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A Palladium-Catalyzed Method for the Preparation of Indoles via the Fischer Indole Synthesis

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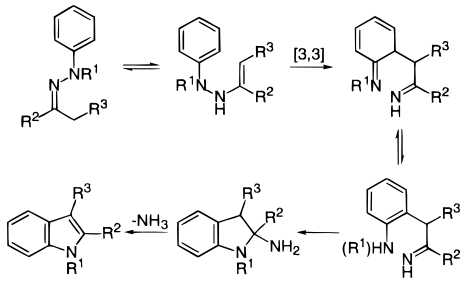
Abstract: A Pd-catalyzed method for the preparation of *N*-aryl benzophenone hydrazones **4** is described. The use of a Pd/BINAP-based catalyst provides hydrazones **4** in good yields. Using 0.1 mol % of a Pd/9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (Xantphos) catalyst, the desired hydrazones are produced in excellent yields. The *N*-aryl benzophenone hydrazones are converted to indole products via an in situ hydrolysis/Fischer cyclization protocol. A procedure that extends this methodology to the synthesis of *N*-alkylindoles via the intermediacy of *N*-aryl-*N*-alkyl benzophenone hydrazones is described. Additionally, the Pd-catalyzed preparation of diaryl benzophenone hydrazones, followed by a hydrolysis/Fischer cyclization protocol, affords *N*-arylindole products in good yields. This methodology provides a means for the preparation of a structurally diverse set of indoles from simple, (usually) commercially available precursors.

Introduction and Background

In 1883, while studying the reactivity of arylhydrazines and arylhydrazones, Emil Fischer found that, under acidic conditions, enolizable arylhydrazones undergo rearrangement and loss of ammonia to provide indole products.[1−3] Subsequent studies suggested a mechanism for the Fischer indole synthesis that proceeds through an initial acid-catalyzed tautomerization of an *N*-arylhydrazone to an ene-hydrazine (Scheme 1). The ene-hydrazine then undergoes [3,3]-sigmatropic rearrangement to produce a bis-imine intermediate; subsequent aromatization of the aniline ring followed by intramolecular nucleophilic attack produces an aminal, which after loss of ammonia affords the indole product.[4] Over 100 years after the initial discovery, the Fischer indole synthesis remains the most commonly employed method for the preparation of indoles.[5,6]

Scheme 1



Due to the rich biological activity of indoles, general and efficient methods for their preparation are continually being developed. Recent reports have described palladium-catalyzed

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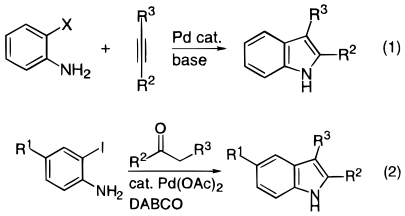
procedures for the preparation of indoles that provide alternatives to traditional methods such as the Fischer indole synthesis. These methods employ *o*-haloaniline precursors, which when react with a variety of unsaturated fragments, forming new C−C and C−N bonds to create the indole nucleus.[7−11] For example, Larock has shown that *o*-haloanilines and internal alkynes are converted to 2,3-disubstituted indole products on treatment with a Pd-catalyst and base (eq 1).[7] Researchers at Merck have demonstrated that 2,3- and 2,3,5-substituted indoles are produced by treatment of an *o*-iodoaniline and a ketone with a catalytic amount of $Pd(OAc)_2$ and 3 equiv of 1,4-diazabicyclo[2,2,2]-octane (DABCO) (eq 2).[8] While these methods are of great



importance, a drawback is the requirement of a bifunctional precursor for the formation of the new C−C and C−N bonds. This means that, to prepare an indole with *n* substituents on the aromatic ring, one must employ an aromatic precursor with $n + 2$ substituents. Issues of cost and availability render the use of less-substituted substrates a desirable goal.

The Fischer indole synthesis provides an efficient method for the conversion of enolizable *N*-arylhydrazones to indole products in which the presence of additional functional groups is not required for the formation of the new C−C and C−N bonds. The preparation of the arylhydrazone precursors, however, is often nontrivial. The requisite *N*-arylhydrazones are most commonly prepared by the condensation of an arylhydrazine with an enolizable ketone. There are a wide variety of easily accessible enolizable ketones, allowing for the variation of substituents on the 2 and 3 positions of the indole nucleus. In contrast, only a limited number of arylhydrazines are commercially available. Generally, arylhydrazines are prepared by the reduction of aryl diazonium salts, which are, in turn, obtained from aniline starting materials.[3,12] Arylhydrazines are toxic, corrosive, and prone to redox chemistry as well as radical decomposition, complicating the preparation, storage, and use of these compounds.[3,12] The difficulties associated with the use of arylhydrazine precursors restricts the ability to readily prepare indoles which are substituted in positions 4−7 by the Fischer indole synthesis.

The introduction of *N*-substituents on an indole also presents a challenging task, as the indole nitrogen is relatively nonnucleophilic. The reaction of indoles with electrophiles is complicated by competitive nucleophilicity at nitrogen and C3.[13,14] Moreover, nucleophilic aromatic substitution reactions to prepare pharmaceutically relevant *N*-arylindoles require particularly electrophilic arenes.[15−19] The most common method employed for the preparation of *N*-arylindoles is the Ullman reaction.[20] This method utilizes either catalytic or stoichiometric amounts of copper at elevated temperatures for the coupling of indoles and aryl halides. Recently, Pd-catalyzed methods for the cross-coupling of indoles with aryl halides have also been developed, but their generality is somewhat limited.[21,22]

Application of the Fischer indole synthesis to the preparation of *N*-alkyl- and *N*-arylindoles provides a unique approach to these compounds in which the indole *N*-substituent is installed prior to formation of the indole nucleus (Scheme 1, R^1 = alkyl or aryl). While it has been demonstrated that *N*-aryl-*N*-alkyl- and *N*,*N*-diarylhydrazones undergo Fischer cyclization to afford the corresponding *N*-substituted indole products,[23−25] the synthesis of *N*,*N*-disubstituted hydrazines is complicated by the presence of two reactive nitrogens and by the instability of the disubstituted products.[12] *N*,*N*-Disubstituted hydrazines are typically prepared by the reduction of the corresponding secondary *N*-nitrosamine, which are, in turn, prepared by the treatment of secondary aniline with HNO_2. Due to the lability of the N−N bond of diarylhydrazines, reduction of the *N*-nitrosodiarylaniline is accompanied by reduction of the desired hydrazine product, resulting in low yields of the diarylhydrazine. *N*-Aryl-*N*-alkylhydrazines may also be prepared by the alkylation of an arylhydrazine. However, this reaction results in a mixture of di-, tri-, and teterasubstituted hydrazines, and the use of protecting groups is required in order to achieve selective substitution.[3,12]

In the past few years, the Pd-catalyzed cross-coupling of amines with aryl halides has been shown to be a useful method in organic synthesis.[26−28] We felt that the extension of this methodology to the preparation of arylhydrazines or arylhydrazones might provide a convenient and practical method for the preparation of arylhydrazine or arylhydrazone precursors for the Fischer indole synthesis. Herein, we describe a full account of our efforts toward this goal.[29]

Results and Discussion

With the aim of circumventing the need to prepare and utilize *N*-arylhydrazines, we worked to developed a palladium-catalyzed method for the synthesis of *N*-arylhydrazones for the Fischer indole synthesis. Our initial attempts at the Pd-catalyzed

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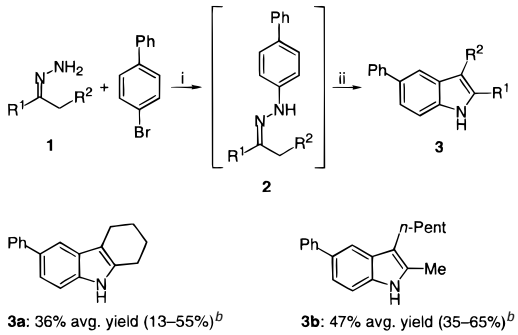
Scheme 2[a]



[a] Reagents and conditions: (i) hydrazone **1** (1 equiv), 4-bromobiphenyl (1 equiv), $Pd(OAc)_2$ (5 mol %), (±)-BINAP (5 mol %), NaO*t*-Bu (1.4 equiv), toluene, 100 °C. (ii) $TsOH \cdot H_2O$ (2 equiv), refluxing EtOH. [b] Yields in parentheses represent the range of yields which were obtained from four experiments run under identical conditions.

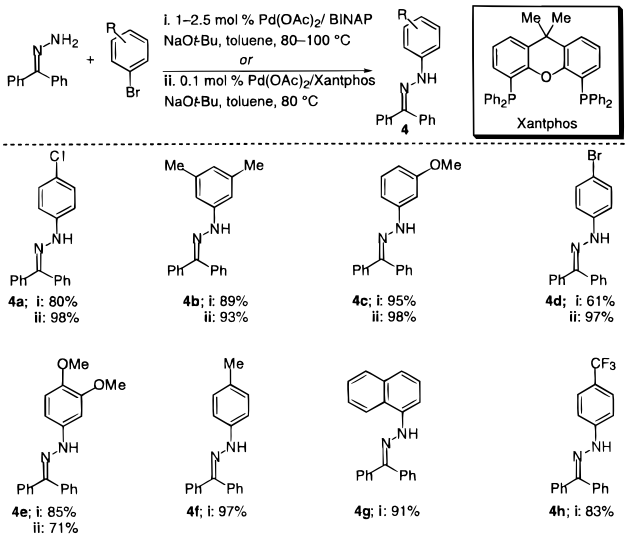
cross-coupling reaction of enolizable hydrazones **1** with aryl halides resulted in the production of the desired enolizable *N*-arylhydrazones **2** (Scheme 2). However, significant amounts of coproducts resulting from the decomposition of the starting hydrazone were also formed, the amounts of which varied in repeated experiments.[30] Enolizable *N*-arylhydrazones **2** are not stable to flash chromatography; therefore, crude **2** was directly subjected to Fischer cyclization. The resulting indole products were obtained in a range of yields, reflecting the varying efficiency with which *N*-arylhydrazone **2** was produced in the cross-coupling reaction.

On further investigation, we found that benzophenone hydrazone undergoes a more efficient cross-coupling reaction with aryl bromides than did enolizable hydrazones **1**. The use of benzophenone hydrazone offers several additional advantages. Hydrazones **1** are prepared in a two-step procedure employing anhydrous hydrazine[31,32] and undergo decomposition on storage. In contrast, benzophenone hydrazone is commercially available, inexpensive, and stable.[31,33] Though the resulting *N*-aryl benzophenone hydrazones could not directly be converted to indole products, we hoped that they would serve as convenient precursors to the necessary enolizable *N*-arylhydrazones for the Fischer indole synthesis.

N-Aryl benzophenone hydrazones **4** were first prepared by a Pd/BINAP-catalyzed cross-coupling reaction of benzophenone hydrazone with aryl bromides (Scheme 3).[29,34,35] In contrast to arylhydrazines and enolizable *N*-arylhydrazones, hydrazones **4** are stable and often crystalline compounds which can be purified either by recrystallization or flash chromatography. Due to the stability of these compounds, even *N*-aryl benzophenone hydrazones with electron-donating groups can be prepared and stored without special precaution (hydrazone **4e**), whereas the corresponding arylhydrazines decompose on contact with air.[3]

While examining the use of a catalyst composed of Pd and the bis-phosphine Xantphos (Xantphos = 9,9-dimethyl-4,5-bis-

Scheme 3



(diphenylphosphino)xanthene)[36–38] for other applications, we found that this catalyst system displayed significantly improved activity over that observed with the Pd/BINAP catalyst system in the cross-coupling of benzophenone hydrazone with aryl bromides. The use of 0.1 mol % $Pd(OAc)_2$ and 0.11 mol % Xantphos, under reaction conditions otherwise identical to those employed in Pd/BINAP-catalyzed reactions, in most instances, gave the desired *N*-aryl benzophenone hydrazones in nearly quantitative yields (Scheme 3, hydrazones **4a**−**d**). Due to the clean conversion of the starting materials to the coupled product, the only purification required in order to obtain analytically pure hydrazones **4a**−**d** was removal of the catalyst and sodium salts by filtration of the crude reaction mixture through a short plug of silica gel. In the preparation of hydrazone **4e**, the use of an electron-rich aryl bromide slows the rate of the coupling reaction; in this instance, Wolff−Kishner-type reduction of benzophenone hydrazone to produce diphenylmethane becomes a competitive reaction, resulting in a diminished yield when the low-catalyst-loading protocol is employed.[39,40] The diphenylmethane byproduct is then removed by recrystallization, and *N*-arylhydrazone **4e** is isolated in pure form.[41] For this substrate, the use of a greater quantity of catalyst is recommended.

We then turned our attention to the cleavage of hydrazones **4** to afford arylhydrazines, which could then be condensed with an enolizable ketone to furnish an enolizable *N*-arylhydrazone for Fischer cyclization. As hydrazones commonly serve as protected ketones, methods for their cleavage have generally been developed with the aim of recovering the ketone portion

(30) Azine byproducts were formed during the coupling reaction of non-benzophenone-derived simple hydrazones, as determined by GC/MS. For discussions on the stability of simple hydrazones, see refs 31−33.

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(34) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2090.

(35) We have also been able to couple benzophenone hydrazone with aryl chlorides employing a Pd/2-dicyclohexylphosphino-2′-dimethylamino-biphenyl-based catalyst system. By this method, hydrazone **4f** was produced in 89% yield from benzophenone hydrazone and 4-chlorotoluene employing 1 mol % of this catalyst mixture. For a discussion on the use of this ligand for Pd-catalyzed cross-coupling reactions of aryl chlorides, see: Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722.

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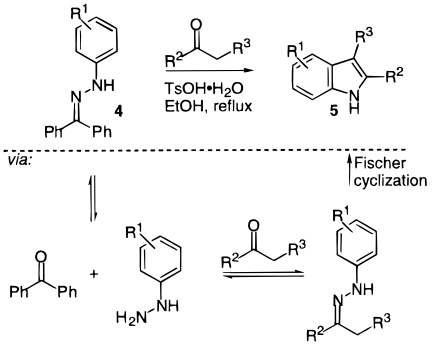
(39) The reaction of 4-bromoveratrole with benzophenone hydrazone requires 12 h to go to completion. In contrast, the coupling reactions to prepare hydrazones **4a**−**d** are complete in 1.5−6 h.

(40) Todd, D. In *Organic Reactions*; Adams, R. Ed.; John Wiley & Sons: New York, 1948; Vol. IV, p 391.

(41) Control experiments showed that, under typical reaction conditions in the absence of Pd, after 16 h approximately 40% of the benzophenone hydrazone undergoes base-promoted Wolff−Kishner reduction to form diphenylmethane. The formation of an *N*-aryl benzophenone hydrazone is not observed without the use of a Pd catalyst.

Scheme 4



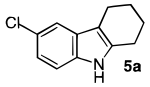
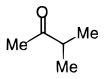
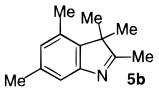
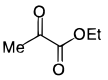
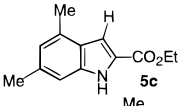
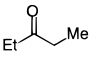
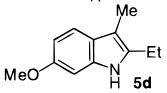
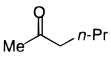
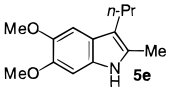
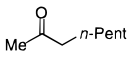
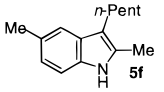
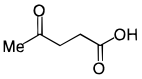
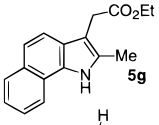
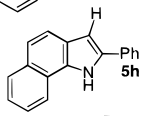
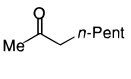
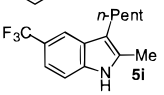
of the molecule.[42] Often, the liberated hydrazine is destroyed by oxidative or reductive means to drive the hydrolysis reaction to completion.[12] Alternatively, acidic hydrolysis of hydrazones affords both the ketone and hydrazine components. As a consequence of the stability of benzophenone hydrazones **4**, the use of strong acids such as hydrochloric acid or *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O) is required in order to effect their hydrolysis. Our initial attempts at the acidic hydrolysis of **4** employing these acids provided modest yields of the desired arylhydrazine products, along with the corresponding aniline byproducts.

The hydrolysis of hydrazones can be driven to completion by trapping the liberated hydrazine with a reactive aldehyde or ketone.[12] We reasoned that employing enolizable ketones in this approach to the hydrolysis of *N*-aryl benzophenone hydrazones **4** would not only facilitate their hydrolysis but also directly provide the desired enolizable *N*-arylhydrazones for Fischer cyclization. Additionally, under the acidic reaction conditions, the resulting enolizable *N*-arylhydrazones should undergo Fischer cyclization to provide the indole product (Scheme 4).

We have found that treatment of hydrazones **4** with an acid (e.g., *p*-TsOH·H_2O) and an enolizable ketone does, in fact, efficiently afford the desired indole products in a one-pot procedure.[29] The reactivity of *N*-arylhydrazones **4** in Fischer cyclization reactions is consistent with previous reports on the reactivity of arylhydrazones in the Fischer indole synthesis.[6] Hydrazones with electron-releasing groups are more susceptible to acid catalysis and, therefore, undergo more facile Fischer cyclization. In contrast, the presence of electron-withdrawing substituents on the aromatic ring decreases the rate of the Fischer cyclization reaction.[3] The presence of strongly deactivating groups, such as in the *p*-CF_3-substituted hydrazone **4h**, precludes efficient Fischer cyclization of this substrate, and less than 5% of the indole product is formed (Table 1, entry 9). Cyclization of *m*-methoxy hydrazone **4c** occurs predominantly *para* to the methoxy group, as is consistent with previous findings,[6] affording 6-methoxyindole **5d** (74% isolated yield) in a 4:1 ratio with the 4-methoxyindole product. In the Fischer cyclization of 3,4-dimethoxy hydrazone **4e**, only the indole product arising from cyclization to the position *para* to a methoxy group was observed (entry 5).

Fischer cyclization of enolizable hydrazones derived from methyl ketones occurs exclusively to the more highly substituted side of the hydrazones (entries 1, 2, 5−7, and 9).[6,43] In instances where there is only one enolizable position on the hydrazone, cyclization onto the methyl group carbon does occur to afford 3-unsubstituted indoles (entries 3 and 8). As shown in entry 2, the use of α-branched ketones provides 3-H indole products. α-Ketoesters may also be employed in this methodology to provide indole 2-carboxylate products (entry 3). The use of toluene as a solvent in this reaction gives optimal yields of the indole product, as is suggested in the literature.[6] The use of α-ketoacids and esters in the Fischer indole synthesis is a common strategy for the preparation of 2-unsubstituted indoles, as the indole 2-carboxylate products may be decarboxylated on heating in the presence of an oxidant.[3,44,45]

Table 1. Synthesis of Indoles

entry	hydrazone	ketone	indole	yield (%)
1	**4a**		 **5a**	95 65[b]
2	**4b**		 **5b**	93
3	**4b**		 **5c**	68[c]
4	**4c**		 **5d**	74[d]
5	**4e**		 **5e**	74[e]
6	**4f**		 **5f**	83 79[b]
7	**4g**		 **5g**	90
8	**4g**		 **5h**	85
9	**4h**		 **5i**	< 5

[a] Reactions were run with 1 equiv of *N*-aryl benzophenone hydrazone, 1.5 equiv of ketone, and 2.0−5.0 equiv of TsOH·H_2O in refluxing EtOH. Yields refer to the average of two isolated yields of >95% purity, as determined by GC, ^{1}H NMR, and, for new compounds, elemental analysis. [b] The intermediate *N*-aryl benzophenone hydrazone **4** was not isolated prior to indolization. Yields are based on the aryl bromide. [c] The reaction was run in toluene at 80 °C. [d] The yield refers only to the isolated 6-methoxyindole product. [e] Indolization was conducted in refluxing THF.

"One-Pot" Protocol. While it is advantageous to be able to isolate and store *N*-aryl benzophenone hydrazones **4**, we have found that it is not necessary to isolate this intermediate. The Pd-catalyzed cross-coupling reaction of benzophenone hydrazone with an aryl bromide affords *N*-arylhydrazone **4** (Scheme 5). The crude product is filtered through a short plug of silica gel, concentrated, and treated with a ketone (1.5 equiv) and *p*-TsOH·H_2O (2 equiv) in refluxing ethanol to afford the indole product. The yields of the indole products obtained by this method are comparable to, though slightly lower than, those obtained when the intermediate hydrazone **4** is isolated prior to the hydrolysis/Fischer cyclization procedure. For instance, indole **5g** is obtained in 70% yield following the "one-pot" protocol (Table 2, entry 6). This protocol allows for the direct conversion

(42) Bergbreiter, D. E.; Momongan, M. In *Comprehensive Organic Synthesis*; Heathcock, C. H. Ed.; Pergamon Press: Oxford, 1991; Vol. 2, pp 523−525.

(43) Hughes, D. L.; Zhao, D. L. *J. Org. Chem.* **1993**, *58*, 228.

Scheme 5

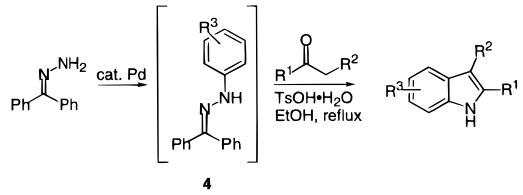
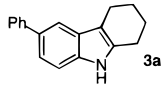
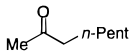
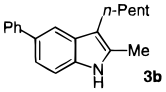
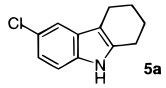
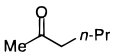
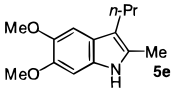
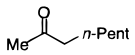
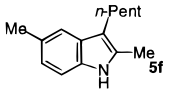
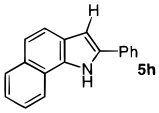


Table 2. "One-Pot" Preparation of Indoles[a]

entry	hydrazone	ketone	indole	yield (%)
1			 **3a**	92[b]
2			 **3b**	81[b]
3	**4a**		 **5a**	65
4	**4e**		 **5e**	54
5	**4f**		 **5f**	79
6	**4g**		 **5h**	70

[a] Pd-catalyzed coupling reactions were run with 1.0 equiv of benzophenone, 1.0 equiv of the aryl halide, 0.1 mol % $Pd(OAc)_2$, 0.11 mol % Xantphos, and 1.4 equiv NaOt-Bu in toluene at 80 °C. Fischer cyclization reactions were run with 1.5 equiv of the ketone and 2 equiv of $TsOH·H_2O$ in refluxing EtOH. Yields are based on benzophenone hydrazone, and refer to the average of two isolated yields of >95% purity, as determined by GC and ^1H NMR. [b] 5 mol % $Pd(OAc)_2$ and 5 mol % (±)-BINAP were employed in the Pd-catalyzed coupling reaction.

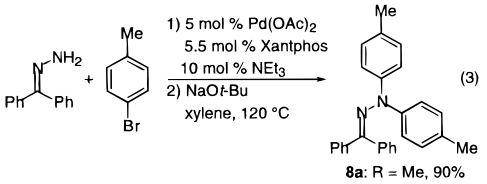
of benzophenone hydrazone and aryl bromides to a variety of indole products.

Preparation of *N*-Alkylindoles. Because of the stability of *N*-aryl benzophenone hydrazones **4**, they readily undergo further substitution at nitrogen to afford *N*,*N*-disubstituted hydrazones. Fischer cyclization of these substrates, under the previously developed hydrolysis/Fischer cyclization conditions, then produces *N*-substituted indole products (Scheme 1, $R^1 \neq H$).[13,14,46] We have found that treatment of hydrazones **4** with lithium diisoproylamide (LDA), followed by addition of an alkyl halide, results in clean formation of *N*-aryl-*N*-alkyl benzophenone hydrazones **6** (Scheme 6). Treatment of crude **6** with a ketone (1.5 equiv) and *p*-$TsOH·H_2O$ (2.0 equiv) in refluxing ethanol then affords the *N*-alkylindole product **7**. Using this methodology, we have been able to prepare several *N*-alkylindoles from *N*-aryl benzophenone hydrazone precursors (Table 3). While alkylation of deprotonated **4** with a reactive alkyl halide such as benzyl bromide, allyl bromide, or methyl iodide proceeds quickly (entries 1 and 3−5), alkylation with *n*-propyl iodide is significantly slower. In this instance, the addition of an equivalent of *N*,*N*,*N*′,*N*′-teteramethylethylenediamine (TMEDA) accelerates the alkylation reaction (entry 2). Epoxides are also found to be suitable alkylating agents (entries 7 and 8), reacting at the less-hindered site, and allow for the introduction of chirality to the indole product. When an optically active epoxide is employed (entry 8, >99% ee), no loss of stereochemical integrity is observed in the final product. Two electrophiles which we have found not to work in the alkylation step, however, are *tert*-butyl bromoacetate and phenethyl tosylate. We believe that basicity of deprotonated **4** is the problem, causing enolization of the *tert*-butyl bromoacetate and E2 elimination of the phenethyl tosylate instead of nucleophilic substitution.

m-Methoxy-substituted *N*-aryl-*N*-alkylhydrazones are efficiently converted to *N*-alkylindole products by this alkylation methodology (entry 3). Indoles **7c** and **7d** are formed in a 3.3:1 ratio; the major product, again, arises from sigmatropic rearrangement to the position *para* to the methoxy group (**7c**). The two products are separable by flash chromatography, providing a 79% combined yield of the two *N*-alkylindole products. While alkylation of *p*-methoxy-substituted *N*-aryl benzophenone hydrazones occurs quite cleanly, attempts to convert the resulting *N*-aryl-*N*-alkylhydrazone to the indole product were unsuccessful. For example, in the reaction of *N*-(*p*-methoxyphenyl)-*N*-benzyl benzophenone hydrazone with levulinic acid, the *N*-arylindole product **7e** is produced as <10% of the crude reaction mixture, as determined by GC/MS analysis (entry 4). The major products from this reaction are benzophenone and *N*-(3,4-dimethoxyphenyl)benzylamine, which arises from cleavage of the N−N bond.[47]

Preparation of *N*-Arylindoles. We have also found that *N*,*N*-diaryl benzophenone hydrazones can be prepared by the Pd-catalyzed cross-coupling reaction of benzophenone hydrazone with aryl bromides. The choice of ligand is crucial to the successful Pd-catalyzed preparation of *N*,*N*-diarylhydrazones. Of the Pd/mono- and bis-phosphine catalysts that we have surveyed, the Pd/Xantphos combination is the only catalyst system that effects the complete conversion of an *N*-aryl benzophenone hydrazone and an aryl bromide to the *N*,*N*-diarylhydrazone.

Using 5 mol % $Pd(OAc)_2$, 5.5 mol % Xantphos, and NaO*t*-Bu (2.4 equiv) in *m*-xylene at 120 °C, benzophenone hydrazone (1.0 equiv) and 4-bromotoluene (2.5 equiv) are converted to bis(*p*-tolyl) benzophenone hydrazone **8a** in 90% yield after flash chromatography (eq 3). To avoid consuming 5% of the



benzophenone hydrazone for the reduction of $Pd(OAc)_2$ to the active Pd(0) catalyst, triethylamine is added to a mixture of Pd-$(OAc)_2$ and Xantphos in xylene at room temperature to effect the catalyst activation prior to the addition of the remaining reagents.

Unsymmetrically substituted *N*,*N*-diaryl benzophenone hydrazones may also be prepared in a one-pot procedure. An

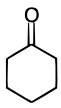
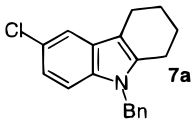
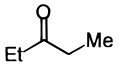
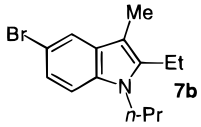
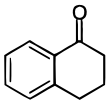
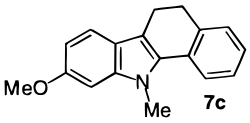
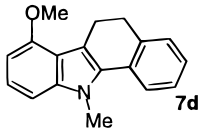
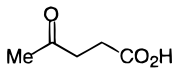
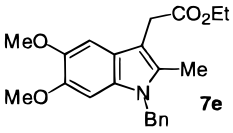
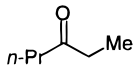
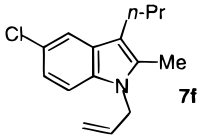
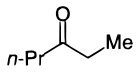
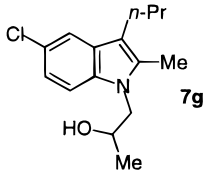
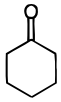
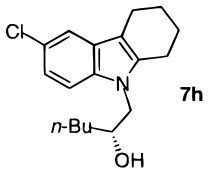
(44) The use of aldehydes in this procedure does initially produce 2-H indole products. However, due to the low reaction pH, the 2-H indole products undergo oligomerization, resulting in low to moderate isolated yields of the desired indole product (see ref 45). We are currently investigating alternative approaches for the preparation of 2-H indoles from aldehydes and hydrazones **4**.

(45) Smith, G. F. In *Advances In Heterocyclic Chemistry*; Academic Press: New York, 1963; Vol. 2, p 300.

(46) Heany, H.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1973**, 499.

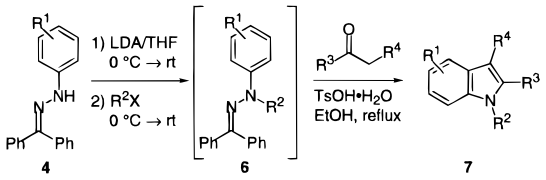
(47) *p*-Methoxy-substituted arylhydrazines are particularly prone to N−N bond cleavage. See ref 3.

Table 3. Synthesis of *N*-Alkylindoles[a]

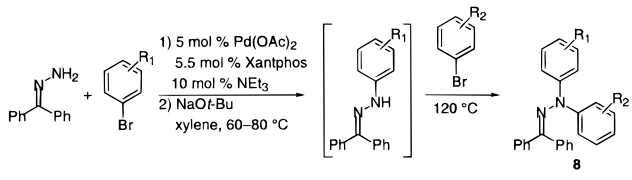
entry	hydrazone	electrophile	ketone	indole	yield (%)
1	**4a**	BnBr		 **7a**	86
2	**4d**	*n*-PrI		 **7b**	76[b]
3	**4c**	MeI		 **7c**	59
				 **7d**	20
4	**4e**	BnBr		 **7e**	<10[c]
5	**4a**			 **7f**	77
6	**4a**			 **7g**	80[d]
7	**4a**			 **7h**	81[d]

[a] Alkylation reactions were run with 1 equiv of hydrazone **4**, 1.1 equiv of LDA, and 1.2−1.5 equiv of the electrophile in THF. Fischer cyclization reactions were run with 1.5 equiv of the ketone and 2.0 equiv TsOH·H_2O in refluxing EtOH. Yields refer to the average of two isolated yields of >95% purity, as determined by GC, ^{1}H NMR, and elemental analysis. [b] 1.1 equiv of TMEDA was employed in the alkylation reaction. [c] Estimated on the basis of an uncorrected GC ratio. [d] Fischer cyclization was conducted with 3 equiv of ketone and 3 equiv of TsOH·H_2O.

Scheme 6



Scheme 7

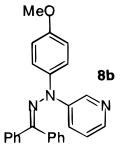
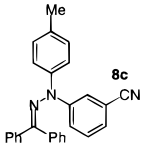
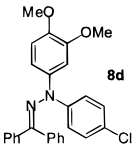


N-arylhydrazone is readily formed from benzophenone hydrazone (1.0 equiv) and an aryl bromide (1.0 equiv) at 60−80 °C (Pd/Xantphos catalyst). Upon completion of the first coupling reaction (as judged by GC analysis), a second aryl halide is added via syringe (Scheme 7). The reaction mixture is then heated to 120 °C to allow for the second coupling reaction to occur. The more electron-rich and, therefore, less reactive aryl halide is employed in the first step, as it is the more facile of the two coupling reactions. Again, purification by flash chromatography affords the desired unsymmetrically substituted *N*,*N*-diarylhydrazones in good yields (Table 4).

van Leeuwen and co-workers have shown that, when complexed to Pd, Xantphos has a relatively large bite angle (111.7°),[36,48] which results in a longer Pd−P bond;[37,49] this may account for the superiority of Xantphos relative to BINAP as a

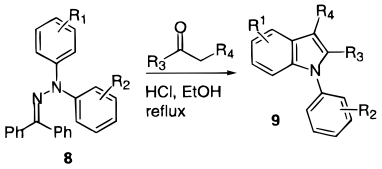
(48) In comparison, the bite angle of BINAP is 92°. See ref 49.

Table 4. Preparation of *N*,*N*-Diarylhydrazones

entry	R^1	R^2	diaryl hydrazone	yield (%)
1	4-MeO	3-pyridyl	 **8b**	73
2	4-Me	3-CN	 **8c**	86
3	3,4-dimethoxy	4-Cl	 **8d**	81

[a] Reactions were run with 5 mol % $Pd(OAc)_2$, 5.5 mol % Xantphos, 10 mol % NEt_3, 1.0 equiv of benzophenone hydrazone, 1.0 equiv of the first aryl bromide, 1.5 equiv of the second aryl halide, and 2.4 equiv of NaO*t*-Bu in *m*-xylene (1 mL/mmol of benzophenone hydrazone). Yields refer to the average of two isolated yields of >95% purity, as determined by ^{1}H NMR.

Scheme 8



8 **9**

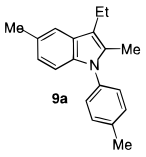
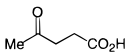
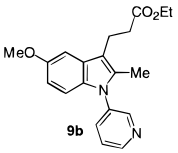
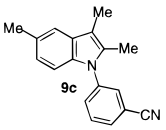
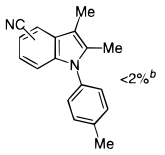
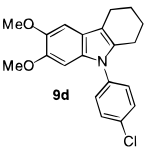
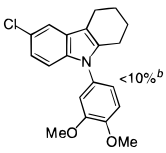
ligand in these transformations. This large bite angle produces a large coordination sphere for the reacting ligands, which may account for the improved reactivity with the sterically demanding *N*-aryl benzophenone hydrazones **4**. Additionally, the long Pd−P bond reduces the ability of phosphorus to act as a σ-donor to Pd, forming a relatively electron deficient metal center. The increased Lewis acidity of the Pd catalyst may improve its ability to coordinate nonnucleophilic hydrazones **4**, thereby assisting in the formation of the Pd−N bond and facilitating the coupling reaction.

When the hydrolysis/Fischer cyclization methodology is employed, *N*,*N*-diaryl benzophenone hydrazones are converted to *N*-arylindole products on treatment with a ketone (1.5 equiv) and concentrated hydrochloric acid in refluxing ethanol (Scheme 8). Following this protocol, symmetrically substituted hydrazone **8a** and 3-pentanone are converted to 2-ethyl-3,5-dimethyl-*N*-(*p*-tolyl)indole (**9a**) in 68% yield (Table 5, entry 1). The only observed coproduct in the crude reaction mixture was an equivalent of benzophenone.

Ishii and co-workers have shown that Fischer cyclization of unsymmetrically substituted *N*,*N*-diarylhydrazones occurs predominantly to the more electron rich arene, as it is more susceptible to interaction with an acid catalyst.[23] In the indolization of hydrazone **8b**, the only product detected is that which is produced by cyclization to the methoxy-substituted arene (Table 5, entry 2). Under the acidic reaction conditions, the pyridine nitrogen is protonated. The resulting pyridinium ring is strongly deactivated toward acid-catalyzed Fischer cyclization.[3] In the indolization of hydrazones **8c** and **8d**, products formed by cyclization to the less electron rich arene are

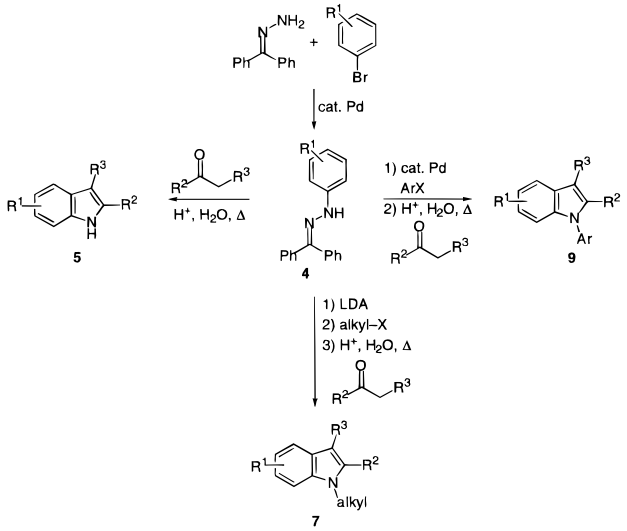
(49) Dierkes, P.; van Leeuwen, P. W. N. M. *J. Chem. Soc., Dalton Trans.* **1999**, 1519.

Table 5 Synthesis of *N*-Arylindoles[a]

entry	hydrazone	ketone	major product	yield (%)	minor product
1	**8a**		 **9a**	68	---
2	**8c**		 **9b**	76	---
3	**8d**		 **9c**	80	 <2%[b]
4	**8e**		 **9d**	80	 <10%[b]

[a] Fischer cyclization reactions were run with 1.0 equiv of the diarylhydrazone, 1.5 equiv of the ketone, and concentrated HCl (1 mL/mmol **8**) in refluxing EtOH (5 mL/mmol **8**). Yields refer to the average of two isolated yields of >95% purity, as determined by GC, ^{1}H NMR, and elemental analysis. [b] Estimated on the basis of an uncorrected GC ratio.

Scheme 9



5 **4** **9** **7**

observed. Nevertheless, the major products resulting from cyclization to the more electron rich arene rings are isolated in good yields (entries 3 and 4).

Conclusions

In summary, we have found that *N*-arylhydrazones **4** are efficiently prepared from commercially available benzophenone hydrazone and a variety of aryl bromides utilizing either a Pd/BINAP- or a $Pd(OAc)_2$/Xantphos-based catalyst system (Scheme 9). These *N*-aryl benzophenone hydrazones serve as protected arylhydrazines, which are deprotected and subjected to Fischer cyclization in a one-pot procedure to provide indole products. Hydrazones **4** are further elaborated by alkylation or a second

arylation reaction to produce *N*-aryl-*N*-alkylhydrazones **6** and *N*,*N*-diarylhydrazones **8**. When the hydrolysis/Fischer cyclization procedure is employed, hydrazones **6** and **8** are readily converted to *N*-alkylindole **7** and *N*-arylindole **9** products, respectively.

Experimental Section

General Considerations. All nonaqueous reactions were run in oven-dried glassware under a slight positive pressure of argon unless otherwise stated. Toluene was distilled from sodium under Ar. Sodium *tert*-butoxide was purchased from Aldrich Chemical Co.; the bulk of this material was stored under nitrogen in a Vacuum Atmospheres glovebox. Small portions (1−2 g) were removed from the glovebox in glass vials, stored in a desiccator with anhydrous calcium sulfate for periods of up to 2 weeks, and weighed in the air. Benzophenone hydrazone was purchased from Aldrich Chemical Co. and used as received. Anhydrous *m*-xylene was purchased from Aldrich Chemical Co. and used without further purification. Alternately, *m*-xylene was distilled under Ar from CaH_2 and stored under Ar. TMEDA and NEt_3 were distilled under vacuum from CaH_2 and stored under Ar. Xantphos was prepared by the method of van Leeuwen and co-workers.[36] Cyclohexanone hydrazone and 2-octanone hydrazone were prepared by the method of Newkome.[31] All other reagents were commercially available and used without further purification unless otherwise noted. Preparative flash chromatography was performed using ICN Flash Silica Gel, 230−400 mesh. Yields refer to the average of two isolated yields of 95% or higher purity, as determined by GC, ^{1}H NMR, and elemental analysis for new compounds. All products were characterized by ^{1}H NMR, ^{13}C NMR, and infrared (IR) spectroscopy. New compounds were further characterized by C, H analysis from E & R Microanalytical Laboratories. NMR spectra were obtained in $CDCl_3$ on a Varian XL-300 MHz, Varian Unity 300 MHz, or Varian VXR 500-MHz spectrometer. All ^{1}H NMR spectra are reported in δ units, ppm downfield from tetramethylsilane as an internal standard. All ^{13}C NMR spectra are reported in ppm relative to the central line of the triplet for $CDCl_3$ at 77 ppm. IR spectra were recorded on an ASi ReactIR 1000 instrument (solids were measured neat on a DiComp probe). Gas chromatography analyses were performed on a Hewlett-Packard 6890 gas chromatograph, with an FID and a 25-m capillary column with a dimethylpolysiloxane stationary phase. Melting points were determined using a Haake Buchler melting point apparatus and are uncorrected.

6-Phenyl-1,2,3,4-tetrahydrocarbazole (3a). Cyclohexanone hydrazone[31] (112 mg, 1.0 mmol) was dissolved in toluene (0.5 mL) in an oven-dried test tube. 4-Bromobiphenyl (233 mg, 1.0 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), and (±)-BINAP (31 mg, 0.05 mmol) were then added, followed by additional toluene (0.5 mL). The test tube was capped with a septum, purged briefly with Ar, and heated to 100 °C for 2 min (the reaction mixture turned green and then black during this time period). The reaction mixture was cooled to room temperature, the septum was removed, and NaO*t*-Bu (134 mg, 1.4 mmol) was added, followed by toluene (1 mL). The test tube was recapped with the septum and purged briefly with Ar, and the resulting purple solution was heated at 100 °C for 8 h. (***Caution!*** *Hydrazine may be evolved during this reaction*). The reaction mixture was cooled to room temperature, diluted with Et_2O (10 mL), and filtered through a short pad of Celite, and the filter cake was rinsed with Et_2O (20 mL). The filtrate was then concentrated to afford the crude product. The crude product was then heated with *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O) (380 mg, 2.0 mmol) in EtOH (5 mL) at reflux for 48 h. The reaction mixture was then cooled to room temperature, the septum was removed, and the reaction mixture was diluted with Et_2O (15 mL). The resulting heterogeneous mixture was then filtered through a pad of silica gel (∼1 in.), and the silica gel was rinsed with an additional portion of Et_2O (20−50 mL). The filtrate was concentrated, and the crude product was purified by flash chromatography (5 → 10% EtOAc/hexanes) to afford **3a** as a white solid (98 mg, 40% yield). Mp: 142−143 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51−7.34 (m, 3 H), 7.48−7.23 (m, 6 H), 2.85−2.67 (m, 4 H), 1.93 (s, 4 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 142.8, 135.1, 134.9, 132.6, 128.5, 128.3, 127.3, 126.1, 120.7, 116.3, 110.5, 110.5, 23.2, 23.1, 20.9. IR (neat, cm^{-1}): 3409, 2929, 2851, 1596, 1471. Anal. Calcd for $C_{18}H_{17}N$: C, 87.41; H, 6.93. Found: C, 87.14; H, 6.96.

2-Methyl-3-pentyl-5-phenylindole (3b). The procedure described for the preparation of indole **3a** was used to convert 2-octanone hydrazone[50] (142 mg, 1.0 mmol) and 4-bromobiphenyl (233 mg, 1.0 mmol) to the title compound. Purification of the crude product by flash chromatography (5 → 10% EtOAc/hexanes) afforded **3b** as a viscous pale yellow oil (132 mg, 48% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (dd, J = 0.9, 11.7 Hz, 2H), 7.66 (dd, J = 1.2, 8.2 Hz, 2 H), 7.45−7.42 (m, 2 H), 7.35 (dd, J = 1.8, 8.2 Hz, 1 H), 7.32−7.28 (m, 2 H), 2.71 (t, J = 7.5 Hz, 2 H), 2.37 (s, 3 H), 1.67−1.61 (m, 2 H), 1.36−1.32 (m, 4 H), 0.88 (t, J = 7.2 Hz, 3 H). ^{13}C{^{1}H} NMR (500 MHz, $CDCl_3$): δ142.9, 134.7, 132.5, 131.3, 129.3, 128.6, 127.3, 126.1, 120.5, 116.7, 112.9, 110.3, 31.8, 30.5, 24.1, 22.6, 14.1, 11.7. IR (neat, cm^{-1}): 3409, 2925, 2853, 1599, 1471, 1309. Anal. Calcd for $C_{20}H_{23}N$: C, 86.59; H, 8.36. Found: C, 86.32; H, 8.37.

Pd-Catalyzed Preparation of *N*-Arylhydrazones 4. Procedure A: 1.0 mol % Pd/(*S*)-BINAP. Benzophenone hydrazone (1.96 g, 10.0 mmol), the aryl bromide (10.0 mmol), $Pd(OAc)_2$ (23 mg, 0.10 mmol), and (*S*)-BINAP (63 mg, 0.10 mmol) were dissolved in toluene (5 mL) in a flame-dried Schlenk flask fitted with a septum and stirred at room temperature until the solution became homogeneous. The septum was removed, and NaO*t*-Bu (1.34 g, 14.0 mmol) was added, followed by additional toluene (5 mL). The reaction vessel was recapped with the septum, purged briefly with Ar, and heated at 80 °C until the aryl bromide was consumed, as determined by GC analysis. The reaction mixture was cooled to room temperature, diluted with Et_2O (10 mL), and filtered through a short pad of Celite, and the filter cake was rinsed with Et_2O (20 mL). The filtrate was then concentrated to afford the crude product. Recrystallization or flash chromatography afforded the analytically pure *N*-aryl benzophenone hydrazone **4**.

Procedure B: 1.0 mol % Pd/(±)-BINAP. Benzophenone hydrazone (1.1 equiv), $Pd(OAc)_2$ (1.0 mol %), and (±)-BINAP (1.5 mol %) were suspended in toluene (1.7 mL/mmol benzophenone hydrazone) in an oven-dried test tube fitted with a septum. The test tube was purged briefly with Ar, heated at 100 °C for 3 min, and then cooled to 25 °C. The septum was removed, and to the resulting purple solution were added the aryl bromide (1.0 equiv), NaO*t*-Bu (1.4 equiv), and an additional portion of toluene (0.3 mL/mmol benzophenone hydrazone). The test tube was recapped with the septum, purged briefly with Ar, and heated at 100 °C until the aryl bromide was consumed, as determined by GC analysis. The reaction mixture was cooled to room temperature and filtered through a short pad of Celite, and the filter cake was rinsed with Et_2O (20 mL). The filtrate was then concentrated to afford the crude product. Recrystallization or flash chromatography afforded analytically pure *N*-aryl benzophenone hydrazone **4**.

Procedure C: 0.10 mol % $Pd(OAc)_2$/Xantphos. A flame-dried Schlenk flask was evacuated, backfilled with Ar, and charged with $Pd(OAc)_2$ (2.0 mg, 0.01 mmol), Xantphos (6.0 mg, 0.011 mmol), and toluene (1 mL). The flask was then capped with a septum, and the reaction mixture was stirred at room temperature under Ar for approximately 5 min. The septum was removed, and benzophenone hydrazone (1.96 g, 10.0 mmol), the aryl halide (10.0 mmol), and NaO*t*-Bu (1.34 g, 14 mmol) were added to the flask, followed by an additional portion of toluene (9 mL). The Schlenk flask was recapped with the septum, evacuated, and backfilled with Ar, and the evacuation−backfill cycle was repeated two more times. The solution was then heated to 80 °C until the benzophenone hydrazone and aryl halide were consumed, as determined by GC analysis. The reaction mixture was then cooled to room temperature, the septum was removed, and the reaction mixture was diluted with Et_2O (15 mL). The resulting heterogeneous mixture was then filtered through a pad of silica gel (∼1 in.), and the silica gel was rinsed with an additional portion of Et_2O (20−50 mL). The filtrate was then concentrated to afford the crude product as an orange or brown solid. When further purification was required, recrystallization from MeOH afforded the pure *N*-aryl benzophenone hydrazone.

***N*-(4-Chlorophenyl) Benzophenone Hydrazone 4a.** Procedure A was used to convert benzophenone hydrazone and 4-bromochlorobenzene (1.92 g, 10.0 mmol) to the title product in crude form. Recrystallization from hot isopropyl alcohol (100 mL) afforded *N*-(4-

(50) Braddock, L. L.; Willard, M. L. *J. Org. Chem.* **1953**, *18*, 3.

chlorophenyl) benzophenone hydrazone as yellow crystals (1.97 g, 64% yield). The mother liquor was concentrated, and the residue was purified by flash chromatography (5% EtOAc/hexanes) to afford an additional 550 mg (18% yield) of the title product. The products were combined to afford 2.52 g (82% total yield) of **4a**. Mp: 125−127 °C; lit. mp 121−122 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61−7.52 (m, 5 H), 7.46 (s, 1 H), 7.30−7.28 (m, 5 H), 7.18 (d, J = 9.2 Hz, 2 H), 7.00 (d, J = 9.2 Hz, 2 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 144.8, 143.1, 138.0, 132.5, 129.7, 129.3, 129.0, 128.2, 126.5, 124.6, 113.9. IR (neat, cm^{-1}): 3327, 3034, 1598, 1552, 1494. Anal. Calcd for $C_{19}H_{15}N_2Cl$: C, 74.39; H, 4.93. Found: C, 74.55; H, 5.01.

***N*-(4-Chlorophenyl) Benzophenone Hydrazone 4a (Alternative Procedure).** Procedure C was used to convert benzophenone hydrazone and 4-bromochlorobenzene (1.92 g, 10.0 mmol) to **4a** in 1.5 h. *N*-(4-Chlorophenyl) benzophenone hydrazone (3.00 g, 9.87 mmol, 98% yield) was obtained in 98% purity, without recrystallization, as determined by ^{1}H NMR and GC analysis. Spectral data were in accord with those of previously prepared analytically pure samples.

***N*-(3,5-Dimethylphenyl) Benzophenone Hydrazone 4b.** Using procedure A, benzophenone hydrazone was coupled with 5-bromo-*m*-xylene (1.36 mL, 10.0 mmol) in 22 h. Recrystallization of the crude product from hot EtOH (20 mL) gave the title compound as an orange solid (2.13 g, 71% yield). The mother liquor was concentrated, and the residue was purified by flash chromatography (2% EtOAc/hexanes) to afford additional product (469 mg, 16% yield). The products were combined to give 2.60 g (87% total yield) of **4b**. Mp: 90−92 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60−7.50 (m, 5 H), 7.42 (s, 1 H), 7.35−7.27 (m, 5 H), 6.72 (s, 2 H), 6.50 (s, 1 H), 2.27 (s, 6 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 144.5,143.7, 138.9,138.4, 132.8, 129.6, 129.1, 128.1, 127.8, 126.4, 121.9, 110.7, 21.5. IR (neat, cm^{-1}): 3339, 3057, 3026, 1598, 1552. Anal. Calcd for $C_{21}H_{20}N_2$: C, 83.96; H, 6.71. Found: C, 84.18; H, 6.78.

***N*-(3,5-Dimethylphenyl) Benzophenone Hydrazone 4b (Alternative Procedure).** Procedure C was used to convert benzophenone hydrazone and 5-bromo-*m*-xylene (1.36 mL, 10.0 mmol) to **4b** in 4 h. *N*-(3,5-Dimethylphenyl) benzophenone hydrazone **4b** (2.80 g, 9.31 mmol, 93% yield) was obtained in 99% purity without recrystallization. Spectral data were in accord with those of previously prepared analytically pure samples.

***N*-(3-Methoxyphenyl) Benzophenone Hydrazone 4c.** Using procedure B, benzophenone hydrazone (614 mg, 3.00 mmol) was coupled with 3-bromoanisole (346 μL, 2.73 mmol) in 2.5 h. Purification of the crude product by flash chromatography (6% EtOAc/hexanes) afforded analytically pure **4c** as a brown solid (800 mg, 97% yield). Mp: 120−123 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61−7.52 (m, 5 H), 7.49 (s, 1 H), 7.34−7.27 (m, 5 H), 7.12 (t, J = 8.2 Hz, 1 H), 6.78 (t, J = 2.2 Hz, 1 H), 6.58−6.54 (m, 1 H), 6.41 (dd, J = 8.2, 2.4 Hz), 3.81 (s, 3 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 160.7, 145.9, 144.2, 138.2, 132.7, 129.8, 129.6, 129.0, 128.0, 127.9, 126.4, 105.7, 98.9, 55.2. IR (neat, cm^{-1}): 3331, 3057, 1601, 1555, 1506, 1490, 1285, 1263, 1205, 1183, 1120, 1034, 767, 690. Anal. Calcd for $C_{20}H_{18}N_2O$: C, 79.44; H, 6.00. Found: C, 79.64; H, 5.83.

***N*-(3-Methoxyphenyl) Benzophenone Hydrazone 4c (Alternative Procedure).** Procedure C was used to convert benzophenone hydrazone and 3-bromoanisole (1.27 mL, 10.0 mmol) to the title product in 6 h. Filtration through silica gel and concentration in vacuo afforded **4c** as a viscous orange oil. This oil was dissolved in Et_2O (10 mL), and the solution was concentrated in vacuo. This cycle was repeated two more times to afford **4c** as an orange solid (2.95 g, 9.80 mmol, 98% yield) in >99% purity, as determined by GC and ^{1}H NMR analysis. Spectral data were in accord with those of previously prepared analytically pure samples.

***N*-(4-Bromophenyl) Benzophenone Hydrazone 4d.**[51] Procedure C was used to convert benzophenone hydrazone and 1,4-dibromobenzene (2.36 g, 10.0 mmol) to the title product in 4 h. *N*-(4-Bromophenyl) benzophenone hydrazone (3.51 g, 9.67 mmol, 97% yield) was obtained in 98% purity without recrystallization, as determined by ^{1}H NMR and GC analysis. Mp: 107−108 °C; lit. mp 118 °C.[51] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.51−7.59 (m, 5 H), 7.46 (s, 1 H), 7.28−7.34 (m, 7 H), 6.93−6.96 (m, 2 H). ^{13}C{^{1}H} NMR (75 MHz): δ 144.8, 143.5, 137.9, 132.4, 131.9, 129.6, 129.3, 128.9, 128.2, 128.1, 126.4, 114.4, 111.7. IR (neat, cm^{-1}): 3328, 3060, 3031, 1657, 1594, 1492, 1445.

***N*-(3,4-Dimethoxyphenyl) Benzophenone Hydrazone (4e).** Using procedure B, benzophenone hydrazone (307 mg, 1.50 mmol) was coupled with 4-bromoveratrole (196 μL, 1.36 mmol) in 14 h, with the modification that $Pd(OAc)_2$ and (±)-BINAP were employed at 1.5 and 2.3 mol %, respectively. Purification of the crude product by flash chromatography (15% EtOAc/hexanes) afforded **4e** as a brown powder (395 mg, 87% yield). Mp: 98−100 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59−7.38 (m, 5 H), 7.36−7.30 (m, 5 H), 6.83−6.77 (m, 2 H), 6.52 (d, J = 2.4 Hz, 1 H), 3.91 (s, 3 H), 3.84 (s, 3 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 149.9, 143.5, 143.0, 139.3, 138.4, 132.8, 129.6, 129.1, 128.1, 127.8, 126.3, 112.5, 103.9, 98.0, 56.5, 55.8. IR (neat, cm^{-1}): 3304, 1613, 1579, 1513, 1490, 1451. Anal. Calcd for $C_{21}H_{20}N_2O_2$: C, 75.88; H, 6.06. Found: C, 75.68; H, 5.95.

***N*-(3,4-Dimethoxyphenyl) Benzophenone Hydrazone 4e (Alternative Procedure).** Procedure C was used to convert benzophenone hydrazone and 4-bromoveratrole (1.44 mL, 10.0 mmol) to the title product in 12 h. GC analysis of the crude reaction indicated that the mixture contained 70% **4e** and 8% diphenylmethane. Recrystallization from hot MeOH (75 mL) afforded the pure title product as orange crystals (2.32 g, 6.99 mmol, 70% yield). Spectral data were in accord with those of previously prepared analytically pure samples.

***N*-(4-Methylphenyl) Benzophenone Hydrazone 4f.**[52] General procedure B was used to convert benzophenone hydrazone (294 mg, 1.50 mmol) and 4-bromotoluene (167 μL, 1.36 mmol) to the crude title product. Purification by flash chromatography (3.5% EtOAc/hexanes) afforded **4f** as a viscous yellow oil (390 mg, 99% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59−7.51 (m, 5 H), 7.33−7.25 (m, 5 H), 7.07−6.97 (m, 4 H), 2.27 (s, 3 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 143.5, 142.4, 138.5, 132.8, 129.7, 129.6, 129.3, 129.2, 129.1, 128.1, 127.8, 126.3, 112.9, 20.6. IR (neat, cm^{-1}): 3332, 3063, 3020, 1613, 1521, 1518. Anal. Calcd for $C_{20}H_{18}N_2$: C, 83.88; H, 6.34. Found: C, 84.02; H, 6.36.

***N*-(1-Naphthyl) Benzophenone Hydrazone 4g.** Using procedure A, benzophenone hydrazone was coupled with 1-bromonaphthalene (1.39 mL, 10.0 mmol) in 3.5 h. Recrystallization of the crude product from hot EtOH (150 mL) afforded the analytically pure title compound as an orange/red solid (1.69 g, 53% yield). The mother liquor was concentrated, and the residue was purified by flash chromatography (2% EtOAc/hexanes) to afford additional product (1.06 g, 33% yield). The products were combined to afford **4g** (2.75 g, 86% total yield). Mp: 99−101 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19 (s, 1 H), 7.78 (t, J = 7.1 Hz, 2 H), 7.71−7.59 (m, 5 H), 7.57−7.22 (m, 10 H). ^{13}C-{^{1}H} NMR (125 MHz, $CDCl_3$): δ 146.2, 139.2, 138.1, 134.1, 132.7, 129.8, 129.5, 129.0, 128.7, 128.3, 128.2, 126.7, 126.6, 125.5, 124.9, 121.9, 121.7, 119.8, 118.9, 107.9. IR (neat, cm^{-1}): 3327, 3057, 1579, 1552, 1521, 1478. Anal. Calcd for $C_{23}H_{18}N_2$: C, 85.68; H, 5.63. Found: C, 85.71; H, 5.87.

***N*-(4-Trifluoromethyphenyl) Benzophenone Hydrazone 4h.** Procedure B was employed to couple benzophenone hydrazone (917 mg, 4.49 mmol) with 4-bromobenzotrifluoride (571 μL, 4.08 mmol), except that cesium carbonate was used in lieu of NaO*t*-Bu, $Pd(OAc)_2$ and (±)-BINAP were employed at 2.5 and 3.4 mol %, respectively, and the reaction was conducted in toluene at reflux for 48 h. Purification of the crude product by flash chromatography (5% EtOAc/hexanes) afforded **4h** as a yellow solid (1.12 g, 81% yield). Mp: 85−86 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68−7.56 (m, 5 H), 7.48 (d, J = 8.3 Hz, 2 H), 7.36−7.30 (m, 5 H), 7.12 (d, J = 8.3 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.0, 146.1, 137.8, 132.3, 129.8, 129.5, 129.0, 128.6, 128.3, 126.7, 126.7, 126.6, 126.5, 126.4. IR (neat, cm^{-1}): 3340, 3060, 1613, 1526. Anal. Calcd for $C_{20}H_{15}F_3N_2$: C, 70.58; H, 4.44. Found: C, 70.74; H, 4.34.

Procedure D: Fischer Cyclization of Hydrazones 4 to Indoles 5. Hydrazone **4** (1.0 equiv), ketone (1.5 equiv), and *p*-TsOH·H_2O (2.0 equiv) were dissolved in EtOH (5 mL/mmol **4**), and the solution was heated at reflux until **4** was consumed, as determined by GC analysis.

(51) Humphries, J. E.; Bloom, E.; Evans, R. *J. Chem. Soc.* **1923**, *123*, 1770.

(52) Bush, M.; Schaffner, S. *Chem. Ber.* **1923**, *56*, 1612.

The reaction mixture was cooled to room temperature, diluted with Et_2O (5 mL), and neutralized with a saturated $NaHCO_3$ solution. The aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined organic extracts were dried (K_2CO_3), filtered, and concentrated under vacuum. Purification of the crude product by flash chromatography afforded the analytically pure indole product.

6-Chloro-1,2,3,4-tetrahydrocarbazole 5a.[53] Procedure D was used to convert hydrazone **4a** (306 mg, 1.0 mmol) and cyclohexanone (160 μL, 1.5 mmol) to the title product. Purification of the crude product by flash chromatography (10% EtOAc/hexanes) gave **5a** as a white solid (188 mg, 91% yield). Mp: 142−143 °C; lit. mp 143−144 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (s, 1 H), 7.41 (d, J = 1.9 Hz, 1 H), 7.17 (d, J = 8.6 Hz, 1 H), 7.05 (dd, J = 2.0, 8.6 Hz, 1 H), 2.73−2.64 (m, 4 H), 1.92−1.85 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.6, 133.9, 129.0, 124.7, 120.9, 117.3, 111.1, 110.1, 23.3, 20.9. IR (neat, cm^{-1}): 3405, 2941, 2845, 1579, 1467, 1436. Anal. Calcd for $C_{12}H_{12}NCl$: C, 70.07; H, 5.88. Found: C, 70.18; H, 6.13.

2,3,3,4,6-Pentamethyl-3*H*-indole 5b. Procedure D was used to convert hydrazone **4b** (300 mg, 1.0 mmol) and 3-methyl-2-butanone (160 μL, 1.5 mmol) to the title product. Purification of the crude product by flash chromatography (30% EtOAc/hexanes) afforded the title compound as a yellow oil (168 mg, 90% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18 (s, 1 H), 6.78 (s, 1 H), 2.41 (s, 3 H), 2.35 (s, 3 H), 2.24 (s, 3 H), 1.36 (s, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 187.8, 154.2, 139.4, 137.2, 132.1, 127.8, 118.2, 53.8, 21.1, 20.7, 17.5, 15.0. IR (neat, cm^{-1}): 2968, 2926, 1722, 1695, 1583. Anal. Calcd for $C_{13}H_{17}N$: C, 82.05; H, 10.59. Found: C, 81.97; H, 10.30.

4,5-Dimethylindole-2-carboxylic Acid Ethyl Ester 5c. Hydrazone **4b** (300 mg, 1.0 mmol), ethyl pyruvate (160 μL, 1.5 mmol), and *p*-TsOH·H_2O (380 mg, 2.0 mmol) were dissolved in toluene (5 mL), and the solution was heated to reflux until **4b** was consumed, as determined by GC analysis (12 h). The reaction solution was cooled to room temperature, neutralized with a saturated $NaHCO_3$ solution, and extracted with EtOAc (3 × 10 mL). The combined EtOAc extracts were dried over anhydrous K_2CO_3, filtered, and concentrated in vacuo to afford the crude product as a brown oil. Purification by flash chromatography (10% EtOAc/hexanes) afforded indole **5c** as a white solid (147 mg, 68% yield). Mp: 108 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.77 (s, 1 H), 7.71 (dd, J = 1.0, 2.1 Hz, 1 H), 7.03 (s, 1 H), 6.79 (s, 1 H), 4.40 (q, J = 7.1 Hz, 2 H), 2.52 (s, 3 H), 2.43 (s, 3 H), 1.42 (t, J = 7.1 Hz, 3 H). ^{13}C{^{1}H} (75 MHz, $CDCl_3$): δ 162.1, 137.1, 135.7, 131.7, 126.1, 125.5, 122.8, 108.9, 107.2, 60.8, 21.9, 18.6, 14.5. IR (neat, cm^{-1}): 3321, 2973, 2917, 2904, 2858, 1686, 1580, 1524, 1432. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96. Found: C, 72.13; H, 6.95.

2-Ethyl-3-methyl-6-methoxyindole 5d. Procedure D was used to convert hydrazone **4c** (302 mg, 1.0 mmol) and 3-pentanone (160 μL, 1.5 mmol) to an approximately 4:1 mixture of the 6-methoxy- and 4-methoxyindole regioisomeric products, as determined by GC and ^{1}H NMR analysis. Purification of the crude product by flash chromatography (10% Et_2O/hexanes) afforded isomerically pure **5d** as a white solid (141 mg, 74% yield). Mp: 105−107 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59 (s, 1 H), 7.34 (d, J = 8.8 Hz, 1 H), 6.75 (dd, J = 2.4, 8.3 Hz, 1 H), 3.84 (s, 3 H), 2.72 (q, J = 7.65 Hz, 2 H), 2.20 (s, 3 H), 1.25 (t, J = 7.6 Hz, 3 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 115.7, 135.6, 135.2, 123.9, 118.5, 108.3, 105.8, 94.4, 55.7, 19.3, 14.1, 8.3. IR (neat, cm^{-1}): 3416, 2961, 2919, 1570, 1458, 1327. Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99. Found: C, 75.95; H, 7.80.

5,6-Dimethoxy-2-methyl-3-propylindole 5e. Procedure D was used except that hydrazone **4e** (692 mg, 2.10 mmol), 2-hexanone (1.28 mL, 10.4 mmol), water (1.0 mL, 56.0 mmol), and *p*-TsOH·H_2O (3.96 g, 20.8 mmol) were heated in THF (50 mL) at reflux for 22 h. Purification of the crude product by flash chromatography (20 → 25% EtOAc/hexanes) afforded the title compound as a yellow oil (361 mg, 74% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57 (br s, 1 H), 6.94 (s, 1 H), 6.73 (s, 1 H), 3.92 (s, 3 H), 3.85 (s, 3 H), 2.61 (t, J = 7.3 Hz, 2 H), 2.29 (s, 3 H), 1.63 (sext, J = 7.3 Hz, 2 H), 0.96 (t, J = 7.3 Hz, 3 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 145.9, 144.3, 129.3, 129.2, 121.5, 111.8, 100.6, 94.4, 60.4, 56.3, 26.2, 23.8, 14.1, 11.6. IR (neat, cm^{-1}): 3369, 2930, 1485, 1464, 1328, 1209, 1158, 756. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21. Found: C, 72.31; H, 8.46.

(53) Welch, W. M. *Synthesis* **1977**, 645.

2,5-Dimethyl-3-pentylindole 5f. Procedure D was used to convert hydrazone **4f** (387 mg, 1.35 mmol) and 2-octanone (317 μL, 2.03 mmol) to the title product. Purification of the crude product by flash chromatography (NEt_3-deactivated silica gel, 10% EtOAc/hexanes) afforded **5f** as a yellow oil (225 mg, 77% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (br s, 1 H), 7.26 (s, 1 H), 7.15 (d, J = 8.1 Hz, 1 H), 6.92 (d, J = 8.1 Hz, 1 H), 2.64 (t, J = 7.5 Hz, 2 H), 2.44 (s, 3 H), 2.34 (s, 3 H), 1.62−1.56 (m, 2 H), 1.31 (m, 4 H), 0.88 (t, J = 6.5 Hz, 3 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 133.5, 130.7, 129.0, 127.9, 122.1, 117.9, 111.9, 109.8, 31.8, 30.5, 24.1, 22.6, 21.6, 14.1, 11.6. IR (neat, cm^{-1}): 3041, 2926, 2856, 1459, 1305, 759. Anal. Calcd for $C_{15}H_{21}N$: C, 83.67; H, 9.83. Found: C, 83.55; H, 10.02.

(2-Methylbenzo[*g*]indol-3-yl)acetic Acid Ethyl Ester 5g. Procedure D was used to convert hydrazone **4g** (322 mg, 1.0 mmol) and levulinic acid (180 μL, 1.5 mmol) to the title product. Purification of the crude product by flash chromatography (20% EtOAc/hexanes) provided **5g** as a white solid (238 mg, 89% yield). Mp: 157−159 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.61 (s, 1 H), 7.91 (t, J = 7.5 Hz, 2 H), 7.66 (d, J = 8.6 Hz, 1 H), 7.51−7.44 (m, 2 H), 7.39−7.35 (m, 1 H), 4.15 (q, J = 7.1 Hz, 3 H), 3.74 (s, 3 H), 2.49 (s, 3 H), 1.24 (t, J = 7.2 Hz, 3 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 172.3, 130.8, 129.9, 129.2, 128.8, 125.2, 124.1, 123.3, 121.2, 120.2, 119.1, 118.5, 106.2,60.8, 30.5, 14.2, 11.6. IR (neat, cm^{-1}): 3343, 2990, 1704, 1429, 1399. Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41. Found: C, 76.24; H, 6.30.

2-Phenylbenzo[*g*]indole 5h. Procedure D was used to convert hydrazone **4g** (322 mg, 1.0 mmol) and acetophenone (170 μL, 1.5 mmol) to the title product. Purification of the crude product by flash chromatography (5% EtOAc/hexanes) afforded **5h** as a white solid (200 mg, 82% yield). Mp: 164−165 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.02 (s, 1 H), 8.07 (d, J = 8.2 Hz, 1 H), 7.93 (d, J = 8.2 Hz, 1 H), 7.74−7.70 (m, 3 H), 7.56−7.41 (m, 5 H), 7.35−7.32 (m, 1 H), 6.96 (s, 1 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 136.2, 132.5, 131.3, 130.5, 129.1, 129.0, 127.4, 125.9, 125.6, 125.3, 123.9, 121.5, 121.2, 120.6, 119.3, 101.7. IR (neat, cm^{-1}): 3341, 3037, 1602, 1486, 1450, 1390. Anal. Calcd for $C_{18}H_{13}N$: C, 88.86; H, 5.39. Found: C, 88.62; H, 5.60.

2-Methyl-3-pentyl-5-trifluoromethylindole 5i. Hydrazone **4h** (34 mg, 0.10 mmol), 2-hexanone (62 μL, 0.50 mmol), and *p*-TsOH·H_2O (190 mg, 1.0 mmol) were heated in EtOH (1 mL) at reflux for 48 h. The crude reaction mixture was worked up according to procedure D. Purification of the crude product by flash chromatography (15% EtOAc/hexanes) afforded <1 mg of the title compound (<5% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (br s, 1 H), 7.76 (s, 1 H), 7.32 (m, 2 H), 2.68 (t, J = 7.4 Hz, 3 H), 2.40 (s, 3 H), 1.70−1.50 (m, 4 H), 0.95 (t, J = 7.4 Hz, 3 H). EI-MS: m/z 241 (M^+), 212 (base peak).

"One-Pot" Synthesis of 6-Phenyl-1,2,3,4-tetrahydrocarbazole 3a from Benzophenone Hydrazone. Benzophenone hydrazone (98 mg, 0.50 mmol) and 4-bromobiphenyl (117 mg, 0.50 mmol) were coupled according to procedure A. The crude product was heated with cyclohexanone (78 μL, 0.75 mmol) and *p*-TsOH·H_2O (190 mg, 1.0 mmol) according to procedure D, except that THF (1 mL) was added to solubilize the intermediate *N*-(*p*-phenyl-phenyl) benzophenone hydrazone. Purification of the crude product by flash chromatography (10% EtOAc/hexanes) afforded **3a** as a white solid (117 mg, 95% yield). Spectral data were in accord with those of previously prepared analytically pure samples.

"One-Pot" Synthesis of 2-Methyl-3-pentyl-5-phenylindole 3b from Benzophenone Hydrazone. Benzophenone hydrazone (98 mg, 0.50 mmol) and 4-bromobiphenyl (117 mg, 0.50 mmol) were coupled according to procedure A. The crude product was heated with 2-octanone (70 μL, 0.75 mmol) and *p*-TsOH·H_2O (190 mg, 1.0 mmol) according to procedure D, except that THF (1 mL) was added to solubilize the intermediate *N*-(4-phenyl-phenyl) benzophenone hydrazone. Purification of the crude product by flash chromatography (10% EtOAc/hexanes) afforded **3b** as a clear oil (109 mg, 79% yield). Spectral data were in accord with those of previously prepared analytically pure samples.

Procedure E: Alkylation of *N*-Aryl Benzophenone Hydrazones 4. Lithium diisopropylamide (LDA, 1.2 M/THF) was prepared by adding diisopropylamine (1.2 equiv) via syringe to THF in an oven-dried flask that was under Ar and capped with a septum. The flask

was cooled to 0 °C, *n*-BuLi (1.6 M in hexane, 1.1 equiv) was added dropwise, and the resulting solution was stirred at 0 °C for 30 min.

An oven-dried flask was charged with the *N*-aryl benzophenone hydrazone (1.0 equiv) and THF (1.0 mL/mmol of **4**), capped with a septum, placed under Ar, and cooled to 0 °C. Freshly prepared LDA was transferred via cannula to the reaction mixture, which was then stirred at room temperature for 30 min. The reaction mixture was cooled to 0 °C, and the alkyl halide (1.2 equiv) and, when needed, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) (1.2 equiv), were added to the reaction mixture, which was then stirred at room temperature or with heating until the *N*-arylhydrazone was consumed, as ascertained by TLC analysis.

On completion of the alkylation reaction, the septum was removed, and the reaction mixture was concentrated in vacuo to afford the crude *N*-aryl-*N*-alkylhydrazone **6**, which was used without further purification. In instances when TMEDA was employed, the crude reaction mixture was diluted with Et_2O (5 mL) and then washed with a saturated $CuSO_4$ solution (3 × 5 mL) to remove the TMEDA. The organic layer was then dried over K_2CO_3, filtered, and concentrated under vacuum to afford the crude product, which was used without further purification.

General Procedure F: Fischer Cyclization of *N*-Aryl-*N*-alkyl Benzophenone Hydrazones 6 to *N*-Alkylindoles 7. The crude *N*-aryl-*N*-alkylhydrazone **6** was dissolved in EtOH (5.0 mL/mmol **6**); the ketone (1.5 equiv) and *p*-TsOH·H_2O (2.0 equiv) were then added, and the solution was heated to reflux (80 °C bath temperature) until hydrazone **6** was consumed, as ascertained by TLC analysis. The reaction mixture was then cooled to room temperature, neutralized with a saturated $NaHCO_3$ solution, and extracted with Et_2O (2 × 10 mL). The combined Et_2O extracts were dried over K_2CO_3, filtered, and concentrated in vacuo to afford crude **7**. Purification by flash chromatography afforded the analytically pure *N*-alkylindole product.

6-Chloro-*N*-benzyl-1,2,3,4-tetrahydrocarbazole 7a.[54] Procedure E was used to convert *N*-(4-chlorophenyl)-*N*-benzyl benzophenone hydrazone **4a** (306 mg, 1.0 mmol) and benzyl bromide (131 μL, 1.1 mmol) to *N*-(4-chlorophenyl)-*N*-benzyl benzophenone hydrazone which, in crude form, was obtained as a viscous yellow oil.

Procedure F was used to convert crude *N*-(4-chlorophenyl)-*N*-benzyl benzophenone hydrazone (∼1 mmol) and cyclohexanone (156 μL, 1.5 mmol) to 6-chloro-*N*-benzyl-1,2,3,4-tetrahydrocarbazole. Purification by flash chromatography (2% EtOAc/hexanes) afforded analytically pure **7a** as a pale yellow oil, which solidified on standing (250 mg, 85% yield). Mp: 95−97 °C; lit. mp 97.5−98.5 °C.[54] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (d, *J* = 2.0 Hz, 1 H), 7.19−7.26 (m, 3 H), 7.06 (d, *J* = 8.5 Hz, 1 H), 7.01 (d, *J* = 8.5 Hz, 1 H), 6.94 (d, *J* = 6.7 Hz, 2 H), 5.15 (s, 2 H), 2.69 (t, *J* = 6.0 Hz, 2 H), 2.59 (t, *J* = 6.0 Hz, 2 H), 1.82−1.91 (m, 4 H). ^{13}C{^{1}H} (125 MHz, $CDCl_3$): δ 137.7, 137.1, 134.8, 128.7, 128.5, 127.2, 127.0, 124.5, 120.7, 117.3, 109.6, 77.3, 77.0, 76,7, 46.2, 23.0, 22.9(8), 22.1, 20.9. IR (neat, cm^{-1}): 3062, 3025, 2941, 2925, 2852, 1602, 1573, 1495, 1453, 1441. Anal. Calcd for $C_{19}H_{18}NCl$: C, 77.15; H, 6.13. Found: C, 76.99; H, 6.19.

5-Bromo-2-ethyl-3-methyl-*N*-propylindole 7b. Procedure E was used to convert *N*-(4-bromophenyl) benzophenone hydrazone **4d** (351 mg, 1.0 mmol) and *n*-propyl iodide (107 μL, 1.5 mmol) in the presence of TMEDA (181 μL, 1.2 mmol) to *N*-(4-bromophenyl)-*N*-propyl benzophenone hydrazone. After deprotonation of the hydrazone with LDA and addition of *n*-propyl iodide and TMEDA, the reaction mixture was heated to 40 °C. Upon consumption of **4d**, the solution was cooled to room temperature, diluted with Et_2O (20 mL), and washed with a saturated $CuSO_4$ solution (2 × 10 mL) to remove the TMEDA. The combined Et_2O layers were then dried over anhydrous K_2CO_3, filtered, and concentrated to afford the crude product as a viscous yellow oil.

Procedure F was used to convert crude *N*-(4-bromophenyl)-*N*-propyl benzophenone hydrazone (∼1 mmol) and 3-pentanone (158 μL, 1.5 mmol) to 5-bromo-2-ethyl-3-methyl-*N*-propylindole. Purification by flash chromatography (2% EtOAc/hexanes) afforded analytically pure **7b** as a clear oil (215 mg, 0.78 mmol, 78% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (dd, *J* = 0.5, 1.9 Hz, 1 H), 7.18 (dd, *J* = 1.9, 8.6 Hz, 1 H), 7.09 (dd, *J* = 0.5, 8.6 Hz, 1 H), 3.96 (t, *J* = 7.6 Hz, 2 H), 2.74 (q, *J* = 7.6 Hz, 2 H), 2.20 (s, 3 H), 1.73 (q, *J* = 7.5 Hz, 2 H), 1.18 (t, *J* = 7.6 Hz, 3 H), 0.93 (t, *J* = 7.5 Hz, 3 H). ^{13}C{^{1}H} (125 MHz, $CDCl_3$): δ 139.3, 134.3, 130.2, 122.9, 120.5, 111.7, 110.3, 105.4, 44.9, 23.8, 17.8, 14.5, 11.5, 8.6. IR (neat, cm^{-1}): 2968, 2933, 2875, 1569, 1468, 1414. Anal. Calcd for C_{14} $H_{18}NBr$: C, 60.01; H, 6.47. Found: C, 60.33; H, 6.73.

7-Methoxy-6,11-dihydro-5*H*-benzo[*a*]carbazole 7c and 9-Methoxy-6,11-dihydro-5*H*-benzo[*a*]carbazole 7d. Procedure E was used to convert 3-methoxyphenyl benzophenone hydrazone **4c** (302 mg, 1.0 mmol) and methyl iodide (94 μL, 1.5 mmol) to *N*-(3-methoxyphenyl)-*N*-methyl benzophenone hydrazone.

Following procedure F, the crude alkylated hydrazone and α-tetralone (200 μL, 1.5 mmol) were converted to a 3.3:1 mixture of indoles **7c** and **7d**. Purification by flash chromatography (2% EtOAc/hexanes) afforded analytically pure indoles **7c** and **7d** (indole **7c**, 155 mg, 0.59 mmol, 59% yield; indole **7d**, 53 mg, 0.20 mmol, 20% yield).

7c. Mp: 120−121 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (d, *J* = 7.6 Hz, 1 H), 7.42 (d, *J* = 8.2 Hz, 1 H), 7.25 (dd, *J* = 7.4, 12.9 Hz, 2 H), 7.12 (t, *J* = 7.4 Hz, 1 H), 6.75−6.81 (m, 2 H). ^{13}C{^{1}H}: δ 156.55, 139.9, 137.2, 133.9, 128.4, 126.4, 125.5, 121.7, 120.4, 119.3, 113.9, 109.1, 93.1, 55.7, 32.6, 30.7, 20.2. IR (neat, cm^{-1}): 3002, 2944, 2889, 2834, 1619, 1600, 1571, 1536, 1492. Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51. Found: C, 82.00; H, 6.45.

7d. Mp: 132−134 °C. ^{1}H NMR: δ 7.58 (d, *J* = 6.0 Hz, 1 H), 7.25−7.32 (m, 2 H), 7.09−7.18 (m, 2 H), 6.94 (d, *J* = 8.1 Hz, 1 H), 6.50 (d, *J* = 7.8 Hz, 1 H), 3.97 (s, 3 H), 3.92 (s, 3 H), 3.15 (dd, *J* = 6.6, 8.1 Hz, 2 H), 2.91−2.96 (m, 2 H). ^{13}C{^{1}H} (75 Hz, $CDCl_3$): δ 154.6, 140.5, 137.9, 133.5, 129.5, 128.4, 126.4, 125.8, 122.6, 122.1, 116.0, 113.9, 1.2.7, 99.5, 55.2, 32.9, 31.0, 21.6. IR (neat, cm^{-1}): 2989, 2958, 2929, 1580, 1499, 1465, 1461. Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51. Found: C, 82.07; H, 6.47.

Attempted Cyclization to (*N*-Benzyl-5,6-dimethoxy-2-methylindol-3-yl)acetic Acid Ethyl Ester 7e. Procedure E was used to convert *N*-(3,4-dimethoxyphenyl) benzophenone hydrazone **4e** (332 mg, 1.0 mmol) and benzyl bromide (178 μL, 1.5 mmol) to *N*-(3,4-dimethoxyphenyl)-*N*-benzyl benzophenone hydrazone.

Following procedure F, the crude *N*-aryl-*N*-alkyl benzophenone hydrazone was treated with levulinic acid (154 μL) and *p*-TsOH·H_2O (380 mg) in refluxing EtOH (5.0 mL). Analysis of the neutralized crude reaction mixture by GC/MS showed that it contained benzophenone (∼54%), bis(4-methoxyphenyl)amine (∼35%), and indole **7e** (∼8%).

5-Chloro-2-methyl-3-propyl-*N*-allylindole 7f. Procedure E was used to convert *N*-(4-chlorophenyl) benzophenone hydrazone (4a) (150 mg, 0.427 mmol) and allyl bromide (66 μL, 0.598 mmol) to *N*-(4-chlorophenyl)-*N*-allyl benzophenone hydrazone which, in its crude form, was obtained as a viscous yellow oil.

Procedure F was used to convert the crude *N*-(4-chlorophenyl)-*N*-allyl benzophenone hydrazone (∼0.424 mmol) and 2-hexanone (78 μL, 0.636 mmol) to 5-chloro-2-methyl-3-propyl-*N*-allylindole. Purification by flash chromatography (4% EtOAc/hexanes) afforded analytically pure **7f** as a yellow oil (81 mg, 77% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (s, 1 H), 7.07 (m, 2 H), 5.88 (m, 1 H), 5.07 (d, *J* = 10.5 Hz, 1 H), 4.71 (d, *J* = 17.0 Hz, 1 H), 4.62 (s, 2 H), 2.64 (t, *J* = 7.3 Hz, 2 H), 2.29 (s, 3 H), 1.60 (m, 2 H), 0.92 (t, *J* = 7.3 Hz, 3 H). ^{13}C{^{1}H} (75 MHz, $CDCl_3$): δ 134.4, 134.0, 133.2, 129.1, 124.3, 120.5, 117.6, 116.0, 111.7, 109.7, 45.3, 26.3, 24.0, 14.0, 10.1. IR (neat, cm^{-1}): 3084, 1471, 923, 790. Anal. Calcd for $C_{15}H_{18}ClN$: C, 72.72; H, 7.32. Found: C, 72.81; H, 7.32.

5-Chloro-2-methyl-3-propyl-*N*-(2-hydroxypropyl)indole 7g. Procedure E was used to convert *N*-(4-chlorophenyl) benzophenone hydrazone **4a** (120 mg, 0.391 mmol) and propylene oxide (85 μL, 0.585 mmol) to *N*-(4-chlorophenyl)-*N*-(2-hydroxypropyl) benzophenone hydrazone. The reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (3 × 15 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated, and the crude product was purified by flash chromatography (22% EtOAc/hexanes). Using procedure F, *N*-(4-chlorophenyl)-*N*-(2-hydroxypropyl) benzophenone hydrazone (∼0.42 mmol), 2-hexanone (123 μL, 1.0 mmol), and *p*-TsOH·H_2O (190 mg, 1.0 mmol) were refluxed in EtOH to afford 5-chloro-2-methyl-3-propyl-*N*-(2-hydroxypropyl)indole. Purification by flash chromatography (28% EtOAc/hexanes) afforded analytically pure

(54) Kotschetkow, N. K.; Kutcherova, N. F.; Yevdakov, V. P. *Zh. Obshch. Khim.* **1956**, *26*, 3144.

7g as a yellow oil (85 mg, 82% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (d, J = 1.8 Hz, 1 H), 7.15 (d, J = 8.6 Hz, 1 H), 7.04 (dd, J = 8.6, 1.8 Hz, 1 H), 4.10 (m, 1 H), 3.95 (m, 2 H), 2.61 (t, J = 7.3 Hz, 2 H), 2.33 (s, 3 H), 1.70 (br, 1 H), 1.61 (m, 2 H), 1.22 (d, J = 6.2 Hz, 3 H), 0.92 (t, J = 7.3 Hz, 3 H). ^{13}C{^{1}H} (75 MHz, $CDCl_3$): δ 134.7, 134.3, 129.1, 124.5, 120.6, 117.6, 111.9, 110.0, 67.3, 50.8, 26.3, 24.0, 20.5, 14.1, 10.6. IR (neat, cm^{-1}): 3402, 1471. Anal. Calcd for $C_{15}H_{20}$ClNO: C, 67.79; H, 7.58. Found: C, 67.67; H, 7.56.

(*R*)-6-Chloro-*N*-(2-hydroxyhexyl)-1,2,3,4-tetrahydrocarbazole 7h. Procedure E was used to convert *N*-(4-chlorophenyl) benzophenone hydrazone **4a** (90 mg, 0.293 mmol) and (*R*)-1,2-epoxyhexane (71 μL, 0.586 mmol) to (*R*)-*N*-(4-chlorophenyl)-*N*-(2-hydroxyhexyl) benzophenone hydrazone. The reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (3 × 15 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated, and the crude product was purified by flash chromatography (13% EtOAc/hexanes). Using procedure F, (*R*)-*N*-(4-chlorophenyl)-*N*-(2-hydroxyhexyl) benzophenone hydrazone (~0.29 mmol), cyclohexanone (123 mL, 1.0 mmol), and *p*-TsOH·H_2O (190 mg, 1.0 mmol) were refluxed in EtOH to afford (*R*)-6-chloro-*N*-(2-hydroxyhexyl)-1,2,3,4-tetrahydrocarbazole. Purification by flash chromatography (16% EtOAc/hexanes) afforded analytically pure **7h** as a yellow oil (75 mg, 84% yield). The enantiomeric excess of **7h** was determined to be >99% by HPLC analysis (Chiralcel OD column) using 7.5% 2-propanol/hexanes at a flow rate of 0.5 mL/min. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 (s, 1 H), 7.20 (d, J = 8.5 Hz, 2 H), 7.08 (d, J = 8.5 Hz, 1 H), 4.02 (m, 3 H), 2.70 (m, 3 H), 1.91 (m, 4 H), 1.52 (m, 8 H), 0.93 (t, J = 6.7 Hz, 3 H). ^{13}C{^{1}H} (75 MHz, $CDCl_3$): δ 137.4, 134.9, 128.5, 124.6, 120.7, 117.3, 110.0, 109.5, 71.2, 49.5, 34.3, 27.7, 23.1, 23.0, 22.7, 22.5, 20.9, 14.0. IR (neat, cm^{-1}): 3423, 2932, 2856, 1467, 1443. $[\alpha]^{25}_D = -3.7°$ (*c* 8.0, $CHCl_3$). Anal. Calcd for $C_{18}H_{24}$ClNO: C, 70.69; H, 7.91. Found: C, 70.74; H, 7.82.

***N*,*N*-Bis-(*p*-tolyl) Benzophenone Hydrazone 8a.** An oven-dried test tube was charged with $Pd(OAc)_2$ (11 mg, 0.05 mmol), Xantphos (32 mg, 0.055 mmol), NEt_3 (15 μL, 0.10 mmol), and *m*-xylene (0.5 mL). The test tube was capped with a septum and purged with Ar (~1 min), and the solution was stirred at room temperature under Ar for approximately 15 min. During this time, the initially red homogeneous solution became yellow and heterogeneous. The septum was removed, and the test tube was charged with benzophenone hydrazone (196 mg, 1.0 mmol) and 4-bromotoluene (308 μL, 2.5 mmol). The septum was replaced, and the reaction mixture was purged with Ar (~1 min). The reaction solution was then heated to 120 °C for 3 h and cooled to room temperature, the septum was removed, and the solution was diluted with Et_2O (5 mL). The resulting heterogeneous mixture was filtered through a short plug of silica gel, and the silica gel was rinsed with an additional portion of Et_2O (20 mL). The filtrate was concentrated in vacuo to afford the crude product. Purification by flash chromatography (2% EtOAc/hexanes) afforded the pure title product as a viscous yellow oil (337 mg, 0.90 mmol, 90% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (dd, J = 2.0, 4.0 Hz, 2 H), 7.36−7.31 (m, 3 H), 7.09−7.15 (m, 3 H), 6.87−6.93 (m, 6 H), 6.76 (d, J = 8.4 Hz, 4 H), 2.24 (s, 6 H). ^{13}C{^{1}H} (125 MHz, $CDCl_3$): δ 161.2, 146.1, 138.9, 137.4, 132.3, 129.3(3), 129.2(9), 128.5, 128.1, 127.9, 127.7, 127.6, 121.7, 20.7. IR (neat, cm^{-1}): 3056, 3025, 2921, 1613, 1507, 1443. Anal. Calcd for $C_{27}H_{24}N_2$: C, 86.13; H, 6.43. Found: C, 85.77; H, 6.76.

Procedure G: Preparation of Unsymmetrically Substituted Diarylhydrazones 8. An oven-dried test tube was charged with $Pd(OAc)_2$ (11 mg, 0.05 mmol), Xantphos (32 mg, 0.055 mmol), NEt_3 (15 μL, 0.10 mmol), and *m*-xylene (0.5 mL), capped with a septum, and purged with Ar (~1 min). The solution was stirred at room temperature under Ar for approximately 15 min. During this time, the initial red homogeneous solution became yellow and heterogeneous. The septum was removed, and benzophenone hydrazone (196 mg, 1.0 mmol), the first aryl bromide (1.0 mmol), and NaO*t*-Bu (231 mg, 2.4 mmol) were added to the test tube, followed by an additional portion of *m*-xylene (0.5 mL). The test tube was recapped with the septum and briefly purged with Ar (~1 min), and the test tube was then heated to 60−80 °C. The disappearance of benzophenone hydrazone and aryl halide was monitored by GC analysis; reaction times ranged from 10 to 30 min. Once the first coupling reaction to form the monoarylhydrazone was complete, the second aryl bromide (1.5 mmol) was added via syringe to the reaction mixture. In instances where solid aryl bromides were used, the aryl bromide was dissolved in *m*-xylene (0.5 mL), and the resulting solution was added to the reaction mixture via syringe. The reaction solution was then heated to 120 °C until the monoarylhydrazone was consumed, as determined by TLC analysis. The reaction mixture was then cooled to room temperature, the septum was removed, and the reaction solution was diluted with Et_2O (5 mL). The resulting heterogeneous mixture was filtered through a short pad of silica gel, and the silica gel was rinsed with an additional portion of Et_2O (10−30 mL). The filtrate was concentrated in vacuo to afford the crude product. Purification by flash chromatography afforded the analytically pure diarylhydrazone.

***N*-(4-Methoxyphenyl)-*N*-(3-pyridyl) Benzophenone Hydrazone 8b.** Procedure G was used to convert benzophenone hydrazone (196 mg, 1.0 mmol), 4-bromoanisole (125 μL, 1.0 mmol), and 3-bromopyridine (144 μL, 1.5 mmol) to the title product. Purification by flash chromatography (25% EtOAc/hexanes) afforded **8b** as a viscous yellow oil, of >95% purity, as determined by ^{1}H NMR analysis (273 mg, 0.72 mmol, 72% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.26 (d, J = 3.0 Hz, 1 H), 8.15 (dd, J = 1.25, 4.75 Hz, 1 H), 7.62−7.64 (m, 2 H), 7.32−7.39 (m, 3 H), 7.15−7.26 (m, 4 H), 7.09 (dd, J = 4.5, 8.5 Hz, 1 H), 6.88−6.90 (m, 2 H), 6.69−6.71 (m, 2 H), 6.62−6.63 (m, 2 H). ^{13}C (125 MHz, $CDCl_3$): δ 161.9, 157.0, 145.9, 141.7, 138.9(5), 138.8(8), 138.2, 136.8, 129.6, 128.1, 128.0, 127.9, 127.8, 127.5, 123.2, 122.8, 114.3, 55.3. IR (neat, cm^{-1}): 3056, 2954, 2836, 1605, 1580, 1511, 1492, 1443. EI-MS *m*/*z*: (M^+) calcd for $C_{25}H_{21}N_3O$ 379.1684, obsd 379.1691.

***N*-(*p*-Tolyl)-*N*-(3-cyanophenylbenzophenone) Benzophenone Hydrazone 8c.** Procedure G was used to convert benzophenone hydrazone (196 mg, 1.0 mmol), 4-bromotoluene (120 μL, 1.0 mmol), and 3-bromobenzonitrile (273 mg, 1.5 mmol) to the title product. Purification by flash chromatography (5% EtOAc/hexanes) afforded analytically pure **8c** as a viscous yellow oil (334 mg, 86% yield). The product contained 1−2% of what appeared to be *N*-(*p*-tolyl)-*N*-(3-*tert*-butylbenzoate) benzophenone hydrazone, as determined by ^{1}H NMR. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62−7.64 (m, 2 H), 7.39−7.42 (m, 1 H), 7.33−7.36 (m, 2 H), 7.12−7.25 (m, 7 H), 6.85−6.90 (m, 4 H), 6.63 (dd, J = 2.0, 6.5 Hz, 2 H), 2.24 (s, 3 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 163.6, 149.9, 143.0, 138.0, 136.7, 135.4, 130.0, 129.8, 129.3, 128.2, 128.1, 128.0, 127.9, 126.1, 123.8, 120.7, 119.6, 119.3, 112.3, 21.0. IR (neat, cm^{-1}): 3060, 3027, 2229, 1594, 1574, 1507, 1443, 1432. Anal. Calcd for $C_{27}H_{21}N_3$: C, 83.69; H, 5.46. Found: C, 83.84; H, 5.61.

***N*-(3,4-Dimethoxyphenyl)-*N*-(4-chlorophenyl) Benzophenone Hydrazone 8d.** Procedure G was used to convert benzophenone hydrazone (196 mg, 1.0 mmol), 4-bromoveratrole (140 μL, 1.0 mmol), and 4-bromochlorobenzene (287 mg, 1.5 mmol) to the title product. Purification by flash chromatography (10% EtOAc/hexanes) afforded analytically pure **8d** as a bright yellow solid (358 mg, 81% yield). Mp: 103−105 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (dd, J = 1.2, 8.25 Hz, 2 H), 7.31−7.34 (m, 2 H), 7.13−7.26 (m, 5 H), 6.86−6.90 (m, 4 H), 6.60 (d, J = 8.5 Hz, 1 H), 6.38 (dd, J = 2.5, 8.5 Hz, 1 H), 6.23 (d, J = 2.5 Hz, 1 H). ^{13}C{^{1}H} (125 MHz, $CDCl_3$): δ 161.8, 149.0, 148.5, 146.7, 140.0, 138.6, 137.3, 129.6, 128.5, 128.4, 128.1, 127.9(2), 127.8(8), 125.9, 118.5, 118.2, 111.3, 110.2, 56.0, 55.6. IR (neat, cm^{-1}): 3056, 3002, 2935, 2902, 2833, 1588, 1513, 1486, 1441. Anal. Calcd for $C_{27}H_{23}N_2O_2Cl$: C, 73.21; H, 5.23. Found: C, 73.53; H, 5.12.

Procedure H: Fischer Cyclization of Diarylhydrazones 8 to *N*-Aryl Indoles 9. Diarylhydrazone **8** (1.0 equiv) and the ketone (1.5 equiv) were dissolved in EtOH (4.0 mL/mmol **8**), and concentrated HCl (1.0 mL/mmol **8**) was then added to the solution. The reaction mixture was heated to reflux (80 °C bath temperature) until the diarylhydrazone was consumed, as determined by TLC; reaction times ranged from 1.5 to 3 h. The reaction mixture was then cooled to room temperature, neutralized with a saturated $NaHCO_3$ solution, and extracted with Et_2O (3 × 10 mL). The Et_2O extracts were dried over anhydrous K_2CO_3, filtered, and concentrated in vacuo to afford the crude product. Purification by flash chromatography afforded the analytically pure *N*-arylindole.

3,5-Dimethyl-2-ethyl-*N*-(*p*-tolyl)indole 9a. Procedure H was used

to convert *N*,*N*-bis-(*p*-tolyl) benzophenone hydrazone **8a** (337 mg, 0.90 mmol, 1.0 equiv) and 3-pentanone (285 μL, 2.5 mmol, 3.0 equiv) to the title product. Purification by flash chromatography (2% EtOAc/hexanes) afforded analytically pure **9a** as a white solid (150 mg, 0.57 mmol, 63% yield). Mp: 49−50 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26−7.32 (m, 2 H), 7.17−7.20 (m, 3 H), 6.88−6.89 (m, 2 H), 2.64 (q, J = 7.5 Hz, 2 H), 2.45 (s, 3 H), 2.43 (s, 3 H), 2.29 (s, 3 H), 0.97 (t, J = 7.5 Hz, 3 H). ^{13}C{^{1}H} (75 MHz, $CDCl_3$): δ 139.1, 137.2, 135.9, 135.8, 129.8, 128.7, 128.4, 128.0, 122.4, 117.6, 109.5, 106.4, 21.5, 21.2, 18.0, 14.4 8.7. IR (neat, cm^{-1}): 3035, 2962, 2917, 2860, 1513, 1478, 1459. Anal. Calcd for $C_{19}H_{21}N$: C, 86.65; H, 8.04. Found: C, 86.89; H, 8.07.

(2-Methyl-5-methoxy-*N*-pyridylindol-3-yl)acetic Acid Ethyl Ester 9b. General procedure H was used to convert *N*-(3,4-dimethoxyphenyl)-*N*-(4-chlorophenyl) benzophenone hydrazone **8d** (273 mg, 0.72 mmol, 1.0 equiv) and levulinic acid (111 μL, 1.10 mmol, 1.5 equiv) to the title product. Purification by flash chromatography (50% EtOAc/hexanes) afforded analytically pure **9b** as a viscous pale yellow oil (159, 68% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.63−8.67 (m, 2H), 7.68 (ddd, J = 1.6, 2.5, 8.1 Hz, 1 H), 7.46 (ddd, J = 0.7, 4.8, 8.1 Hz, 1 H), 7.05 (d, J = 2.1 Hz, 1 H), 6.95 (dd, J = 0.5, 8.8 Hz, 1 H), 6.75 (dd, J = 2.4, 8.8 Hz, 1 H), 4.15 (q, J = 7.1 Hz, 2 H), 3.85 (s, 3 H), 3.71 (s, 2 H), 1.26 (t, J = 7.1 Hz, 3 H). ^{13}C{^{1}H} (75 MHz, $CDCl_3$): δ 171.5, 154.6, 148.9, 148.4, 135.0, 134.7, 134.6, 132.2, 128.5, 123.8, 111.4, 110.1, 106.3, 100.4, 60.7, 55.8, 30.8, 14.2, 11.2. IR (neat, cm^{-1}): 2981, 2935,1731, 1588, 1484, 1428. Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21. Found: C, 70.08; H, 6.51.

***N*-(3-Cyanophenyl)-2,3,5-trimethylindole 9c.** Procedure H was used to convert *N*-(*p*-tolyl)-*N*-(3-cyanophenyl) benzophenone hydrazone **8d** (314 mg. 0.81 mmol, 1.0 equiv) and 2-butanone (110 μL, 1.22 mmol, 1.5 equiv) to the title product. Purification by flash chromatography (2% EtOAc/hexanes) afforded analytically pure **9c** as a pale yellow oil (161 mg, 0.62 mmol, 76% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (dt, J = 1.5, 7.0 Hz, 1 H), 7.60−7.63 (m, 2 H), 7.56−7.58 (m, 1 H), 7.23−7.32 (m, 1 H), 6.95−6.97 (m, 2 H), 2.46 (s, 3 H), 2.27(5) (s, 3 H), 2.27 (s, 3 H). ^{13}C{^{1}H} (75 MHz): δ 139.4, 135.1, 132.1, 132.0, 130.9, 130.2, 130.3, 129.4, 129.2, 123.1, 118.0, 117.9, 113.5, 109.0, 108.8, 21.4, 11.1, 8.9. IR (neat, cm^{-1}): 3062, 2919, 2861, 2232, 1598, 1582, 1484, 1436. Anal. Calcd for $C_{18}H_{16}N_2$: C, 83.05; H, 6.19. Found: C, 82.98; H, 6.17.

***N*-(4-Chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydrocarbazole 9d.** Procedure H was used to convert *N*-(3,4-dimethoxyphenyl)-*N*-(4-chlorophenyl) benzophenone hydrazone **8d** (110 mg, 0.250 mmol, 1.0 equiv) and cyclohexanone (40 μL, 0.375 mmol, 1.5 equiv) to the title product. Purification by flash chromatography (10% EtOAc/hexanes) afforded analytically pure **9d** as a white solid (72 mg, 0.21 mmol, 86% yield). Mp: 112−115 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (d, J = 8.5 Hz, 2 H), 7.29 (d, J = 8.5 Hz, 2 H), 6.95 (s, 1 H), 6.72 (s, 1 H), 3.95 (s, 3 H), 3.82 (s, 3 H), 2.70−2.76 (m, 2 H), 2.51−2.57 (m, 2 H), 1.85−1.90 (m, 4 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 146.4, 144.9, 136.7, 133.9, 132.4, 130.4, 131.0, 129.5, 128.1, 120.4, 111.0, 100.0, 93.7, 56.4, 56.3, 23.4, 23.3, 23.2, 21.2. IR (neat, cm^{-1}): 2929, 2850, 2838, 1488, 1476, 1461. Anal. Calcd for $C_{20}H_{20}NO_2Cl$: C, 70.27; H, 5.90. Found: C, 70.39; H, 5.98.

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