (14.8 mL, 97.0 mmol, 1.25 equiv) and then dimethyl sulfoxide (78 mL, deoxygenated by nitrogen sparging for 30 min, water content 454 ppm by Karl Fisher titration). The mixture was heated to an internal temperature of 75 °C and stirred for 8 h. After cooling to room temperature, the reaction mixture was filtered over a pad of Celite (4.5 cm diameter, 1 cm height), and the pad was washed with isopropyl acetate (2 × 50 mL). The mixture was poured into a 1.0 M aqueous solution of a pH 7 sodium phosphate buffer (100 mL), forming a triphasic mixture (dark brown top layer, green middle layer, blue bottom layer). The bottom two layers (green and blue) were separated and extracted with isopropyl acetate (100 mL). The combined organic extracts were washed with water (100 mL) and a saturated, aqueous solution of brine (100 mL) and then dried over anhydrous sodium sulfate. The drying agent was removed by filtration, and the solution was concentrated *in vacuo* to afford a brown oil. The oil was purified by flash column chromatography over silica gel (0−15% ethyl acetate in hexanes gradient) to afford product $\mathbf{9}_{Boc}$ as a light yellow

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solid (17.86 g, 90%). R_f (10% ethyl acetate in hexanes): 0.23 (UV). Mp (ethyl acetate/hexanes): 66−69 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.07 (br s, 1H), 7.19 (d, J = 8.8 Hz, 2H), 6.59 (d, J = 8.8 Hz, 2H), 3.05 (s, 3H), 1.33 (br s, 9H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 155.3, 147.1, 128.6, 122.0, 113.1, 79.5, 37.0 (br), 27.8. IR (solid) (cm^{-1}): 3284 (m), 1681 (s), 1360 (s), 1148 (s), 820 (s). HRMS (ESI): m/z [M + H − C_4H_8]$^+$ calcd for $C_8H_{10}ClN_2O_2$, 201.0425; found, 201.0425.

The Boc hydrazine $\mathbf{9}_{\mathbf{Boc}}$ (15.00 g, 58.43 mmol, 1.00 equiv) was dissolved in methanol (30 mL) after stirring for 15 min. The solution was cooled to an internal temperature of 4 °C with an ice−water bath, and a light purge of nitrogen was applied to the headspace, venting to the back of the hood. Chlorotrimethylsilane (11.5 mL, 87.64 mmol, 1.50 equiv) was added dropwise at a rate such that the internal temperature did not exceed 6.0 °C (15 min). The reaction mixture was warmed to room temperature and stirred for 5 h. A crystalline slurry formed during the process. The stirring was suspended, toluene (30 mL) was added, and the meniscus was marked. Additional toluene (60 mL) was added, and the slurry was concentrated *in vacuo* to the marked line. The slurry was cooled to an internal temperature of 4 °C with an ice−water bath and held for 30 min. The crystals were collected by filtration, washed with toluene (2 × 30 mL), and then dried at an ambient temperature under reduced pressure until a constant weight was achieved. Salt **9** was obtained as white crystals (10.82 g, 96%) and was stored under nitrogen at −20 °C. DSC (methanol/toluene), T_{onset} 118.79 °C, T_{peak} 190.04 °C (ΔH_D 164.2 kJ/mol). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.36 (br s, 1H), 8.58 (br s, 1H), 7.36 (app d, J = 8.8 Hz, 2H), 7.13 (app d, J = 8.9 Hz, 2H), 2.76 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 142.6, 129.0, 126.0, 117.6, 33.8. IR (solid) (cm^{-1}): 2658 (m), 1491 (m), 1092 (m), 820 (s), 663 (s). HRMS (ESI): m/z [M + H]$^+$ calcd for $C_7H_{10}ClN_2$, 157.0527; found, 157.0527.

*2-Methyl-1-(3,5-dimethoxyphenyl)hydrazine Hydrochloride (**10**).* To a dried flask equipped with a thermocouple were added copper(I) iodide (170 mg, 0.894 mmol, 0.040 equiv), ligand **L1** (325 mg, 1.34 mmol, 0.060 equiv), and potassium carbonate (4.63 g, 33.52 mmol, 1.50 equiv). The vessel was flushed and then maintained under a nitrogen atmosphere. 1-Bromo-3,5-dimethoxybenzene (5.00 g, 22.34 mmol, 1.00 equiv) was added, followed by hydrazine **7** (4.27 mL, 27.93 mmol, 1.25 equiv) and then dimethyl sulfoxide (22 mL, deoxygenated by nitrogen sparging for 30 min, water content 709.760 ppm by Karl Fisher titration). The mixture was heated to an internal temperature of 75 °C and stirred for 16 h. After cooling to room temperature, the maroon reaction mixture was filtered over a pad of Celite (3 cm diameter, 1 cm height) (air exposure turns the reaction mixture green), and the pad was washed with isopropyl acetate (3 × 25 mL). The mixture was poured into a 0.5 M aqueous solution of a pH 7 sodium phosphate buffer (50 mL), forming a triphasic mixture (dark brown top layer, green middle layer, blue bottom layer), and the bottom two layers (green and blue) were separated and extracted with isopropyl acetate (50 mL). The combined organic extracts were washed with water (50 mL) and a saturated, aqueous solution of brine (50 mL) and then dried over anhydrous sodium sulfate. The drying agent was removed by filtration, and the solution was concentrated *in vacuo* to afford a brown oil. The oil was purified by flash column chromatography over silica gel (0−25% ethyl acetate in hexanes gradient) to afford product $\mathbf{10}_{\mathbf{Boc}}$ as a light yellow oil (5.90 g, 94%). R_f (20% ethyl acetate in hexanes): 0.30 (UV). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.87 (br s, 1H), 5.90 (t, J = 1.8 Hz, 1H), 5.73 (s, J = 2.0 Hz, 2H), 3.66 (s, 6H), 3.03 (s, 3H), 1.35 (br s, 9H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 161.7, 155.9, 150.5, 91.4, 90.8, 79.9, 55.3, 37.5, 28.4. IR (thin film) (cm^{-1}): 3325 (w), 1696 (m), 1599 (m), 1144 (s), 816 (m). HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{14}H_{23}N_2O_4$, 283.1652; found, 283.1659.

The Boc hydrazine $\mathbf{10}_{\mathbf{Boc}}$ (5.00 g, 17.71 mmol, 1.00 equiv) was dissolved in methanol (10 mL). The solution was cooled to an internal temperature of 1 °C with an ice−water bath, and a light purge of nitrogen was applied to the headspace, venting to the back of the hood. Chlorotrimethylsilane (3.44 mL, 26.57 mmol, 1.50 equiv) was added dropwise at a rate such that the internal temperature did not exceed 5.0 °C (15 min). The reaction mixture was warmed to room temperature and stirred for 15 h. Toluene (10 mL) was added, and the solution was concentrated *in vacuo* to afford a rapidly crystallizing gel. Additional toluene (20 mL) was added, and the mixture was concentrated *in vacuo*. Toluene (20 mL) was added, and the crystals were collected by filtration, washed with methyl *tert*-butyl ether (2 × 20 mL), and then dried at an ambient temperature under reduced pressure until a constant weight was achieved. Salt **10** was obtained as off-white (yellowish) crystals (3.54 g, 91%) and was stored under nitrogen at −20 °C. DSC (methanol/toluene), T_{onset} 104.10 °C, T_{peak} 202.31 °C (ΔH_D 215.0 kJ/mol). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.00−11.40 (br m, 2H), 8.18−8.45 (br m, 1H), 6.34 (s, 1H), 6.31 (s, 1H), 6.15 (s, 1H), 3.71 (s, 6H), 2.75 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 161.1, 145.5, 94.6, 94.3, 55.3, 33.8. IR (solid) (cm^{-1}): 2628 (br), 1606 (m), 1465 (m), 1200 (s), 831 (s). HRMS (ESI): m/z [M + H]$^+$ calcd for $C_9H_{15}N_2O_2$, 183.1128; found, 183.1134.

*2-Methyl-1-(3,5-dinitrophenyl)hydrazine Hydrochloride (**11**).* To a dried flask equipped with a thermocouple were added copper(I) iodide (153 mg, 0.802 mmol, 0.040 equiv), ligand **L1** (291 mg, 1.20 mmol, 0.060 equiv), and potassium carbonate (4.15 g, 30.06 mmol, 1.50 equiv). The vessel was flushed and then maintained under a nitrogen atmosphere. 1-Bromo-3,5-dinitrobenzene (5.00 g, 20.04 mmol, 1.00 equiv) was added, followed by hydrazine **7** (3.83 mL, 25.05 mmol, 1.25 equiv) and then dimethyl sulfoxide (20 mL, deoxygenated by nitrogen sparging for 30 min, water content 709.306 ppm by Karl Fisher titration). The mixture was heated to an internal temperature of 75 °C and stirred for 5 h. After cooling to room temperature, the black reaction mixture was filtered over a pad of Celite (3 cm diameter, 1 cm height), and the pad was washed with isopropyl acetate (3 × 50 mL). The mixture was poured into a 0.5 M aqueous solution of a pH 7 sodium phosphate buffer (50 mL), and the layers were separated with the aid of a flashlight. The aqueous layer was extracted with isopropyl acetate (3 × 50 mL). The combined organic extracts were washed with water (50 mL) and a saturated, aqueous solution of brine (50 mL) and then dried over anhydrous sodium sulfate. The drying agent was removed by filtration, and the solution was concentrated *in vacuo* to afford a black residue. The residue was purified by flash column chromatography over silica gel (0−30% ethyl acetate in hexanes gradient) to afford product $\mathbf{11}_{\mathbf{Boc}}$ as a red oil that crystallized to a yellow solid (5.56 g, 94%). R_f (20% ethyl acetate in hexanes): 0.25 (UV). Mp (ethyl acetate/hexanes): 115−116 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.19 (s, 1H), 8.16 (t, J = 1.8 Hz, 1H), 7.70 (d, J = 1.7 Hz, 2H), 3.13 (s, 3H), 1.38 (br s, 9H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 154.8, 150.4, 148.9, 110.5, 107.1, 80.6, 37.1 (br), 27.7 (br). IR (solid) (cm^{-1}): 1688 (s), 1543 (s), 1346 (s), 1144 (s), 726 (s). HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{12}H_{17}N_4O_6$, 313.1143; found, 313.1152.

The Boc hydrazine $\mathbf{11}_{\mathbf{Boc}}$ (5.00 g, 16.01 mmol, 1.00 equiv) was dissolved in methanol (50 mL). The solution was cooled to an internal temperature of 2.5 °C with an ice−water bath, and a light purge of nitrogen was applied to the headspace, venting to the back of the hood. Chlorotrimethylsilane (4.15 mL, 32.02 mmol, 2.00 equiv) was added dropwise at a rate such that the internal temperature did not exceed 5.0 °C (15 min). The reaction mixture was warmed to room temperature and stirred for 15 h, whereupon yellow needles formed. The solvent was concentrated *in vacuo* by 80%, then toluene (20 mL) was added, and the solution was concentrated again *in vacuo* by 80%. Additional toluene (15 mL) was added, and the crystals were collected by then dried at an ambient temperature under reduced pressure until a constant weight was achieved. Salt **11** was obtained as beige needles (3.87 g, 97%) and was stored under nitrogen at −20 °C. DSC (methanol/toluene), T_{onset} 155.35 °C, T_{peak} 187.73 °C (ΔH_D 275.5 kJ/mol), T_{peak} 312.00 °C (ΔH_D 312.8 kJ/mol). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.00−12.00 (br s, 2H), 9.55 (br s, 1H), 8.31 (s, 1H), 8.26 (s, 2H), 2.81 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 148.6, 146.6, 114.5, 110.2, 34.4. IR (solid) (cm^{-1}): 2658 (br), 1536 (s), 1338 (s), 1174 (w), 723 (s). HRMS (ESI): m/z [M + H]$^+$ calcd for $C_7H_9N_4O_4$, 213.0618; found, 213.0623.

*Ethyl 5-(2-Methylhydrazinyl)thiophene-2-carboxylate Sesquihydrochloride (**12**).* To a dried flask equipped with a thermocouple were added copper(I) iodide (318 mg, 1.67 mmol, 0.040 equiv), ligand **L1** (606 mg, 2.50 mmol, 0.060 equiv), and potassium carbonate (8.73 g,

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62.5 mmol, 1.50 equiv). The vessel was flushed and then maintained under a nitrogen atmosphere. Ethyl 5-bromothiophene-2-carboxylate (10.0 g, 41.7 mmol, 1.00 equiv) was added, followed by hydrazine **7** (7.97 mL, 52.1 mmol, 1.25 equiv) and then dimethyl sulfoxide (62.5 mL, deoxygenated by nitrogen sparging for 30 min, water content 207.336 ppm by Karl Fisher titration). The mixture was heated to an internal temperature of 80 °C and stirred for 14 h. After cooling to room temperature, the reaction mixture was filtered over a pad of Celite (4.5 cm diameter, 1 cm height), and the filter was washed with dichloromethane (2 × 100 mL). The mixture was poured into a 0.50 M aqueous solution of a pH 7 sodium phosphate buffer (100 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 50 mL). The combined organic extracts were washed with water (100 mL) and a saturated, aqueous solution of brine (100 mL) and then dried over anhydrous sodium sulfate. The drying agent was removed by filtration, and the solution was concentrated *in vacuo* to afford a dark oil. The oil was purified by flash column chromatography over silica gel (0−25% ethyl acetate in hexanes gradient) to afford product $\mathbf{12}_{\mathbf{Boc}}$ as a red gel (10.42 g, 83%). After extended storage (>2 mo) at 4 °C, the material crystallized. R_f (15% ethyl acetate in hexanes): 0.27 (UV). Mp (ethyl acetate/hexanes): 74−75 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, J = 4.0 Hz, 1H), 6.54 (br s, 1H), 6.20 (d, J = 4.0 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 3.21 (s, 3H), 1.45 (s, 9H), 1.34 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 162.6, 161.9, 155.5, 134.2, 119.7, 106.2, 81.8, 60.6, 37.3, 28.1, 14.3. IR (thin film) (cm^{-1}): 3276 (br w), 1677 (br m), 1450 (m), 1148 (s), 1085 (s). HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{13}H_{21}N_2O_4$, 301.1216; found, 301.1219.

The Boc hydrazine $\mathbf{12}_{\mathbf{Boc}}$ (8.00 g, 26.63 mmol, 1.00 equiv) was dissolved in methanol (16 mL). The solution was cooled to an internal temperature of 2.3 °C with an ice−water bath, and a light purge of nitrogen was applied to the headspace, venting to the back of the hood. Chlorotrimethylsilane (8.70 mL, 66.58 mmol, 2.50 equiv) was added dropwise at a rate such that the internal temperature did not exceed 5.0 °C (15 min). The reaction mixture was warmed to room temperature and stirred for 2.5 h. A crystalline slurry formed during the process. The stirring was suspended, toluene (16 mL) was added, and the meniscus was marked. Additional toluene (40 mL) was added, and the slurry was concentrated *in vacuo* to the marked line. The slurry was cooled to an internal temperature of 4 °C with an ice−water bath and held for 30 min. The crystals were collected by filtration, washed with toluene (2 × 16 mL), and then dried at an ambient temperature under reduced pressure until a constant weight was achieved. Salt **12** was obtained as bone-colored crystals (5.92 g) and was stored under nitrogen at −20 °C. The exact protonation state of the salt was difficult to determine by NMR spectroscopy due to broad resonances. The solid was found to be 78.3 wt % free base (4.64 g) by quantitative NMR. The theoretical yield of the free base is 5.33 g, corresponding to a corrected, isolated yield of 87%. This observed potency of 78.3% did not correspond to a monohydrochoride (84.6 wt %) or a dihydrochloride (73.3 wt %) salt but rather a sesquihydrochloride (78.5 wt %). As calculated as a sesquihydrochloride salt, this would represent an 87% isolated yield of the salt **12** having 99.7 wt % purity. DSC (methanol/toluene), T_{onset} 125.98 °C, T_{peak} 148.95 °C (ΔH_D144.6 kJ/mol). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.80−12.30 (br s, 1.5H), 9.47 (br s, 1H), 7.56 (d, J = 4.0 Hz, 1H), 6.76 (d, J = 3.9 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 2.75 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 161.4, 154.2, 133.7, 122.7, 113.4, 60.7, 34.0, 14.3. IR (solid) (cm^{-1}): 3168 (w), 2691 (m), 1696 (m), 1457 (m). 1260 (s), 1085 (s). HRMS (ESI): m/z [M + H]$^+$ calcd for $C_8H_{13}N_2O_2S$, 201.0692; found, 201.0692.

*2-Methoxy-3-(2-methylhydrazinyl)pyridinium Bistetrafluoroborate (**13**).* To a dried flask equipped with a thermocouple was added *tert*-amyl alcohol (200 mL, water content 145.9 ppm by Karl Fisher titration). The solvent was deoxygenated by nitrogen sparging for 30 min, and then palladium acetate (351 mg, 1.53 mmol, 0.030 equiv) and X-Phos (1.51 g, 3.06 mmol, 0.060 equiv) were added against a current of nitrogen. The suspension was heated to an internal temperature of 65 °C (temperature ramp took 15 min), forming a very dark solution, and then cooled to room temperature, forming a light slurry. Powered sodium hydroxide (2.89 g, 71.48 mmol, 1.40 equiv), 3-bromo-2-methoxypyridine (6.31 mL, 51.06 mmol, 1.00 equiv), and hydrazine **7** (9.77 mL, 63.82 mmol, 1.25 equiv) were added sequentially, and the mixture was heated to an internal temperature of 90 °C under a nitrogen atmosphere. The initially dark solution becomes a reddish slurry, then a black suspension. After 2 h, the mixture is cooled to room temperature and filtered through a pad of Celite (4.5 cm diameter, 1 cm height), and the pad was washed with dichloromethane (3 × 50 mL). The combined filtrates were concentrated *in vacuo* to afford a dark oil. The oil was purified by flash column chromatography over silica gel (0−25% ethyl acetate in hexanes gradient). The product $\mathbf{13}_{\mathbf{Boc}}$ was isolated as a syrup that, upon storage, at 4 °C slowly (1−2 days) solidifies to a waxy solid (12.30 g, 95%). R_f (25% ethyl acetate in hexanes): 0.55 (UV). Mp (ethyl acetate/hexanes): 49−51 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.55 (br s, 1H), 7.52 (dd, J = 4.9, 1.6 Hz, 1H), 6.84 (dd, J = 7.6, 5.0 Hz, 1H), 6.75 (dd, J = 7.6, 1.3 Hz, 1H), 3.88 (s, 3H), 3.05 (s, 3H), 1.32 (br s, 9H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 155.2, 151.3, 134.8, 131.7, 117.2, 116.2, 79.5, 52.7, 36.8 (br), 27.8. IR (solid) (cm^{-1}): 3358 (w), 1692 (s), 1364 (s), 1148 (s), 805 (m). HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{12}H_{20}N_3O_3$, 254.1499; found, 254.1497.

The Boc hydrazine $\mathbf{13}_{\mathbf{Boc}}$ (12.30 g, 48.56 mmol, 1.0 equiv) was dissolved in toluene (61.5 mL). The solution was cooled to an internal temperature of 5 °C with an ice−water bath, and a light purge of nitrogen was applied to the headspace, venting to the back of the hood. The tetrafluoroboric acid-diethyl ether complex (14.4 mL, 101 mmol, 2.08 equiv) was added dropwise under vigorous stirring at a rate such that the internal temperature did not exceed 6 °C (1 h), forming a grainy slurry. Rapid addition of the acid will cause gelling; though after further agitation, it will break down to a slurry. The slurry was aged for an additional 1 h at room temperature. The product was collected by filtration, washed with toluene (2 × 61 mL), and then dried at an ambient temperature under reduced pressure until a constant weight was achieved. The salt **13** was obtained as a light beige solid (15.64 g) and was stored under nitrogen at −20 °C. The exact protonation state of the salt (i.e., mono or bistetrafluoroborate) was difficult to determine by NMR spectroscopy due to broad resonances. The solid was 45.1 wt % as analyzed by quantitative NMR as the free base, corresponding to 7.05 g. The theoretical yield of the free base is 7.44 g, corresponding to a corrected, isolated yield of 95%. As calculated as a bistetrafluoroborate salt, this would represent a 95% isolated yield of the salt **13** having 96.8 wt % purity. DSC (toluene), T_{onset} 107.27 °C, T_{peak} 165.44 °C (ΔH_D 185.1 kJ/mol). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.58 (br s, 2H), 7.83 (dd, J = 5.0, 1.5 Hz, 1H), 7.31 (dd, J = 7.6, 1.5 Hz, 1H), 7.08 (v br s, integration impeded by broadening), 7.01 (dd, J = 7.6, 5.1 Hz, 1H), 3.94 (s, 3H), 2.86 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 153.6, 140.0, 127.5, 123.3, 117.6, 54.0, 34.8. IR (solid) (cm^{-1}): 3127 (br), 1561 (m), 1271 (m), 984 (s), 764 (m). HRMS (ESI): m/z [M + H]$^+$ calcd for $C_7H_{12}N_3O$, 154.0975; found, 154.0970.

The labeled compounds ($\mathbf{13}_{\mathbf{OCD3}}$, $\mathbf{13}_{\mathbf{NHCD3}}$, and $\mathbf{13}_{\mathbf{15N}}$) were prepared analogously.

2-(Methoxy-d_3)-3-(2-methylhydrazinyl)pyridinium Bistetrafluoroborate ($\mathbf{13}_{\mathbf{OCD3}}$): 10.47 mmol scale. 96% yield for the CN coupling and 84% yield for the HBF_4 salt formation. White solid (3.13 g, 42.2 wt % calculated as free base). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.59 (br s, 2H), 7.84 (dd, J = 5.0, 1.5 Hz, 1H), 7.32 (dd, J = 7.6, 1.5 Hz, 1H), 7.02 (dd, J = 7.7, 5.0 Hz, 1H), 6.79 (v br s, integration impeded by broadening), 2.86 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 153.7, 140.1, 127.5, 123.4, 117.7, 53.3 (app septet, J = 22.5 Hz), 34.9. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_7H_9D_3N_3O$, 157.1163; found, 157.1167.

2-Methoxy-3-(2-(methyl-d_3)hydrazinyl)pyridinium Bistetrafluoroborate ($\mathbf{13}_{\mathbf{NHCD3}}$): 6.11 mmol scale. 92% yield for the CN coupling and 89% yield for the HBF_4 salt formation. White solid (1.74 g, 44.4 wt % calculated as free base). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.57 (br s, 2H), 8.06 (br s, 1H), 7.83 (dd, J = 4.9, 1.5 Hz, 1H), 7.31 (dd, J = 7.6, 1.4 Hz, 1H), 7.01 (dd, J = 7.4, 5.2 Hz, 1H), 3.94 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 154.1, 140.2, 127.9, 124.1, 118.1, 54.6, 34.6 (app septet, J = 21.3 Hz). HRMS (ESI): m/z [M + H]$^+$ calcd for $C_7H_9D_3N_3O$, 157.1163; found, 157.1168.

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*2-Methoxy-3-(2-methylhydrazinyl-1-^{15}N)pyridinium Bistetrafluoroborate (**13**$_{15N}$):* 4.37 mmol scale. 86% yield for the CN coupling and 90% yield for the HBF_4 salt formation. White solid (1.20 g, 43.4 wt % calculated as free base). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.58 (br s, 2H), 8.04 (br s, 2H), 7.84 (dd, J = 5.0, 1.5 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7.01 (dd, J = 7.6, 5.1 Hz, 1H), 3.94 (s, 3H), 2.86 (d, J = 2.6 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 153.8 (d, J = 2.9 Hz), 140.1, 127.7 (d, J = 7.3 Hz), 123.7, 117.8, 54.3, 35.0. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_7H_{12}{}^{15}NN_2O$, 155.0945; found, 155.0951.

*2-Methoxy-5-(2-methylhydrazinyl)pyridinium Bistetrafluoroborate (**14**).* To a dried pear-shaped flask equipped with a thermocouple was added *tert*-amyl alcohol (100 mL, water content 150.9 ppm by Karl Fisher titration). The solvent was deoxygenated by nitrogen sparging for 30 min, and then palladium acetate (347 mg, 1.52 mmol, 0.030 equiv) and X-Phos (1.49 g, 3.03 mmol, 0.060 equiv) were added against a current of nitrogen. The suspension was heated to an internal temperature of 65 °C (temperature ramp took 15 min), forming a very dark solution, and then cooled to room temperature, forming a slight slurry. Separately, to a dried 500 mL round-bottomed flask were added powered sodium hydroxide (2.83 g, 70.74 mmol, 1.40 equiv), 5-bromo-2-methoxypyridine (6.88 mL, 50.53 mmol, 1.00 equiv), and hydrazine **7** (9.66 mL, 63.16 mmol, 1.25 equiv) under nitrogen. The dark palladium mixture in the pear-shaped flask was transferred to the round-bottomed flask using a wide bore (16 gauge) cannula. The cherry red suspension was heated to an internal temperature of 90 °C under nitrogen. The mixture changes from a cherry red suspension to a thick, pinkish-beige suspension and then finally to a black slurry. After 3 h, the mixture is cooled to room temperature and filtered through a pad of Celite (4.5 cm diameter, 1 cm height), and the pad was washed with *tert*-amyl alcohol (2 × 20 mL). The combined filtrates were concentrated *in vacuo* to afford a dark oil. The oil was purified by flash column chromatography over silica gel (0−60% ethyl acetate in hexanes gradient). The product **14**$_{Boc}$ was isolated as a thick, tan syrup (11.76 g, 92%). R_f (30% ethyl acetate in hexanes): 0.50 (UV). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.72 (br s, 1H), 7.52 (d, J = 2.7 Hz, 1H), 7.06 (dd, J = 8.8, 2.9 Hz, 1H), 6.68 (d, J = 8.8 Hz, 1H), 3.75 (s, 3H), 3.07 (s, 3H), 1.33 (br s, 9H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 157.7, 155.4, 139.1, 129.9, 125.0, 110.3, 79.5, 52.8, 37.3 (br), 27.8. IR (thin film) (cm^{-1}): 3302 (w), 1692 (m), 1487 (m), 1364 (m), 1148 (s). HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{12}H_{20}N_3O_3$, 254.1499; found, 254.1506.

The Boc hydrazine **14**$_{Boc}$ (9.25 g, 36.52 mmol, 1.00 equiv) was dissolved in toluene (46 mL). The solution was cooled to an internal temperature of 0.2 °C with an ice−water bath, and a light purge of nitrogen was applied to the headspace, venting to the back of the hood. The tetrafluoroboric acid-diethyl ether complex (11.0 mL, 76.69 mmol, 2.10 equiv) was added dropwise under vigorous stirring at a rate such that the internal temperature did not exceed 5 °C (1 h), forming a grainy slurry. Rapid addition of the acid will cause gelling; though after further agitation, it will break down to a slurry. The slurry was aged for an additional 1.5 h at room temperature. The product was collected by filtration, washed with ethyl acetate (2 × 25 mL), and then dried at an ambient temperature under reduced pressure until a constant weight was achieved. If toluene is used as the cake wash, the salt will clump upon storage. The salt **14** was obtained as a light beige solid (11.79 g) and was stored under nitrogen at −20 °C. The exact protonation state of the salt (i.e., mono or bistetrafluoroborate) was difficult to determine by NMR spectroscopy due to broad resonances. The solid was 45.1 wt % as analyzed by quantitative NMR as the free base, corresponding to 5.32 g. The theoretical yield of the free base is 5.59 g, corresponding to a corrected, isolated yield of 95%. As calculated as a bistetrafluoroborate salt, this would represent a 95% isolated yield of the salt **14** having 97.0 wt % purity. DSC (toluene), T_{onset} 123.68 °C, T_{peak} 192.55 °C (ΔH_D182.5 kJ/mol). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.46 (br s, 2H), 7.98 (d, J = 2.8 Hz, 1H), 7.54 (dd, J = 8.9, 2.9 Hz, 1H), 6.89 (d, J = 8.8 Hz, 1H), 3.83 (s, 3H), 2.78 (br s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 160.7, 136.8, 133.8, 132.7, 111.3, 54.0, 34.3. IR (solid) (cm^{-1}): 3157 (br), 1565 (m), 1025 (s), 1006 (s), 839 (m). HRMS (ESI): m/z [M + H]$^+$ calcd for $C_7H_{12}N_3O$, 154.0975; found, 154.0979.

*5-Methoxy-2-(2-methylhydrazinyl)pyridinium Bishydrochloride (**15**).* To a dried flask equipped with a thermocouple were added copper(I) iodide (397 mg, 2.08 mmol, 0.040 equiv), ligand **L1** (758 mg, 3.13 mmol, 0.060 equiv), and potassium carbonate (10.91 g, 78.18 mmol, 1.50 equiv). The vessel was flushed and then maintained under a nitrogen atmosphere. 2-Bromo-5-methoxypyridine (6.54 mL, 52.12 mmol, 1.00 equiv) was added, followed by hydrazine **7** (9.97 mL, 65.2 mmol, 1.25 equiv) and then dimethyl sulfoxide (52 mL, deoxygenated by nitrogen sparging for 30 min, water content 655.8 ppm by Karl Fisher titration). The mixture was heated to an internal temperature of 80 °C and stirred for 16 h. After cooling to room temperature, the reaction mixture was filtered over a pad of Celite (4.5 cm diameter, 1 cm height), and the pad was washed with isopropyl acetate (2 × 50 mL). The mixture was poured into a 1.0 M aqueous solution of a pH 7 sodium phosphate buffer (100 mL), forming a triphasic mixture (dark brown top layer, green middle layer, blue bottom layer). The bottom two layers (green and blue) were separated and extracted with isopropyl acetate (100 mL). The combined organic extracts were washed with water (100 mL) and a saturated, aqueous solution of brine (100 mL) and then dried over anhydrous sodium sulfate. The drying agent was removed by filtration, and the solution was concentrated *in vacuo* to afford a brown oil. The oil was purified by flash column chromatography over silica gel (0−30% acetone in hexanes gradient) to afford product **15**$_{Boc}$ as a white solid (11.18 g, 85%). R_f (15% acetone in hexanes): 0.19 (UV). Mp (acetone/hexanes): 96−97.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.16 (br s, 1H), 7.82 (d, J = 2.8 Hz, 1H), 7.26 (dd, J = 8.9, 2.8 Hz, 1H), 6.49 (d, J = 8.9 Hz, 1H), 3.72 (s, 3H), 3.06 (s, 3H), 1.28 (br s, 9H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 155.7 (br), 153.5, 149.6, 133.2, 124.8, 107.1, 79.2 (br), 55.9, 37.3 (br), 27.9. IR (solid) (cm^{-1}): 3217 (br w), 1700 (s), 1364 (m), 1141 (s), 823 (s). HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{12}H_{20}N_3O_3$, 254.1499; found, 254.1507.

The Boc hydrazine **15**$_{Boc}$ (10.00 g, 39.48 mmol, 1.00 equiv) was dissolved in methanol (50 mL) and then cooled to an internal temperature of 0.5 °C with an ice−water bath, and a light purge of nitrogen was applied to the headspace, venting to the back of the hood. Chlorotrimethylsilane (15.2 mL, 118.4 mmol, 3.00 equiv) was added dropwise at a rate such that the internal temperature did not exceed +5.0 °C (30 min). The reaction mixture was allowed to warm to room temperature and was stirred for 15 h, forming a white slurry after 30 min. The stirring was suspended, the meniscus was marked, and then toluene (50 mL) was added. The mixture was concentrated to the marked line; then additional toluene (50 mL) was added. The slurry was stirred for 30 min; then the crystals were isolated by filtration and then dried at an ambient temperature under reduced pressure until a constant weight was achieved. Salt **15** was obtained as a light beige solid (8.85 g) and was stored under nitrogen at −20 °C. The exact protonation state of the salt (i.e., mono or bishydrochloride) was difficult to determine by NMR spectroscopy due to broad resonances. The solid was 64.5 wt % as analyzed by quantitative NMR as the free base, corresponding to 5.71 g. The theoretical yield of the free base is 6.05 g, corresponding to a corrected, isolated yield of 94%. As calculated as a bishydrochloride salt, this would represent a 94% isolated yield of the salt **15** having 95.1 wt % purity. DSC (methanol/toluene), T_{onset} 147.29 °C, T_{peak} 196.84 °C (ΔH_D 234.9 kJ/mol). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.79−12.36 (br m, 3H), 7.85 (d, J = 2.9 Hz, 1H), 7.47 (dd, J = 9.1, 2.9 Hz, 1H), 6.91 (d, J = 9.0 Hz, 1H), 3.77 (s, 3H), 2.74 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 150.9, 149.2, 129.7, 127.5, 111.2, 56.3, 35.3. IR (solid) (cm^{-1}): 2479 (br w), 1629 (w), 1349 (w), 1278 (s), 842 (m). HRMS (ESI): m/z [M + H]$^+$ calcd for $C_7H_{12}N_3O$, 154.0975; found, 154.0979.

*2-Methoxy-6-(2-methylhydrazinyl)pyridinium Bistetrafluoroborate (**16**).* To a dried flask equipped with a thermocouple were added copper(I) iodide (310 mg, 1.59 mmol, 0.040 equiv), ligand **L1** (580 mg, 2.39 mmol, 0.060 equiv), and potassium carbonate (8.35 g, 59.81 mmol, 1.50 equiv). The vessel was flushed and then maintained under a nitrogen atmosphere. 2-Bromo-6-methoxypyridine (5.00 mL, 39.87 mmol, 1.00 equiv) was added, followed by hydrazine **7** (7.63 mL, 49.84 mmol, 1.25 equiv) and then dimethyl sulfoxide (40 mL, deoxygenated by nitrogen sparging for 30 min, water content 205.85 ppm by Karl Fisher titration). The mixture was heated to an internal temperature of 80 °C and stirred for 1 h. After cooling to room temperature, the

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reaction mixture was filtered over a pad of Celite (4.5 cm diameter, 1 cm height), and the pad was washed with isopropyl acetate (2 × 76 mL). The mixture was poured into a 0.5 M aqueous solution of a pH 7 sodium phosphate buffer (76 mL), and the layers were separated. The aqueous layer was extracted with isopropyl acetate (76 mL), and the combined organic extracts were washed with water (76 mL) and a saturated, aqueous solution of brine (76 mL) and then dried over anhydrous sodium sulfate. The drying agent was removed by filtration, and the solution was concentrated *in vacuo* to afford a green-brown oil. The oil was purified by flash column chromatography over silica gel (0−20% ethyl acetate in hexanes gradient) to afford product $\mathbf{16}_{\mathbf{Boc}}$ as a colorless oil that rapidly crystallized (9.21 g, 91%). R_f (15% ethyl acetate in hexanes): 0.43 (UV). Mp (ethyl acetate/hexanes): 74−75.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.50 (s, 1H), 7.44 (t, J = 7.8 Hz, 1H), 6.09 (d, J = 7.9 Hz, 1H), 6.04 (d, J = 7.8 Hz, 1H), 3.74 (s, 3H), 3.08 (s, 3H), 1.28 (br s, 9H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 162.9, 157.8, 156.0 (br), 140.1, 98.9, 97.6, 79.2 (br), 52.4, 37.3 (br), 27.8. IR (solid) (cm^{-1}): 3317 (m), 1674 (s), 1364 (m), 1141 (s), 757 (m). HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{12}H_{20}N_3O_3$, 254.1499; found, 254.1505.

The Boc hydrazine $\mathbf{16}_{\mathbf{Boc}}$ (5.00 g, 19.74 mmol, 1.00 equiv) was dissolved in toluene (25 mL). The solution was cooled to an internal temperature of 1.2 °C with an ice−water bath, and a light purge of nitrogen was applied to the headspace, venting to the back of the hood. The tetrafluoroboric acid-diethyl ether complex (5.62 mL, 40.47 mmol, 2.05 equiv) was added dropwise under vigorous stirring at a rate such that the internal temperature did not exceed 5 °C (1 h), forming a grainy slurry. Rapid addition of the acid will cause gelling; though after further agitation, it will break down to a slurry. The slurry was aged for an additional 1.5 h at room temperature. The product was collected by filtration, washed with ethyl acetate (2 × 10 mL), and then dried at an ambient temperature under reduced pressure until a constant weight was achieved. If toluene is used as the cake wash, the salt will clump upon storage. Ssalt **16** was obtained as a white solid (5.99 g) and was stored under nitrogen at −20 °C. The exact protonation state of the salt (i.e., mono or bistetrafluoroborate) was difficult to determine by NMR spectroscopy due to broad resonances. The solid was 45.8 wt % as analyzed by quantitative NMR as the free base, corresponding to 2.74 g. The theoretical yield of the free base is 3.02 g, corresponding to a corrected, isolated yield of 91%. As calculated as a bistetrafluoroborate salt, this would represent a 91% isolated yield of the salt **16** having 98.3 wt % purity. DSC (toluene), T_{onset} 104.39 °C, T_{peak} 192.91 °C (ΔH_D 214.4 kJ/mol). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.67 (br s, 3 H), 9.25 (br s, 1H), 7.64 (t, J = 7.9 Hz, 1H), 6.38 (app t, J = 7.3 Hz, 2H), 3.88 (s, 3H), 2.87 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 163.3, 153.9, 141.8, 102.2, 101.0, 54.1, 35.6. IR (solid) (cm^{-1}): 3112 (w), 1632 (m), 1286 (m), 1002 (s), 782 (m). HRMS (ESI): m/z [M + H]$^+$ calcd for $C_7H_{12}N_3O$, 154.0975; found, 154.0979.

*3-(2-Methylhydrazinyl)pyridinium Bishydrochloride (**17**).* To a dried flask equipped with a thermocouple were added copper(I) iodide (477 mg, 2.51 mmol, 0.040 equiv), ligand **L1** (911 mg, 3.76 mmol, 0.060 equiv), and potassium carbonate (13.12 g, 93.99 mmol, 1.50 equiv). The vessel was flushed and then maintained under a nitrogen atmosphere. 3-Bromopyridine (6.10 mL, 62.66 mmol, 1.00 equiv) was added, followed by hydrazine **7** (12.00 mL, 78.33 mmol, 1.25 equiv) and then dimethyl sulfoxide (63 mL, deoxygenated by nitrogen sparging for 30 min, water content 96.40 ppm by Karl Fisher titration). The mixture was heated to an internal temperature of 80 °C and stirred for 3 h. After cooling to room temperature, the reaction mixture was filtered over a pad of Celite (4.5 cm diameter, 1 cm height), and the pad was washed with isopropyl acetate (2 × 100 mL). The mixture was poured into a 0.5 M aqueous solution of a pH 7 sodium phosphate buffer (100 mL), and layers were separated. The aqueous layer was extracted with isopropyl acetate (100 mL). The combined organic extracts were washed with water (50 mL) and a saturated, aqueous solution of brine (50 mL) and then dried over anhydrous sodium sulfate. The drying agent was removed by filtration, and the solution was concentrated *in vacuo* to afford a brown oil. The oil was purified by flash column chromatography over silica gel (0−100% ethyl acetate in hexanes gradient) to afford product $\mathbf{17}_{\mathbf{Boc}}$ as a golden brown gel (11.56 g, 83%). R_f (75% ethyl acetate in hexanes): 0.38 (UV). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.19 (s, 1H), 7.96−7.97 (m, 2H), 7.19 (dd, J = 8.2, 4.6 Hz, 1H), 6.94 (ddd, J = 8.3, 2.7, 1.3, 1H), 3.09 (s, 3H), 1.33 (br s, 9H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 155.2, 144.1 (br), 139.9, 134.5, 123.7 (br), 118.1, 79.7, 37.2 (br), 27.8. IR (thin film) (cm^{-1}): 3299 (br w), 1700 (s), 1364 (m), 1148 (s), 7.08 (w). HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{11}H_{18}N_3O_2$, 224.1394; found, 224.1399.

The Boc hydrazine (11.56 g, 39.48 mmol, 1.00 equiv) was dissolved in methanol (23 mL) then cooled to an internal temperature of 2.3 °C with an ice−water bath and a light purge of nitrogen was applied to the headspace, venting to the back of the hood. Chlorotrimethylsilane (17.0 mL, 129.4 mmol, 2.50 equiv) was added dropwise at a rate such that the internal temperature did not exceed +5.0 °C (30 min). The reaction mixture was allowed to warm to room temperature and was stirred for 15 h. Toluene (23 mL) was added, then the stirring was suspended, and the meniscus was marked. Additional toluene (46 mL) was added, and the mixture was concentrated to the marked line. The slurry was cooled to an internal temperature of 3.5 °C with an ice−water bath and was stirred for 30 min. The crystals were isolated by filtration, washed with toluene (2 × 23 mL), and then dried at an ambient temperature under reduced pressure until a constant weight was achieved. The salt **17** was obtained as a light beige solid (8.95 g) and was stored under nitrogen at −20 °C. The exact protonation state of the salt (i.e., mono or bishydrochloride) was difficult to determine by NMR spectroscopy due to broad resonances. The solid was 61.4 wt % as analyzed by quantitative NMR as the free base, corresponding to 5.50 g. The theoretical yield of the free base is 6.38 g, corresponding to a corrected, isolated yield of 86%. As calculated as a bishydrochloride salt, this would represent an 86% isolated yield of the salt **17** having 97.8 wt % purity. DSC (methanol/toluene), T_{onset} 124.83 °C, T_{peak} 218.25 °C (ΔH_D 142.4 kJ/mol). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.83 (br s, 3H), 9.83 (br s, 1H), 8.63 (d, J = 1.7 Hz, 1H), 8.44 (br d, J = 5.1 Hz, 1H), 8.19 (dd, J = 8.4, 1.5 Hz, 1H), 7.92 (dd, J = 8.6, 1.5 Hz, 1H), 2.81 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 143.5, 133.9, 130.2, 127.28, 127.25, 34.0. IR (solid) (cm^{-1}): 2564 (br w), 1629 (w), 1561 (m), 805 (m), 675 (m). HRMS (ESI): m/z [M + H]$^+$ calcd for $C_6H_{10}N_3$, 124.0869; found, 124.0871.

*1-(2,6-Dichlorophenyl)-2-methylhydrazinium Hydrochloride (**44**).* The precursor was prepared as in ref 6a. For the final step, removal of the *N*-formyl group, the following procedure was followed. A solution of *N*′-(2,6-dichlorophenyl)-*N*-methylformylhydrazide (8.00 g, 36.5 mmol, 1.00 equiv) in ethanol (16.0 mL) was cooled to an internal temperature of 2.3 °C whereupon a light slurry formed. Chlorotrimethylsilane (9.5 mL, 73.0 mmol, 2.00 equiv) was added slowly at a rate such that the internal temperature did not exceed 5.0 °C (∼10 min). The slurry was warmed to room temperature during which, at approximately 10 °C, a yellow solution formed. After 30 min, the product began to crystallize from solution. After stirring for a total of 2 h, a 50 vol% solution of ethanol in toluene (24 mL) was added, and the slurry was cooled to an internal temperature of 1.8 °C with an ice−water bath and held for 30 min. The crystals were collected by washed with toluene (2 × 16 mL). After drying to a constant weigh under a vacuum, salt **44** was isolated as white crystals (6.42 g, 77%) and was stored under nitrogen at −20 °C. DSC (ethanol/toluene), T_{onset} 163.70 °C, T_{peak} 225.26 °C (ΔH_D 148.7 kJ/mol). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.93 (br m, 2H), 7.72 (br s, 1H), 7.55−7.58 (m, 2H), 7.36 (t, J = 8.1 Hz, 1H), 2.81 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 136.0, 132.6, 129.6, 129.1, 36.2. IR (solid) (cm^{-1}): 3213 (w), 2572 (w), 1573 (m), 1446 (m), 1144 (m), 779 (s). HRMS (ESI): m/z [M + H]$^+$ calcd for $C_7H_8Cl_2N_2$, 191.0137; found, 191.0142.

Synthesis of Unalkylated Hydrazine Salts. *3,5-Dimethoxyphenylhydrazine Hydrochloride (**10$_H$**):* white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.22 (br s, 1H), 8.24 (br s, 1H), 6.20 (d, J = 1.2 Hz, 2H), 6.10 (t, J = 2.0 Hz, 1H), 3.70 (s, 6H).

*3,5-Dinitrophenylhydrazine Hydrochloride (**11$_H$**).* **Caution**! The stability of product $\mathbf{11}_H$ toward friction and shock was not investigated. Caution must be exercised with this compound. To a dried flask was added copper(I) iodide (122 mg, 0.641 mmol, 0.040 equiv), ligand **L1** (232 mg, 0.958 mmol, 0.060 equiv), potassium carbonate (3.32 g, 24.02 mmol, 1.50 equiv), 1-bromo-3,5-dinitrobenzene (4.00 g, 15.87 mmol,

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1.00 equiv) and *tert*-butyl carbazate (2.64 g, 19.98 mmol, 1.25 equiv). The vessel was flushed and then maintained under a nitrogen atmosphere. DMSO (16 mL, deoxygenated by nitrogen sparging for 30 min, water content 141.811 ppm by Karl Fisher titration) was added. The mixture stirred at room temperature for 3 days. When attempting to run this reaction at 75 °C, we observed significant pressure build-up and a greatly reduced yield of product (2.7%). The reaction mixture was filtered over a pad of Celite (4.5 cm diameter, 1 cm heightt), and the pad was washed with isopropyl acetate (2 × 40 mL). The mixture was poured into a 0.5 M aqueous solution of a pH 7 sodium phosphate buffer (120 mL), and layers were separated with the aid of a flashlight. The aqueous layer was extracted with isopropyl acetate (3 × 20 mL). The combined organic extracts were washed with water (80 mL) and a saturated, aqueous solution of brine (80 mL) and then dried over anhydrous sodium sulfate. The drying agent was removed by filtration, and the solution was concentrated *in vacuo* to afford a black oil. The oil was purified by flash column chromatography over silica gel (0−40% ethyl acetate in hexanes gradient). Fractions were pooled that contained the desired molecular weight (298.96 g/mol) and concentrated *in vacuo* to afford the product as a dark gel (2.21 g). We did not fully characterize this product.

The dark gel from above was dissolved in methanol (22 mL) then a light purge of nitrogen was applied to the headspace, venting to the back of the hood. Chlorotrimethylsilane (2.00 mL, 15.0 mmol, 2.00 equiv) was added dropwise over 5 min. The reaction mixture was allowed to stir for 24 h, forming a thick precipitate. Toluene (22 mL) was added, and the precipitate was collected by filtration. The cake was washed with toluene (2 × 11 mL) and dried at an ambient temperature under reduced pressure until a constant weight was achieved. The product $\mathbf{11_H}$ was obtained as a bone-colored solid (860 mg, 23% from aryl bromide) and was stored in a plastic vial, not glass, under nitrogen at −20 °C. DSC (methanol/toluene), T_{onset} 204.43 °C, T_{peak} 233.39 °C (ΔH_D: − 658.04 kJ/mol). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.53 (br s, 2H), 9.48 (br s, 1H), 8.31 (m, 1H), 8.18 (m, 1H), 6.19 (br s, 1H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 148.4, 148.0, 113.6, 109.5. IR (solid) (cm^{-1}): 3291 (w), 2878 (br m), 1532 (s), 1131 (s), 1088 (m). HRMS (ESI): m/z [M + H]$^+$ calcd for $C_6H_7N_4O_4$, 199.0462; found, 199.0460.

*Ethyl 5-Hydrazinylthiophene-2-carboxylate Hydrochloride (**12$_H$**).* Di-*tert*-butyl 1-(5-ethoxycarbonylthiophen-2-yl)hydrazine-1,2-dicarboxylate was prepared according to Moody.[15] To a solution of di-*tert*-butyl 1-(5-ethoxycarbonylthiophen-2-yl)hydrazine-1,2-dicarboxylate (3.28 g, 8.49 mmol, 1.00 equiv) in methanol (6.5 mL) was charged chlorotrimethylsilane (3.30 mL, 25.5 mmol, 3.00 equiv) over 5 min. After 1 h, a thick precipitate was formed, and an additional charge of chloromethylsilane (3.30 mL, 25.5 mmol, 3.00 equiv) and methanol (6.5 mL) was added. After an additional 6 h, methanol (6.5 mL) was added to the thick precipitate. The slurry stirred for an additional 17 h (23 h total). The slurry was filtered, and the needles were washed with methanol (2 × 7 mL) to afford the product as an off-white (peach) solid (1.20 g). Unlike **12**, this compound was found to be a monohydrochloride.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.39 (br s, 3H), 9.40 (br s, 1H), 7.54 (d, J = 4.2 Hz, 1H), 6.54 (d, J = 4.0 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 161.6, 157.0, 133.8, 120.7, 110.0, 60.5, 14.3. IR (solid) (cm^{-1}): 3168 (w), 2691 (m), 1696 (s), 1457 (m), 1260 (s). HRMS (ESI): m/z [M + H]$^+$ calcd for $C_7H_{11}N_2O_2S$, 187.0536; found, 187.0538.

*3-Hydrazinyl-2-methoxypyridinium Bistetrafluoroborate (**13$_H$**).* The dihydrochloride salt was prepared according to Houk and Garg.[18b] The salt (3.50 g, 16.5 mmol, 1.00 equiv) was partitioned between dichloromethane (50 mL) and a solution of 1 N aqueous sodium hydroxide (50 mL). The layers were split, the aqueous layer was extracted with dichloromethane (2 × 25 mL), and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford the free base as a tea-colored oil (2.12 g, 92%).

The free base was dissolved in toluene (15 mL), and the tetrafluoroboric acid-diethyl ether complex (4.73 mL, 33.0 mmol, 2.00 equiv) was added dropwise under vigorous stirring over 1 h. The solids were collected by filtration, washed with toluene (2 × 10 mL), and dried at an ambient temperature under reduced pressure until a constant weight was achieved. The product $\mathbf{13_H}$ was obtained as a white solid (4.34 g). The solid was 42.8 wt % as analyzed by quantitative NMR as the free base, corresponding to a product that was obtained in 81% yield and 97 wt % purity. The NMR spectrum was similar to the bishydrochloride. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.90 (br s, 3H), 7.77 (dd, J = 5.0, 1.4 Hz, 1H), 7.20 (dd, J = 7.7, 1.4 Hz, 1H), 6.99 (dd, J = 7.6, 5.0 Hz, 1H), 3.93 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 152.6, 138.6, 129.4, 120.8, 117.2, 53.6.

*5-Hydrazinyl-2-methoxypyridinium Bistetrafluoroborate (**14$_H$**).* The free base (5-hydrazinyl-2-methoxypyridine) was prepared according to Cook.[27] 5-Hydrazinyl-2-methoxypyridine (6.20 g, 44.6 mmol, 1.00 equiv) was stirred in toluene (56 mL) forming a red suspension. The tetrafluoroboric acid-diethyl ether complex (13.0 mL, 93.6 mmol, 2.10 equiv) was added dropwise under vigorous stirring over 1 h. A dark, gummy precipitate separated. The toluene was decanted from the gum, and ethyl acetate (56 mL) was added. The mixture was stirred for 14 h, becoming a slurry. The solids were collected by filtration, washed with ethyl acetate (2 × 10 mL), and dried at an ambient temperature under reduced pressure until a constant weight was achieved. The product $\mathbf{14_H}$ was obtained as a reddish-brown solid (10.18 g). The solid was 40.6 wt % as analyzed by quantitative NMR as the free base, corresponding to a product that was obtained in 73% yield and 92.0 wt % purity. The NMR spectrum was consistent with the product $\mathbf{14_H}$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.82 (br s, 4H), 7.89 (d, J = 2.7 Hz, 1H), 7.46 (dd, J = 8.9, 2.9 Hz, 1H), 6.86 (d, J = 8.9 Hz, 1H), 3.82 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 159.5, 136.4, 132.8, 130.5, 111.1, 54.2.

*2-Hydrazinyl-5-methoxypyridinium Bishydrochloride (**15$_H$**).* A solution of the commercially available free base, 2-hydrazinyl-5-methoxypyridine (80 wt %, 1.00 g, 5.75 mmol, 1.00 equiv) in methanol (5.0 mL), was cooled in an ice-water bath for 10 min, then chlorotrimethylsilane (2.2 mL, 17.2 mmol, 3.0 equiv) was added dropwise over 10 min. The reaction mixture was allowed to warm to room temperature and stir for 1 h. The slurry was filtered, and the solids were washed with methyl *tert*-butyl ether (2 × 5 mL) to afford salt $\mathbf{15_H}$ as a tan solid (1.09 g). The solid was 60.8 wt % as analyzed by quantitative NMR as the free base (663 mg), corresponding to a product that was obtained in 89% yield and 92.7 wt % purity. The NMR spectrum was consistent with the product $\mathbf{15_H}$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.77 (br s, 5H), 7.87 (d, J = 2.6 Hz, 1H), 7.44 (dd, J = 9.1, 2.9 Hz, 1H), 6.90 (d, J = 9.0 Hz, 1H), 3.77 (s, 3H). This compound had concentration-dependent instability in DMSO solution, complicating ^{13}C NMR spectra acquisition. The solution stability was better in methanol, and resonances were confirmed by 2D HSQC and HMBC spectroscopy. ^{1}H NMR (400 MHz, MeOD-d_4): δ 7.63 (dd, J = 9.4, 2.7 Hz, 1H), 7.58 (dd, J = 2.7, 0.6 Hz, 1H), 6.96 (dd, J = 9.4, 0.6 Hz, 1H), 3.83 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, MeOD-d_4): δ 152.3, 151.2, 134.8, 121.5, 113.4, 57.2.

*2-Hydrazinyl-6-methoxypyridinium Bistetrafluoroborate (**16$_H$**).* A solution of the commercially available free base, 2-hydrazinyl-6-methoxypyridine (745 mg, 5.09 mmol, 1.00 equiv) in toluene (4.0 mL), was cooled in an ice-water bath to an internal temperature of 5.0 °C. The tetrafluoroboric acid-diethyl ether complex (1.48 mL, 10.7 mmol, 2.10 equiv) was added dropwise under vigorous stirring over 15 min. A dark red, gummy precipitate separated that broke down into a free-flowing slurry after 30 min of stirring. The slurry was filtered, and the solids were washed with methyl *tert*-butyl ether (2 × 8 mL) to afford salt $\mathbf{16_H}$ as reddish solids (1.37 g). The solid was 44.0 wt % as analyzed by quantitative NMR as the free base (603 mg), corresponding to a product that was obtained in 81% yield and 99.5 wt % purity. The NMR spectrum was consistent with the product $\mathbf{16_H}$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.92 (br s, 3H), 8.99 (br s, 1H), 7.61 (app t, J = 7.9 Hz, 1H), 7.46 (br s, 1H), 6.38 (d, J = 7.8 Hz, 1H), 6.35 (d, J = 7.9 Hz, 1H), 3.88 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 163.1, 155.1, 141.4, 101.4, 100.7, 53.8.

Synthesis of Indoles and Byproducts. *3-Phenyl-2,3,4,9-tetrahydro-1H-carbazole (**19**).* From **8**, to a vial containing **8** (500 mg, 3.15 mmol, 1.00 equiv) and ketone **18** (560 mg, 3.15 mmol, 1.00

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equiv) was added absolute ethanol (5.0 mL, deoxygenated by nitrogen sparging for 20 min). The mixture was placed under nitrogen heated to an internal temperature of 50 °C for 20 min. The mixture was then cooled to room temperature, and the solvent was concentrated *in vacuo* to afford a residue. To the residue was added water (5.0 mL), and the resulting slurry was stirred for 10 min. The solids were isolated by filtration, then dried at 50 °C under vacuum until a constant weight was achieved. Product **19** was isolated as a white powder (746 mg, 96%).

From $\mathbf{8}_{\mathbf{Boc}}$, to a vial containing $\mathbf{8}_{\mathbf{Boc}}$ (200 mg, 0.900 mmol, 1.00 equiv) and ketone **18** (160 mg, 0.900 mmol, 1.00 equiv) was added absolute ethanol (2.0 mL, deoxygenated by nitrogen sparging for 20 min), followed by chlorotrimethylsilane (180 μL, 1.35 mmol, 1.50 equiv). The mixture was placed under nitrogen heated to an internal temperature of 50 °C for 1 h. The mixture was then cooled to room temperature, and the solvent was concentrated *in vacuo* to afford a residue. To the residue was added water (5.0 mL), and the resulting slurry was stirred for 10 min. The solids were isolated by filtration, washed with water (3 × 5.0 mL), and then dried at 50 °C under vacuum until a constant weight was achieved. Product **19** was isolated as a white powder (200 mg, 90%). This compound's spectra matched the literature report.[28] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (br s, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.34−7.39 (m, 4H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.24−7.28 (m, 1H), 7.16 (app t, *J* = 7.4 Hz, 1H), 7.10 (app t, *J* = 7.3 Hz, 1H), 3.08−3.15 (m, 2H), 2.91−2.98 (m, 1H), 2.81−2.87 (m, 2H), 2.22−2.26 (m, 1H), 2.10−2.20 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 146.7, 136.0, 133.6, 128.4, 127.5, 127.3, 126.2, 121.0, 119.2, 117.7, 110.4, 110.2, 41.1, 30.3, 29.2, 23.4. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{18}N$, 248.1434; found, 248.1432.

*3-Phenyl-2,3,4,9-tetrahydro-1H-carbazol-3-ol (**21**).* To a round-bottomed flask were added salt **8** (1.00 g, 6.30 mmol, 1.00 equiv) and ketone **20** (1.20 g, 6.30 mmol, 1.00 equiv). Absolute ethanol (10 mL, deoxygenated by nitrogen sparging for 20 min) was added, and the mixture was stirred at room temperature. The reaction initially becomes homogeneous and then a white precipitate forms. After 24 h, the solvent was evaporated and the product was purified by flash column chromatography over silica gel using a 0−70% ethyl acetate in hexanes gradient. The indole **21** was isolated as a white solid (1.54 g, 93%). Repeating the reaction with phenylhydrazine hydrochloride ($\mathbf{8}_{\mathbf{H}}$, 300 mg) under similar conditions (50 °C) for 7 h afforded 428 mg (79%) of **21**. R_f (20% ethyl acetate in hexanes): 0.26 (UV). Mp (ethyl acetate/hexanes): 152.5−153.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.66 (br s, 1H), 7.54 (app d, *J* = 7.3 Hz, 2H), 7.30−7.34 (m, 3H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.22 (app t, *J* = 7.3 Hz, 1H), 6.99 (app t, *J* = 7.1 Hz, 1H), 6.92 (app t, *J* = 7.1 Hz, 1H), 5.04 (s, 1H), 3.08 (d, *J* = 15.8 Hz, 1H), 2.88−2.96 (m, 1H), 2.82 (d, *J* = 15.8 Hz, 1H), 2.54 (dt, *J* = 16.4, 4.8 Hz, 1H), 2.23 (ddd, *J* = 14.0, 9.3, 5.7 Hz, 1H), 1.98 (dt, *J* = 12.8, 5.2 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 149.7, 136.1, 133.6, 127.7, 127.4, 126.2, 125.1, 120.0, 118.0, 117.0, 110.5, 107.1, 71.7, 35.9, 35.6, 20.3. IR (solid) (cm^{-1}): 3515 (m), 3288 (br), 1211 (m), 749 (s), 693 (s). HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{18}NO$, 264.1383; found, 264.1382.

*1-(8-Chloro-6,11-dihydro-5H-benzo[a]carbazol-2-yl)ethan-1-one (**23**).* To a round-bottomed flask were added salt **9** (1.00 g, 5.18 mmol, 1.00 equiv) and ketone **22** (957 mg, 1.00 equiv). Absolute ethanol (10 mL, deoxygenated by nitrogen sparging for 20 min) was added, and the mixture was sealed under nitrogen and heated to an internal temperature of 80 °C for 26 h. The initial slurry dissolved, and then a yellow precipitate formed after 30 min. The yellow slurry was allowed to cool to room temperature, and then the solvent was removed *in vacuo*. The yellow powder was broken down with a spatula and slurried in water (10 mL) for 10 min, then filtered, and washed with water (2 × 5 mL). Product **23** was dried at 50 °C under a vacuum until a constant weight was achieved. The dried indole **23** (1.45 g) was found to be 93 wt % by quantitative NMR (1.35 g, 88% corrected yield). Further purification was hampered by the insolubility of the product, though it can be recrystallized by dissolving in boiling tetrahydrofuran (20 mL/g **23**), allowing cooling to room temperature, standing for 24 h, slowly removing 25% of the solvent *in vacuo*, and finally collecting the large yellow plates by filtration. The recovery is typically 80% of theory. Repeating the reaction with 4-chlorophenylhydrazine hydrochloride ($\mathbf{9}_{\mathbf{H}}$, 200 mg) under identical conditions afforded 287 mg of **23**, which was 78.5 wt % by quantitative NMR (225 mg, 69% corrected). R_f (30% ethyl acetate in hexanes): 0.47 (UV). Mp (ethanol/water): 252−254 °C. Mp (recrystallized, tetrahydrofuran): 264−265 °C. Characterization was performed on the recrystallized material. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.85 (s, 1H), 8.27 (d, *J* = 1.6 Hz, 1H), 7.80 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.56 (d, *J* = 2.0 Hz, 1H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.40 (d, *J* = 8.6 Hz, 1H), 7.10 (dd, *J* = 8.6, 2.1 Hz, 1H), 3.07 (app t, *J* = 7.6 Hz, 2H), 2.92 (app t, *J* = 7.5 Hz, 2H), 2.62 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 197.4, 141.6, 135.63, 135.61, 133.9, 128.9, 128.5, 127.6, 127.0, 123.7, 121.8, 120.5, 117.8, 112.9, 111.1, 28.9, 26.6, 18.7. IR (solid) (cm^{-1}): 3273 (m), 1659 (s), 1409 (s), 1247 (s), 820 (m). HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{15}ClNO$, 296.0837; found, 296.0836.

*4,6-Dimethoxy-2-(4-nitrobenzyl)-3-phenyl-1H-indole (**29**).* To a round-bottomed flask were added ketone **28** (1.00 g, 3.51 mmol, 1.00 equiv) and salt **10** (766 mg, 3.51 mmol, 1.00 equiv). Absolute ethanol (10 mL, deoxygenated by nitrogen sparging for 20 min) was added, and the mixture was heated to an internal temperature of 80 °C under a nitrogen atmosphere. After 22 h, the deep red reaction mixture was cooled to room temperature, and the crystalline slurry was concentrated *in vacuo* to afford reddish-brown solids. The solids were broken down and stirred in water (10 mL) for 30 min, then filtered. The cake was washed with additional water (2 × 5 mL) and deliquored on the filter until a sandy, free-flowing solid was obtained (∼10 min). The solids were dissolved off the filter with dichloromethane (∼20 mL), and the solvent was concentrated *in vacuo*. The residue was slurried in toluene (10 mL) for 10 min and concentrated *in vacuo*. The sample was placed under nitrogen, toluene (5.0 mL) was added, and the mixture was brought to reflux, forming a dark red solution. Heating was discontinued, heptane (2.0 mL) was added, and the solution was allowed to cool to room temperature. At an internal temperature of approximately 53 °C, crystallization began. Once the slurry reached room temperature, it was stirred for an additional 15 min; then the red crystals were isolated by dried at room temperature under reduced pressure until a constant weight was achieved (1.22 g, 83%). Repeating this reaction with 3,5-dimethoxyphenylhydrazine hydrochloride ($\mathbf{10}_{\mathbf{H}}$, 136 mg) under identical conditions (1.5 h) afforded the indole **29** as red crystals (193 mg, 69%). R_f (25% ethyl acetate in hexanes): 0.35 (UV). Mp (toluene/heptane): 142−145 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.96 (s, 1H), 8.14 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz), 6.45 (s, 1H), 6.14 (s, 1H), 4.08 (s, 2H), 3.76 (s, 3H), 3.75 (s, 3H), 3.62 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 157.4, 156.4, 153.9, 148.4, 146.0, 137.2, 131.4, 129.7, 129.2, 128.0, 123.6, 113.8, 112.7, 111.0, 91.4, 87.0, 55.2, 54.9, 31.4. IR (solid) (cm^{-1}): 3396 (m), 1506 (s), 1345 (m), 1148 (m), 801 (s). HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{23}N_2O_5$, 419.1601; found, 419.1587.

*1-Ethoxy-1-(4-methoxyphenyl)-3-(4-nitrophenyl)propan-2-one (**30**):* dark oil (6%). R_f (20% ethyl acetate in hexanes): 0.34). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.12 (d, *J* = 8.7 HZ, 2H), 7.31 (d, *J* = 8.7 Hz, 4H), 6.96 (d, *J* = 8.8 Hz, 2H), 5.01 (s, 1H), 4.08 (d, *J* = 16.9 Hz, 1H), 3.99 (d, *J* = 17.0 Hz, 1H), 3.76 (s, 3H), 3.45 (dq, *J* = 16.8, 7.0 Hz, 2H), 1.17 (t, *J* = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 205.1, 159.3, 146.3, 142.7, 131.0, 128.7, 123.1, 114.1, 85.7, 64.3, 55.1, 43.8, 15.1. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{20}NO_5$, 330.1336; found, 330.1347.

*4,6-Dimethoxy-3-(4-methoxyphenyl)-2-methyl-1H-indole (**33**).* To a suspension of the salt **10** (100 mg, 0.457 mmol, 1.00 equiv) in ethanol (1.00 mL, deoxygenated by nitrogen sparging for 30 min) was added ketone **31** (71.8 μL, 0.457 mmol, 1.00 equiv), and the mixture was heated to an internal temperature of 80 °C for 30 min. The mixture was cooled to approximately 50 °C, and water (2.00 mL) was added. The slurry was cooled to room temperature and stirred for 30 min. The product **33** was isolated as a beige solid (106 mg, 78%). R_f (20% ethyl acetate in hexanes): 0.26 (UV). Mp (ethanol/water): 164−165 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.83 (s, 1H), 7.23 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.42 (d, *J* = 2.0 Hz, 1H), 6.11 (d, *J* = 2.0 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.61 (s, 3H), 2.23 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 156.9, 155.8, 153.4, 136.7, 131.5,

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128.9, 128.5, 112.5, 112.0, 111.0, 91.1, 86.8, 55.2, 54.9, 54.8, 11.8. IR (solid) (cm^{-1}): 3332 (br m), 1558 (m), 1457 (m), 1196 (s), 1126 (s). HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{18}H_{20}NO_3$, 298.1438; found, 298.1449.

*4,6-Dimethoxy-2-methyl-3-(4-nitrophenyl)-1H-indole (**34**).* To a suspension of the salt **10** (100 mg, 0.457 mmol, 1.00 equiv) in ethanol (1.00 mL, deoxygenated by nitrogen sparging for 30 min) was added ketone **32** (86.2 mg, 0.457 mmol, 1.00 equiv), and the mixture was heated to an internal temperature of 80 °C for 4 h. The mixture was cooled to approximately 50 °C, and water (2.00 mL) was added. The slurry was cooled to room temperature and stirred for 30 min. The product **34** was isolated as deep red crystals (125 mg, 88%). R_f (50% ethyl acetate in hexanes): 0.66 (UV). Mp (ethanol/water): 195−197 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.25 (s, 1H), 8.19 (d, J = 8.9 Hz, 2H), 7.58 (d, J = 8.9 Hz, 2H), 6.48 (d, J = 1.8 Hz, 1H), 6.21 (d, J = 1.8 Hz, 1H), 3.77 (s, 3H), 3.68 (s, 3H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 156.4, 153.2, 144.4, 143.9, 137.0, 131.7, 131.0, 110.9, 110.1, 91.8, 87.0, 55.2, 54.9, 12.1. IR (solid) (cm^{-1}): 3362 (br w), 1592 (m), 1491 (m), 1327 (s), 1107 (s). HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{17}H_{17}N_2O_4$, 313.1183; found, 313.1196.

*3-(4-Methoxyphenyl)-2-methyl-4,6-dinitro-1H-indole (**38**).* To a suspension of the salt **11** (100 mg, 0.457 mmol, 1.00 equiv) in ethanol (1.00 mL, deoxygenated by nitrogen sparging for 30 min) was added ketone **31** (62.3 μL, 0.457 mmol, 1.00 equiv), and the mixture was heated to an internal temperature of 80 °C for 2 h. The mixture was cool to room temperature and concentrated *in vacuo*. The residue was partitioned between a 1.0 M aqueous solution of a pH 7 sodium phosphate buffer (10 mL) and ethyl acetate (10 mL). The layers were separated, and the organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford a dark residue. The crude was purified by flash column chromatography over silica gel (0−40% ethyl acetate in hexanes gradient) to afford three products of increasing polarity. The first product to elute was a 54:46 (**35**/**36**) ratio of products as a yellow solid (20.3 mg combined mass, 15%). The second product was 3,5-dinitroaniline (**37**, 44.9 mg, 61%) as a yellow solid, and the third product was the indole **38** (18.2 mg, 14%) as a red solid. R_f (40% ethyl acetate in hexanes): 0.32 (UV). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.81 (s, 1H), 8.56 (d, J = 2.0 Hz, 1H), 8.46 (d, J = 2.0 Hz, 1H), 7.10 (d, J = 8.6 Hz, 2H), 6.96 (d, J = 8.6 Hz, 2H), 3.80 (s, 3H), 2.43 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 158.0, 146.1, 139.6, 139.0, 136.0, 130.4, 125.9, 121.9, 113.8, 113.3, 111.61, 111.58, 55.0, 12.7. IR (solid) (cm^{-1}): 3325 (br w), 1498 (m), 1342 (m), 1323 (m), 1245 (s). HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{16}H_{14}N_3O_5$, 28.0928; found, 328.0929.

*1-((3,5-Dinitrophenyl)amino)-1-(4-methoxyphenyl)propan-2-one (**35**) and 2-((3,5-Dinitrophenyl)amino)-1-(4-methoxyphenyl)-propan-1-one (**36**).* R_f (25% ethyl acetate in hexanes): 0.42 (UV). The resonances due to the 3,5-dinitroaniline fragment could not be assigned conclusively to a methoxyphenylpropanone backbone. Data for the backbones are as follows. ^{1}H NMR (400 MHz, DMSO-d_6) **35**: δ 7.44 (d, J = 8.6 Hz, 2H), 6.99 (d, J = 8.4 Hz, 2H), 5.68 (d, J = 7.1 Hz, 1H), 3.74 (s, 3H), 2.10 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) **35**: δ 203.5, 159.2, 129.1, 128.1, 114.6, 64.9, 55.1, 26.7. ^{1}H NMR (400 MHz, DMSO-d_6) **36**: δ 8.14 (d, J = 8.9 Hz, 2H), 7.10 (d, J = 8.8 Hz, 2H), 5.53 (app pentet, J = 7.2 Hz, 1H), 3.88 (s, 3H), 1.49 (d, J = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) **36** δ: 197.8, 163.7, 131.0, 127.1, 114.2, 55.6, 52.4, 18.4. The remaining resonances are as follows. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.95 (br t, J = 2.0 Hz, 1H), 7.93 (br t, J = 2.0 Hz, 1H), 7.89 (br s, 2H), 7.86 (br s, 2H), 7.79 (d, J = 7.1 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 149.5, 148.9, 148.7, 148.6, 112.0 (br), 111.5 (br), 104.6, 104.3. HRMS (ESI): m/z $[M - H]^-$ calcd for $C_{16}H_{14}N_3O_6$, 344.0888; found, 344.0886.

*3,5-Dinitroaniline (**37**).* This compound's ^{1}H NMR spectrum matched a commercially available sample. R_f (20% ethyl acetate in hexanes): 0.31 (UV). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.90 (br s, 1H), 7.74 (d, J = 2.0 Hz, 2H), 6.52 (br s, 2H).

*(E)-1-(3,5-Dinitrophenyl)-2-(1-(4-nitrophenyl)propan-2-ylidene)-hydrazine (**39**).* To a suspension of the salt **11** (100 mg, 0.457 mmol, 1.00 equiv) in ethanol (1.00 mL, deoxygenated by nitrogen sparging for 30 min) was added ketone **32** (75.9 mg, 0.457 mmol, 1.00 equiv), and the mixture was heated to an internal temperature of 80 °C for 24 h. The mixture was cool to room temperature and concentrated *in vacuo*. The residue was partitioned between a 1.0 M aqueous solution of a pH 7 sodium phosphate buffer (15 mL) and ethyl acetate (15 mL). The layers were separated with the aid of a flashlight, and any rag layer or solid precipitates were retained in the organic phase. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford a dark residue. The crude was purified by flash column chromatography over silica gel (0−40% ethyl acetate in hexanes gradient) to afford 23.1 mg of a dark yellow solid, approximately 80% pure by NMR. This material was further purified by bringing a suspension of the material in methanol (7 mL) to reflux and then cooling and concentrating to ∼5 mL under a stream of nitrogen. The product **39** was isolated as fine yellow needles (9.9 mg, 7%). The *E* configuration of the hydrazone was determined by nOesy analysis. A cross peak was observed between the proton on the nitrogen and the methyl group adjacent to the hydrazone. R_f (40% ethyl acetate in hexanes): 0.50 (UV). Mp (methanol): 211 °C (decomposition). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.99 (s, 1H), 8,21 (d, J = 8.7 Hz, 2H), 8.08−8.15 (m, 3H), 7.56 (d, J = 8.6 Hz, 2H), 3.81 (s, 2H), 1.92 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 149.2, 148.7, 148.1, 146.3, 145.9, 130.4, 123.4, 111.3, 106.4, 43.9, 16.0. IR (solid) (cm^{-1}): 3340 (w), 1536 (s), 1502 (m), 1338 (s), 727 (m). HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{15}H_{14}N_5O_6$,360.0939; found, 360.0936.

*Ethyl (S)-4-(1-tert-Butylsulfonamido)-2-isopropoxy-2-oxoethyl-5-phenyl-6H-thieno[2,3-b]pyrrole-2-carboxylate (**41**).* To a round-bottomed flask were added ketone[16] **40** (1.00 g, 2.81 mmol, 1.00 equiv, 94:6 er) and thiophene salt **12** (720 mg, 2.81 mmol, 1.00 equiv). 1-Butanol (7.20 mL, deoxygenated by nitrogen sparging for 30 min) was added, followed by pyridine (114 μL, 1.41 mmol, 0.50 equiv), and the mixture was heated to an internal temperature of 90 °C under a nitrogen atmosphere. After 10 h, the reaction was cooled to room temperature, and an additional charge of salt **12** (720 mg, 2.81 mmol, 1.00 equiv) and pyridine (114 μL, 1.41 mmol, 0.50 equiv) were added under a nitrogen atmosphere. The mixture was stirred at an internal temperature of 90 °C for an additional 14 h, after which it was cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between water (10 mL) and ethyl acetate (10 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford a dark orange-brown gel. The gel was purified by flash column chromatography over silica gel (0−50% ethyl acetate in hexanes gradient) to afford a semipure product contaminated with **43**. We observed a white precipitate in a stretch of early eluting fractions. These fractions were collected and concentrated *in vacuo* to afford a dark yellow solid. This yellow solid was slurried in methyl *tert*-butyl ether (10 mL) and filtered to afford a bone-colored solid (20 mg) identified as pyridine **42** (2% with respect to total **12** charged). The semipure product **41** was subjected to additional purification by flash column chromatography over silica gel (0−5% methyl *tert*-butyl ether in dichloromethane) to afford pure **41**, which tenaciously retains methyl *tert*-butyl ether. Drying in a vacuum oven for 48 h at 50 °C afforded a light yellow foam (770 mg, 54%, 94:6 er).

Repeating this reaction with desmethyl salt $\mathbf{12_H}$ (313 mg, 1.41 mmol, 1.00 equiv), ketone **40** (500 mg, 1.41 mmol, 1.00 equiv) in 1-butanol (3.60 mL, deoxygenated by nitrogen sparging for 30 min) at an internal temperature of 90 °C for 2 h under nitrogen, led to formation of the cyclized product **43**. The expected hydrazone from condensation of $\mathbf{12_H}$ and **40**, and the desired product **43** were both observed in the reaction mixture in low to trace amounts. After reaction workup as above, and purification of the crude by flash column chromatography over silica gel (5 to 35% ethyl acetate in hexanes gradient), the product was isolated semipure as a red gel. Methanol (25 mL) was added to the gel and the mixture was brought to a boil for 5 min. Cooling to room temperature caused **43** to crystallize as fine white needles that were collected by Buchner filtration, and washed with methanol (2 × 5 mL) (325 mg, 50%). R_f (25% ethyl acetate in hexanes): 0.28 (UV). R_f (5% methyl *tert*-butyl ether in dichloromethane): 0.50. $[\alpha]_D^{22}$ +107.4° (c 10.0

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mg/mL, methanol). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.09 (s, 1H), 8.15 (s, 1H), 8.13 (d, J = 8.0 Hz, 1H), 7.60 (app d, J = 7.5 Hz, 2H), 7.53 (app t, J = 7.6 Hz, 2H), 7.43 (app t, J = 7.3 Hz, 1H), 5.23 (d, J = 8.7 Hz, 1H), 4.90 (septet, J = 6.2 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H), 1.20 (d, J = 6.2 Hz, 3H), 1.08 (d, J = 6.2 Hz, 3H), 1.06 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 170.2, 162.9, 138.3, 138.1, 131.6, 128.88, 128.84, 128.16, 128.14, 127.0, 124.6, 109.4, 68.9, 60.6, 58.7, 53.3, 23.5, 21.4, 21.3, 14.4. IR (solid) (cm^{-1}): 3276 (br w), 1722 (m), 1685 (m), 1513 (m), 1282 (s), 1070 (s). HRMS (ESI): m/z [M + NH$_4$]$^+$ calcd for $C_{24}H_{34}N_3O_6S_2$, 524.1884; found, 524.1875.

*Diethyl Dithieno[2,3-b:3′,2′-e]pyridine-2,6-dicarboxylate (**42**).* A positive NOE was observed between the singlet at 8.60 ppm and the singlet at 8.11 ppm. R_f (20% ethyl acetate in hexanes): 0.39 (UV). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (s, 1H), 8.11 (s, 2H), 4.46 (q, J = 7.1 Hz, 4H), 1.45 (t, J = 7.1 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 163.0, 162.2, 133.8, 130.1, 129.5, 127.8, 62.1, 14.3. IR (solid) (cm^{-1}): 1703 (s), 1528 (m), 1286 (m), 1066 (s), 731 (s). HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{15}H_{14}NO_4S_2$, 336.0359; found, 336.0358.

*Ethyl 5-(5-(tert-Butylsulfonamido)-6-oxo-3-phenyl-5,6-dihydropyridazin-1(4H)-yl)thiophene-2-carboxylate (**43**).* R_f (25% ethyl acetate in hexanes): 0.29 (UV). Mp (methanol): 174−176 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.94−7.97 (m, 2H), 7.70 (d, J = 4.0 Hz, 1H), 7.69 (s, 1H), 7.50−7.59 (m, 3H), 7.39 (d, J = 4.3 Hz, 1H), 4.70 (ddd, J = 12.7, 8.8, 7.2 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 3.47 (dd, J = 16.9, 6.8 Hz, 1H), 3.20 (dd, J = 16.9, 12.8 Hz, 1H), 1.35 (s, 9H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 164.0, 162.0, 154.3, 148.0, 134.4, 132.4, 130.8, 128.8, 126.6, 124.4, 114.5, 60.6, 59.2, 49.7, 31.4, 23.8, 14.2. IR (solid) (cm^{-1}): 1681 (br m), 1442 (m), 1245 (s), 1122 (s), 1088 (s). HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{21}H_{26}N_3O_5S_2$, 464.1308; found, 464.1300.

*6,8-Dichloro-3-phenyl-2,3,4,9-tetrahydro-1H-carbazole (**45**).* To a round-bottomed flask was added salt **44** (1.00 g, 4.40 mmol, 1.00 equiv) and ketone **18** (781 mg, 4.40 mmol, 1.00 equiv). Isopropanol (10 mL, deoxygenated by nitrogen sparging for 30 min) was added, and the mixture was heated to an internal temperature of 50 °C under nitrogen. A green-black solution formed. After 3 h, the reaction mixture was cooled to room temperature and concentrated *in vacuo* to afford a dark residue. The residue was partitioned between ethyl acetate (10 m) and water (10 mL), and the layers were separated. The now reddish organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude was purified by flash column chromatography over silica gel (0−10% ethyl acetate in hexanes gradient) to afford two products. The first product to elute was pure **47** (104 mg, 8%) as a white solid. The second was a golden oil containing a mixture of product (673 mg). By quantitative NMR: **45** (462 mg, 33%), **48** (154 mg, 11%), **49** (14.8 mg, 1%), and **50** (37 mg, 2%). Repeating this reaction with 2,6-dichlorophenylhydrazine hydrochloride (**44$_H$**, 1.00 g) under identical conditions for 6 days afforded the following: **45** (280 mg, 19%), **47** (183 mg, 14%), **48** (57 mg, 4%), **49** (<1%, trace), and **50** (16.7 mg, 1%).

*Preparation of Authentic Markers **45, 47−50**.* A general procedure was followed, and 1.00 g of the parent hydrazine hydrochloride salt and **18** (1.00 equiv) were heated in ethanol (10 mL/g hydrazine salt) to 80 °C for 1 h. The reaction was cooled to room temperature and then partitioned between EtOAc (15 mL/g) and a saturated aqueous solution of sodium bicarbonate (10 mL/g). The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford a solid residue. The residue was purified by flash column chromatography over silica gel (0−10% ethyl acetate in hexanes gradient) to afford the desired indole.

*6,8-Dichloro-3-phenyl-2,3,4,9-tetrahydro-1H-carbazole (**45**):* 40%, white crystals. R_f (5% ethyl acetate in hexanes): 0.35 (UV). Mp (ethyl acetate/hexanes): 126−127 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.31 (s, 1H), 7.39 (d, J = 1.6 Hz, 1H), 7.28−7.37 (m, 4H), 7.18−7.26 (m, 1H), 7.13 (d, J = 1.6 Hz, 1H), 2.79−3.06 (m, 4H), 2.65 (dd, J = 15.1, 10.5 Hz, 1H), 1.95−2.14 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 146.3, 137.8, 131.5, 129.4, 128.3, 126.9, 126.1, 122.8, 119.0, 115.8, 115.6, 109.7, 40.2, 29.7, 28.7, 23.0. IR (solid) (cm^{-1}): 3437 (m), 1469 (m), 1293 (m), 1073 (m), 700 (s). HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{18}H_{16}Cl_2N$, 316.0654; found, 316.0664.

*8-Chloro-3-phenyl-2,3,4,9-tetrahydro-1H-carbazole (**47**):* 70%, light yellow crystals. R_f (5% ethyl acetate in hexanes): 0.44 (UV). Mp (ethyl acetate/hexanes): 108−109 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.05 (s, 1H), 7.29−7.40 (m, 5H), 7.18−7.25 (m, 1H), 7.06 (d, J = 7.6 Hz, 1H), 6.89−6.96 (m, 1H), 2.79−3.07 (m, 4H), 2.69 (dd, J = 15.1, 10.6 Hz, 1H), 1.98−2.15 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 146.5, 135.8, 132.8, 129.1, 128.3, 126.9, 126.0, 119.6, 119.1, 116.2, 115.2, 109.6, 40.5, 29.8, 29.1, 23.0. IR (solid) (cm^{-1}): 3448 (m), 1487 (m), 1323 (m), 1178 (m), 999 (m). HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{18}H_{17}ClN$, 282.1044; found, 282.1055.

*7,8-Dichloro-3-phenyl-2,3,4,9-tetrahydro-1H-carbazole (**48**):* 66%, white solid. R_f (5% ethyl acetate in hexanes): 0.36 (UV). Mp (ethyl acetate/hexanes): 170−172 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.27 (s, 1H), 7.30−7.41 (m, 5H), 7.19−7.27 (m, 1H), 7.12 (d, J = 8.3 Hz, 1H), 2.80−3.08 (m, 4H), 2.63−2.74 (m, 1H), 1.98−2.12 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 146.4, 136.9, 133.7, 128.3, 127.4, 126.9, 126.1, 122.4, 119.8, 117.0, 113.3, 110.0, 40.3, 29.7, 28.8, 23.0. IR (solid) (cm^{-1}): 3452 (m), 1450 (m), 1319 (w), 1159 (m), 1003 (w). HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{18}H_{16}Cl_2N$, 316.0654; found, 316.0665.

*5,8-Dichloro-3-phenyl-2,3,4,9-tetrahydro-1H-carbazole (**49**):* 37%, white crystals. R_f (5% ethyl acetate in hexanes): 0.36 (UV). Mp (ethyl acetate/hexanes): 156−158 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.42 (s, 1H), 7.28−7.38 (m, 4H), 7.17−7.26 (m, 1H), 7.03 (d, J = 8.2 Hz, 1H), 6.92 (d, J = 8.1 Hz, 1H), 3.32 (br dd, J = 15.1, 4.2 Hz, 1H), 2.93−3.01 (m, 1H), 2.80−2.93 (m, 3H), 1.94−2.09 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 146.4, 137.3, 133.6, 128.4, 126.9, 126.1, 125.4, 122.8, 120.2, 119.4, 114.2, 109.4, 40.5, 31.0, 29.0, 23.1. IR (solid) (cm^{-1}): 3422 (m), 1461 (m), 1319 (m), 1147 (s), 1129 (m). HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{18}H_{16}Cl_2N$, 316.0654; found, 316.0669.

*8-Chloro-6-isopropoxy-3-phenyl-2,3,4,9-tetrahydro-1H-carbazole (**50**).* R_f (5% ethyl acetate in hexanes): 0.26 (UV). Mp (ethyl acetate/hexanes): 114−115 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.83 (s, 1H), 7.30−7.36 (m, 4H), 7.18−7.24 (m, 1H), 6.86 (d, J = 2.1 Hz, 1H), 6.71 (d, J = 2.1 Hz, 1H), 4.49 (septet, J = 6.1 Hz, 1H), 2.94−3.04 (m, 1H), 2.76−2.94 (m, 3H), 2.64 (dd, J = 15.2, 10.5, 1H), 1.95−2.12 (m, 2H), 1.22 (d, J = 6.0 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 151.0, 146.5, 136.6, 128.9, 128.4, 128.2, 126.8, 126.0, 115.0, 111.1, 109.3, 102.7, 70.6, 40.5, 29.8, 29.2, 23.1, 21.9. IR (solid) (cm^{-1}): 3336 (br m), 1588 (m), 1208 (m), 1114 (s), 965 (m). HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{21}H_{23}ClNO$, 340.1463; found, 340.1468.

*3-Butyl-7-methoxy-1H-pyrrolo[2,3-c]pyridine (**52**).* To a round-bottomed flask was added salt **13** (1.00 g, 45.1 wt % calculated as free base, 2.94 mmol, 1.00 equiv). Absolute ethanol (10 mL, deoxygenated by nitrogen sparging for 20 min) was added, followed by freshly distilled hexanal (**51**, 406 μL, 3.24 mmol, 1.10 equiv), and the homogeneous solution was heated to an internal temperature of 50 °C under a nitrogen atmosphere for 2 h. The solution was cooled to room temperature and poured into a 0.5 M aqueous solution of a pH 7 sodium phosphate buffer (20 mL). The solution was extracted with ethyl acetate (2 × 15 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford a dark residue. The residue was purified by flash column chromatography over silica gel (0−25% ethyl acetate in hexanes gradient). The desired product **52** was isolated as a white solid (280 mg, 46%). *N*-Methyl analogue **54** was isolated as a colorless oil (69 mg, 11%) and the 4-azaindole **55** was isolated as a light tan oil that became a wax upon standing (95 mg, 15%). Repeating the reaction with 3-hydrazinyl-2-methoxypyridinium bistetrafluoroborate (**13$_H$**, 300 mg, 42.8% calculated as free base) under identical conditions for 30 h afforded the desired indole **52** as a white solid (104 mg, 55%) and the 4-azaindole **55** as a light tan oil that became a wax upon standing (33 mg, 16%). R_f (15% ethyl acetate in hexanes): 0.34 (UV). Mp (ethyl acetate/hexanes): 73−75 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.35 (br s, 1H), 7.59 (d, J = 5.8 Hz, 1H), 7.17 (br s, 1H), 7.10 (d, J = 5.6 Hz, 1H), 3.98 (s, 3H), 2.64 (t, J = 7.6 Hz, 2H), 1.59 (quintet, J = 7.5 Hz, 2H),

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1.33 (quintent, J = 7.4 Hz, 2H), 0.90 (t, J = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 150.7, 133.6, 133.0, 124.7, 120.4, 115.4, 108.5, 52.4, 32.2, 24.2, 21.9, 13.8. IR (solid) (cm^{-1}): 1625 (m), 1375 (s), 1297 (s), 1077 (m), 1039 (m). HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{12}H_{17}N_2O$, 205.1335; found, 205.1334.

*3-Butyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one (**53**).* Note that this compound was wot observed when methylhydrazine **13** or hydrazine $\mathbf{13_H}$ was used as the HBF_4 salt. R_f (10% methanol in dichloromethane): 0.44 (UV). Mp (methanol/dichloromethane): 234−235 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 11.58 (br s, 1H), 10.78 (br s, 1H), 7.04 (d, J = 2.3 HZ, 1H), 6.83 (t, J = 6.1 Hz, 1H), 6.41 (d, J = 6.8 Hz, 1H), 2.55 (t, J = 7.5 Hz, 2H), 1.54 (quintet, J = 7.5 Hz, 2H), 1.32 (app sextet, J = 7.4 Hz, 2H), 0.89 (t, J = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 155.1, 129.4, 123.9, 123.8, 123.7, 116.9, 32.5, 24.1, 21.9, 13.8. IR (solid) (cm^{-1}): 3131 (br), 1644 (s), 1398 (s), 1103 (m), 749 (s). HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{11}H_{15}N_2O$, 191.1179; found, 191.1186.

*3-Butyl-7-methoxy-1-methyl-1H-pyrrolo[2,3-c]pyridine (**54**).* R_f (15% ethyl acetate in hexanes): 0.53 (UV). ^1H NMR (400 MHz, DMSO-d_6): δ 7.57 (d, J = 5.6 Hz, 1H), 7.17 (s, 1H), 7.08 (d, J = 5.6 Hz, 1H), 3.97 (s, 3H), 3.95 (s, 3H), 2.61 (t, J = 7.5 Hz, 2H), 1.58 (quintet, J = 7.5 Hz, 2H), 1.33 (quintet, J = 7.4 Hz, 2H), 0.90 (t, J = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 151.2, 133.8, 133.6, 130.1, 120.7, 114.4, 108.7, 52.6, 35.5, 32.1, 23.9, 21.9, 13.8. IR (solid) (cm^{-1}): 1610 (m), 1543 (m), 1312 (s), 1249 (m), 805 (m). HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{13}H_{19}N_2O$, 219.1492; found, 219.1499.

*3-Butyl-5-ethoxy-1-methyl-1H-pyrrolo[3,2-b]pyridine (**55**).* R_f (15% ethyl acetate in hexanes): 0.47 (UV). ^1H NMR (400 MHz, DMSO-d_6): δ 10.75 (br s, 1H), 7.60 (d, J = 8.7 Hz, 1H), 7.22 (d, J = 2.3 Hz, 1H), 6.47 (d, J = 8.6 Hz, 1H), 4.32 (q, J = 7.0 Hz, 2H), 2.66 (t, J = 7.5 Hz, 2H), 1.67 (quintet, J = 7.5 Hz, 2H), 1.23−1.39 (m, 5H), 0.91 (t, J = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 158.0, 141.2, 124.8, 124.5, 122.0, 114.4, 104.1, 60.2, 31.8, 23.2, 21.9, 14.7, 13.8. IR (solid) (cm^{-1}): 3179 (br), 1565 (m), 1248 (s), 1107 (s), 719 (s). HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{13}H_{19}N_2O$, 219.1492; found, 219.1499.

*Ethyl 5-Methoxy-1H-pyrrolo[3,2-b]pyridine-2-carboxylate (**57**).* To a round-bottomed flask was added salt **14** (1.00 g, 45.1 wt % calculated as free base, 2.94 mmol, 1.00 equiv). Absolute ethanol (10 mL, deoxygenated by nitrogen sparging for 20 min) was added, followed by ethyl pyruvate (**56**, 367 μL, 3.24 mmol, 1.10 equiv), and the homogeneous solution was heated to an internal temperature of 50 °C under a nitrogen atmosphere for 15 h. The solution was cool to room temperature and concentrated *in vacuo*. The residue was partitioned between a 0.5 M aqueous solution of a pH 7 sodium phosphate buffer (15 mL) and isopropyl acetate (10 mL). The layers were separated, and the aqueous layer was extracted with isopropyl acetate (10 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford a yellow solid. The crude was purified by flash column chromatography over silica gel (0−100% ethyl acetate in hexanes gradient) to afford product **57** as an off-white (beige) solid (585 mg, 90%). The remaining chromatography fractions eluting after the product were concentrated *in vacuo* and purified by flash column chromatography over silica gel (5−15% acetone in dichloromethane gradient) to afford the 6-azaindole isomer **58** as a light yellow solid (4.9 mg, 1%). Compound **58**'s ^1H NMR spectrum matched a commercially available sample. Repeating the reaction with 5-hydrazinyl-2-methoxypyridinium bistetrafluoroborate ($\mathbf{14_H}$, 1.00 g, 40.6% calculated as the free base) under similar conditions (80 °C, 8 days) afforded, after flash column chromatography over silica gel (0−10% methanol in dichloromethane gradient) the hydrazone **59** as a golden-colored solid (427 mg, 62%) and the desmethylated indole **60** as a beige solid (49 mg, 8%). R_f (25% ethyl acetate in hexanes): 0.46 (UV). Mp (ethyl acetate/hexanes): 134−135 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 12.01 (br s, 1H), 7.76 (d, J = 8.9 Hz, 1H), 7.01 (s, 1H), 6.76 (d, J = 8.9 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 3.87 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 161.0, 159.9, 140.4, 128.3, 126.8, 124.0, 109.5, 106.2, 60.6, 52.9, 14.3. IR (solid) (cm^{-1}): 3317 (m), 1685 (s), 1521 (m), 1204 (s), 775 (s). HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{11}H_{13}N_2O_3$, 221.0921; found, 221.0928.

*Ethyl 5-Methoxy-1H-pyrrolo[2,3-c]pyridine-2-carboxylate (**58**).* This compound's ^1H NMR spectrum matched a commercially available sample. R_f (10% acetone in dichloromethane): 0.29 (UV). ^1H NMR (400 MHz, C_6D_6): δ 8.09 (s, 1H), 7.92 (br s, 1H), 6.97 (s, 1H), 6.86 (d, J = 1.0 Hz, 1H), 4.04 (q, J = 7.1 Hz, 2H), 3.98 (s, 3H), 1.98 (t, J = 7.2 Hz, 3H).

*Ethyl (E)-2-(2-(6-Methoxypyridin-3-yl)hydrazinylidene)-propanoate (**59**).* The E configuration of the hydrazone was determined by nOesy analysis. A cross peak was observed between the proton on the nitrogen and the methyl group adjacent to the hydrazone. R_f (5% methanol in dichloromethane): 0.49 (UV). Mp (methanol/dichloromethane): 118−119 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 9.80 (s, 1H), 8.08 (d, J = 2.7 Hz, 1H), 7.62 (dd, J = 8.9, 2.8 Hz, 1H), 6.79 (d, J = 8.8 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.80 (s, 3H), 2.04 (s, 3H), 1.26 (t, J = 7.1 Hz, 3). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 164.8, 158.6, 135.9, 132.0, 131.7, 125.7, 110.5, 60.2, 53.0, 14.2, 11.7. IR (solid) (cm^{-1}): 3284 (m), 1662 (m), 1368 (m), 1144 (s), 1029 (s). HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{11}H_{16}N_3O_3$, 238.1186; found, 238.1181.

*Ethyl 5-Hydroxy-1H-pyrrolo[3,2-b]pyridine-2-carboxylate (**60**).* R_f (5% methanol in dichloromethane): 0.23 (UV). ^1H NMR (400 MHz, DMSO-d_6): δ 12.11 (br s, 1H), 11.47 (br s, 1H), 7.57 (d, J = 9.5 Hz, 1H), 6.48 (d, J = 1.6 Hz, 1H), 6.25 (d, J = 9.5 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 161.8, 160.5, 130.4, 128.2, 125.4, 121.2, 118.4, 98.8, 60.4, 14.2. IR (solid) (cm^{-1}): 3183 (br w), 1681 (m), 1569 (m), 1211 (m), 812 (m). HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{10}H_{11}N_2O_3$, 207.0764; found, 207.0769.

*2-(5-Methoxy-1H-indol-3-yl)phenylmethanol (**62**).* To a round-bottomed flask were added salt **15** (1.00 g, 64.5 wt % calculated as free base, 4.21 mmol, 1.00 equiv) and isochroman-3-ol (**61**, 632 mg, 4.21 mmol, 1.00 equiv). Isopropanol (10 mL, deoxygenated by nitrogen sparging for 30 min) was added, and the mixture was heated to an internal temperature of 80 °C, forming a light yellow solution. After 24 h, the mixture was cooled to room temperature and concentrated *in vacuo* to afford a yellow-brown residue. The residue was partitioned between a 0.5 M aqueous solution of a pH 7 sodium phosphate buffer (30 mL) and isopropyl acetate (15 mL). The layers were separated, and the aqueous layer was extracted with isopropyl acetate (2 × 15 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford a yellow-brown oil. The crude was purified by flash column chromatography over silica gel (0−100% ethyl acetate in dichloromethane gradient) to afford the product **62** as an off-white (beige) solid (367 mg, 34%). The *N*-methyl analogue **63** was isolated as a golden brown gel (27.6 mg, 2%). The isopropyl ether product **66** was isolated as a dark residue (53.3 mg, 4%). The benzyl chloride product **67** was isolated impure. It was subsequently slurried in methanol (4 mL) then isolated by filtration to afford **67** as an off-white (yellow) solid (43.5 mg, 4% yield). Aniline **69** was isolated as a dark residue (67.8 mg, 13%). Repeating this reaction with 2-hydrazinyl-5-methoxypyridinium bishydrochloride ($\mathbf{15_H}$, 400 mg, 60.8 wt % calculated as free base) and isochroman-3-ol (**61**) under identical conditions for 48 h afforded the product **62** (60.5 mg, 13%). R_f (50% ethyl acetate in dichloromethane): 0.17 (UV). Mp (ethyl acetate/dichloromethane): 150−151 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 11.72 (br s, 1H), 8.02 (d, J = 2.7 Hz, 1H), 7.62 (d, J = 2.4 Hz, 1H), 7.57−7.61 (m, 1H), 7.41−7.47 (m, 1H), 7.39 (d, J = 2.7 Hz, 1H), 7.29−7.37 (m, 2H), 5.14 (t, J = 5.3 Hz, 1H), 4.48 (d, J = 5.4 Hz, 2H), 3.79 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 151.0, 143.8, 139.8, 133.3, 132.8, 129.6, 128.6, 127.0, 126.2, 125.9, 118.5, 112.3, 109.4, 61.2, 55.9. IR (solid) (cm^{-1}): 3355 (br w), 1580 (w), 1200 (m), 1029 (m), 757 (s). HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{15}H_{15}N_2O_2$, 255.1128; found, 255.1136.

*(2-(5-Methoxy-1-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)phenyl)-methanol (**63**).* R_f (50% ethyl acetate in dichloromethane): 0.43. ^1H NMR (400 MHz, C_6D_6): δ 8.37 (d, J = 2.7 Hz, 1H), 7.62 (dd, J = 7.1, 1.5 Hz, 1H), 7.52 (dd, J = 7.3, 1.4 Hz, 1H), 7.41 (d, J = 2.7 Hz, 1H), 7.24 (app quintd, J = 7.5, 1.5 Hz, 2H), 7.08 (s, 1H), 4.63 (s, 2H), 3.40 (s,

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3H), 3.26 (s, 3H), 2.86 (br s, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, C_6D_6): δ 152.6, 144.4, 140.3, 134.65, 134.57, 131.08, 129.9, 129.5, 128.2, 127.4, 120.4, 112.9, 110.8, 63.8, 56.1, 31.3. IR (solid) (cm^{-1}): 3280 (br w), 1491 (m), 1215 (m), 1029 (m), 757 (s). HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{16}H_{17}N_2O_2$, 269.1285; found, 269.1289.

*3-(2-(Isopropoxymethyl)phenyl)-5-methoxy-1H-pyrrolo[2,3-b]-pyridine (**66**).* R_f (50% ethyl acetate in dichloromethane): 0.57. ^1H NMR (400 MHz, DMSO-d_6): δ 11.72 (br s, 1H), 8.02 (d, J = 2.7 Hz, 1H), 7.60 (d, J = 2.6 Hz, 1H), 7.54 (br d, J = 7.3 Hz, 1H), 7.27−7.43 (m, 3H), 4.40 (s, 2H), 3.79 (s, 3H), 3.59 (app septet, J = 6.1 Hz, 1H), 1.09 (d, J = 6.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 151.0, 143.8, 136.5, 133.7, 133.3, 129.8, 129.7, 127.6, 126.0, 125.9, 118.5, 112.2, 109.4, 70.3, 67.6, 55.9, 22.0. HRMS (ESI): m/z $[M + NH_4]^+$ calcd for $C_{18}H_{24}N_3O_2$, 314.1863; found, 314.1870.

*3-(2-(Chloromethyl)phenyl)-5-methoxy-1H-pyrrolo[2,3-b]-pyridine (**67**).* R_f (50% ethyl acetate in dichloromethane): 0.66. ^1H NMR (400 MHz, DMSO-d_6): δ 11.83 (br s, 1H), 8.05 (d, J = 2.6 Hz, 1H), 7.59−7.67 (m, 2H), 7.46−7.49 (m, 2H), 7.36−7.41 (m, 2H), 4.78 (s, 2H), 3.79 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 151.0, 143.8, 135.3, 134.2, 133.6, 131.0, 130.6, 128.8, 127.0, 125.4, 118.5, 111.8, 109.1, 55.9, 45.3. IR (solid) (cm^{-1}): 3116 (br w), 1491 (w), 1215 (m), 1032 (m), 749 (s). HRMS (ESI): m/z $[M - H]^-$ calcd for $C_{15}H_{12}ClN_2O$, 271.0644; found, 271.0649.

*2-(2-(Isochroman-3-yl)-2-methylhydrazinyl)-5-methoxypyridine (**68**).* This product was isolated from a different experiment run in *tert*-amyl alcohol. ^1H NMR (400 MHz, DMSO-d_6): δ 7.77 (d, J = 2.9 Hz, 1H), 7.26 (dd, J = 9.0, 2.9 Hz, 1H), 7.11−7.17 (m, 2H), 7.02−7.11 (m, 2H), 6.81 (d, J = 8.9 Hz, 1H), 6.37−6.61 (m, 1H), 6.51 (br s, 1H), 4.90 (d, J = 15.0 Hz, 1H), 4.77 (d, J = 15.0 Hz, 1H), 4.51 (dd, J = 10.0, 3.4 Hz, 1H), 3.72 (s, 3H), 3.01 (dd, J = 16.3, 10.0 Hz, 1H), 2.73 (d, J = 16.0 Hz, 1H), 2.66 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 155.1, 149.2, 134.4, 133.5, 133.2, 128.2, 126.4, 125.7, 124.8, 123.9, 106.9, 90.2, 66.7, 55.9, 38.5 (obscured by DMSO, identified by HSQC), 30.6. UPLCMS (LRMS, ESI): m/z $[M + H]^+$ calcd for $C_{16}H_{20}N_3O_2$, 286.2; found, 286.2.

*5-Methoxypyridin-2-amine (**69**).* This compound's ^1H NMR spectrum matched a commercially available sample. ^1H NMR (400 MHz, DMSO-d_6): δ 7.63 (d, J = 3.1 Hz, 1H), 7.09 (dd, J = 8.9. 3.1 Hz, 1H), 6.41 (d, J = 8.9 Hz, 1H), 5.42 (br s, 2H), 3.67 (s, 3H).

*6-(tert-Butyl)-2-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]-indole (**71**).* To a round-bottomed flask was added salt **16** (1.00 g, 45.8 wt % calculated as free base, 2.99 mmol, 1.00 equiv) and 4-*tert*-butylcyclohexanone (**70**, 466 mg, 2.99 mmol, 1.00 equiv). *n*-Butanol (10 mL, deoxygenated by nitrogen sparging for 30 min) was added, and the mixture was heated to an internal temperature of 90 °C, forming a light yellow solution. After a total of 8 h, the mixture was cooled to room temperature and concentrated *in vacuo* to afford a yellow-brown residue. The residue was partitioned between dichloromethane (10 mL) and a saturated aqueous solution of sodium bicarbonate (10 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford a yellow solid. The solids were slurried in 10 v/v% methyl *tert*-butyl ether in hexanes (10 mL) for 15 min. The solids were collected by Buchner filtration to afford 685 mg of a light beige powder. The mother liquor was concentrated *in vacuo* to afford a red gel that was purified by flash column chromatography over silica gel (0−5% methanol in dichloromethane gradient). Fractions containing the product were combined and concentrated *in vacuo* to afford additional product **71** (65 mg) as beige solids. The total amount of **71** isolated was 750 mg (97%).

Repeating this reaction with 2-hydrazinyl-6-methoxypyridinium bistetrafluoroborate ($\mathbf{16_H}$, 380 mg, 44.0 wt % calculated as free base) under identical conditions (30 h) afforded the indole **71** as an orange solid (296 mg, 95%). R_f (15% ethyl acetate in hexanes): 0.35. Mp (hexanes): 167−168 °C (dec). ^1H NMR (400 MHz, DMSO-d_6): δ 10.97 (br s, 1H), 7.65 (d, J = 8.3 Hz, 1H), 6.40 (d, J = 8.3 Hz, 1H), 3.82 (s, 3H), 2.55−2.77 (m, 3H), 2.27 (app dd, J = 13.0, 12.0 Hz, 1H), 2.03 (dd, J = 11.4, 4.0 Hz, 1H), 1.30−1.51 (m, 2H), 0.95 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 159.0, 145.8, 131.2, 127.9, 113.7, 107.1, 101.2, 52.5, 44.6, 32.0, 27.1, 24.0, 23.2, 21.6. IR (solid) (cm^{-1}): 3354 (m), 2948 (m), 1621 (w), 1215 (s), 1025 (s), 809 (s). HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{16}H_{23}N_2O$, 259.1805; found, 259.1811.

*8-(tert-Butyl)-6,7,8,9-tetrahydro-5H-pyrido[3,2-b]indole (**72**).* To a round-bottomed flask were added salt **17** (1.00 g, 61.4 wt % calculated as free base, 4.99 mmol, 1.00 equiv) and 4-*tert*-butylcyclohexanone (**70**, 777 mg, 4.99 mmol, 1.00 equiv). *n*-Butanol (10 mL, deoxygenated by nitrogen sparging for 30 min) was added, and the mixture was heated to an internal temperature of 90 °C, forming a light yellow solution. After 10 h, a dark orange solution formed. The mixture was cooled to room temperature and concentrated *in vacuo* to afford a yellow-brown residue. The residue was partitioned between dichloromethane (10 mL) and a saturated aqueous solution of sodium bicarbonate (10 mL). The pH of the aqueous later was 9. The layers were separated, and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel (0−20% methanol in dichloromethane gradient) to afford the product **72** as an off-white (beige) solid (765 mg, 67%. The fractions containing the minor product were combined and concentrated *in vacuo* to afford a beige solid. This appeared to be some sort of salt form of **73**. The salt was partitioned between a saturated, aqueous solution of sodium bicarbonate (5 mL) and dichloromethane (5 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford the isomeric 6-azaindole **73** as an off-white solid (69 mg, 6%). This reaction was repeated with 3-hydrazinylpyridinium bishydrochloride ($\mathbf{17_H}$, 319 mg) under identical conditions. In this case, the conversion of the hydrazone to the product was very slow taking 2 weeks for full conversion of the hydrazone. At reaction completion, there was a thick precipitate of an unidentified, highly insoluble material that needed to be filtered off. Work up and purification as above afforded the indole **72** as a beige solid (49.9 mg, 13%). The isomeric 6-azaindole **73** was identified as a trace product in the reaction, though it was not found during isolation. R_f (10% methanol in dichloromethane): 0.49. Mp (methanol/dichloromethane): 232−233 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 10.86 (s, 1H), 8.16 (d, J = 4.5 Hz, 1H), 7.56 (d, J = 7.6 Hz, 1H), 6.95 (dd, J = 7.9, 4.6 Hz, 1H), 277−2.90 (m, 2H), 2.65−2.77 (m 1H), 2.31 (dd, J = 14.1, 10.9 Hz, 1H), 2.07 (dd, J = 11.0, 5.0 Hz, 1H), 1.28−1.54 (m, 2H), 0.97 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 145.3, 140.8, 138.9, 128.8, 116.9, 115.1, 109.1, 44.7, 32.3, 27.4, 24.2, 23.9, 21.3. IR (solid) (cm^{-1}): 2944 (w), 1480 (w), 1412 (m), 1360 (m), 764 (s). HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{15}H_{21}N_2$, 229.1699; found, 229.1705.

*6-(tert-Butyl)-6,7,8,9-tetrahydro-5H-pyrido[3,4-b]indole (**73**).* R_f (10% methanol in dichloromethane): 0.35. Mp (methanol/dichloromethane): 215−216 °C (dec). ^1H NMR (400 MHz, DMSO-d_6): δ 11.12 (br s, 1H), 8.54 (br s, 1H), 8.00 (br d, J = 3.2 Hz, 1H), 7.34 (br d, J = 4.8 Hz, 1H), 2.63−2.90 (m, 3H), 2.31 (app t, J = 12.9 Hz, 1H), 2.07 (dd, J = 11.4, 4.2 Hz, 1H), 1.29−1.53 (m 2H), 0.97 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 139.1, 137.2, 133.2 (br), 132.9, 131.4, 112.0 (br), 108.4, 44.8, 32.3, 27.4, 24.2, 23.6, 21.7. IR (solid) (cm^{-1}): 2948 (w), 1573 (m), 1364 (m), 1141 (m), 801 (s). HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{15}H_{21}N_2$, 229.1699; found, 229.1705.

*2-Methylquinoline (**74**).* A mixture of salt **8** (500 mg, 3.15 mmol, 1.00 equiv), acetaldehyde diethyl acetal (920 μL, 6.30 mmol, 2.00 equiv), and ethanol (5.0 mL) was heated to an internal temperature of 80 °C under nitrogen for 29 h. The reaction was cooled to room temperature, then poured into a saturated, aqueous solution of sodium bicarbonate (10 mL), and extracted with dichloromethane (1 × 10 mL, then 2 × 5 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford a dark oil. The oil was purified by flash column chromatography over silica gel (0−25% ethyl acetate in hexanes gradient) to give a semipure product. A second purification by flash column chromatography over silica gel (0−2% ethyl acetate in dichloromethane gradient) afforded **74** as a light yellow oil (73.4 mg, 16%) that was identical to a commercially available sample.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00203.

Rate experiments, ligand byproduct identification, stability studies and isotope labeling experiments, ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra, and DSC traces (PDF)

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Notes

The author declares no competing financial interest.

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■ REFERENCES

(1) (a) Robinson, B. The Fischer Indole Synthesis. *Chem. Rev.* **1963**, *63*, 373. (b) Joule, J. A.; Mills, K. *Heterocyclic Chemistry Fourth ed.*; Blackwell Science: Oxford, 2000; p 354−356. (c) Kürti, L.; Czakó, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier Academic Press: Oxford, 2005; p 172−173 and references therein.

(2) (a) Fischer, E.; Jourdan, F. Ueber die Hydrazine der Brenztraubensäure. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2241. (b) Fischer, E.; Hess, O. Synthese von Indolderivaten. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 559.

(3) (a) Hughes, D. L.; Zhao, D. Mechanistic Studies of the Fischer Indole Reaction. *J. Org. Chem.* **1993**, *58*, 228. (b) Hughes, D. L. Progress in the Fischer Indole Reaction. A Review. *Org. Prep. Proced. Int.* **1993**, *25*, 607.

(4) Çelebi-Ölçüm, N.; Boal, B. W.; Huters, A. D.; Garg, N. K.; Houk, K. N. Why Do Some Fischer Indolizations Fail? *J. Am. Chem. Soc.* **2011**, *133*, 5752. Please also see footnote 16 in ref 18b.

(5) Hammerum, S.; Sølling, T. I. The Proton Affinities of Imines and the Heats of Formation of Immonium Ions Investigated with Composite ab Initio Methods. *J. Am. Chem. Soc.* **1999**, *121*, 6002.

(6) (a) Robinson, F. P.; Brown, R. K. Further Evidence for the Dienone-Imine Intermediate in the Fischer Indole Synthesis. An Uncatalyzed Fischer Reaction under Mild Conditions. *Can. J. Chem.* **1964**, *42*, 1940. (b) Schiess, P.; Grieder, A. Zur Kenntnis der Indolreaktion nach *Fischer*, I. Thermische und Säurekatalysierte Reaktionen von *N*, *N*′-Dimethyl-*N*-Phenyl-*N*′-alkenylhydrazinen. *Helv. Chim. Acta* **1974**, *57*, 2643. (c) Przheval'skii, N. M.; Kletskii, M. E.; Grandberg, I. I.; Kostromina, L. Yu. Mechanism of the Fischer Reaction. Rearrangement of Cyclohexanone *N*-Methylphenylhydrazone and *N*,*N*′-Dimethyl-*N*-phenyl-*N*′-(1-cyclohexenyl)hydrazine to 9-Methyl-1,2,3,4-tetrahydrocarbazole. *Khim. Geterotsikl. Soedin.* **1985**, *6*, 779.

(7) Bernhardson, D. J.; Widlicka, D. W.; Singer, R. A. Cu-Catalyzed Couplings of Heteroaryl Primary Amines and (Hetero)aryl Bromides with 6-Hydroxypicolinamide Ligands. *Org. Process Res. Dev.* **2019**, *23*, 1538.

(8) Mauger, C.; Mignani, G. The Synthesis of Important Pharmaceutical Building Blocks by Palladium-Catalyzed Coupling Reaction: Access to Various Arylhydrazines. *Adv. Synth. Catal.* **2005**, *347*, 773.

(9) For details, please see the Supporting Information.

(10) Brosse, N.; Pinto, M. F.; Jamart-Grégoire, B. New Synthesis of 1,1-Substituted Hydrazines by Alkylation of *N*-Acyl- or *N*-Alkyloxycarbonylaminophthalimide Using the Mistunobu Protocol. *J. Org. Chem.* **2000**, *65*, 4370.

(11) We briefly examined an aldehyde/ketone competition reaction with the nonenolizable aldehyde, 4-propanoylbenzaldehyde with **8**, and did not observe any indole products. Instead, higher molecular weight products were observed, possibly arising from aldol-like reactions. Compound **8** remained unchanged.

(12) House, H. O.; Berkowitz, W. F. The Stereochemistry of the Neber Rearrangement. *J. Org. Chem.* **1963**, *28*, 2271. For step 4 of this synthesis, we instead dehydrated using *p*-TsOH (5 mol%) in refluxing toluene (8.8 mL/g) with a Dean−Stark trap to collect the water over 1 h. After cooling to room temperature, the reaction mixture was washed with a saturated, aqueous solution of sodium bicarbonate (5 mL/g), water (5 mL/g) and then a saturated aqueous solution of brine (5 mL/g). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford a brown mass that was dissolved in a minimum of 2 vol% triethylamine in toluene and passed through a plug of silica (23 g silica/g crude), eluting with 2 vol% triethylamine in toluene. The solution was collected from the column until just before a yellow colored band eluted. Concentration of the filtrate *in vacuo* affords light yellow crystals of the olefin.

(13) Terminal nitrogen methylation is expected to reduce the equilibrium constant of the initial bimolecular step (i.e., **1** + **2** → **3**), especially for acyclic ketones. Hine, J.; Evangelista, R. A. Iminium-Ion Formation and Deuterium Exchange by Acetone in the Presence of Pyrrolidine, Pyrazolidine, Isoxazolidine, and Their Acyclic Analogues. *J. Am. Chem. Soc.* **1980**, *102*, 1649.

(14) Szmuszkovicz, J.; Glenn, E. M.; Heinzelman, R. V.; Hester, J. B.; Youngdale, G. A. Synthesis and Antiinflammatory Activity of 2,3-Bis(*p*-methoxyphenyl)indole and Related Compounds. *J. Med. Chem.* **1966**, *9*, 527. A small amount of a compound corresponding to a product similar to **35**/**36** was observed by LC-MS monitoring but was lost to isolation.

(15) For example, see: Inman, M.; Carbone, A.; Moody, C. J. Two-Step Route to Indoles and Analogues from Haloarenes: A Variation on the Fischer Indole Synthesis. *J. Org. Chem.* **2012**, *77*, 1217.

(16) Yang, C.-F.; Shen, C.; Wang, J.-Y.; Tian, S.-K. A Highly Diastereoselective Decarboxylative Mannich Reaction of *β*-Keto Acids with Optical Active *N*-Sulfinyl *α*-Imino Esters. *Org. Lett.* **2012**, *14*, 3092.

(17) Ishii, H. Nucleophilic Displacement of the Methoxy Group in Abnormal Fischer Indolization of 2-Methoxyphenylhydrazones. *Acc. Chem. Res.* **1981**, *14*, 275. Supporting this hypothesis, running the reaction with the HBF_4 salt of **44** led to diminished efficiency (11%, **45**; 14%, **47**; 5%, **48**; 1%, **49**).

(18) (a) Jeanty, M.; Blu, J.; Suzenet, F.; Guillaumet, G. Synthesis of 4- and 6-Azaindoles via the Fischer Reaction. *Org. Lett.* **2009**, *11*, 5142. (b) Simmons, B. J.; Hoffmann, M.; Champagne, P. A.; Picazo, E.; Yamakawa, K.; Morrill, L. A.; Houk, K. N.; Garg, N. K. Understanding and Interrupting the Fischer Azaindolization Reaction. *J. Am. Chem. Soc.* **2017**, *139*, 14833.

(19) Murakami, Y. Peculiarity of Methoxy Group-Substituted Phenylhydrazones in Fischer Indole Synthesis. *Proc. Jpn. Acad., Ser. B* **2012**, *88*, 1. See also reference 23

(20) Shiao, M.-J.; Tarng, K.-Y. A Facile Synthesis of Bromo-2-Alkoxypyridines. *Heterocycles* **1990**, *31*, 819.

(21) Prepared according to ref 10, from *N*-Boc-aminophthalimide and deuteromethanol-d_4.

(22) Prepared from ^{15}N-labeled potassium phthalimide. Labeled *N*-Boc-aminophthalimide was prepared according to Brosse, N.; Pinto, M. F.; Jamart-Grégoire, B. Synthesis of *N*-(Protected)aminophthalimides: Application to the Synthesis of Singly Labelled Isoniazid. *J. Chem. Soc.*,

Perkin Trans. 1 **1998**, 3685. This was converted to $\mathbf{13}_{15N}$ according to ref 10.

(23) (a) Allen, C. F. H.; Wilson, C. V. The Use of N^{15} as a Tracer Element in Chemical Reactions. The Mechanism of the Fischer Indole Synthesis. *J. Am. Chem. Soc.* **1943**, *65*, 611. (b) Clusius, K.; Weisser, H. R. Reaktionen mit ^{15}N. III. Zum Mechanismus der Fischer'schen Indolsynthese. *Helv. Chim. Acta* **1952**, *35*, 400. Further support for this comes from researchers at Merck using a particularly suited substrate (c) Conn, R. S. E.; Douglas, A. W.; Karady, S.; Corley, E. G.; Lovell, A. V.; Shinkai, I. An Unsual Fischer Indole Synthesis with 4-Keto Acids: An Indole Incorporating the Terminal Hydrazine Nitrogen. *J. Org. Chem.* **1990**, *55*, 2908.

(24) Cottet, F.; Cottier, L.; Descotes, G. New Syntheses of Isochromene. *Synthesis* **1987**, *5*, 497.

(25) Yu, H.; Qi, C.; Tempest, P. Pyrazole Compounds as Modulators of FSHR and Uses Thereof. WO 2015/196335 A1, 2015.

(26) Green, S. P.; Wheelhouse, K. M.; Payne, A. D.; Hallett, J. P.; Miller, P. W.; Bull, J. A. On the Use of Differential Scanning Calorimetry for Thermal Hazard Assessment of New Chemistry: Avoiding Explosive Mistakes. *Angew. Chem., Int. Ed.* **2020**, *59*, 2.

(27) Knutson, D. E.; Kodali, R.; Divović, B.; Treven, M.; Stephen, M. R.; Zahn, N. M.; Dobričić, V.; Huber, A. T.; Meirelles, M. A.; Verma, R. S.; Wimmer, L.; Witzigmann, C.; Arnold, L. A.; Chiou, L. C.; Ernst, M.; Mihovilovic, M. D.; Savić, M. M.; Sieghart, W.; Cook, J. M. Design and Synthesis of Novel Deuterated Ligands Functionally Selective for the γ-Aminobutyric Acid Type A Receptor ($GABA_AR$) $\alpha 6$ Subtype with Improved Metabolic Stability and Enhanced Bioavailability. *J. Med. Chem.* **2018**, *61*, 2422.

(28) (a) Chen, J.; Hu, Y. Microwave-Assisted One-Pot Synthesis of 1,2,3,4-Tetrahydrocarbazoles. *Synth. Commun.* **2006**, *36*, 1485. (b) Lim, B. Y.; Jung, B. E.; Cho, C. G. Ene-Hydrazide from Enol Triflate for the Regioselective Fischer Indole Synthesis. *Org. Lett.* **2014**, *16*, 4492.

https://doi.org/10.1021/acs.joc.1c00203
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