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Synthesis of *o*-(Dimethylamino)aryl Ketones, Acridones, Acridinium Salts, and 1*H*-Indazoles by the Reaction of Hydrazones and Arynes

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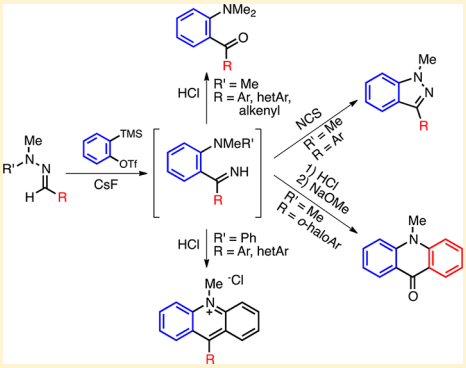
Supporting Information

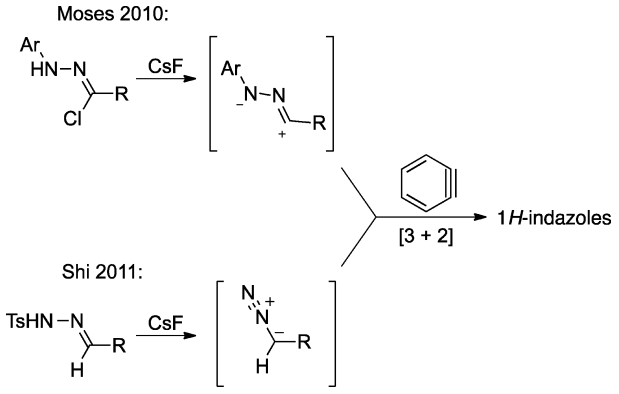
ABSTRACT: A novel, efficient route to biologically and pharmaceutically important *o*-(dimethylamino)aryl ketones, acridones, acridinium salts, and 1*H*-indazoles has been developed starting from readily available hydrazones of aldehydes and *o*-(trimethylsilyl)aryl triflates. The reaction proceeds through arynes under mild conditions, tolerates a wide range of functional groups, and provides the final products in good to excellent yields.



INTRODUCTION

A number of nitrogen-based nucleophiles have been shown to react with arynes: aryl and alkyl amines,[1,2] enamines,[3] sulfonamides,[1] amides,[4] enamides,[5] nitrogen-containing heterocycles,[6,7] and imines.[8] Two recent approaches to 1*H*-indazoles involve a [3 + 2] cycloaddition between arynes and 1,3-dipoles generated in situ from *N*-tosylhydrazones[9] and hydrazonoyl chlorides.[10] (Scheme 1).

Scheme 1. Known Couplings of Hydrazone-Derived Dipoles and Benzyne



While there has been considerable recent interest in aryne-based methodologies, no reaction of arynes and readily available 1,1-dialkylhydrazones had been reported until our communication in 2011.[11] In the present account, we wish to provide a more comprehensive report on the scope and limitations of the reaction of 1,1-dialkylhydrazones and arynes, which leads to various biologically and pharmaceutically important products.

RESULTS AND DISCUSSION

Ketimine Generation and Subsequent Transformations. In a preliminary study, it was observed that the reaction of the *N*,*N*-dimethylhydrazone derived from benzyl phenyl ketone and *o*-(trimethylsilyl)phenyl triflate[12] plus CsF at 65 °C in MeCN provided 2,3-diphenyl-2*H*-azirine in a 47% yield plus diphenylmethylamine, along with unreacted starting material. It appears that these products are formed by initial reaction of the hydrazone nitrogen with the very electrophilic aryne to generate a highly basic aryl anion, which deprotonates one of the methylene protons next to the hydrazone functionality (Scheme 2). An intramolecular S_N2 reaction follows, which leads to formation of the azirine and phenyldimethylamine, which is further converted into diphenylmethylamine by reaction with the benzyne. Although this route to an azirine is not described in the literature, better ways of synthesizing azirines have been previously reported.[13]

We felt that if the possibility for proton abstraction in the hydrazone substrate could be eliminated, attack of the aryl anion on the activated imine might afford a five-membered ring dinitrogen heterocycle. To our surprise, the reaction between benzaldehyde *N*,*N*-dimethylhydrazone (**1**) and the benzyne precursor **2** under reaction conditions identical to those used in the reaction of the ketone hydrazone did not yield the expected 1,2-dihydroindazole. Instead, the *o*-(dimethylamino)phenyl imine **3** was obtained in a 76% yield (Scheme 3).

Formation of the acyclic product **3** can be rationalized as follows (Scheme 3). After formation of the dinitrogen-containing five-membered ring heterocycle **1b**, a proton shift occurs from

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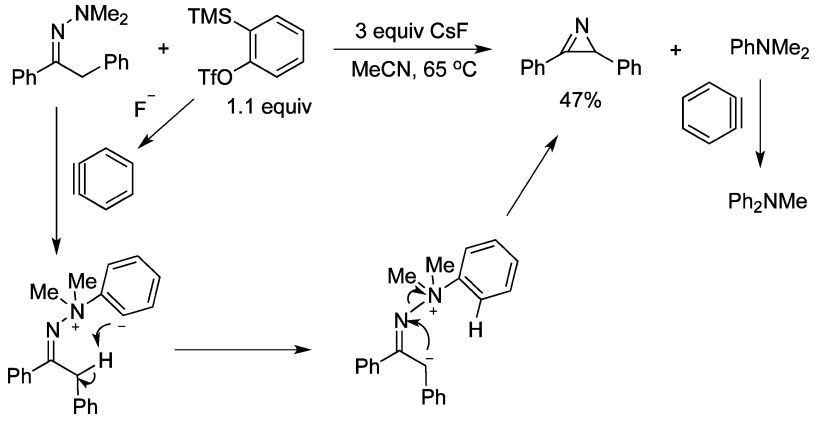
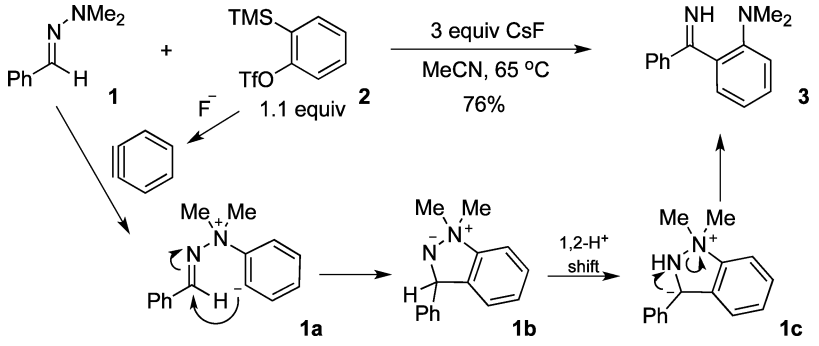
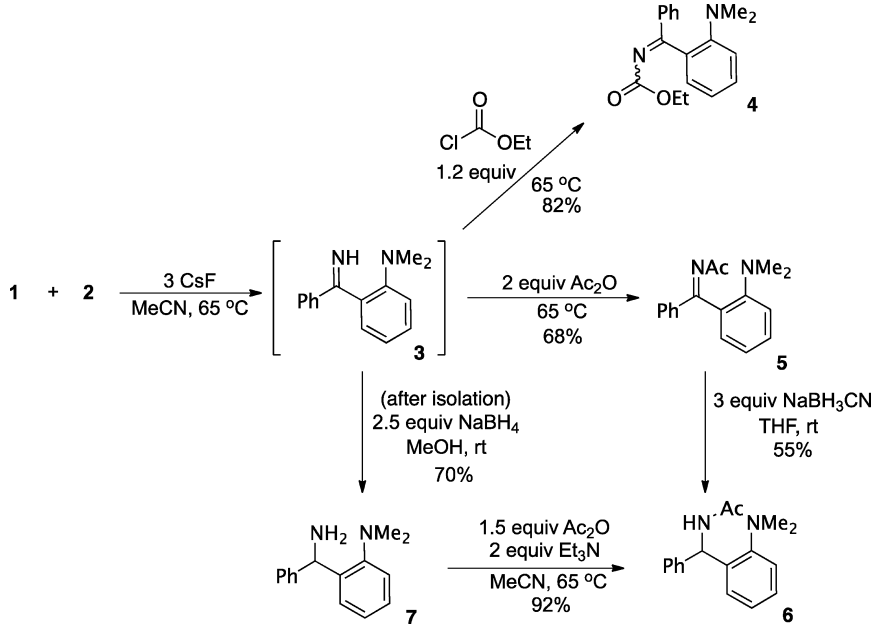
Scheme 2. Azirine Formation from a Ketone-Derived Hydrazone



Scheme 3. Imine Formation from an Aldehyde-Derived Hydrazone



Scheme 4. One-Pot Transformations of the Generated Imine 3



the benzylic position to the highly basic amide anion. The resulting dipole **1c** can undergo ring-opening to afford the final product **3**. It is possible that the proton shift from **1b** to **1c** occurs without any participation of the solvent, since the reaction also proceeds in less acidic THF,[14] although the yield of the final product drops to 43%.

The imine **3** can be acetylated without isolation by adding ethyl chloroformate to the reaction to yield the corresponding ethyl carbamate **4** in an 82% yield (Scheme 4). An analogous reaction of the imine **3** with Ac_2O provides the *N*-acetylimine derivative **5** in a 68% yield. Reduction of the latter with $NaBH_3CN$ in THF leads to formation of the reduced *N*-acetylamine **6** in a 55% yield. The same compound **6** can be obtained after $NaBH_4$ reduction of the imine **3** to the amine **7** (70%), followed by acetylation of the amino group with Ac_2O (92% yield).

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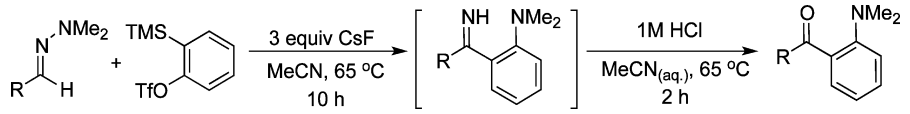
Table 1. Reaction of 1,1-Dimethylhydrazones with Arynes:[a] Substrate Scope



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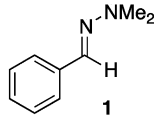
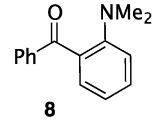
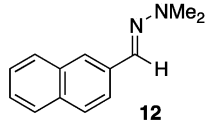
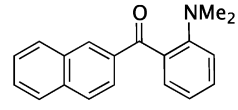
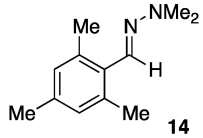
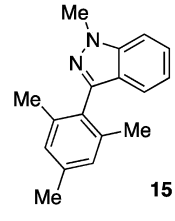
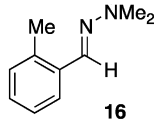
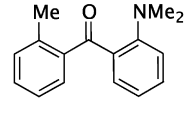
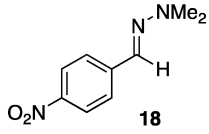
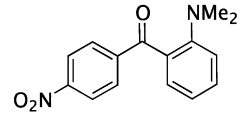
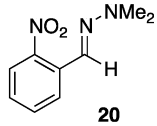
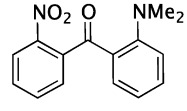
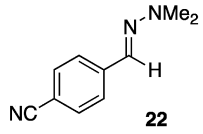
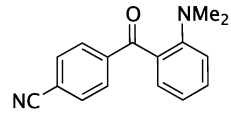
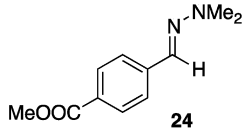
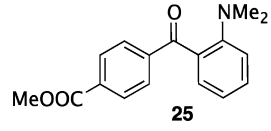
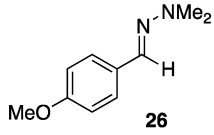
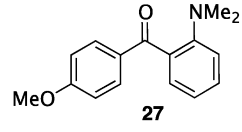
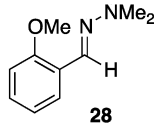
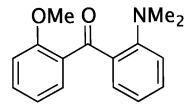
1	 **1**	 **8**	93
2	 **12**	 **13**	91
3	 **14**	 **15**	33
4	 **16**	 **17**	78
5	 **18**	 **19**	88
6	 **20**	 **21**	0[c]
7	 **22**	 **23**	92
8	 **24**	 **25**	94
9	 **26**	 **27**	91
10	 **28**	 **29**	74

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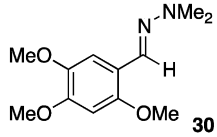
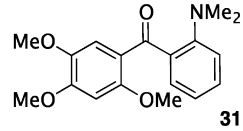
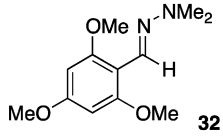
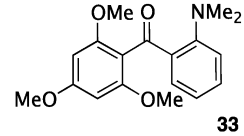
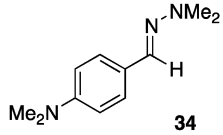
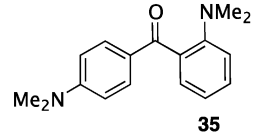
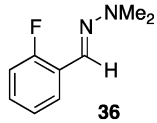
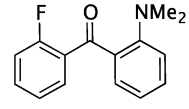
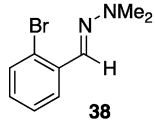
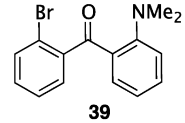
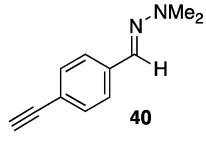
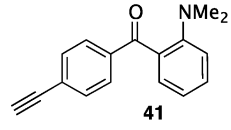
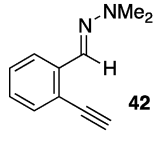
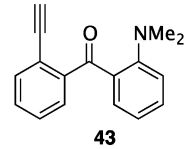
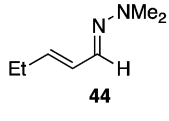
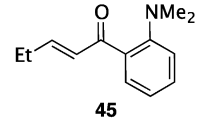
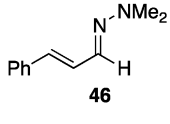
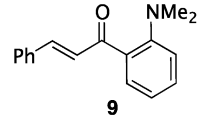
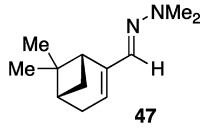
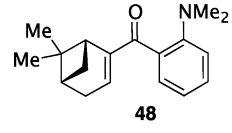
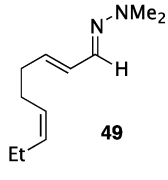
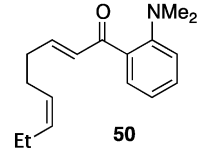
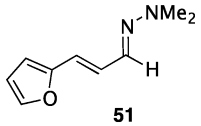
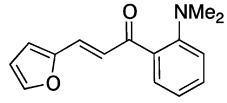
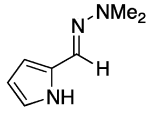
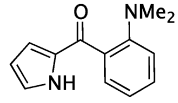
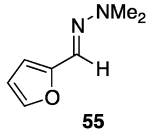
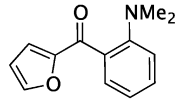
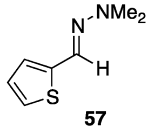
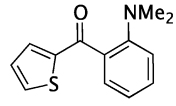
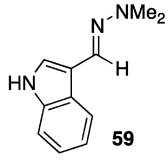
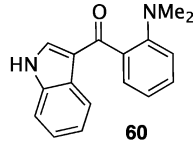
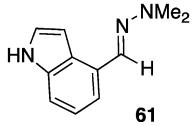
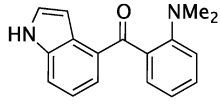
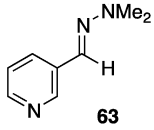
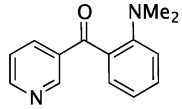
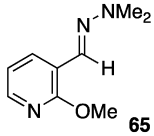
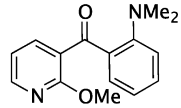
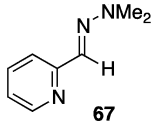
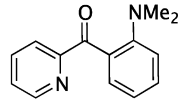
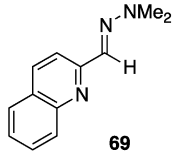
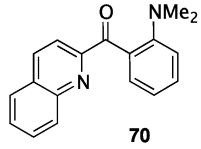
Table 1. continued

entry	starting hydrazone	product	yield[b] (%)
11	 **30**	 **31**	67
12	 **32**	 **33**	0[d]
13	 **34**	 **35**	45
14	 **36**	 **37**	61
15	 **38**	 **39**	85
16	 **40**	 **41**	100
17	 **42**	 **43**	0[c]
18	 **44**	 **45**	77
19	 **46**	 **9**	91
20	 **47**	 **48**	63
21	 **49**	 **50**	82

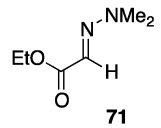
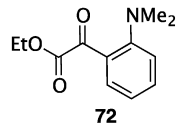
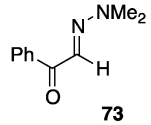
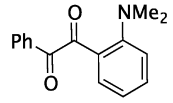
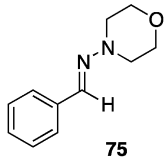
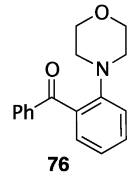
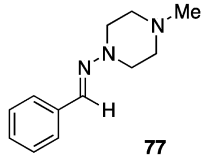
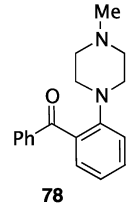
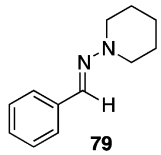
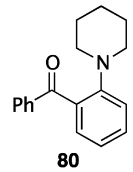
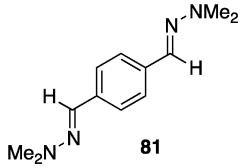
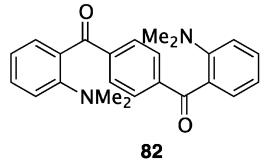
dx.doi.org/10.1021/jo302378w | J. Org. Chem. 2012, 77, 11232−11256

Table 1. continued

entry	starting hydrazone	product	yield[b] (%)
22	 **51**	 **52**	85
23	 **53**	 **54**	81
24	 **55**	 **56**	90
25	 **57**	 **58**	85
26	 **59**	 **60**	21
27	 **61**	 **62**	84
28	 **63**	 **64**	55
29	 **65**	 **66**	78
30	 **67**	 **68**	82
31	 **69**	 **70**	84

dx.doi.org/10.1021/jo302378w | J. Org. Chem. 2012, 77, 11232−11256

Table 1. continued

entry	starting hydrazone	product	yield[b] (%)
32	 **71**	 **72**	32
33	 **73**	 **74**	66
34	 **75**	 **76**	89
35	 **77**	 **78**	0[c]
36	 **79**	 **80**	85
37	 **81**	 **82**	84[e]

[a]Reaction conditions: 0.25 mmol of substrate, 1.1 equiv of 2-(trimethylsilyl)phenyl trifluoromethane-sulfonate and 3.0 equiv of CsF in 5 mL of MeCN were heated in a closed vial at 65 °C for 10 h. Then, 3 mL of 1 M HCl was added, and the mixture was heated at 65 °C for 2 h. [b]Isolated yield. [c]A mixture of unidentified products was produced. [d]One of the major products was very polar, presumably a cyclic intermediate analogous to intermediate **1b**. [e]2.2 equiv of benzyne precursor and 5.0 equiv of CsF were used.

Synthesis of Aminoaryl Ketones. As expected, the imine formed can also be easily hydrolyzed to the corresponding ketone under aqueous HCl conditions. Running the aryne coupling and hydrolysis reaction in the same vessel, *o*-(dimethylamino)phenyl ketone **8** was isolated in a 93% yield (Table 1, entry 1). Running the reaction at room temperature slightly lowers the yield from 93 to 84%. The high efficiency and mild reaction conditions for this overall transformation are of great importance, since *o*-(dimethylamino)aryl ketones are generally prepared through pathways involving harsh and regiorandom Friedel–Crafts reaction conditions[15] or nucleophilic aromatic substitutions of *o*-fluoroaryl ketones, which are not very readily available, by amino or proamino nucleophiles.[16,17]

o-(Dimethylamino)aryl ketones are quite important from a biological standpoint. Compound D-205 (**9**) has shown significant anti-inflammatory activity[15b] (Figure 1). The quinolinyl and isoquinolinyl ketones **10** and **11** have been found to be very efficient agonists of the cannabinoid CB2 receptor.[18] Some aminoaryl ketones are found in nature,[19] and some are employed as starting materials in the preparation of chiral 1,3-diamine-based reagents and ligands[16] and in recently reported ruthenium-catalyzed derivatization processes.[20]

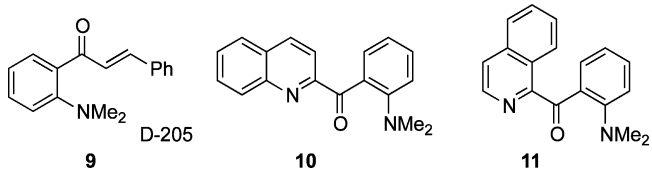


Figure 1. Pharmaceutically important *o*-(dimethylamino)aryl ketones.

The importance of *o*-(dimethylamino)aryl ketones encouraged us to evaluate the scope of this novel aryne coupling

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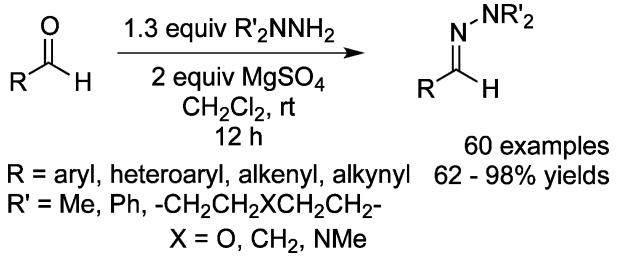
reaction. Various hydrazones have been prepared by reacting the corresponding aldehydes with 1,1-disubstituted hydrazines in CH_2Cl_2 in the presence of $MgSO_4$ (Scheme 5).[21] The yields of the hydrazones have ranged from 62 to 98%.

Scheme 5. Preparation of 1,1-Disubstituted Hydrazones



We first examined other 1,1-dimethylhydrazones. The 2-naphthyl-substituted substrate **12** provided the corresponding ketone **13** in a 91% yield (Table 1, entry 2). Surprisingly, the mesityl hydrazone **14** did not provide the expected product (entry 3). Presumably because of steric hindrance, the presumed cyclic intermediate did not undergo a proton shift but retained its cyclic structure. The oxidized and demethylated product **15** has been obtained in a 33% yield. In contrast, a less hindered hydrazone **16** with only one methyl group in the position *ortho* to the reacting functionality cleanly furnished the expected aminoaryl ketone **17** in a 78% yield (entry 4). The *p*-nitrobenzaldehyde hydrazone **18** provided the corresponding ketone **19** in an 88% yield (entry 5). In a similar manner, the *p*-methoxybenzaldehyde hydrazone **26** provided the product **27** in a 91% yield (entry 9). These results suggest that there is very little electronic effect of the substituents on the efficiency of this transformation. A messy mixture was observed when the *o*-nitrobenzaldehyde substrate **20** (entry 6) was employed, presumably due to the instability of the anticipated cyclic intermediate analogous to intermediate **1b**. Other electron-withdrawing substituents, such as cyano and ester groups, resulted in clean formation of the corresponding aminoaryl ketones **23** and **25** in 92 and 94% yields, respectively (entries 7 and 8). An electron-donating methoxy group in the *ortho* position leads to aminoaryl ketone **29** in a 74% yield (entry 10, compare with the *o*-nitro-substituted substrate **20**). Interestingly, the 2,4,5-trimethoxy-substituted substrate **30** provides the corresponding product **31** in a 67% yield (entry 11), while the 2,4,6-trimethoxy-substituted substrate **32** (entry 12) results in formation of a very polar compound, presumably analogous to intermediate **1b**. All of our attempts to open the proposed cyclic structure or to dequaternarize the presumed ammonium fragment of the cyclic intermediate failed to provide any recognizable product. One should note a similarity between entries 3 and 12, where both starting materials have substituents at the 2 and 6 positions of the aromatic ring, which evidently causes some disruption in the corresponding rearrangement of **1b** to **1c**. The *p*-dimethylamino-substituted substrate **34** led to formation of the corresponding ketone **35** in a low 45% yield, likely due to a competing reaction of the nitrogen of the aniline moiety (entry 13). Halides in the *ortho* position of the aryl ring are well tolerated in this methodology, providing the corresponding fluoro- and bromo-containing aminoaryl ketones **37** and **39** in 61 and 85% yields, respectively (entries 14 and 15). Alkynyl functionality in the *para* position of the phenyl ring afforded the corresponding product **41** in a quantitative yield (entry 16). It is noteworthy that aminoaryl ketone **41** can potentially be quite useful for further elaboration via Sonogashira coupling reactions.[22] In contrast, alkynyl functionality in the *ortho* position is not tolerated in this transformation (entry 17, compare with the *o*-nitro substrate **20**), providing a mixture of mostly unidentified products.

Unfortunately, 2-alkynal hydrazones did not provide the desired aminoketones, but an inseparable mixture of mostly unidentified products.[23] However, alkenyl functionality is well tolerated in this transformation. Products **45** (entry 18) and **9** (entry 19) have been obtained in 77 and 91% yields, respectively, from such hydrazones. It is noteworthy that the aminoketone **9** has been previously reported to exhibit significant biological activity.[15b] The chiral (−)-myrtenal-derived hydrazone **47**, the remote alkene-containing hydrazone **49**, and the furan-containing alkenal hydrazone **51** all provided the expected aminoaryl ketones in good yields (63−85%, entries 20−22).

To our delight, despite benzyne's dienophilic nature,[24] electron-rich pyrrole-, furan-, and thiophene-containing hydrazones have undergone the transformation with good efficiency, providing the 2-pyrrolyl (entry 23), 2-furyl (entry 24), and 2-thienyl (entry 25) ketones **54**, **56**, and **58** in 81, 90, and 85% yields, respectively. Unfortunately, the indole-derived hydrazone **59** with the substitution at the C-3 position provided the desired aminoaryl ketone **60** in only a 21% yield (entry 26), along with a number of unidentified side products. However, the isomeric hydrazone **61** with the substitution at the C-4 position of the indole system efficiently provided the corresponding product **62** in an 84% yield (entry 27).

Despite the well-documented reactivity of pyridines with arynes,[7,25] a number of substituted pyridines provided the expected aminoaryl ketones in high yields. Thus, hydrazones derived from nicotinaldehyde (**63**), 2-methoxynicotinaldehyde (**65**), and picolinaldehyde (**67**) provided the corresponding products in 55, 78, and 82% yields, respectively (entries 28−30). The high efficiency of the transformations for the pyridine-derived hydrazones suggests a significant difference in the nucleophilicities of the NMe_2 groups in the hydrazones and the nitrogen atoms in the pyridine rings toward the benzyne. The 2-quinolinyl-derived hydrazone **69** provided the expected product **70** in an 84% yield (entry 31). It is noteworthy that the aminoketone **70** has been previously reported to exhibit significant biological activity.[18]

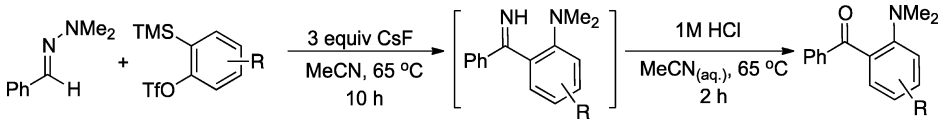
Ester- and ketone-containing hydrazones **71** and **73** provided the corresponding aminoaryl 1,2-dicarbonyl compounds in 32 and 66% yields, respectively (entries 32 and 33). Unfortunately, our attempts to cyclize the compound **72** into an isatin heterocycle were not successful.

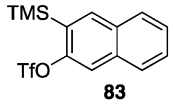
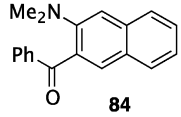
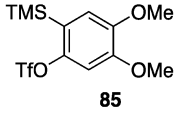
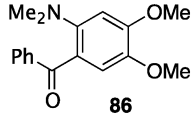
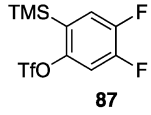
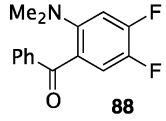
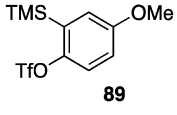
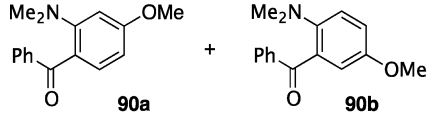
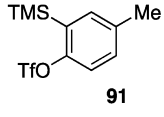
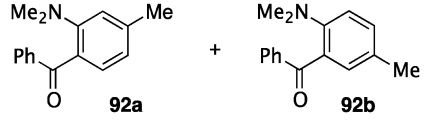
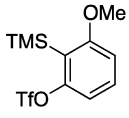
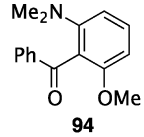
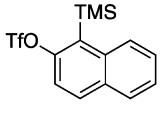
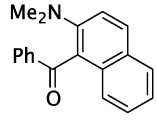
The nature of the hydrazone moiety can be modified as well. The 1-aminomorpholine-derived substrate **75** afforded the corresponding ketone **76** in an 89% yield (entry 34). The apparent high reactivity of the remote NMe unit in the piperazine-derived hydrazone **77** resulted in the formation of unidentified products with none of the expected aminoaryl ketone isolated. However, the piperidine-derived hydrazone **79** cleanly furnished the desired product **80** in an 85% yield (entry 36).

As an interesting application of our method, we were able to obtain a double aryne insertion product **82** from a substrate derived from terephthalaldehyde in an 84% yield (entry 37).

Next, we examined the reactivity of various aryne precursors toward our model substrate **1** (Table 2). The symmetrical naphthalyne precursor **83** afforded the corresponding aminoaryl ketone **84** in a 77% yield (entry 1). The electron-rich

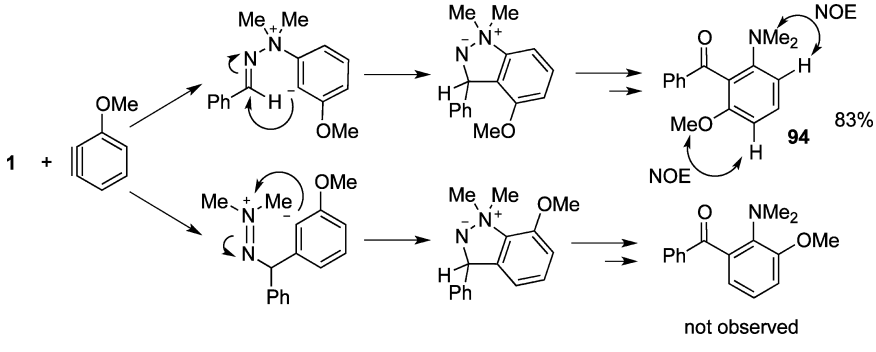
Table 2. Reaction of 1,1-Dimethylhydrazones with Arynes: Aryne Scope[a]



entry	aryne precursor	product	yield[b] (%)
1	 **83**	 **84**	77
2	 **85**	 **86**	83
3	 **87**	 **88**	62
4	 **89**	 **90a** **90b**	81[c]
5	 **91**	 **92a** **92b**	85[d]
6	 **93**	 **94**	83[e]
7	 **95**	 **96**	82[e]

[a]Reaction conditions: 0.25 mmol of benzaldehyde dimethylhydrazone, 1.1 equiv of aryne precursor and 3.0 equiv of CsF in 5 mL of MeCN were heated in a closed vial at 65 °C for 10 h. Then, 3 mL of 1 M HCl was added, and the mixture was heated at 65 °C for 2 h. [b]Isolated yield. [c]A separable ~1/1 mixture of regioisomers was produced. [d]An inseparable ~1/1 mixture of regioisomers was produced. [e]See the Experimental Section for the structure determination of this product.

Scheme 6. Reaction with Unsymmetrical 3-Methoxybenzyne



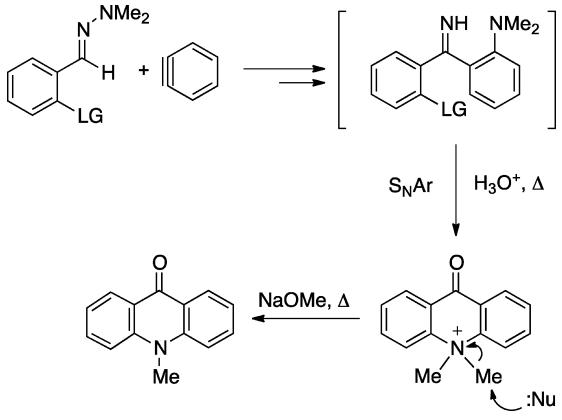
dx.doi.org/10.1021/jo302378w | J. Org. Chem. 2012, 77, 11232–11256

symmetrical dimethoxybenzyne afforded the expected product in a 83% yield (entry 2), while the electron-deficient 4,5-difluorobenzyne afforded the ketone **88** in a lower 62% yield, which is generally the case for this highly reactive difluorobenzyne.[26] The unsymmetrical 4-methoxy- and 4-methylsilylaryl triflates provided ~1/1 mixtures of regioisomers in 81 and 85% yields, respectively (entries 4 and 5). The lack of regiocontrol in these two reactions is good evidence that the transformation being studied indeed occurs via benzyne intermediates.

The reaction of the 1,1-dimethylhydrazone derived from benzaldehyde with the unsymmetrical aryne precursor 3-methoxy-2-(trimethylsilyl)phenyl triflate resulted in the formation of a single regioisomer **94** in an 83% yield (entry 6). The regiochemistry of the product affirms that it is the NMe_2 group that initially attacks the benzyne, not the nucleophilic carbon through the substrate's alternative resonance structure as is the case with enamines[3] (Scheme 6).[27] Similar regiocontrol is observed with the unsymmetrical naphthalyne precursor **95**. A single regioisomer **96**, resulting from attack of the dimethylamino group of the hydrazone at the more electrophilic C-2 position of the naphthalyne,[28] was produced in an 82% yield (entry 7).

Synthesis of *N*-Methylacridones. We envisioned that the NMe_2 group of the aminoketones generated by our process could further undergo an intramolecular S_NAr reaction if there was a favorably positioned leaving group *ortho* to the ketone. This would lead to the formation of a cationic *N*,*N*-dimethylacridinium salt, which should undergo in situ demethylation to the more stable *N*-methylacridone in the presence of the nucleophilic fluoride media or the addition of a base, such as NaOMe (Scheme 7).[29] This latter heterocycle is a prominent naturally occurring scaffold[30] with many of its members exhibiting a wide range of biological activities, including antitumor,[31] antimalarial,[32] and antiplasmodial[33] activities.

Scheme 7. Plausible Pathway of the Formation of *N*-Methylacridones



To our delight, a closer examination of the reaction of the *o*-bromobenzaldehyde hydrazone (Table 1, entry 15) indicated that along with the 85% yield of the aminoketone **39**, *N*-methylacridone was generated in a 7% yield. Upon heating the *o*-aminoketone **39** in MeCN at 100 °C, the ketone quantitatively cyclized to the desired acridone. After optimizing the reaction conditions, we found that *N*-methylacridone (**97**) could be obtained in one-pot in a 95% yield (Table 3, entry 1) by reacting the *o*-bromobenzaldehyde hydrazone **38** with the benzyne precursor **2** in the presence of CsF and subsequently hydrolyzing the imine and at the same time inducing the cyclization in the presence of aqueous HCl at 100 °C. Further addition of a solution of NaOMe and heating the mixture at 100 °C presumably assists in dequaternarizing the initially formed *N*,*N*-dimethylacridinium salt.

Excellent yields (91 and 94%) have also been observed using the corresponding *o*-chloro- and *o*-fluorobenzaldehyde hydrazones **98** (entry 2) and **36** (entry 3). The 1-bromo-2-naphthaldehyde-derived hydrazone provided the polycyclic acridone **100** in a 45% yield (entry 4). Unfortunately, the reaction of 2-fluoro-6-iodobenzaldehyde dimethylhydrazone with benzyne resulted in the formation of a mixture of unidentified products, likely due to a competitive S_NAr reaction with the iodo- and fluoro-substituents (entry 5). The dihalogenated substrates **103** and **105** provided the corresponding acridones **104** and **106** in 84 and 79% yields, respectively (entries 6 and 7). It is noteworthy that the presence of the halide moiety at the C-2 position of the acridone **106** allows further elaboration of this heterocyclic structure by various, well-known Pd-catalyzed processes. As a representative example of such methodologies, we have successfully obtained the Suzuki–Miyaura coupling product **119** in a 75% yield (Scheme 8).[34]

The nitro-substituted acridone **108** was obtained using our aryne methodology, but the limited solubility of the product produced only a modest 59% yield of this acridone (entry 8). The mono- and dimethoxy-substituted *o*-halobenzaldehyde hydrazones **109** and **111** successfully provided the corresponding *N*-methylacridones in 87 and 77% yields, respectively (entries 9 and 10). Despite similarities between the oxygenated substrates **111** and **113**, the final S_NAr step in the latter case was rather sluggish, and the desired product **114** was obtained in only a 38% yield (entry 11).

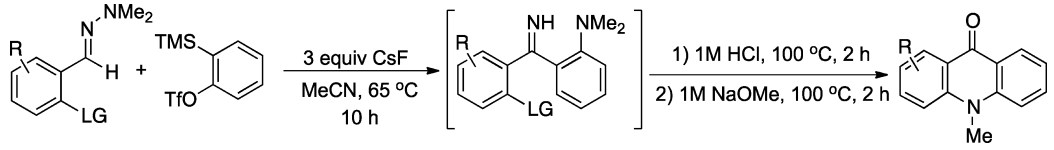
Unfortunately, applying our methodology to an indole system was not successful; none of the desired product was formed under our optimized conditions when hydrazone **115** was employed (entry 12). However, the pyridine-derived hydrazone **117** led to formation of the desired aza-acridone derivative **118** in a 48% yield (entry 13). The latter compound is a type of benzonaphthyridinone, some of which have shown antimicrobial,[35] trypanocidal,[36] and anticancer[37] activities. They have also been shown to reverse the multidrug resistance of tumor cells.[38]

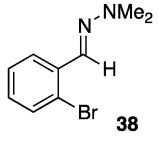
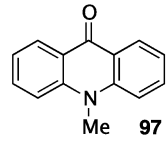
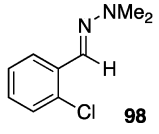
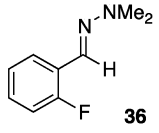
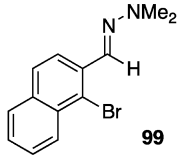
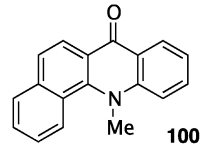
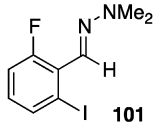
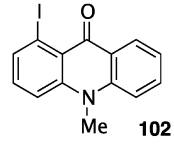
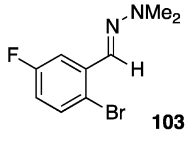
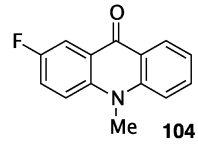
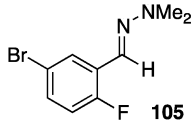
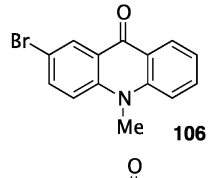
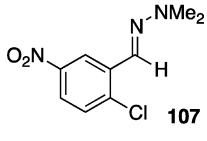
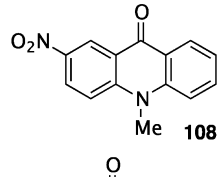
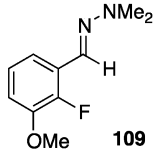
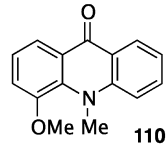
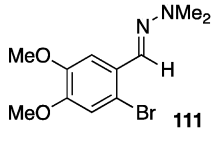
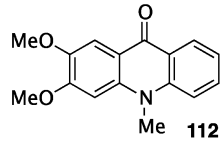
A number of naturally occurring acridones have been synthesized utilizing our methodology. The use of the unsymmetrical 3-methoxy-2-(trimethylsilyl)phenyl triflate **93** in the above transformation resulted in the formation of a single regioisomer **120** in an 87% yield with regioselectivity analogous to that described above (Table 2, entry 6). It is noteworthy that compound **120** is a naturally occurring acridone,[39] and its demethylated derivative **121** has been shown to exhibit anti-HIV activity.[40] We obtained the latter pharmaceutically important product in a 94% yield after HI-induced demethylation of the acridone **120** (i.e., in a 75% overall yield via 3 steps starting from *o*-fluorobenzaldehyde) (Scheme 9).

The use of the unsymmetrical 3,5-dimethoxy-2-(trimethylsilyl)-phenyl triflate **122**[41] in a reaction with *o*-fluorobenzaldehyde dimethylhydrazone resulted in the formation of compound **123** in a 78% yield as a single regioisomer (Scheme 10). Compound **123** is found in nature,[42] as well as its 1-demethylated[33] and 1,3-bisdemethylated[43] derivatives. The latter has also been shown to have significant antipsoriatic activity[44] and has been previously made from compound **123** using an HBr-mediated ether cleavage.[45] It is also noteworthy that the compound **123** has

dx.doi.org/10.1021/jo302378w | J. Org. Chem. 2012, 77, 11232–11256

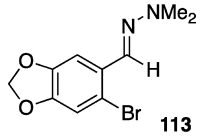
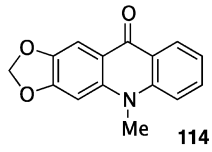
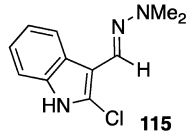
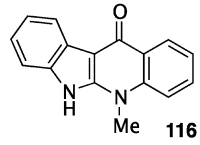
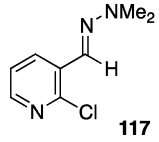
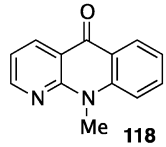
Table 3. Synthesis of *N*-Methylacridones[a]



entry	starting hydrazone	product	yield[b] (%)
1	 **38**	 **97**	95
2	 **98**	**97**	91
3	 **36**	**97**	94
4	 **99**	 **100**	45
5	 **101**	 **102**	0
6	 **103**	 **104**	84
7	 **105**	 **106**	79
8	 **107**	 **108**	59
9	 **109**	 **110**	87
10	 **111**	 **112**	77

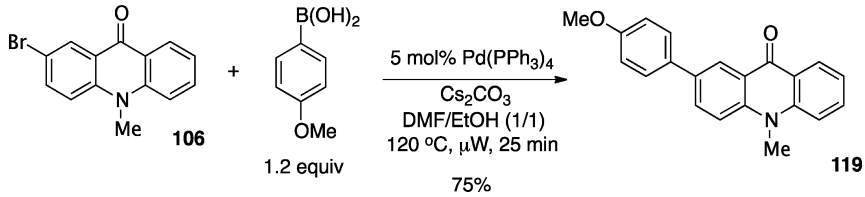
dx.doi.org/10.1021/jo302378w | *J. Org. Chem.* 2012, 77, 11232−11256

Table 3. continued

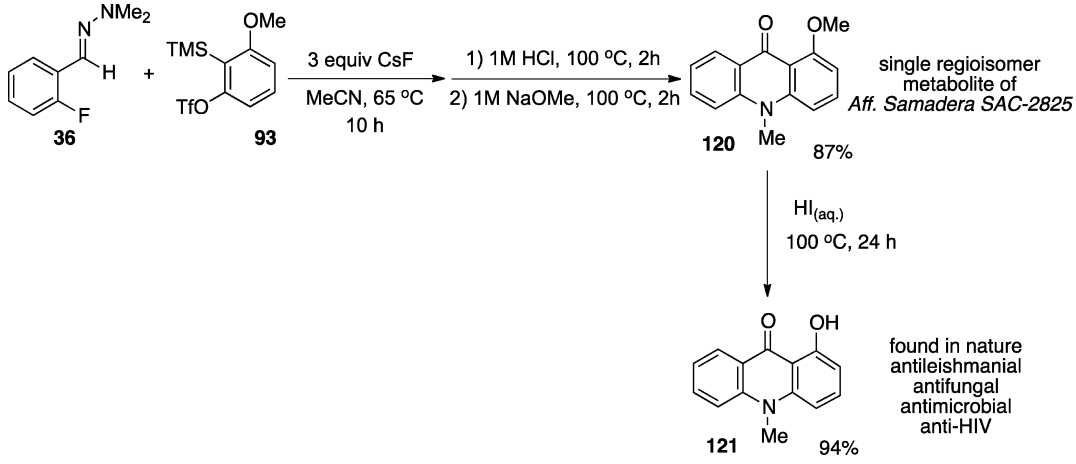
entry	starting hydrazone	product	yield[b] (%)
11	 **113**	 **114**	38
12	 **115**	 **116**	0
13	 **117**	 **118**	48

[a]Reaction conditions: 0.25 mmol of substrate, 1.1 equiv of benzyne precursor and 3.0 equiv of CsF in 5 mL of MeCN were heated in a closed vial at 65 °C for 10 h. Then, 3 mL of 1 M HCl was added, and the mixture was heated at 100 °C for 2 h. Then, 5 mL of 1 M NaOMe was added, and the mixture was heated at 100 °C for 2 h. [b]Isolated yield.

Scheme 8. Suzuki–Miyaura Coupling of an Acridone



Scheme 9. Synthesis of a Naturally Occurring Acridone



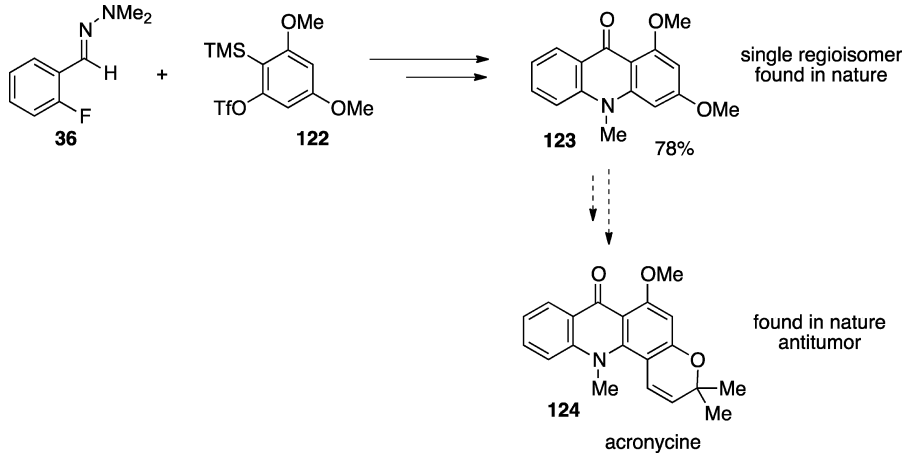
been previously used as a precursor to acronycine (**124**),[46] an alkaloid long known for its antitumor properties.[47]

The analogous reaction of the unsymmetrical 3,5-dimethoxy-2-(trimethylsilyl)phenyl triflate with the methoxy-analogue of **36** resulted in the formation of acridone **125** after additional exposure of the unreacted, uncyclized aminoaryl ketone to elevated temperatures because of incomplete cyclization under our standard S_NAr reaction conditions. The acridone **125** was isolated in a 60% yield as a single isomer from the aminobenzophenone. The compound **125** is found in nature (Scheme 11).[48] Synthesis of its 1,3,6-trisdemethylated derivative by HBr-mediated demethylation is described in the literature.[49] The latter is an immediate precursor to the natural product acrimarine-G.[49,50]

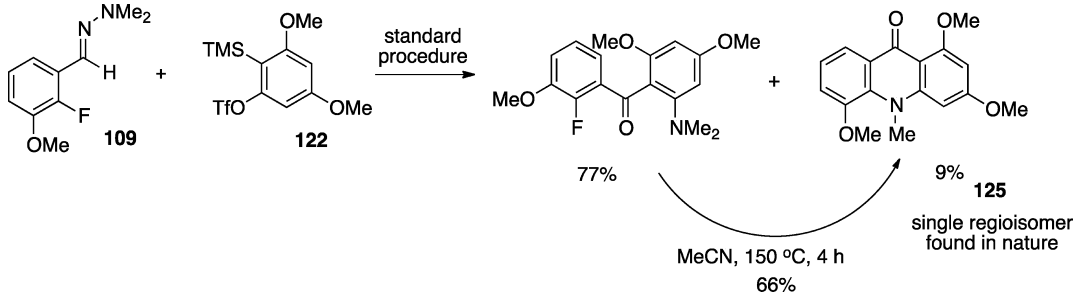
Synthesis of Acridinium Salts. To further extend the scope of our methodology, we reacted the *N*-methyl-*N*-phenyl hydrazone of benzaldehyde (**126**) with benzyne under our optimized reaction conditions for the synthesis of aminoaryl ketones (Scheme 12). To our surprise, instead of the expected ketone, a very polar compound **127** was obtained with its spectrum identical to that reported in the literature.[51] The

dx.doi.org/10.1021/jo302378w | J. Org. Chem. 2012, 77, 11232–11256

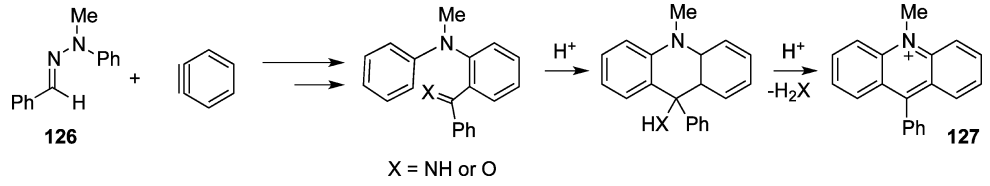
Scheme 10. Synthesis of a Naturally Occurring Acridone



Scheme 11. Synthesis of a Naturally Occurring Acridone



Scheme 12. Plausible Pathway for Acridinium Salt Formation

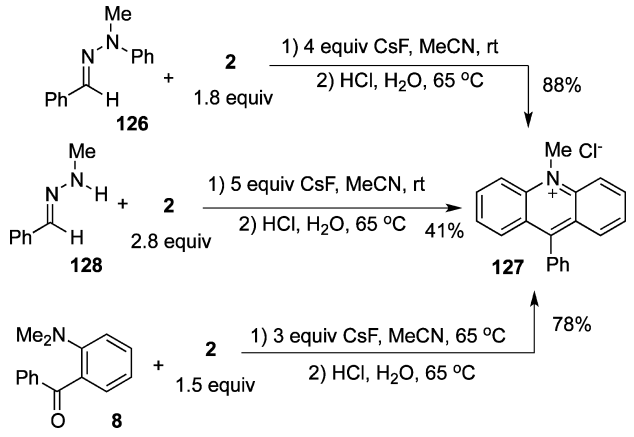


formation of the *N*-methylacridinium salt **127** can be rationalized in the following way (Scheme 12). After ketimine formation, the acid added to the reaction mixture apparently catalyzes an intramolecular Friedel–Crafts reaction of the imine (or of the previously hydrolyzed ketone) with the neighboring phenyl group leading to the formation of a 6-membered ring heterocycle.[52] Subsequent deamination (or dehydration) of the intermediate leads to formation of the acridinium salt **127**.

A related finding has been recently reported by Greaney's group, where the cyclization of a secondary amine derivative with simultaneous dehydration leads to formation of an acridine.[4] It has been found that reacting the hydrazone with 1.8 equiv of the aryne precursor in the presence of 4 equiv of CsF in acetonitrile at room temperature affords, after HCl-catalyzed cyclization and aromatization, the desired product **127** in an 88% yield (Scheme 13).

The same product **127** can be formed in a 41% yield starting from the *N*-methyl hydrazone **128**. Presumably, the first equivalent of benzyne arylates the hydrazone nitrogen,[53] essentially forming the starting substrate for the subsequent benzyne insertion/Friedel–Crafts cyclization/aromatization sequence. Also, it has been found that the reaction of (dimethylamino)aryl ketone **8** (obtained from benzaldehyde dimethylhydrazone and

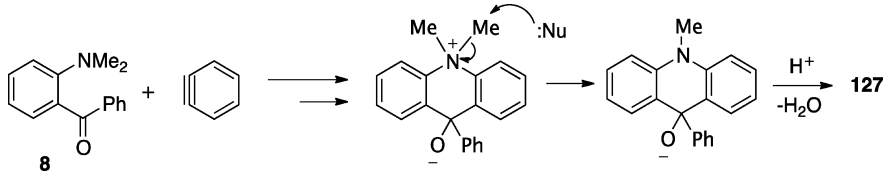
Scheme 13. Various Routes to Acridinium Salt Formation



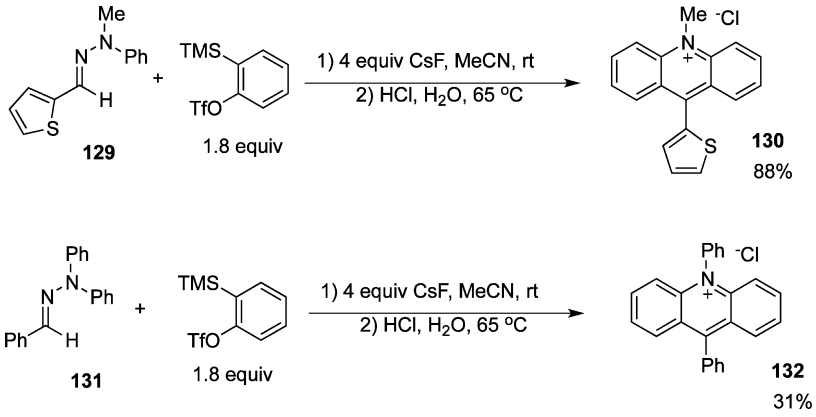
benzyne as reported in Table 1, entry 1) with benzyne leads to formation of the same acridinium salt **127**. This result can be rationalized in the following way (Scheme 14). After nucleophilic attack of the dimethylamino group onto the benzyne, the expected annulation reaction occurs,[54] and dequaternarization of the diaryldimethylammonium fragment follows (presumably assisted

dx.doi.org/10.1021/jo302378w | J. Org. Chem. 2012, 77, 11232–11256

Scheme 14. Plausible Pathway for Acridinium Salt Formation



Scheme 15. Synthesis of Substituted Acridinium Salts

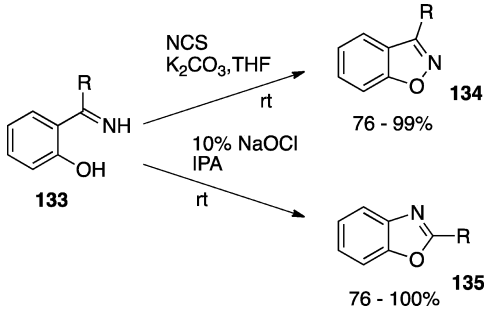


by the fluoride). Following the addition of hydrochloric acid to the reaction mixture, loss of the hydroxyl group (as water) from the molecule results in formation of the stable aromatic acridinium salt **127**, which was formed in a 78% yield using this approach.

Acridinium salts are an intriguing class of compounds used for DNA intercalation studies[51] and as NAD^+ analogues.[55] Recently, their analogues, quinolinium salts, have been shown to be effective photocatalysts for the direct oxygenation of benzene to phenol.[56] Our methodology provides a convenient approach to the synthesis of derivatized acridinium salts. Using the 2-thienaldehyde-derived substrate **129** in place of the model hydrazone **126** in our chemistry afforded the thiophene-containing acridinium chloride **130** in an 88% yield (Scheme 15). The *N,N*-diphenylhydrazone **131** afforded the *N*-phenyl acridinium salt **132** in a 31% yield. The lower yield is presumably due to difficulties in removing the phenyl group during the dequaternization step.

Synthesis of 1*H*-Indazoles by the Chlorination and Subsequent Cyclization of *ortho*-Aminoaryl Ketimines. Recently, a convenient method for the preparation of isomeric benzoxazoles was described by Chen and co-workers (Scheme 16).[57] In that process, *o*-hydroxyaryl ketimines **133** are intramolecularly cyclized to benzisoxazoles **134** or benzoxazoles **135** upon exposure to chlorinating conditions involving respectively (a) NCS in the presence of K_2CO_3 or (b) 10% NaOCl.

Scheme 16. Synthesis of Isomeric Benzoxazoles by the Chen Group



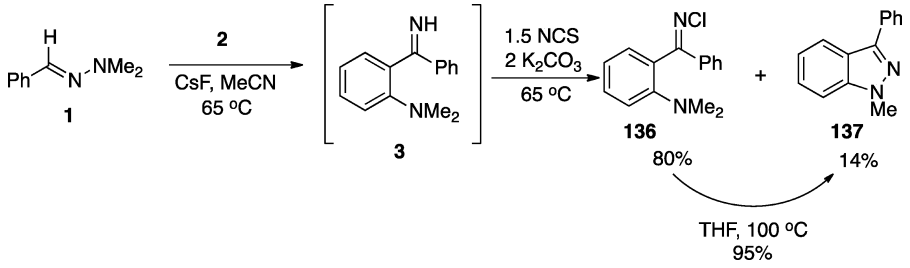
Because of the similar nature of *o*-hydroxyaryl ketimines and our *o*-aminoaryl ketimines **3**, we attempted to induce a similar cyclization to 1*H*-indazoles through a one-pot synthesis of aminoaryl ketimines by the reaction of hydrazones with arynes, followed by chlorination with NCS (Scheme 17).[58] When the reaction mixture containing ketimine **3** was subjected to NCS/K_2CO_3 at 65 °C, only 14% of the desired indazole was isolated. The major product of the reaction, *N*-chloroketimine **136**, was isolated in an 80% yield. The latter cyclized to the desired indazole **137** in a 90% yield upon exposure to elevated temperatures (100 °C) in THF. We noticed that the key cyclization is more facile in THF (as compared to MeCN). However, running the first step (the reaction with the benzyne) in acetonitrile, followed by evaporation and immediate addition of THF, unavoidably causes some hydrolysis of the labile ketimine **3** to the corresponding ketone. We could obtain the indazole **137** in only a 50% yield using the procedure with the two different solvents.

Subjecting the original reaction mixture of the ketimine **3** to the NCS-chlorinating conditions and, after a complete imine-to-chloroimine conversion (as detected by TLC), heating at 130 °C resulted in only a 34% isolated yield of the desired product **137**. This result suggests interference of the constituents of the reaction mixture with the intramolecular cyclization step. If one extracts the reaction mixture after the NCS-chlorination step (performed at 65 °C with no K_2CO_3) from water (thus, separating the desired products from all possible water-soluble constituents) and subsequently exposes the reaction mixture to 130 °C in acetonitrile, the desired indazole **137** is formed in a 66% yield in a pseudo-one-pot fashion (Scheme 18).

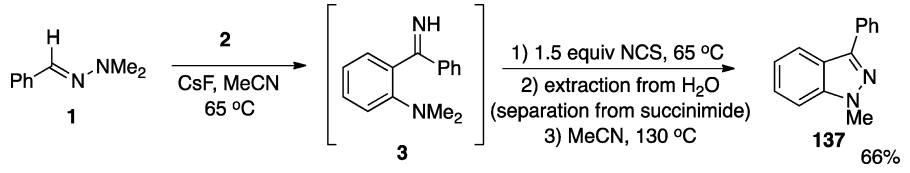
An alternative route to indazoles from *o*-aminoaryl aldehydes **138** has been recently described by Rebek Jr. (Scheme 19).[59] When reacting the latter compounds with hydroxylamine hydrochloride at elevated temperatures, the hydroxyl group of the *o*-aminoaryl aldoximes **139** formed in situ is intramolecularly replaced by the neighboring amino group (after activation by

dx.doi.org/10.1021/jo302378w | J. Org. Chem. 2012, 77, 11232−11256

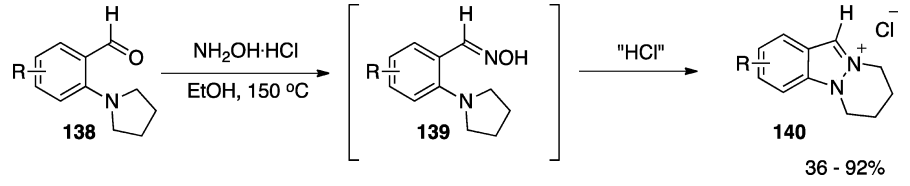
Scheme 17. Attempts to Develop a One-Pot Synthesis of 1*H*-Indazoles



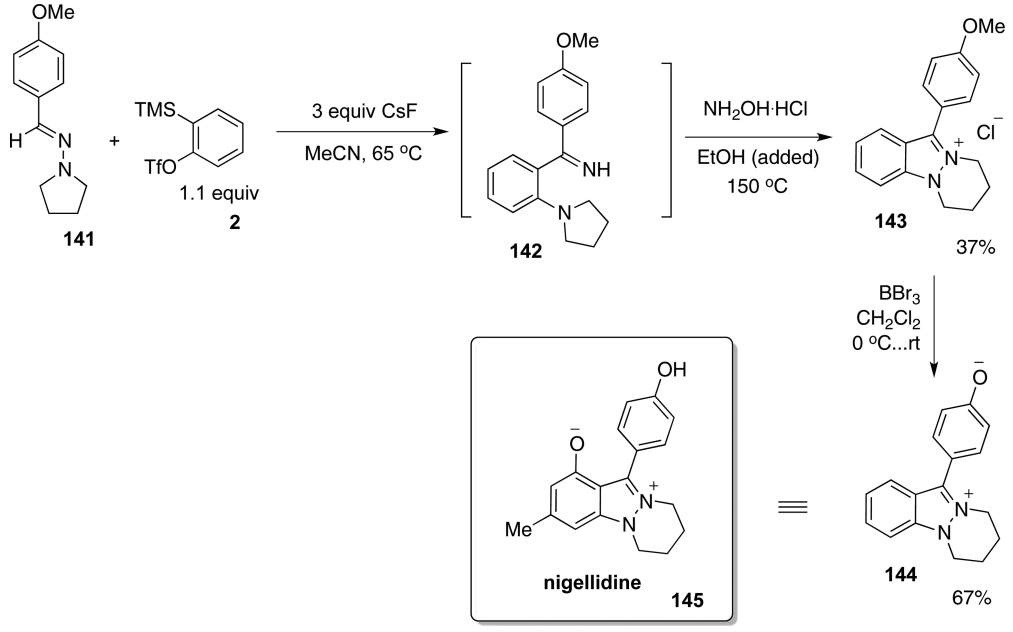
Scheme 18. Optimization of the Synthesis of Indazoles from Ketimines



Scheme 19. Synthesis of Indazoles by Rebek



Scheme 20. Synthesis of a Nigellidine Analogue



the HCl present in the reaction media), thus leading to the desired indazole moiety **140**.

Although no attempts to run this transformation on analogous ketones have been reported, we decided to use this approach for the synthesis of an analogue of the natural alkaloid nigellidine (**145**). Nigellidine and its sulfated analogue have been isolated[60] from the seeds of the common spice *Nigella sativa*. After the reaction of the pyrrolidine-derived hydrazone **141** with the silylaryl triflate **2** in the presence of CsF in MeCN at 65 °C, hydroxylamine hydrochloride was added to the imine formed in situ, and the reaction was kept at 150 °C for an additional 24 h. As a result, we could successfully isolate the tricyclic compound **143**, albeit in a low 37% yield (Scheme 20). Subsequent BBr_3-mediated demethylation[61] furnished the desired nigellidine analogue **144** in a 67% yield.

■ CONCLUSIONS

In summary, we have developed a novel, efficient route to *o*-(dimethylamino)aryl ketones, acridones, acridinium salts, and 1*H*-indazoles starting from readily available aldehydes,

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1,1-dimethylhydrazine and *o*-(trimethylsilyl)aryl triflates. In the formation of *o*-(dimethylamino)aryl ketones, the reaction proceeds through a cyclization−ring-opening pathway with intermediate formation of a dihydroindazole. In the case of acridones, the initial transformation is followed by an additional intramolecular S_NAr reaction and demethylation. In the case of acridinium salts, the initial transformation is followed by an intramolecular acid-catalyzed Friedel−Crafts cyclization. In the case of indazoles, after the benzyne-induced cyclization and subsequent ring-opening, the resulting *o*-aminoaryl ketimine can be cyclized to a 1*H*-indazole by chlorination of the imine by NCS, followed by intramolecular displacement of the chloride. Additionally, an analogue of nigellidine **144** has been synthesized in only two steps from the starting hydrazone **141** and the commercially available benzyne precursor **2**. This array of methods should prove useful for the preparation of a variety of biologically and pharmaceutically important structures. A representative number of naturally occurring and medicinally relevant compounds have been obtained using our methodology. A variety of functional groups are compatible with the reaction conditions.

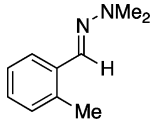
EXPERIMENTAL SECTION

General Information. The ^1H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz, respectively. Chemical shifts are reported in δ units (ppm) by assigning the TMS resonance in the ^1H NMR spectrum as 0.00 ppm and the $CDCl_3$ resonance in the ^{13}C NMR spectrum as 77.23 ppm. All coupling constants (J) are reported in Hertz (Hz). All commercial reagents were used directly as obtained. Thin layer chromatography was performed using commercially prepared 60-mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm). All melting points were obtained using an automated melting point apparatus and are uncorrected. High resolution mass spectra (HRMS) were obtained using a Q-TOF mass spectrometer (APCI at a voltage of 70 eV).

The characterization of compounds **1**, **8**, **9**, **12**−**14**, **18**−**20**, **22**, **24**, **26**, **27**, **32**, **36**, **38**−**40**, **44**−**46**, **55**−**57**, **63**, **64**, **71**, **75**, **76**, **79**, **94**, **97**, **98**, **120**, **121**, **153**, and **163** can be found in our earlier reports.[11]

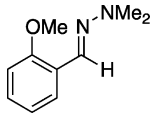
Synthesis of the Hydrazones. The starting hydrazones were prepared according to the procedure described in our recent communication.[11a]

*o-Tolylaldehyde dimethylhydrazone (**16**).*



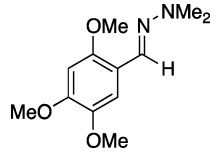
Yellow liquid: ^1H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 3.00 (s, 6H), 7.10−7.23 (m, 3H), 7.44 (s, 1H), 7.81 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 43.2, 125.2, 126.3, 127.4, 130.7, 131.5, 134.9; HRMS (APCI) calcd for $[M + H]^+$ $C_{10}H_{15}N_2$ 163.1230, found 163.1228.

*2-Methoxybenzaldehyde dimethylhydrazone (**28**).*



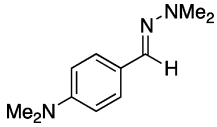
Light yellow liquid: ^1H NMR (400 MHz, $CDCl_3$) δ 2.97 (s, 6H), 3.85 (s, 3H), 6.86 (d, J = 8.2 Hz, 1H), 6.93 (t, J = 7.5 Hz, 1H), 7.20 (td, J = 8.3, 1.7 Hz, 1H), 7.61 (s, 1H), 7.85 (dd, J = 7.7, 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.3, 55.7, 111.0, 121.1, 125.2, 125.6, 128.5, 129.1, 156.7; HRMS (APCI) calcd for $[M + H]^+$ $C_{10}H_{15}N_2O$ 179.1179, found 179.1176.

*2,4,5-Trimethoxybenzaldehyde dimethylhydrazone (**30**).*



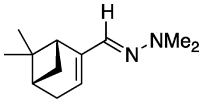
Pale brown solid: mp 60−63 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.87 (s, 6H), 3.76 (s, 3H), 3.82 (s, 3H), 3.83 (s, 3H), 6.42 (s, 1H), 7.36 (s, 1H), 7.53 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.4, 56.2, 56.4, 56.8, 97.6, 107.8, 117.6, 129.7, 143.8, 149.6, 151.5; HRMS (APCI) calcd for $[M + H]^+$ $C_{12}H_{19}N_2O_3$ 239.1390, found 239.1388.

*4-(N,N-Dimethylamino)benzaldehyde dimethylhydrazone (**34**).*



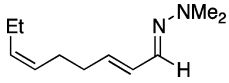
Red solid: mp 67−68 °C (lit.[62] mp 65−67 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 2.90 (s, 6H), 2.97 (s, 6H), 6.70 (d, J = 8.8 Hz, 2H), 7.32 (s, 1H), 7.48 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.8, 43.6, 112.6, 125.5, 127.2, 135.9, 150.5; HRMS (APCI) calcd for $[M + H]^+$ $C_{11}H_{18}N_3$ 192.1495, found 192.1493.

*(−)-Myrtenal dimethylhydrazone (**47**).*



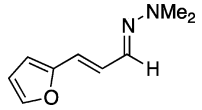
Pale yellow liquid: ^1H NMR (400 MHz, $CDCl_3$) δ 0.81 (s, 3H), 1.14 (d, J = 8.8 Hz, 1H), 1.32 (s, 3H), 2.07−2.16 (m, 1H), 2.34−2.47 (m, 3H), 2.81 (s, 6H), 2.97 (t, J = 5.4 Hz, 1H), 5.61 (s, 1H), 7.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 26.4, 31.6, 32.3, 37.9, 40.4, 41.3, 43.3, 124.6, 136.8, 146.8; HRMS (APCI) calcd for $[M + H]^+$ $C_{12}H_{21}N_2$ 193.1699, found 193.1698.

*(2E,6Z)-Nonadienal dimethylhydrazone (**49**).*



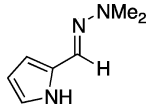
Red-brown liquid: ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, J = 7.5 Hz, 3H), 2.02 (quintet, J = 7.3, 2H), 2.13−2.19 (m, 4H), 2.81 (s, 6H), 5.27−5.42 (m, 2H), 5.77−5.84 (m, 1H), 6.17−6.23 (m, 1H), 6.99 (d, J = 8.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 20.8, 27.0, 33.0, 43.2, 128.3, 129.5, 132.5, 135.2, 137.0; HRMS (APCI) calcd for $[M + H]^+$ $C_{11}H_{21}N_2$ 181.1699, found 181.1697.

*(E)-3-(2-Furyl)-2-propenal dimethylhydrazone (**51**).*



Black solid: mp 37−39 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.90 (s, 6H), 6.26 (d, J = 3.3 Hz, 1H), 6.35−6.43 (m, 2H), 6.82 (dd, J = 15.8, 9.1 Hz, 1H), 7.04 (d, J = 9.2 Hz, 1H), 7.35 (d, J = 1.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.0, 108.0, 111.8, 119.3, 126.5, 134.7, 142.3, 153.6; HRMS (APCI) calcd for $[M + H]^+$ $C_9H_{13}N_2O$ 165.1022, found 165.1024.

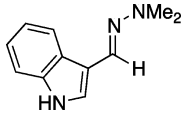
*2-Pyrrolecarbaldehyde dimethylhydrazone (**53**).*



Black solid: mp 43−46 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.86 (s, 6H), 6.22 (d, J = 12.5 Hz, 2H), 6.76 (s, 1H), 7.28 (s, 1H), 9.03 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.6, 109.1, 109.4, 119.1, 127.8, 130.3; HRMS (APCI) calcd for $[M + H]^+$ $C_7H_{12}N_3$ 138.1026, found 138.1026.

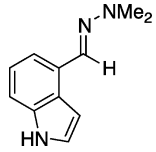
dx.doi.org/10.1021/jo302378w | J. Org. Chem. 2012, 77, 11232−11256

*Indole-3-carbaldehyde dimethylhydrazone (**59**).*



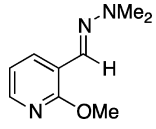
This compound was obtained as a brown solid using 2 mL of MeOH as a cosolvent: mp 90−93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.97 (s, 6H), 7.18 (d, J = 2.7 Hz, 1H), 7.23−7.29 (m, 3H), 7.74 (s, 1H), 8.35−8.40 (m, 1H), 8.57 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.9, 111.5, 114.6, 120.8, 122.1, 123.0, 125.0, 125.2, 133.1, 137.0; HRMS (APCI) calcd for $[M + H]^+$ $C_{11}H_{14}N_3$ 188.1182, found 188.1181.

*Indole-4-carbaldehyde dimethylhydrazone (**61**).*



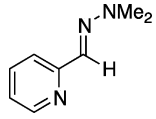
Black oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.02 (s, 6H), 7.09−7.30 (m, 5H), 7.62 (s, 1H), 8.31 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.0, 103.1, 110.5, 119.1, 121.8, 124.2, 124.5, 128.6, 134.6, 136.4; HRMS (APCI) calcd for $[M + H]^+$ $C_{11}H_{14}N_3$ 188.1182, found 188.1180.

*2-Methoxy-3-pyridinecarboxaldehyde dimethylhydrazone (**65**).*



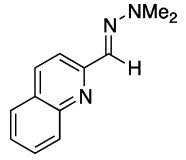
Colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.98 (s, 6H), 3.97 (s, 3H), 6.85 (dd, J = 7.4, 4.9 Hz, 1H), 7.38 (s, 1H), 7.98−8.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.1, 53.5, 117.4, 120.2, 126.6, 132.8, 145.3, 160.7; HRMS (APCI) calcd for $[M + H]^+$ $C_9H_{14}N_3O$ 180.1131, found 180.1130.

*2-Pyridinecarboxaldehyde dimethylhydrazone (**67**).*



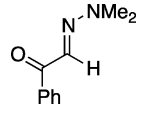
Pale brown liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.01 (s, 6H), 7.03 (ddd, J = 7.2, 4.8, 1.3 Hz, 1H), 7.24 (s, 1H), 7.56 (t, J = 7.7, 1H), 7.73 (d, J = 8.1 Hz, 1H), 8.45 (d, J = 4.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.8, 118.9, 121.6, 131.8, 136.3, 149.2, 156.1; HRMS (APCI) calcd for $[M + H]^+$ $C_8H_{12}N_3$ 150.1026, found 150.1027.

*2-Quinolinecarboxaldehyde dimethylhydrazone (**69**).*



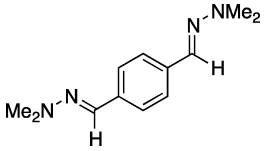
Brown-red semisolid: mp 67−68 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.92 (s, 6H), 7.26 (t, J = 7.5 Hz, 1H), 7.31 (s, 1H), 7.51 (ddd, J = 8.5, 7.0, 1.5 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.80−7.95 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.7, 117.6, 125.7, 127.5, 127.7, 128.7, 129.5, 131.3, 135.8, 148.1, 156.5; HRMS (APCI) calcd for $[M + H]^+$ $C_{12}H_{14}N_3$ 200.1182, found 200.1180.

*2-Oxo-2-phenylacetaldehyde dimethylhydrazone (**73**).*



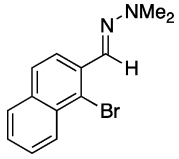
This compound was obtained as a pale yellow solid from phenylglyoxal monohydrate using 3 equiv (instead of 2) of $MgSO_4$: mp 41−42 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.19 (s, 6H), 7.05 (s, 1H), 7.40 (t, J = 7.4 Hz, 2H), 7.48 (t, J = 7.3 Hz, 1H), 7.96 (dd, J = 8.3, 1.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.8, 126.3, 128.1, 129.8, 131.7, 138.5, 189.7; HRMS (APCI) calcd for $[M + H]^+$ $C_{10}H_{13}N_2O$ 177.1022, found 177.1021.

*1,4-Benzenedicarboxaldehyde bis(dimethylhydrazone) (**81**).*



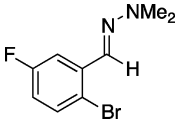
Pale yellow solid: mp 164−165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.96 (s, 12H), 7.22 (s, 2H), 7.53 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.1, 127.0, 133.0, 136.1; HRMS (APCI) calcd for $[M + H]^+$ $C_{12}H_{19}N_4$ 219.1604, found 219.1602.

*1-Bromo-2-naphthaldehyde dimethylhydrazone (**99**).*



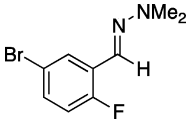
White solid: mp 80−82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.11 (s, 6H), 7.48 (t, J = 7.4 Hz, 1H), 7.58 (t, J = 7.6 Hz, 1H), 7.74 (d, J = 8.7 Hz, 1H), 7.78−7.80 (m, 2H), 8.13 (d, J = 8.6 Hz, 1H), 8.36 (d, J = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.1, 122.2, 124.2, 126.4, 127.3, 127.6, 127.7, 128.4, 131.6, 132.9, 133.9, 134.1; HRMS (APCI) calcd for $[M + H]^+$ $C_{13}H_{14}BrN_2$ 277.0335, found 277.0331.

*2-Bromo-5-fluorobenzaldehyde dimethylhydrazone (**103**).*



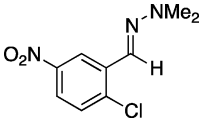
Colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.05 (s, 6H), 6.77 (ddd, J = 8.7, 7.7, 3.2 Hz, 1H), 7.33 (s, 1H), 7.43 (dd, J = 8.8, 5.3 Hz, 1H), 7.61 (dd, J = 10.3, 3.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.9, 112.5 ($^2J_{CF}$ = 24.4 Hz), 115.4 ($^2J_{CF}$ = 23.6 Hz), 116.3 ($^4J_{CF}$ = 2.9 Hz), 128.8 ($^4J_{CF}$ = 2.7 Hz), 134.1 ($^3J_{CF}$ = 8.2 Hz), 137.8 ($^3J_{CF}$ = 8.1 Hz), 162.3 ($^1J_{CF}$ = 244.9 Hz); HRMS (APCI) calcd for $[M + H]^+$ $C_9H_{11}BrFN_2$ 245.0084, found 245.0082.

*5-Bromo-2-fluorobenzaldehyde dimethylhydrazone (**105**).*



Colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.02 (s, 6H), 6.88 (dd, J = 10.3, 8.7 Hz, 1H), 7.19−7.25 (m, 2H), 7.98 (dd, J = 6.6, 2.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.9, 117.3 (J_{CF} = 3.0 Hz), 117.3 (J_{CF} = 22.9 Hz), 122.3, 127.0 (J_{CF} = 11.7 Hz), 128.0 (J_{CF} = 3.8 Hz), 130.6 (J_{CF} = 8.4 Hz), 159.1 ($^1J_{CF}$ = 247.8 Hz); HRMS (APCI) calcd for $[M + H]^+$ $C_9H_{11}BrFN_2$ 245.0084, found 245.0082.

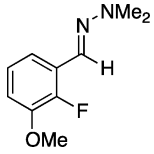
*2-Chloro-5-nitrobenzaldehyde dimethylhydrazone (**107**).*



Orange solid: mp 87−91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.09 (s, 6H), 7.25 (s, 1H), 7.39 (d, J = 8.8 Hz, 1H), 7.86 (dd, J = 8.8, 2.7 Hz, 1H), 8.69 (d, J = 2.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.8, 120.5, 121.2, 123.6, 130.6, 136.3, 137.2, 147.1; HRMS (APCI) calcd for $[M + H]^+$ $C_9H_{11}ClN_3O_2$ 228.0534, found 228.0532.

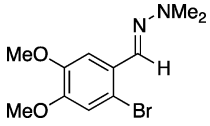
dx.doi.org/10.1021/jo302378w | J. Org. Chem. 2012, 77, 11232−11256

*2-Fluoro-3-methoxybenzaldehyde dimethylhydrazone (**109**).*



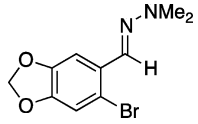
Colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.00 (s, 6H), 3.86 (s, 3H), 6.79 (td, J = 8.2, 1.6 Hz, 1H), 7.00 (td, J = 8.1, 1.5 Hz, 1H), 7.38 (s, 1H), 7.44 (ddd, J = 8.0, 6.3, 1.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.9, 56.4, 111.5, 116.9, 123.9 (J_{CF} = 4.7 Hz), 124.5 (J_{CF} = 6.4 Hz), 125.8 (J_{CF} = 7.6 Hz), 148.0 (J_{CF} = 10.6 Hz), 150.3 ($^1J_{CF}$ = 247.9 Hz) (extra signals due to C−F coupling); HRMS (APCI) calcd for $[M + H]^+$ $C_{10}H_{14}FN_2O$ 197.1085, found 197.1083.

*2-Bromo-4,5-dimethoxybenzaldehyde dimethylhydrazone (**111**).*



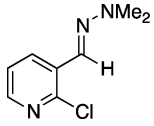
White solid: mp 90−91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.91 (s, 6H), 3.78 (s, 3H), 3.84 (s, 3H), 6.88 (s, 1H), 7.33 (s, 1H), 7.37 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.1, 56.1, 56.3, 108.1, 113.3, 115.1, 128.2, 131.6, 148.7, 149.2; HRMS (APCI) calcd for $[M + H]^+$ $C_{11}H_{16}BrN_2O_2$ 287.0390, found 287.0389.

*6-Bromopiperonal dimethylhydrazone (**113**).*



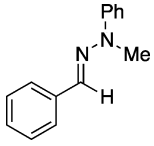
White solid: mp 55−57 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.97 (s, 6H), 5.92 (s, 2H), 6.93 (s, 1H), 7.38 (s, 1H), 7.39 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.1, 101.9, 105.7, 112.5, 113.7, 129.7, 131.4, 147.9; HRMS (APCI) calcd for $[M + H]^+$ $C_{10}H_{12}BrN_2O_2$ 271.0077, found 271.0077.

*2-Chloro-3-pyridinecarboxaldehyde dimethylhydrazone (**117**).*



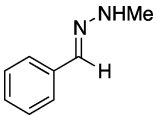
Pale yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.05 (s, 6H), 7.14−7.19 (m, 1H), 7.29 (s, 1H), 8.15−8.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.9, 122.9, 125.3, 131.5, 133.9, 147.4, 148.5; HRMS (APCI) calcd for $[M + H]^+$ $C_8H_{11}ClN_3$ 184.0636, found 184.0634.

*N-Methyl-N-phenylbenzaldehyde hydrazone (**126**).*



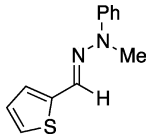
White solid: mp 105−106 °C (lit.[63] mp 107−109 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.44 (s, 3H), 6.95 (tt, J = 7.0, 1.3 Hz, 1H), 7.23−7.44 (m, 7H), 7.51 (s, 1H), 7.72 (d, J = 7.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.3, 115.5, 120.8, 126.3, 127.9, 128.8, 129.3, 132.1, 137.0, 148.1; HRMS (APCI) calcd for $[M + H]^+$ $C_{14}H_{15}N_2$ 211.1230, found 211.1228. The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.[64]

*Benzaldehyde methylhydrazone (**128**).*



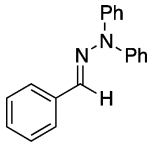
Colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.98 (s, 3H), 7.23−7.29 (m, 1H), 7.34 (t, J = 8.0 Hz, 2H), 7.53 (s, 1H), 7.56 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.7, 125.7, 127.8, 128.5, 135.4, 136.2; HRMS (APCI) calcd for $[M + H]^+$ $C_8H_{11}N_2$ 135.0917, found 135.0917.

*N-Methyl-N-phenyl-2-thienaldehyde hydrazone (**129**).*



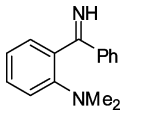
Pale yellow solid: mp 82−83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.40 (s, 3H), 6.94 (t, J = 6.3 Hz, 1H), 7.02 (t, J = 4.1 Hz, 1H), 7.11 (d, J = 3.5 Hz, 1H), 7.21 (d, J = 5.1 Hz, 1H), 7.31−7.36 (m, 4H), 7.68 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.5, 115.4, 120.9, 125.1, 125.6, 127.1, 127.4, 129.3, 142.9, 147.7; HRMS (APCI) calcd for $[M + H]^+$ $C_{12}H_{13}N_2S$ 217.0794, found 217.0790.

*Benzaldehyde diphenylhydrazone (**131**).*



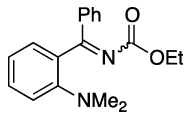
Colorless solid: mp 124−125 °C (lit.[65] mp 125−126 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18−7.33 (m, 8H), 7.38 (t, J = 7.4 Hz, 2H), 7.47 (d, J = 7.0 Hz, 4H), 7.66 (d, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 122.8, 124.8, 126.6, 128.4, 128.8, 130.1, 135.7, 136.4, 143.9; HRMS (APCI) calcd for $[M + H]^+$ $C_{19}H_{17}N_2$ 273.1386, found 273.1396.

Synthesis of Aminoaryl Ketimines and Derivatives. *N,N-Dimethyl-2-[imino(phenyl)methyl]aniline (**3**).*



To a mixture of benzaldehyde dimethylhydrazone (0.25 mmol), CsF (0.75 mmol, 3 equiv) and 5 mL of acetonitrile in a 10 mL vial, *o*-(trimethylsilyl)phenyl triflate (0.28 mmol, 1.1 equiv) was added. The vial was capped, and the reaction mixture was allowed to stir for 10 h at 65 °C. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired ketamine **3**. Yellow oil (42.8 mg, 76%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.67 (s, 6H), 6.94 (t, J = 7.4 Hz, 1H), 7.01 (d, J = 8.2 Hz, 1H), 7.17 (d, J = 7.3 Hz, 1H), 7.30−7.46 (m, 4H), 7.72 (d, J = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.6, 117.7, 120.6, 128.3, 128.4, 130.3, 130.4, 130.6, 131.5, 139.1, 151.5, 178.4; HRMS (APCI) calcd for $[M + H]^+$ $C_{15}H_{17}N_2$ 225.1386, found 225.1385.

*Ethyl [(2-(dimethylamino)phenyl)(phenyl)methylene]carbamate (**4**).*

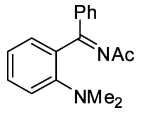


To a mixture of benzaldehyde dimethylhydrazone (0.25 mmol), CsF (0.75 mmol, 3 equiv) and 5 mL of acetonitrile in a 10 mL vial, *o*-(trimethylsilyl)phenyl triflate (0.28 mmol, 1.1 equiv) was added. The vial was capped, and the reaction mixture was allowed to stir for 10 h at 65 °C. After cooling to room temperature, ethyl chloroformate (0.3 mmol, 1.2 equiv) was added, and the mixture was heated at 65 °C for an additional 2 h. After cooling to room temperature, 25 mL of dichloromethane was added to the residue, and the reaction mixture was poured into 25 mL of water in a separatory funnel. After shaking the layers, the organic fraction was separated, and the aqueous layer was extracted with dichloromethane (2 × 10 mL). All organic fractions were combined and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired product **4**. Yellow oil (60.5 mg, 82%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (t, J = 7.1 Hz, 3H), 2.66 (s, 6H), 4.14 (q, J = 7.1 Hz, 2H), 6.92 (t, J = 7.5 Hz, 1H), 6.97 (d, J = 8.3 Hz, 1H), 7.23 (d, J = 7.5 Hz, 1H), 7.33−7.38 (m, 3H),

dx.doi.org/10.1021/jo302378w | J. Org. Chem. 2012, 77, 11232−11256

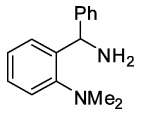
7.46 (t, J = 7.4 Hz, 1H), 7.69 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 43.2, 62.3, 117.6, 120.0, 127.4, 128.3, 129.4, 130.4, 131.1, 131.8, 137.2, 151.5, 163.1, 173.3; HRMS (APCI) calcd for $[M + H]^+$ $C_{18}H_{21}N_2O_2$ 297.1598, found 297.1595.

*N-[(2-(Dimethylamino)phenyl)(phenyl)methylene]acetamide (**5**).*



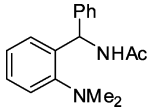
To a mixture of benzaldehyde dimethylhydrazone (0.25 mmol), CsF (0.75 mmol, 3 equiv) and 5 mL of acetonitrile in a 10 mL vial, *o*-(trimethylsilyl)phenyl triflate (0.28 mmol, 1.1 equiv) was added. The vial was capped, and the reaction mixture was allowed to stir for 10 h at 65 °C. After cooling to room temperature, acetic anhydride (0.5 mmol, 2 equiv) was added, and the mixture was heated at 65 °C for an additional 2 h. After cooling to room temperature, 25 mL of dichloromethane was added to the residue, and the reaction mixture was poured into 25 mL of water in a separatory funnel. After shaking the layers, the organic fraction was separated, and the aqueous layer was extracted with dichloromethane (2 × 10 mL). All organic fractions were combined and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired product **5**. Yellow oil (45.0 mg, 68%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.15 (s, 3H), 2.68 (s, 6H), 6.92 (t, J = 7.4 Hz, 1H), 6.98 (d, J = 8.3 Hz, 1H), 7.12 (dd, J = 7.6, 1.6 Hz, 1H), 7.31−7.42 (m, 3H), 7.43−7.50 (m, 1H), 7.70−7.76 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.2, 43.2, 117.8, 120.1, 127.1, 128.4, 129.5, 130.4, 131.0, 131.6, 137.5, 151.3, 165.7, 185.2; HRMS (APCI) calcd for $[M + H]^+$ $C_{17}H_{19}N_2O$ 267.1492, found 267.1489.

*N,N-Dimethyl-2-[amino(phenyl)methyl]aniline (**7**).*



To a solution of imine **3** (0.20 mmol) in MeOH (4 mL) in a 10 mL vial, $NaBH_4$ (0.50 mmol, 2.5 equiv) was added portionwise. The reaction mixture was allowed to stir for 10 h at room temperature. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired product. Yellow oil (31.5 mg, 70%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01 (br s, 2H, NH_2), 2.63 (s, 6H), 5.75 (s, 1H), 7.09 (t, J = 7.1 Hz, 1H), 7.19−7.24 (m, 3H), 7.28−7.33 (m, 3H), 7.41 (d, J = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.1, 54.3, 121.4, 124.8, 126.8, 127.2, 128.1, 128.2, 128.5, 141.0, 144.7, 152.7; HRMS (APCI) calcd for $[M + H]^+$ $C_{15}H_{19}N_2$ 227.1543, found 227.1545.

*N-[(2-(Dimethylamino)phenyl)(phenyl)methyl]acetamide (**6**).*

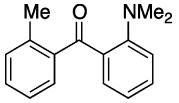


Method A. To a solution of *N*-acetylimine **5** (0.20 mmol) in THF (4 mL) in a 10 mL vial, $NaBH_3CN$ (0.50 mmol, 2.5 equiv) was added portionwise. The reaction mixture was allowed to stir for 10 h at room temperature. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired product in a 55% yield (29.4 mg).

Method B. To a solution of amine **7** (0.20 mmol) in CH_3CN (4 mL) in a 10 mL vial, Ac_2O (0.40 mmol, 2.0 equiv) and Et_3N (0.40 mmol, 2.0 equiv) were added. The reaction mixture was allowed to stir for 2 h at 65 °C. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired product. Pale brown solid (49.4 mg, 92%): mp 97−99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.08 (s, 3H), 2.50 (s, 6H), 6.56 (d, J = 8.6 Hz, 1H), 7.11−7.19 (m, 4H), 7.22−7.35 (m, 5H), 7.58 (d, J = 8.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8, 45.9, 54.6, 122.8, 125.3, 126.7, 126.9, 128.4, 128.8, 129.9, 137.5, 142.7, 152.9, 169.3; HRMS (APCI) calcd for $[M + H]^+$ $C_{17}H_{21}N_2O$ 269.1648, found 269.1653.

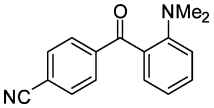
Synthesis of the Aminoaryl Ketones. To a mixture of the appropriate dialkylhydrazone (0.25 mmol), CsF (0.75 mmol, 3 equiv) and 5 mL of acetonitrile in a 10 mL vial, the silylaryl triflate (0.28 mmol, 1.1 equiv) was added. The vial was capped, and the reaction mixture was allowed to stir for 10 h at 65 °C. Then, 3 mL of 1 M HCl was added, and the mixture was heated at 65 °C for an additional 2 h. After cooling to room temperature, 25 mL of dichloromethane was added to the residue, and the reaction mixture was poured into 25 mL of water in a separatory funnel. After shaking the layers, the organic fraction was separated, and the aqueous layer was extracted with dichloromethane (2 × 10 mL). All organic fractions were combined and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired *o*-(dimethylamino)aryl ketone.

*2-(Dimethylamino)-2′-methylbenzophenone (**17**).*



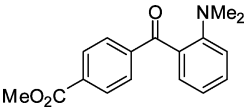
Pale yellow oil (46.4 mg, 78%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.53 (s, 3H), 2.77 (s, 6H), 6.83 (t, J = 7.4 Hz, 1H), 6.97 (d, J = 8.3 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H), 7.27 (d, J = 7.7 Hz, 1H), 7.31−7.41 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 43.8, 116.6, 118.5, 125.3, 129.3, 130.8, 131.1, 131.7, 132.4, 132.5, 138.8, 139.0, 152.3, 199.2; HRMS (APCI) calcd for $[M + H]^+$ $C_{16}H_{18}NO$ 240.1383, found 240.1386.

*4-[2-(Dimethylamino)benzoyl]benzonitrile (**23**).*



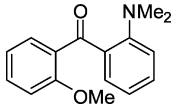
Light orange crystals (57.8 mg, 92%): mp 99−102 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.62 (s, 6H), 6.95 (t, J = 7.4 Hz, 1H), 7.01 (d, J = 8.3 Hz, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.44 (ddd, J = 8.6, 7.3, 1.7 Hz, 1H), 7.69 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.8, 115.8, 117.2, 118.5, 120.0, 128.6, 130.2, 131.1, 132.1, 132.7, 141.5, 152.2, 196.7; HRMS (APCI) calcd for $[M + H]^+$ $C_{16}H_{15}N_2O$ 251.1179, found 251.1186.

*Methyl 4-[2-(dimethylamino)benzoyl]benzoate (**25**).*



Light orange oil (66.7 mg, 94%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.64 (s, 6H), 3.92 (s, 3H), 6.92 (t, J = 7.4 Hz, 1H), 6.99 (d, J = 8.3 Hz, 1H), 7.35 (d, J = 7.6 Hz, 1H), 7.41 (t, J = 8.3 Hz, 1H), 7.83 (d, J = 8.3 Hz, 2H), 8.06 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.7, 52.6, 116.9, 119.6, 129.0, 129.5, 129.8, 131.1, 132.2, 133.5, 141.6, 152.1, 166.6, 197.7; HRMS (APCI) calcd for $[M + H]^+$ $C_{17}H_{18}NO_3$ 284.1281, found 284.1289.

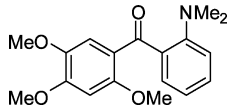
*2-(Dimethylamino)-2′-methoxybenzophenone (**29**).*



Yellow crystals (47.0 mg, 74%): mp 111−113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.79 (s, 6H), 3.68 (s, 3H), 6.77 (t, J = 7.4 Hz, 1H), 6.93 (d, J = 8.4 Hz, 2H), 6.99 (t, J = 7.5 Hz, 1H), 7.32−7.36 (m, 2H), 7.44 (ddd, J = 9.3, 7.6, 1.9 Hz, 1H), 7.52 (dd, J = 7.6, 1.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.9, 55.9, 111.7, 116.1, 118.1, 120.5, 129.7, 129.9, 131.2, 131.9, 132.1, 132.7, 151.9, 158.5, 196.6; HRMS (APCI) calcd for $[M + H]^+$ $C_{16}H_{18}NO_2$ 256.1332, found 256.1335.

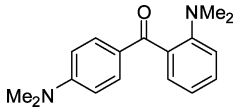
dx.doi.org/10.1021/jo302378w | *J. Org. Chem.* 2012, 77, 11232−11256

*2-(Dimethylamino)-2′,4′,5′-trimethoxybenzophenone (**31**).*



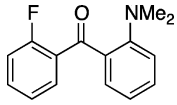
Pale brown solid (52.8 mg, 67%): mp 106−110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.75 (s, 6H), 3.58 (s, 3H), 3.83 (s, 3H), 3.92 (s, 3H), 6.46 (s, 1H), 6.78 (t, J = 7.4 Hz, 1H), 6.90 (d, J = 8.2 Hz, 1H), 7.20−7.32 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.9, 56.3, 56.6, 56.7, 97.3, 114.1, 116.0, 118.4, 120.4, 130.5, 131.2, 131.8, 143.2, 151.3, 153.5, 154.9, 195.8; HRMS (APCI) calcd for $[M + H]^+$ $C_{18}H_{22}NO_4$ 316.1543, found 316.1550.

*2,4′-Bis(dimethylamino)benzophenone (**35**).*



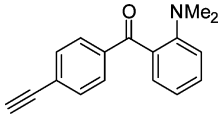
Pale yellow oil (30.4 mg, 45%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.73 (s, 6H), 3.06 (s, 6H), 6.63 (d, J = 9.0 Hz, 2H), 6.87 (t, J = 7.4 Hz, 1H), 6.96 (d, J = 8.3 Hz, 1H), 7.25 (d, J = 8.8 Hz, 1H), 7.34 (t, J = 7.8 Hz, 1H), 7.78 (d, J = 9.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.3, 43.7, 110.6, 116.5, 119.0, 125.4, 130.3, 130.6, 130.8, 132.7, 151.3, 153.6, 197.0; HRMS (APCI) calcd for $[M + H]^+$ $C_{17}H_{21}N_2O$ 269.1648, found 269.1650.

*2-(Dimethylamino)-2′-fluorobenzophenone (**37**).*



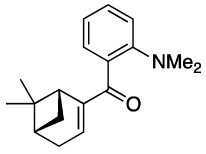
Yellow oil (37.3 mg, 61%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.73 (s, 6H), 6.88 (t, J = 7.5 Hz, 1H), 6.98 (d, J = 8.1 Hz, 1H), 7.04−7.10 (m, 1H), 7.20 (td, J = 7.6, 1.1 Hz, 1H), 7.37−7.43 (m, 2H), 7.45−7.51 (m, 1H), 7.68 (td, J = 7.4, 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.8, 115.9, 116.1, 116.5, 118.9, 120.1, 123.6, 123.9, 124.0, 127.7, 127.8, 127.9, 129.7, 131.2, 131.3, 132.4, 133.3, 133.4, 152.1, 159.7, 162.3, 193.8 (extra peaks due to C−F coupling); HRMS (APCI) calcd for $[M + H]^+$ $C_{15}H_{15}FNO$ 244.1132, found 244.1129.

*2-(Dimethylamino)-4′-ethynylbenzophenone (**41**).*



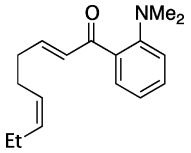
Light orange oil (62.2 mg, quantitative yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66 (s, 6H), 3.23 (s, 1H), 6.92 (t, J = 7.4 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 7.32 (dd, J = 7.7, 1.7 Hz, 1H), 7.40 (ddd, J = 8.7, 7.3, 1.7 Hz, 1H), 7.52 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.7, 80.3, 83.3, 116.8, 119.5, 126.5, 129.2, 129.9, 130.9, 132.0, 132.1, 137.8, 151.9, 197.5; HRMS (APCI) calcd for $[M + H]^+$ $C_{17}H_{16}NO$ 250.1226, found 250.1229.

*[2-(Dimethylamino)phenyl][(1R,5S)-6,6-dimethylbicyclo[3.1.1]-hept-2-en-2-yl]methanone (**48**).*



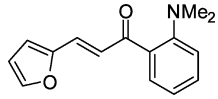
Yellow oil (42.5 mg, 63%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (s, 3H), 1.13 (d, J = 9.1 Hz, 1H), 1.36 (s, 3H), 2.44 (dt, J = 10.7, 3.1 Hz, 1H), 2.51 (dt, J = 9.1, 5.8 Hz, 1H), 2.73 (s, 1H), 3.00−3.05 (m, 6H), 6.44 (s, 1H), 6.86 (t, J = 7.4 Hz, 1H), 6.93 (d, J = 8.2 Hz, 1H), 7.18 (dd, J = 7.5, 1.7 Hz, 1H), 7.30 (t, J = 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 26.2, 31.7, 32.9, 38.0, 40.4, 40.7, 43.8, 116.8, 119.1, 130.0, 130.5, 130.7, 140.9, 149.6, 151.3, 197.6; HRMS (APCI) calcd for $[M + H]^+$ $C_{18}H_{24}NO$ 270.1852, found 270.1857.

*(2E,6Z)-1-[2-(Dimethylamino)phenyl]nona-2,6-dien-1-one (**50**).*



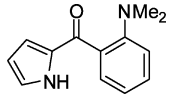
Brown oil (52.5 mg, 82%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J = 7.5 Hz, 3H), 2.03 (p, J = 7.4 Hz, 2H), 2.18−2.34 (m, 4H), 2.78 (s, 6H), 5.28−5.46 (m, 2H), 6.68 (d, J = 15.8 Hz, 1H), 6.86−6.97 (m, 3H), 7.34 (t, J = 7.8 Hz, 1H), 7.41 (d, J = 7.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 20.8, 26.1, 32.8, 44.4, 116.8, 119.9, 127.7, 130.1, 130.6, 131.3, 131.8, 133.0, 147.5, 152.1, 195.8; HRMS (APCI) calcd for $[M + H]^+$ $C_{17}H_{24}NO$ 258.1852, found 258.1848.

*(E)-1-[2-(Dimethylamino)phenyl]-3-(furan-2-yl)prop-2-en-1-one (**52**).*



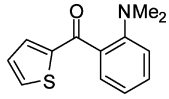
Dark red solid (51.1 mg, 85%): mp 80−81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.82 (s, 6H), 6.45−6.49 (m, 1H), 6.64 (d, J = 3.4 Hz, 1H), 6.93 (t, J = 7.4 Hz, 1H), 7.00 (d, J = 8.2 Hz, 1H), 7.24 (d, J = 15.7 Hz, 1H), 7.37 (t, J = 7.8 Hz, 1H), 7.45−7.53 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.6, 112.7, 115.4, 117.0, 120.1, 124.0, 129.1, 130.6, 131.6, 132.1, 144.8, 152.1, 152.4, 194.8; HRMS (APCI) calcd for $[M + H]^+$ $C_{15}H_{16}NO_2$ 242.1176, found 242.1180.

*[2-(Dimethylamino)phenyl](1H-pyrrol-2-yl)methanone (**54**).*



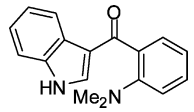
Gray green solid (43.6 mg, 81%): mp 96−99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.81 (s, 6H), 6.24−6.31 (m, 1H), 6.75 (s, 1H), 6.87 (t, J = 7.4 Hz, 1H), 6.97 (d, J = 8.3 Hz, 1H), 7.10 (s, 1H), 7.36 (ddd, J = 8.7, 7.3, 1.8 Hz, 1H), 7.45 (dd, J = 7.6, 1.7 Hz, 1H), 10.23 (br s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.7, 111.0, 116.6, 118.4, 119.5, 125.5, 128.9, 130.9, 131.3, 132.6, 151.3, 187.3; HRMS (APCI) calcd for $[M + H]^+$ $C_{13}H_{15}N_2O$ 215.1179, found 215.1180.

*[2-(Dimethylamino)phenyl](thiophen-2-yl)methanone (**58**).*



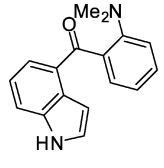
Yellow solid (49.4 mg, 85%): mp 49−51 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.78 (s, 6H), 6.87 (t, J = 7.4 Hz, 1H), 6.98 (d, J = 8.2 Hz, 1H), 7.09 (t, J = 4.4 Hz, 1H), 7.35−7.39 (t, J = 7.6 Hz, 2H), 7.54 (d, J = 3.8 Hz, 1H), 7.66 (d, J = 4.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.7, 116.7, 118.7, 128.1, 129.1, 130.5, 131.7, 134.3, 134.7, 145.0, 151.2, 190.4; HRMS (APCI) calcd for $[M + H]^+$ $C_{13}H_{14}NOS$ 232.0791, found 232.0797.

*[2-(Dimethylamino)phenyl](1H-indol-3-yl)methanone (**60**).*



Red oil (14.0 mg, 21%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.77 (s, 6H), 6.87−6.91 (m, 3H), 7.08 (t, J = 7.4 Hz, 1H), 7.14 (d, J = 8.1 Hz, 1H), 7.32 (t, J = 7.7 Hz, 1H), 7.40−7.45 (m, 2H), 7.70 (d, J = 7.4 Hz, 1H), 8.58 (br s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.0, 110.7, 111.9, 118.6, 120.0, 122.0, 123.1, 125.1, 128.5, 129.9, 133.6, 135.7, 136.2, 150.8, 152.8, 187.0; HRMS (APCI) calcd for $[M + H]^+$ $C_{17}H_{17}N_2O$ 265.1335, found 265.1339.

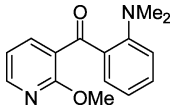
*[2-(Dimethylamino)phenyl](1H-indol-4-yl)methanone (**62**).*



dx.doi.org/10.1021/jo302378w | J. Org. Chem. 2012, 77, 11232−11256

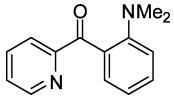
Yellow solid (55.6 mg, 84%): mp 173−176 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.61 (s, 6H), 6.79 (m, 1H), 6.88 (t, J = 7.4 Hz, 1H), 7.02 (d, J = 8.3 Hz, 1H), 7.09−7.17 (m, 2H), 7.27 (d, J = 7.4 Hz, 1H), 7.37 (ddd, J = 8.7, 7.4, 1.6 Hz, 1H), 7.51 (t, J = 2.7 Hz, 2H), 7.66 (d, J = 8.0 Hz, 1H), 11.47 (br s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 43.8, 102.7, 117.2, 117.4, 119.3, 120.7, 125.0, 127.2, 128.8, 129.1, 130.2, 131.3, 131.6, 137.5, 151.4, 198.9; HRMS (APCI) calcd for $[M + H]^+$ $C_{17}H_{17}N_2O$ 265.1335, found 265.1337.

*[2-(Dimethylamino)phenyl](2-methoxypyridin-3-yl)methanone (**66**).*



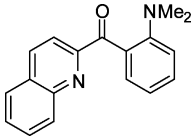
Yellow solid (49.8 mg, 78%): mp 69−71 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.68 (s, 6H), 3.80 (s, 3H), 6.86 (t, J = 7.4 Hz, 1H), 6.92−6.95 (m, 2H), 7.35−7.39 (m, 2H), 7.84 (dd, J = 7.3, 2.0 Hz, 1H), 8.25 (dd, J = 5.0, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.1, 53.8, 116.6, 116.7, 119.3, 123.5, 130.1, 131.5, 132.5, 140.1, 149.7, 152.5, 161.9, 195.4; HRMS (APCI) calcd for $[M + H]^+$ $C_{15}H_{17}N_2O_2$ 257.1285, found 257.1287.

*[2-(Dimethylamino)phenyl](pyridin-2-yl)methanone (**68**).*



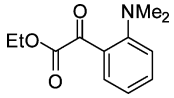
Red oil (46.5 mg, 82%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.69 (s, 6H), 6.89 (t, J = 7.4 Hz, 1H), 7.00 (d, J = 8.6 Hz, 1H), 7.34−7.44 (m, 3H), 7.81 (t, J = 6.9 Hz, 1H), 7.93 (d, J = 7.7 Hz, 1H), 8.66 (d, J = 4.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.9, 117.0, 119.1, 124.2, 126.2, 128.6, 131.4, 132.3, 136.8, 149.3, 152.6, 155.8, 197.1; HRMS (APCI) calcd for $[M + H]^+$ $C_{14}H_{15}N_2O$ 227.1179, found 227.1179.

*[2-(Dimethylamino)phenyl](quinolin-2-yl)methanone (**70**).*



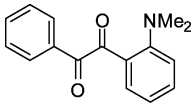
Yellow crystals (58.3 mg, 84%): mp 111−114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.70 (s, 6H), 6.92 (t, J = 7.4 Hz, 1H), 7.03 (d, J = 8.3 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.53 (d, J = 7.7 Hz, 1H), 7.60 (t, J = 7.3 Hz, 1H), 7.72 (t, J = 7.3 Hz, 1H), 7.85 (d, J = 8.1 Hz, 1H), 7.96 (d, J = 8.5 Hz, 1H), 8.17 (d, J = 8.6 Hz, 1H), 8.25 (d, J = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.0, 117.0, 119.0, 120.8, 127.7, 128.3, 128.5, 129.2, 130.0, 130.9, 132.2, 132.5, 136.7, 147.5, 153.0, 155.6, 197.0; HRMS (APCI) calcd for $[M + H]^+$ $C_{18}H_{17}N_2O$ 277.1335, found 277.1343. The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.[18]

*Ethyl 2-[2-(dimethylamino)phenyl]-2-oxoacetate (**72**).*



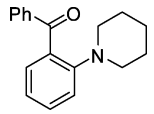
Yellow oil (17.5 mg, 32%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (t, J = 7.1 Hz, 3H), 2.71 (s, 6H), 4.33 (q, J = 7.1 Hz, 2H), 7.16 (t, J = 7.5 Hz, 1H), 7.22 (d, J = 8.1 Hz, 1H), 7.55 (t, J = 7.7 Hz, 1H), 7.73 (d, J = 7.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 45.8, 61.8, 120.1, 123.7, 129.8, 130.9, 134.9, 155.7, 165.3, 189.1; HRMS (APCI) calcd for $[M + H]^+$ $C_{12}H_{16}NO_3$ 222.1125, found 222.1124.

*1-[2-(Dimethylamino)phenyl]-2-phenylethane-1,2-dione (**74**).*



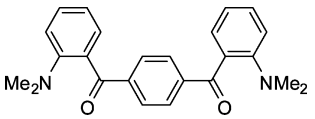
Light brown solid (41.9 mg, 66%): mp 92−93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 6H), 7.27 (d, J = 8.4 Hz, 1H), 7.33 (t, J = 7.5 Hz, 1H), 7.43 (t, J = 7.5 Hz, 2H), 7.53 (t, J = 7.3 Hz, 1H), 7.61 (td, J = 7.7, 1.7 Hz, 1H), 7.83 (d, J = 7.2 Hz, 2H), 7.97 (dd, J = 7.8, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 45.0, 122.9, 126.1, 128.1, 128.7, 130.3, 133.0, 133.2, 134.3, 135.6, 155.8, 189.3, 196.5; HRMS (APCI) calcd for $[M + H]^+$ $C_{16}H_{16}NO_2$ 254.1176, found 254.1176.

*2-(Piperidin-1-yl)benzophenone (**80**).*



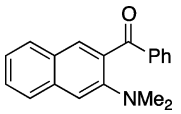
Light brown solid (53.3 mg, 80%): mp 94−95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11−1.17 (m, 4H), 1.24−1.30 (m, 2H), 2.83 (t, J = 5.3 Hz, 4H), 7.01−7.09 (m, 2H), 7.35−7.46 (m, 4H), 7.51 (t, J = 7.4 Hz, 1H), 7.76 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.1, 25.8, 53.7, 118.9, 122.0, 128.0, 130.1, 130.4, 131.8, 132.7, 133.4, 137.7, 152.7, 199.1; HRMS (APCI) calcd for $[M + H]^+$ $C_{18}H_{20}NO$ 266.1539, found 266.1540.

*1,4-Bis(2-dimethylaminobenzoyl)benzene (**82**).*



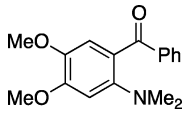
2.2 equiv of the benzyne precursor and 5.0 equiv of CsF were used in this synthesis. Orange solid (78.4 mg, 84%): mp 130−131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.67 (s, 12H), 6.93 (t, J = 7.4 Hz, 2H), 7.00 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 7.6 Hz, 2H), 7.41 (t, J = 7.9 Hz, 2H), 7.81 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.8, 116.9, 119.5, 129.1, 129.6, 131.1, 132.2, 141.1, 152.1, 197.8; HRMS (APCI) calcd for $[M + H]^+$ $C_{24}H_{25}N_2O_2$ 373.1911, found 373.1914.

*[3-(Dimethylamino)naphthalen-2-yl](phenyl)methanone (**84**).*



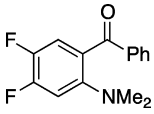
Light orange oil (52.7 mg, 77%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.75 (s, 6H), 7.27 (s, 1H), 7.33 (t, J = 7.5 Hz, 1H), 7.43 (t, J = 7.7 Hz, 2H), 7.49 (t, J = 7.5 Hz, 1H), 7.57 (t, J = 7.4 Hz, 1H), 7.75 (dd, J = 8.2, 3.8 Hz, 2H), 7.83 (s, 1H), 7.87 (d, J = 6.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.0, 112.7, 124.3, 126.7, 127.9, 128.1, 128.4, 128.6, 130.3, 130.9, 133.0, 133.2, 135.6, 137.7, 149.3, 198.2; HRMS (APCI) calcd for $[M + H]^+$ $C_{19}H_{18}NO$ 276.1383, found 276.1386.

*4,5-Dimethoxy-2-(dimethylamino)benzophenone (**86**).*



Yellow crystals (59.0 mg, 83%): mp 101−104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.58 (s, 6H), 3.80 (s, 3H), 3.93 (s, 3H), 6.55 (s, 1H), 6.94 (s, 1H), 7.39 (d, J = 7.6 Hz, 2H), 7.49 (t, J = 7.4 Hz, 1H), 7.76 (d, J = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.3, 56.1, 56.6, 101.6, 114.1, 122.2, 128.1, 129.9, 132.5, 138.6, 143.1, 147.8, 152.1, 197.6; HRMS (APCI) calcd for $[M + H]^+$ $C_{17}H_{20}NO_3$ 286.1438, found 286.1441.

*4,5-Difluoro-2-(dimethylamino)benzophenone (**88**).*

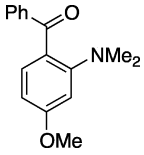


Pale yellow oil (40.7 mg, 62%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.65 (s, 6H), 6.77 (dd, J = 12.9, 6.6 Hz, 1H), 7.17 (dd, J = 10.3, 9.1 Hz, 1H), 7.43 (t, J = 7.7 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.79 (d, J = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.8, 105.7, 105.9, 115.6, 119.4, 119.6, 124.9, 128.5, 130.0, 133.3, 137.3, 142.5, 142.6, 144.9, 145.0, 149.3, 149.4, 150.9, 151.0, 153.4, 153.5, 195.9 (extra signals due to C−F coupling); HRMS (APCI) calcd for $[M + H]^+$ $C_{15}H_{14}F_2NO$ 262.1038, found 262.1041.

*Mixture of (2-(Dimethylamino)-4-methoxyphenyl)(phenyl)-methanone (**90a**) and (2-(Dimethylamino)-5-methoxyphenyl)(phenyl)-methanone (**90b**) (~1/1 Ratio).* The mixture (51.7 mg, 81%) was separated using preparative TLC.

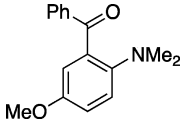
dx.doi.org/10.1021/jo302378w | J. Org. Chem. 2012, 77, 11232−11256

*2-(Dimethylamino)-4-methoxybenzophenone (**90a**).*



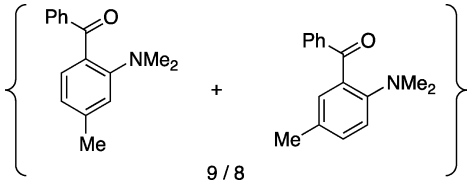
Yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.71 (s, 6H), 3.85 (s, 3H), 6.40 (d, J = 8.5 Hz, 1H), 6.45 (s, 1H), 7.32 (d, J = 8.5 Hz, 1H), 7.41 (t, J = 7.5 Hz, 2H), 7.52 (t, J = 7.4 Hz, 1H), 7.81 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.5, 55.5, 102.1, 103.5, 121.6, 128.2, 130.1, 132.5, 133.9, 138.8, 154.0, 162.9, 197.1; HRMS (APCI) calcd for $[M + H]^+$ $C_{16}H_{18}NO_2$ 256.1332, found 256.1333.

*2-(Dimethylamino)-5-methoxybenzophenone (**90b**).*



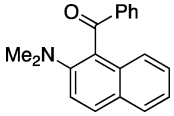
Yellow solid: mp 58−59 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.56 (s, 6H), 3.77 (s, 3H), 6.87 (d, J = 2.8 Hz, 1H), 6.99 (dd, J = 8.9, 2.9 Hz, 1H), 7.04 (d, J = 8.9 Hz, 1H), 7.40 (t, J = 7.6 Hz, 2H), 7.53 (t, J = 7.4 Hz, 1H), 7.80 (d, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.8, 55.9, 114.4, 117.5, 119.7, 128.3, 130.0, 133.0, 133.6, 137.6, 146.1, 154.4, 198.5; HRMS (APCI) calcd for $[M + H]^+$ $C_{16}H_{18}NO_2$ 256.1332, found 256.1334.

*Mixture of 2-(Dimethylamino)-4-methoxy-benzophenone (**92a**) and 2-(dimethylamino)-5-methoxybenzophenone (**92b**) (~1/1 ratio).*



Pale yellow oil (51.0 mg, 85%): ^{1}H NMR of the mixture (400 MHz, $CDCl_3$) δ 2.29 (s, 3H, minor isomer), 2.38 (s, 3H, major isomer), 2.63 (s, 6H, minor), 2.70 (s, 6H, major), 6.71 (d, J = 7.7 Hz, 1H, major), 6.79 (s, 1H, major), 6.93 (d, J = 8.3 Hz, 1H, minor), 7.13 (s, 1H, minor), 7.18−7.26 (m, 2H), 7.41 (t, J = 7.7 Hz, 4H), 7.48−7.57 (m, 2H), 7.78−7.86 (m, 4H); ^{13}C NMR of the mixture (100 MHz, $CDCl_3$) δ 20.6, 22.2, 43.7, 44.1, 117.1, 117.2 (×2), 119.8 (×2), 126.4, 128.3, 129.3, 130.1, 130.5, 130.8, 131.4, 132.2, 132.7, 132.9, 137.9, 138.3, 142.2, 149.8, 152.0, 198.2, 198.8; HRMS (APCI) calcd for $[M + H]^+$ $C_{16}H_{18}NO$ 240.1383, found 240.1384.

*[2-(Dimethylamino)naphthalen-1-yl](phenyl)methanone (**96**).*

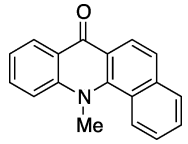


Light orange oil (56.2 mg, 82%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.72 (s, 6H), 7.33−7.43 (m, 5H), 7.53 (t, J = 7.3 Hz, 1H), 7.61−7.66 (m, 1H), 7.78−7.84 (m, 3H), 7.91 (d, J = 8.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.7, 119.3, 124.3, 124.5, 127.3, 127.6, 128.3, 128.6, 129.6, 129.9, 130.8, 131.9, 133.3, 138.6, 149.6, 199.8; HRMS (APCI) calcd for $[M + H]^+$ $C_{19}H_{18}NO$ 276.1383, found 276.1386.

Note: In a 1D-NOE experiment, a correlation of 7.42 (1H) to 2.72 (s, 6H) is observed, and in a ^{1}H−^{1}H COSY experiment, a coupling of 7.42 (1H) to 7.91 (d, 1H) is observed. If the other regioisomer was formed, the latter coupling would be a triplet.

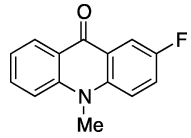
Synthesis of the Acridones. To a mixture of the appropriate dimethylhydrazone (0.25 mmol), CsF (0.75 mmol, 3 equiv) and 5 mL of acetonitrile in a 10 mL vial, the silylaryl triflate (0.28 mmol, 1.1 equiv) was added. The vial was capped, and the reaction mixture was allowed to stir for 10 h at 65 °C. Then 3 mL of 1 M HCl was added, and the mixture was heated at 65 °C for 2 h. Then 5 mL of 1 M NaOMe was added, and the mixture was heated at 100 °C for an additional 2 h. After cooling to room temperature, 25 mL of dichloromethane was added to the residue, and the reaction mixture was poured into 25 mL of water in a separatory funnel. After shaking the layers, the organic fraction was separated, and the aqueous layer was extracted with dichloromethane (2 × 10 mL). All organic fractions were combined and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired acridone.

*N-Methylbenz[c]acridin-7(12H)-one (**100**).*



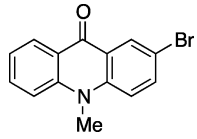
Red brown solid (29.4 mg, 45%): mp 142−145 °C (lit.[66] mp 143−144 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 (s, 3H), 7.36 (t, J = 7.5 Hz, 1H), 7.55 (t, J = 7.7 Hz, 1H), 7.60−7.67 (m, 2H), 7.76 (t, J = 7.8 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H), 8.30 (d, J = 8.5 Hz, 1H), 8.44 (d, J = 8.7 Hz, 1H), 8.53 (d, J = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 45.1, 117.4, 121.7, 122.6, 122.8, 123.5, 124.3, 124.9, 125.0, 127.2, 127.5, 128.4, 129.1, 133.6, 137.6, 144.3, 145.9, 178.0; HRMS (APCI) calcd for $[M + H]^+$ $C_{18}H_{14}NO$ 260.1070, found 260.1070.

*N-Methyl-2-fluoro-9-acridone (**104**).*



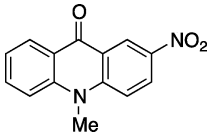
Orange crystals (47.5 mg, 84%): mp 173−176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 7.20 (t, J = 7.5 Hz, 1H), 7.29−7.40 (m, 3H), 7.63 (ddd, J = 8.7, 7.0, 1.8 Hz, 1H), 8.05 (dd, J = 8.8, 2.9 Hz, 1H), 8.41 (dd, J = 8.1, 1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.1, 111.9, 112.1, 114.9, 117.1, 117.1, 121.5, 121.7, 122.1, 122.3, 123.3, 123.4, 127.7, 134.1, 139.1, 142.4, 156.4, 158.8, 177.3 (extra peaks due to C−F coupling); HRMS (APCI) calcd for $[M + H]^+$ $C_{14}H_{11}FNO$ 228.0819, found 228.0823.

*N-Methyl-2-bromo-9-acridone (**106**).*



Brown crystals (56.8 mg, 79%): mp 196−198 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 3H), 7.17−7.27 (m, 2H), 7.39 (d, J = 8.7 Hz, 1H), 7.58−7.68 (m, 2H), 8.40 (dd, J = 8.0, 1.8 Hz, 1H), 8.50 (d, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.9, 114.7, 115.1, 117.0, 121.8, 122.4, 123.6, 127.8, 130.0, 134.2, 136.5, 141.2, 142.3, 176.8; HRMS (APCI) calcd for $[M + H]^+$ $C_{14}H_{11}BrNO$ 288.0019, found 288.0020. The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.[54]

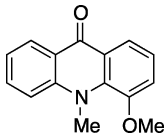
*N-Methyl-2-nitro-9-acridone (**108**).*



Orange solid (37.7 mg, 59%): mp 284−286 °C (decomp.) (lit.[67] mp 287 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (s, 3H), 7.42 (t, J = 7.6 Hz, 1H), 7.60 (d, J = 8.8 Hz, 2H), 7.82 (t, J = 8.2 Hz, 1H), 8.52 (dd, J = 17.8, 9.2 Hz, 2H), 9.39 (s, 1H); ^{13}C NMR (150 MHz, acetone-d_6) δ 34.1, 116.4, 117.3, 121.4, 122.8, 123.3, 127.0, 127.4, 134.7, 141.3, 141.4, 142.9, 146.4, 176.4; HRMS (APCI) calcd for $[M + H]^+$ $C_{14}H_{11}N_2O_3$ 255.0764, found 255.0773. The ^{1}H NMR spectral data are in good agreement with the literature data.[68]

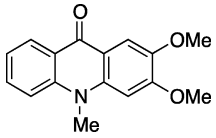
dx.doi.org/10.1021/jo302378w | J. Org. Chem. 2012, 77, 11232−11256

*N-Methyl-4-methoxy-9-acridone (**110**).*



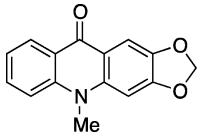
Reddish-yellow solid (52.0 mg, 87%): mp 89−91 °C (lit.[69] mp 90 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H), 3.95 (s, 3H), 7.11−7.27 (m, 3H), 7.47 (d, J = 8.7 Hz, 1H), 7.66 (ddd, J = 8.5, 6.8, 1.7 Hz, 1H), 8.09 (dd, J = 7.7, 1.8 Hz, 1H), 8.43 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.6, 56.6, 115.7, 116.3, 119.3, 121.5, 122.1, 122.9, 125.6, 127.3, 133.8, 135.8, 145.8, 150.1, 178.6; HRMS (APCI) calcd for $[M + H]^+$ $C_{15}H_{14}NO_2$ 240.1019, found 240.1022.

*N-Methyl-2,3-dimethoxy-9-acridone (**112**).*



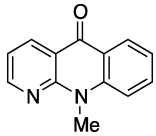
Light brown needles (51.7 mg, 77%): mp 193−196 °C (lit.[70] mp 192−195 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 3.99 (s, 3H), 4.01 (s, 3H), 6.72 (s, 1H), 7.22−7.27 (m, 1H), 7.40 (d, J = 8.7 Hz, 1H), 7.63 (t, J = 7.8 Hz, 1H), 8.52 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.0, 56.4, 56.4, 96.7, 107.0, 114.8, 116.4, 121.2, 122.2, 127.6, 133.1, 138.9, 142.1, 145.4, 154.9, 176.5; HRMS (APCI) calcd for $[M + H]^+$ $C_{16}H_{16}NO_3$ 270.1125, found 270.1132. The ^{1}H NMR spectral data are in good agreement with the literature data.[70]

*N-Methyl-[1,3]dioxolo[4,5-b]acridone (**114**).*



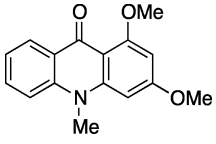
Light brown solid (24.1 mg, 38%): mp 258−260 °C (lit.[70] mp 260−263 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 6.01 (s, 2H), 6.88 (s, 1H), 7.22 (t, J = 7.5 Hz, 1H), 7.43 (d, J = 8.8 Hz, 1H), 7.61 (t, J = 8.0 Hz, 1H), 7.74 (s, 1H), 8.40 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.5, 94.8, 102.3, 104.2, 115.0, 117.5, 121.6, 121.8, 127.4, 133.4, 140.7, 142.0, 144.0, 154.0, 176.8; HRMS (APCI) calcd for $[M + H]^+$ $C_{15}H_{12}NO_3$ 254.0812, found 254.0821. The ^{1}H NMR spectral data are in good agreement with the literature data.[70]

*N-Methylbenzo[b][1,8]naphthyridin-5(10H)-one (**118**).*



Gray brown solid (25.4 mg, 48%): mp 220−221 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.13 (s, 3H), 7.20−7.27 (m, 1H), 7.33 (dd, J = 7.9, 7.0 Hz, 1H), 7.60 (d, J = 8.7 Hz, 1H), 7.77 (ddd, J = 8.7, 6.9, 1.7 Hz, 1H), 8.52 (dd, J = 8.0, 1.8 Hz, 1H), 8.73−8.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.0, 115.6, 117.4, 117.6, 122.1, 122.8, 127.8, 134.6, 137.0, 142.6, 151.3, 153.5, 178.6; HRMS (APCI) calcd for $[M + H]^+$ $C_{13}H_{11}N_2O$ 211.0866, found 211.0867.

*N-Methyl-1,3-dimethoxy-9-acridone (**123**).*

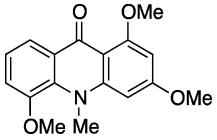


Pale yellow solid (52.3 mg, 78%): mp 158−160 °C (lit.[66] mp 162−163 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.48 (s, 3H), 3.77 (s, 3H), 3.86 (s, 3H), 6.08 (s, 1H), 6.11 (s, 1H), 7.09 (t, J = 7.5 Hz, 1H), 7.13 (d, J = 8.6 Hz, 1H), 7.43 (t, J = 8.6 Hz, 1H), 8.34 (d, J = 9.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.7, 55.5, 56.1, 90.2, 92.4, 108.2, 114.4, 121.3, 124.3, 127.4, 132.8, 141.7, 146.7, 163.1, 164.1, 176.9; HRMS (APCI) calcd for $[M + H]^+$ $C_{16}H_{16}NO_3$ 270.1125, found 270.1129.

The ^{13}C NMR spectral data are in good agreement with the literature data.[71]

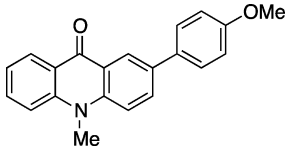
Note: In a 1D-NOE experiment, a correlation of 3.48 (s, 3H) to 7.13 (d, 1H) and 6.11 (s, 1H) is observed. If the other regioisomer had been obtained, a correlation of 3.48 (s, 3H) to one of the OMe groups (3.86 or 3.77 ppm) and lack of 3.48 (s, 3H) to 6.11 (s, 1H) would be expected.

*N-Methyl-1,3,5-trimethoxy-9-acridone (**125**).*



The standard procedure yielded the desired acridone (6.8 mg, 9%) and the uncyclized aminoaryl ketone (64.1 mg, 77%). The latter compound was exposed to 150 °C in 5 mL of MeCN for 4 h while stirring. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford an additional 38.0 mg (51%) of the desired product **125**. Thus, 44.8 mg (60% combined yield) of the acridone **125** was obtained. Brown red solid: mp 128−132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 3.82 (s, 6H), 3.87 (s, 3H), 6.16 (d, J = 2.1 Hz, 1H), 6.28 (d, J = 2.2 Hz, 1H), 7.00 (dd, J = 7.9, 1.5 Hz, 1H), 7.02−7.26 (m, 1H), 7.93 (dd, J = 7.9, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.4, 55.4, 56.1, 56.3, 91.0, 92.5, 108.9, 114.6, 119.0, 121.9, 127.8, 134.5, 149.4, 149.8, 162.4, 163.9, 177.1; HRMS (APCI) calcd for $[M + H]^+$ $C_{17}H_{18}NO_4$ 300.1230, found 300.1239.

*Suzuki−Miyaura Procedure[72] for the Preparation of N-Methyl-2-(4-methoxyphenyl)-9-acridone (**119**).*



To a 2 mL microwave vial was added the bromoacridone **106** (0.28 mmol), *p*-methoxyphenyl boronic acid (1.2 equiv), 1 M Cs_2CO_3 (0.2 mL), and 5 mol % $Pd(PPh_3)_4$ in 1/1 DMF/EtOH (1 mL). The solution was vigorously stirred for 5 min at room temperature, flushed with argon, and then heated to 120 °C under microwave irradiation for 20 min. Upon cooling to room temperature, the resulting reaction mixture was diluted with a saturated solution of Na_2SO_4 and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, concentrated, and purified by column chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired product. Yellow needles (66.3 mg, 75%): mp 218−220 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H), 3.86 (s, 3H), 6.99 (d, J = 8.8 Hz, 2H), 7.26 (ddd, J = 7.9, 5.9, 1.0 Hz, 1H), 7.48 (dd, J = 13.7, 8.8 Hz, 2H), 7.63 (d, J = 8.8 Hz, 2H), 7.68 (ddd, J = 8.8, 7.0, 1.7 Hz, 1H), 7.88 (dd, J = 9.0, 2.4 Hz, 1H), 8.55 (dd, J = 8.0, 1.7 Hz, 1H), 8.72 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.8, 55.6, 114.6, 115.0, 115.6, 121.4, 122.6, 122.8, 124.8, 128.0, 128.1, 132.3, 132.4, 133.7, 133.9, 141.5, 142.5, 159.4, 178.3; HRMS (APCI) calcd for $[M + H]^+$ $C_{21}H_{18}NO_2$ 316.1332, found 316.1335.

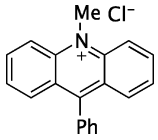
Synthesis of Acridinium Salts. *Method A.* To a mixture of the appropriate *N*,*N*-disubstituted hydrazone (0.25 mmol), CsF (4 equiv) and 5 mL of acetonitrile in a 10 mL vial, the silylaryl triflate (1.8 equiv) was added. The reaction mixture was allowed to stir for 10 h at room temperature. Then 3 mL of 1 M HCl was added, and the mixture was heated at 65 °C for an additional 2 h. After cooling to room temperature, 25 mL of dichloromethane was added to the residue, and the reaction mixture was poured into 25 mL of brine in a separatory funnel. After shaking the layers, the organic fraction was separated, and the aqueous layer was extracted with dichloromethane (2 × 10 mL). All organic fractions were combined and concentrated under reduced pressure. The residue was eluted with hexanes/EtOAc (1/2) using a preparative thin-layer chromatography plate with silica gel. The bright yellow spot of high polarity was collected and put on a short plug of

silica gel. CH_2Cl_2/MeOH (1/1, 15 mL) was run through the plug, and the solvent was evaporated to afford the desired acridinium salt.

Method B. The silylaryl triflate (2.8 equiv) was added to a mixture of benzaldehyde *N*-methylhydrazone (0.25 mmol), CsF (5 equiv) and 5 mL of acetonitrile in a 10 mL vial. The reaction mixture was allowed to stir for 10 h at room temperature. The rest of the procedure follows Method A.

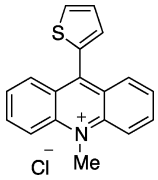
Method C. The silylaryl triflate (1.5 equiv) was added to a mixture of the aminoaryl ketone **8** (0.25 mmol), CsF (3 equiv) and 5 mL of acetonitrile in a 10 mL vial. The vial was capped, and the reaction mixture was allowed to stir for 10 h at 65 °C. The rest of the procedure follows Method A.

*10-Methyl-9-phenylacridin-10-ium chloride (**127**).*



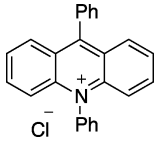
This compound was obtained as a dark yellow-green solid in an 88% yield by Method A (67.4 mg), in a 41% yield by Method B (31.2 mg), and in a 78% yield by Method C (59.9 mg): 201−203 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.04 (s, 3H), 7.44−7.51 (m, 2H), 7.66−7.76 (m, 3H), 7.79 (dd, J = 8.7, 6.7 Hz, 2H), 8.00 (dd, J = 8.7, 1.6 Hz, 2H), 8.38 (ddd, J = 9.0, 6.8, 1.6 Hz, 2H), 8.75 (d, J = 9.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.6, 119.1, 126.3, 128.1, 129.3, 130.0, 130.4, 130.7, 133.2, 139.4, 141.8, 161.7; HRMS (APCI) calcd for $[M]^+$ $C_{20}H_{16}N$ 270.1277, found 270.1278. The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.[51]

*10-Methyl-9-(thiophen-2-yl)acridin-10-ium chloride (**130**).*



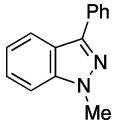
Dark green solid (68.4 mg, 88% by Method A): mp 136−138 °C (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.94 (s, 3H), 7.34−7.41 (m, 2H), 7.72−7.80 (m, 2H), 7.82 (d, J = 5.0 Hz, 1H), 8.18 (d, J = 8.7 Hz, 2H), 8.31 (dd, J = 8.9, 7.1 Hz, 2H), 8.66 (d, J = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.5, 118.9, 127.0, 128.2, 128.3, 129.9, 130.8, 131.6, 132.9, 139.3, 141.4, 154.7; HRMS (APCI) calcd for $[M]^+$ $C_{18}H_{14}NS$ 276.0841, found 276.0849.

*9,10-Diphenylacridin-10-ium chloride (**132**).*



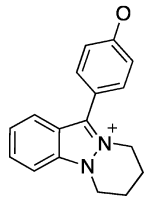
Yellow solid (28.6 mg, 31% by Method A): mp 259−263 °C (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 9.2 Hz, 2H), 7.66−7.70 (m, 2H), 7.71−7.79 (m, 7H), 7.85−7.92 (m, 3H), 8.03−8.12 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 119.6, 126.2, 127.8, 128.0, 128.9, 130.1, 130.2, 130.5, 131.6, 131.8, 133.0, 137.1, 138.4, 142.1, 163.4; HRMS (APCI) calcd for $[M]^+$ $C_{25}H_{18}N$ 332.1434, found 332.1443.

Synthesis of 1-Methyl-3-phenyl-1*H*-indazole (137).



The silylaryl triflate **2** (0.28 mmol, 1.1 equiv) was added to a mixture of the hydrazone **1** (0.25 mmol), CsF (0.75 mmol, 3 equiv) and 5 mL of acetonitrile in a 10 mL vial. The vial was capped, and the reaction mixture was allowed to stir for 10 h at 65 °C. Then NCS (1.5 equiv) was added, and the mixture was heated at 65 °C for an additional 2 h. After cooling to room temperature, 25 mL of CH_2Cl_2 was added to the residue, and the reaction mixture was poured into 40 mL of water in a separatory funnel. After shaking the layers, the organic fraction was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). All organic fractions were combined and concentrated under reduced pressure. The residue was dissolved in 5 mL of acetonitrile and heated at 130 °C for 10 h. After cooling to room temperature, 25 mL of CH_2Cl_2 was added to the residue, and the reaction mixture was poured into 40 mL of water in a separatory funnel. After shaking the layers, the organic fraction was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). All organic fractions were combined and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired 1*H*-indazole **137**. Gray solid (34.2 mg, 66%): mp 81−83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (s, 3H), 7.21 (s, 1H), 7.42 (t, J = 4.3 Hz, 3H), 7.52 (t, J = 7.6 Hz, 2H), 7.99 (d, J = 8.3 Hz, 2H), 8.04 (d, J = 8.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.7, 109.4, 121.1, 121.5, 121.8, 126.5, 127.6, 128.0, 129.0, 133.9, 141.6, 143.9; HRMS (APCI) calcd for $[M + H]^+$ $C_{14}H_{13}N_2$ 209.1073, found 209.1075. The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.[73]

Synthesis of Nigellidine Analogue 144.



The silylaryl triflate **2** (0.28 mmol, 1.1 equiv) was added to a mixture of the hydrazone **141** (0.25 mmol),[74] CsF (0.75 mmol, 3 equiv) and 5 mL of acetonitrile in a 10 mL vial. The vial was capped, and the reaction mixture was allowed to stir for 10 h at 65 °C. Then NH_2OH·HCl (2 equiv) and EtOH (3 mL) were added, and the mixture was heated at 150 °C for 24 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography on silica gel using hexanes/EtOAc (1/1) as the eluent to afford the tricyclic product **143** as a dark brown oil (29.3 mg, 37%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26−2.52 (m, 4H), 3.92 (s, 3H), 4.70 (dt, J = 19.5, 6.1 Hz, 4H), 7.16 (d, J = 8.8 Hz, 2H), 7.47 (t, J = 7.6 Hz, 1H), 7.68 (d, J = 8.8 Hz, 3H), 7.76−7.83 (m, 2H). BBr_3 (1.0 M solution in CH_2Cl_2, 6 equiv)[75] was added dropwise to a solution of the compound **143** in CH_2Cl_2 (5 mL) at 0 °C and stirred at room temperature for 5 h. The mixture was extracted with 10% methanol in CH_2Cl_2 (5 mL × 4), and the organic solution was concentrated under reduced pressure. The residue was washed with hexanes (5 mL × 2), diethyl ether (5 mL × 2), and ethyl acetate (5 mL × 2) and dried in vacuo to afford the desired nigellidine analogue **144**. Black oil (16.4 mg, 67%): ^{1}H NMR (400 MHz, $CDCl_3$ + CD_3OD) δ 2.15−2.38 (m, 4H), 4.56 (dt, J = 31.3, 6.1 Hz, 4H), 6.99 (d, J = 8.6 Hz, 2H), 7.35−7.40 (m, 1H), 7.43 (d, J = 8.6 Hz, 2H), 7.59 (d, J = 8.7 Hz, 1H), 7.68−7.76 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$ + CD_3OD) δ 19.4, 20.3, 47.0, 49.1, 110.2, 113.9, 116.9, 119.4, 122.7, 125.8, 131.5, 133.7, 140.6, 144.8, 160.8. HRMS (APCI) calcd for $[M + H]^+$ $C_{17}H_{17}N_2O$ 265.1335, found 265.1337.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR data for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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