Synthesis of Isoindolo[2,1-*a*]indoles by the Palladium-Catalyzed Annulation of Internal Acetylenes

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A wide variety of substituted isoindolo[2,1-*a*]indoles have been prepared via annulation of internal alkynes by imines derived from *o*-iodoanilines in the presence of a palladium catalyst. This methodology provides an extremely efficient route for the synthesis of these tetracyclic heterocycles from readily available starting materials. The mechanism of this interesting annulation process appears to involve (1) oxidative addition of the aryl iodide to Pd(0), (2) alkyne insertion, (3) addition of the resulting vinylic palladium intermediate to the C−N double bond of the imine, (4) either electrophilic palladation of the resulting *σ*-palladium intermediate onto the adjacent aromatic ring derived from the internal alkyne or oxidative addition of the neighboring aryl carbon−hydrogen bond, and (5) reduction of the tetracyclic product and Pd(0). A variety of internal acetylenes have been employed in this annulation process in which the aromatic ring of the alkyne contains either a phenyl or a heterocyclic ring.

Introduction

The development of efficient and selective synthetic transformations is a major challenge in organic synthesis. Consequently, tandem (domino) processes have been extensively investigated as they are among the most versatile reactions for the efficient, stereocontrolled synthesis of complex organic molecules.[1] It is not surprising, therefore, that transition-metal-catalyzed alkyne annulation processes have received considerable attention for the synthesis of a variety of complex carbo- and heterocycles due to the synthetic efficiency of this methodology.[2] For example, the palladium-catalyzed annulation of internal alkynes has been employed by us for the synthesis of indoles,[3] benzofurans,[4] benzopyrans,[4] isocoumarins,[4,5] indenones,[6] isoquinolines,[7] α-pyrones,[5,8] and polycyclic aromatic hydrocarbons.[9]

Considerable attention has been directed toward the synthesis of compounds containing the indole nucleus, a structural subunit of a wide variety of biologically active natural products.[10] However, the synthesis of functionalized indoles still presents a major challenge in organic synthesis. Isoindolo[2,1-*a*]indoles are a class of these functionalized indoles that have been synthesized by employing classical synthetic organic,[11] photochemical,[12] radical,[13,14] and palladium-mediated[14,15] methodologies. The classical synthetic, photochemical, and radical methods that have been reported all afford relatively low yields of the tetracyclic products and have yet to be employed on targets bearing much functionality. Efficient palladium-catalyzed cyclization methodology has been reported for the synthesis of these heterocycles. However, no reports of highly functionalized products, or indoles containing functional groups other than a carbonyl group at C-6 of the isoindolo[2,1-*a*]indole structure, have appeared.

Due to our continuing interest in the palladium-catalyzed annulation of internal alkynes, we have investigated the reaction of internal alkynes and imines derived from *o*-iodoanilines and aldehydes and have previously communicated that excellent yields of highly functionalized isoindolo[2,1-*a*]indoles can be synthesized by employing this methodology.[16] Herein, we report the full details of this new isoindolo[2,1-*a*]indole synthesis.

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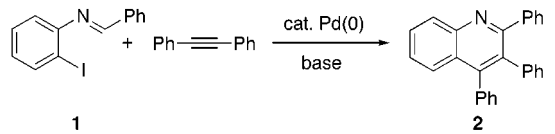
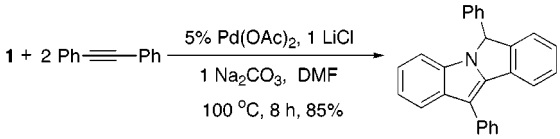
Results and Discussion

The palladium-catalyzed reaction of imine **1** and diphenylacetylene was chosen as the model system for our initial investigation of this annulation process. We anticipated that imine **1** might undergo a reaction with an internal alkyne in the presence of a palladium catalyst to produce the highly substituted quinoline derivative **2** (eq 1). However, when reaction conditions were employed that have been used in much of our previous alkyne annulation chemistry (1 equiv of the aryl imine, 2.0 equiv of the acetylene, 5 mol % $Pd(OAc)_2$, 1 equiv of Na_2CO_3, and 1 equiv of LiCl in DMF at 100 °C),[3-9] none of the anticipated quinoline derivative was observed. Instead, indole **3** was isolated in 85% yield after an 8 h reaction time (eq 2). This surprising result encouraged us to examine the scope and limitations of this intriguing new indole synthesis.

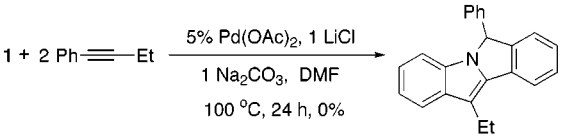


1 **2** (1)



3 (2)

Since the reaction of imine **1** and diphenylacetylene proceeded in high yield with a short reaction time under the reaction conditions that were initially employed, we proceeded to investigate the annulation of **1** with alkynes of differing functionality to expand the scope of this indole synthesis. Many of the alkynes that were employed, however, failed to give yields as good as the reactions that were run with diphenylacetylene. For example, the reaction of imine **1** and 1-phenyl-1-butyne under the reaction conditions that were developed for the diphenylacetylene annulation afforded none of the desired indole **4** (eq 3). Therefore, several optimization reactions were run to improve this reaction (Table 1).



4 (3)

By employing *n*-Bu_4NCl as the chloride source, instead of LiCl, indole **4** was obtained in 65% yield after a 72 h reaction time (entry 1). Upon increasing the amount of Na_2CO_3 to 2 equiv, virtually no increase in yield or decrease in the reaction time was observed (entry 3). Also, no increase in yield was observed by employing *i*-Pr_2NEt as the base (entry 4). However, by increasing the amount of *i*-Pr_2NEt to 2 equiv with 1 equiv of *n*-Bu_4NCl, the yield increased to 75% and the reaction time decreased significantly (entry 5). The yield was not increased, however, by employing 3 equiv of *i*-Pr_2NEt (entry 6). By reducing the amount of the alkyne to 1.2 equiv, indole **4** was isolated in 77% yield (entry 7). Finally, by reducing the amount of alkyne and increasing the concentration of the reaction mixture, the desired product was obtained in 81% yield (entry 8).

Table 1. Synthesis of Indole 4 by the Pd-Catalyzed Annulation of Internal Acetylenes (Eq 3)[a]

entry	base (equiv)	chloride source	time (h)	isolated yield (%)
1	Na_2CO_3 (1)	LiCl	72	0
2	Na_2CO_3 (1)	*n*-Bu_4NCl	72	65
3	Na_2CO_3 (2)	*n*-Bu_4NCl	72	68
4	*i*-Pr_2NEt (1)	*n*-Bu_4NCl	72	63
5	*i*-Pr_2NEt (2)	*n*-Bu_4NCl	36	75
6	*i*-Pr_2NEt (3)	*n*-Bu_4NCl	36	75
7	*i*-Pr_2NEt (2)	*n*-Bu_4NCl	36	77[b]
8	*i*-Pr_2NEt (2)	*n*-Bu_4NCl	36	81[c]

[a] All reactions were run with 0.5 mmol of the imine, 2.0 mmol of 1-phenyl-1-butyne, and 1 equiv of the chloride source in 10 mL of DMF at 100 °C unless otherwise noted. [b] 1.2 equiv of 1-phenyl-1-butyne was used. [c] 1.2 equiv of 1-phenyl-1-butyne and 5 mL of DMF were used.

Table 2. Synthesis of Indole 3 by the Pd-Catalyzed Annulation of Diphenylacetylene[a]

entry	base (equiv)	chloride source	time (h)	isolated yield (%)
1	Na_2CO_3 (1)	LiCl	8	85
2	*i*-Pr_2NEt (2)	*n*-Bu_4NCl	12	84
3	*i*-Pr_2NEt (2)	*n*-Bu_4NCl	12	94[b]
4	*i*-Pr_2NEt (2)	*n*-Bu_4NCl	10	85[c]

[a] All reactions were run with 0.5 mmol of the imine, 2.0 equiv of diphenylacetylene, and 1 equiv of the chloride source in 10 mL of DMF at 100 °C unless otherwise noted. [b] 1.2 equiv of diphenylacetylene was used. [c] 1.2 equiv of diphenylacetylene and 5 mL of DMF were used.

As a consequence of the results reported in Table 1, the reaction of imine **1** and diphenylacetylene was reinvestigated (Table 2). By employing *i*-Pr_2NEt as the base, the desired indole was obtained in an 84% yield (entry 2). However, as in the reaction with 1-phenyl-1-butyne, reducing the amount of alkyne to 1.2 equiv increased the yield to 94% (entry 3). Upon reducing the amount of alkyne and solvent as in Table 1, entry 8, the yield was reduced to 85%.

The results of these optimization studies led to the use of three general reaction procedures for the synthesis of the indoles. Procedure A: 0.5 mmol of the aryl imine, 2.0 equiv of the acetylene, 5 mol % $Pd(OAc)_2$, 1 equiv of Na_2CO_3, and 1 equiv of LiCl in 10 mL of DMF at 100 °C. Procedure B: 0.5 mmol of the aryl imine, 1.2 equiv of the acetylene, 5 mol % $Pd(OAc)_2$, 2 equiv of *i*-Pr_2NEt, and 1 equiv of *n*-Bu_4NCl in 5 mL of DMF at 100 °C. Procedure C: 0.5 mmol of the aryl imine, 1.2 equiv of the acetylene, 5 mol % $Pd(OAc)_2$, 2 equiv of *i*-Pr_2NEt, and 1 equiv of *n*-Bu_4NCl in 10 mL of DMF at 100 °C. The procedure used for these reactions is dependent upon the alkyne that is employed, as one procedure may not give any of the desired indole. In general, alkyl-substituted acetylenes afford better yields when procedure B is employed and diaryl acetylenes afford better yields when procedure C is employed. The other substituted alkynes (ester, hydroxyl) usually afford better yields when procedure A is employed. The indoles that have been synthesized using these procedures are shown in Table 3.

The reaction of imine **1** with a variety of functionalized alkynes has afforded the desired indoles in good to excellent yields. For example, the reaction with diphenylacetylene gave indole **3** in 94% yield by employing procedure C (entry 3). Also, the reaction of **1** with alkyl-

Table 3. Synthesis of Isoindolo[2,1-*a*]indoles by the Pd-Catalyzed Annulation of Internal Alkynes[a]

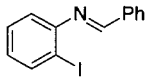
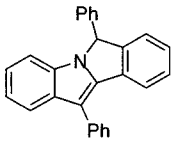
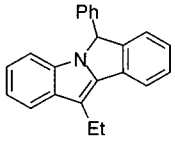
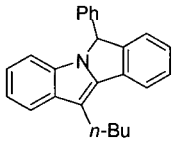
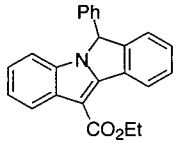
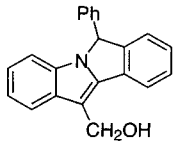
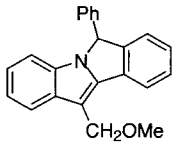
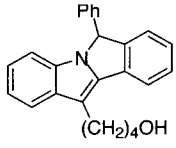
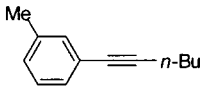
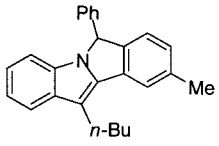
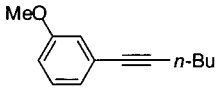
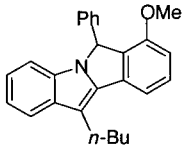
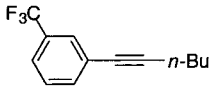
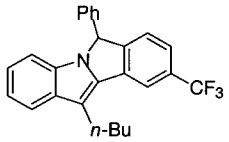
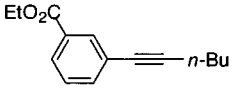
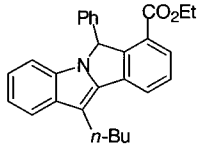
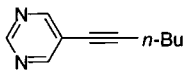
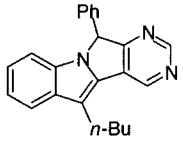
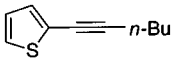
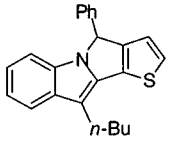
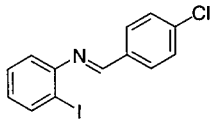
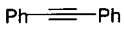
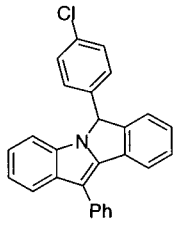
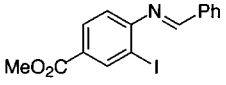
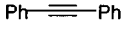
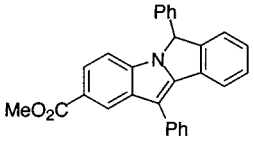
entry	imine	alkyne	procedure, time (h)	product	% yield
1	 **1**		A, 8	 **3**	85
2			B, 10		85
3			C, 12		94
4			A, 72	 **4**	0
5			B, 36		81
6			C, 36		77
7			B, 24	 **5**	81
8			A, 4	 **6**	80
9			A, 24	 **7**	51
10			B, 12	 **8**	46
11			B, 10	 **9**	72
12			B, 36	 **10**	81

Table 3. (Continued)

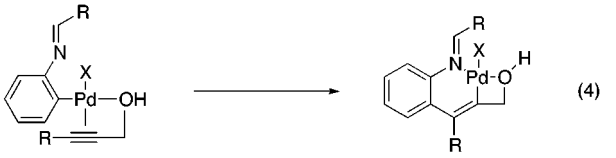
entry	imine	alkyne	procedure, time (h)	product	% yield
13			B, 36	 **11**	78
14			B, 18	 **12**	95
15			B, 18	 **13**	74
16			B, 10	 **14**	93
17			B, 19	 **15**	84
18	 **16**		C, 12	 **17**	93
19	 **18**		C, 18	 **19**	83

[a] See the text for procedures A–C.

substituted alkynes afforded the desired heterocycles in excellent yields by employing procedure B (entries 5 and 7). The annulation with ethyl phenylpropiolate afforded **6** in 80% yield using procedure A (entry 8).

The reaction of 3-phenyl-2-propyn-1-ol gave indole **7** in only 51% yield (entry 9). The low yield associated with this alkyne can possibly be explained by a directive effect of the hydroxyl substituent on the alkyne, which has been

observed previously in analogous indole chemistry[3] and the palladium-catalyzed hydroarylation of propargylic alcohols.[17] This effect appears to direct alkyne insertion so that the palladium adds to the least hindered end of the alkyne (eq 4). Consequently, the tetracyclic product cannot be formed from this vinylpalladium intermediate, which would be expected to undergo unknown side reactions, although no other products were isolated from this reaction (see the latter mechanistic discussion).



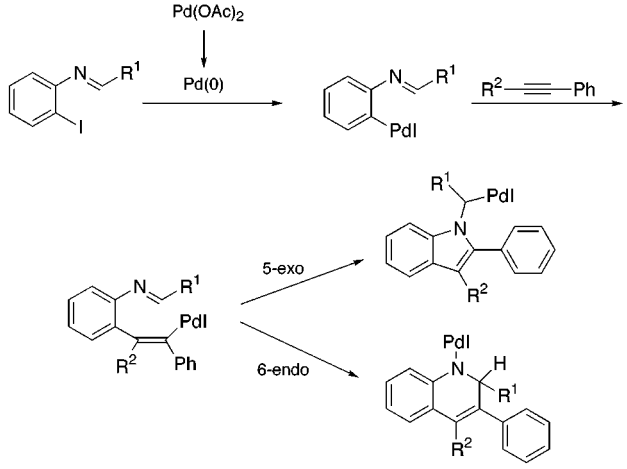
(4)

In an attempt to avoid the directive effect of the propargylic alcohol, 1-phenyl-3-methoxy-1-propyne was subsequently employed in the annulation with imine **1**. However, it appears that the effect of the methyl ether is still significant, as only a low yield of indole **8** was observed (46%, entry 10). 6-Phenyl-5-hexyn-1-ol, which has an additional three-carbon spacer between the triple bond and the free hydroxyl substituent, was also employed in the reaction with imine **1**. A significant increase in yield was observed from this alkyne annulation (72%, entry 11) when compared to that of the propargylic alcohol or its methyl ether, although some effect of the heteroatom may still be operating, since the yield was lower than in the annulation in which 1-phenyl-1-hexyne was employed (compare entries 7 and 11).

We have also investigated the regiochemistry of ring closure onto the aryl group of the acetylene (entries 12−15). This has been done by employing alkynes which bear substituents *meta* to the alkynyl substituent. In the case of the aryl acetylene bearing a methyl group, a single regioisomer, **10**, was obtained in 81% yield (entry 12). Also, a single regioisomer, **11,** was isolated in 78% yield from the annulation using an aryl acetylene bearing an electron-donating methoxy group (entry 13). By ^{1}H NMR spectral analysis, regioisomer **10** was obtained, which has the methyl substituent in the 9-position of the isoindoloindole. However, isoindoloindole **11** has the electron-donating methoxy substituent in the 7-position. The excellent regioselectivity of this ring closure and the reversal of regioselectivity upon switching from the electron-donating methoxy group to the relatively neutral methyl group were rather surprising, so we therefore investigated the use of aryl alkynes bearing electron-withdrawing substituents.

When aryl alkynes bearing electron-withdrawing substituents were employed with imine **1**, single regioisomers were also obtained. For example, isoindoloindole **12** was obtained in which the trifluoromethyl substituent appears in the 9-position, as had been observed with the aryl alkyne bearing a methyl group (entry 14). Surprisingly, an aryl alkyne bearing an electron-withdrawing ester group reacted in such a manner as to place the ester functionality in the 7-position, as had been observed with the aryl alkyne bearing an electron-donating methoxy group (entry 15).

Scheme 1



From these results, it appears that substituents on the aryl ring of the alkyne are able to control the regioselectivity of ring closure by chelation of the palladium in the σ-palladium intermediate that is formed during the reaction (see the latter mechanistic discussion). Thus, products were isolated in which ring closure had occurred to place the oxygen-containing alkoxy or ester functionalities in the 7-position. However, when aryl alkynes were employed that contained trifluoromethyl or methyl substituents, products were isolated with these substituents in the 9-position, presumably due to steric interactions that inhibit ring closure and thus place these groups in the 7-position. Thus, it appears that by the appropriate choice of functionality, it is possible to exclusively prepare one isoindoloindole isomer.

In addition to the previous examples, ring closure onto heterocyclic rings has also been investigated. For example, 5-pyrimidyl-1-hexyne afforded a 93% yield of the desired tetracyclic indole in a short reaction time (entry 16). A thienyl-substituted acetylene also undergoes this annulation process to afford heterocycle **15** in 84% yield (entry 17).

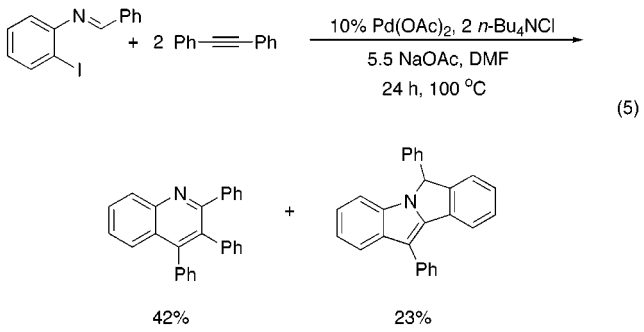
Finally, the annulation of functionalized imines also affords the tetracyclic indoles in good yields. For example, the annulation of imine **16** with diphenylacetylene afforded indole **17** in 93% yield (entry 18). This example not only demonstrates the ease of introduction of additional functionality into the tetracyclic structure, but it also shows the chemoselectivity of the annulation. Imine **18** bearing an electron-withdrawing methyl ester has also been employed with diphenylacetylene to afford indole **19** in good yield (entry 19).

As mentioned previously, the anticipated product from the annulation of imine **1** and diphenylacetylene was the highly substituted quinoline derivative **2** (eq 1). To our surprise, none of this heterocycle was observed and tetracyclic indole **3** was isolated as the only product in 85% yield. From a mechanistic standpoint, these two heterocycles can be formed from two different possible ring closure pathways as illustrated in Scheme 1. Following reduction of $Pd(OAc)_2$ to the actual catalyst Pd(0), oxidative addition of the aryl iodide to Pd(0), and coordination and subsequent insertion of the acetylene, either a 5-*exo* or 6-*endo* addition of the vinylpalladium intermediate across the adjacent carbon−nitrogen double bond can occur. The σ-palladium intermediate resulting from the 5-*exo* cyclization proceeds to form the observed

(17) (a) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron* **1985**, *41*, 5121. (b) Arcadi, A.; Cacchi, S.; Ianelli, S.; Marinelli, F.; Nardelli, M. *Gazz. Chim. Ital.* **1986**, *116*, 725. (c) Arcadi, A.; Bernocchi, E.; Burini, A.; Cacchi, S.; Marinelli, F.; Pietroni, B. *Tetrahedron* **1988**, *44*, 481. (d) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1986**, *27*, 6397.

tetracyclic products, and the 6-*endo* pathway might be expected to form the anticipated quinoline derivative. In this palladium-catalyzed process, however, the 5-*exo* pathway, which forms the tetracyclic products, occurs exclusively.

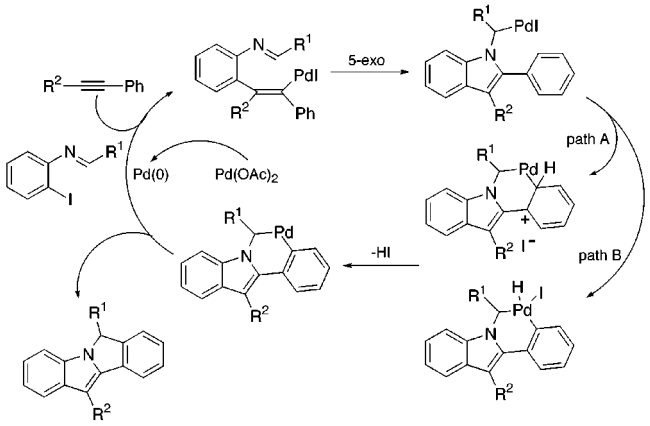
Numerous examples have been reported in the literature in which palladium intermediates can cyclize via *exo* or *endo* pathways in Heck-type reactions. Although the *exo* mode cyclizations have generally been observed to be the dominant ring closure pathway when substrates are employed that can cyclize via either process, various examples of the less favored *endo* mode pathway have been reported.[18] Preliminary data suggest that, by slightly altering the reaction conditions employed in this annulation process, it is possible to promote the formation of quinoline derivatives through the 6-*exo* cyclization pathway (eq 5).[19] However, a significant amount of the tetracyclic product has also generally been observed. Work on this process is continuing.



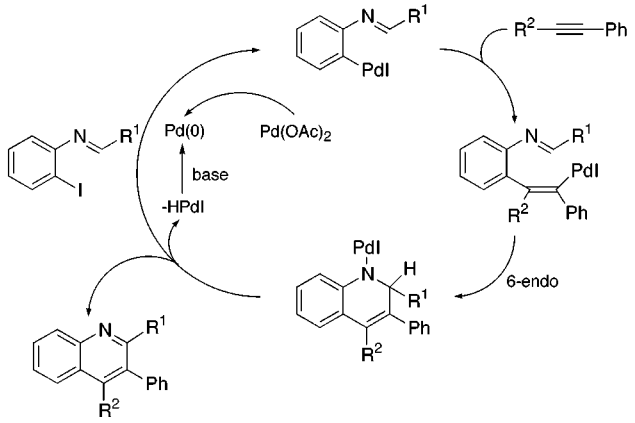
(5)

On the basis of the previous discussion, we propose a mechanism for this remarkable isoindoloindole synthesis involving (1) reduction of $Pd(OAc)_2$ to the actual catalyst Pd(0), (2) oxidative addition of the aryl iodide to Pd(0), (3) coordination and subsequent insertion of the acetylene, (4) a 5-*exo* addition of the vinylpalladium intermediate across the carbon−nitrogen double bond, (5) either electrophilic palladation of the σ-palladium intermediate onto the adjacent aromatic ring (path A) or oxidative addition of the neighboring aryl carbon−hydrogen bond of the aromatic ring to the σ-palladium intermediate to form a Pd(IV) intermediate (path B) and subsequent elimination of HI by base, and (6) regeneration of the Pd(0) catalyst by reductive elimination to form the isoindoloindole as shown in Scheme 2. The reduction of the Pd(II) salt to Pd(0) under the reaction conditions employed is a well-known process and appears to be the key step in virtually all of our annulation chemistry, as are the next two steps, oxidative addition and alkyne insertion. The regiochemistry of alkyne insertion is also consistent with all of our previous annulation work, where steric effects dominate and direct the palladium moiety to the more sterically hindered end of the alkyne. The addition of the resulting vinylic palladium intermediate to the imine double bond is unprecedented. While most organometallics, including allylic palladium species,[20] add to imines to form new carbon−carbon bonds, acylpalladium species have been shown to react with

Scheme 2



Scheme 3



formation of an amide bond,[21] and calculations have been carried out on the addition of methylpalladium species to an imine with C−N bond formation.[22] The resulting benzylic palladium compound cannot undergo β-hydride elimination, but apparently can undergo either electrophilic substitution on the neighboring arene originating in the alkyne or perhaps substitution by a process involving aryl C−H insertion to generate a Pd(IV) intermediate, which then undergoes reductive elimination to the final product.

An alternative mechanism for formation of the isoindoloindole product might involve substitution of the palladium moiety in the vinylic palladium intermediate by the imine functionality to generate an indole iminium salt, which subsequently undergoes intramolecular electrophilic substitution on the neighboring arene. This seems less likely on the basis of the unusual substituent effects reported in entries 12−15 in Table 3. These results seem more consistent with metal coordination to the oxygen-containing methoxy and carboalkoxy substituents.

Likewise, we propose a mechanism for formation of the quinoline heterocycle involving (1) reduction of $Pd(OAc)_2$ to the actual catalyst Pd(0), (2) oxidative addition of the aryl iodide to Pd(0), (3) coordination and subsequent

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(21) (a) Kacker, S.; Kim, J. S.; Sen, A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1251. (b) Dghaym, R. D.; Yaccato, K. J.; Arndtsen, B. A. *Organometallics* **1998**, *17*, 4.

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insertion of the acetylene, (4) a 6-*endo* addition of the vinylic palladium intermediate across the carbon−nitrogen double bond, (5) β-hydride elimination to form the quinoline, and (6) regeneration of the Pd(0) catalyst by reductive elimination of HPdI, as shown in Scheme 3.

Conclusion

We have developed an efficient, palladium-catalyzed synthesis of isoindolo[2,1-*a*]indoles from readily available starting materials. A wide variety of aryl acetylenes in which the aromatic ring of the alkyne contains either a phenyl or a heterocyclic ring undergo this process in moderate to excellent yields with high regioselectivity. In addition, preliminary results indicate that the formation of highly substituted quinoline heterocycles may be possible by slightly altering the reaction conditions employed.

Experimental Section

General Procedures. All ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F), and visualization was effected with short-wavelength UV light (254 nm) and a basic $KMnO_4$ solution [3 g of $KMnO_4$ + 20 g of K_2CO_3 + 5 mL of NaOH (5%) + 300 mL of H_2O]. All melting points are uncorrected. All reagents were used directly as obtained commercially unless otherwise noted. Anhydrous forms of Na_2CO_3, LiCl, DMF, ethyl ether, hexanes, and ethyl acetate were purchased from Fisher Scientific Co. All palladium salts were donated by Johnson Matthey Inc. and Kawaken Fine Chemicals Co. Ltd. PPh_3 was donated by Kawaken Fine Chemicals Co. Ltd. Compounds **3**−**6** and **9**−**14** have been previously reported.[16] Methyl 3-iodo-4-aminobenzoate was prepared according to a previous literature procedure.[23] The following starting materials were prepared as indicated.

General Procedure for the Synthesis of the Aryl Alkynes. To a solution of the iodo- or bromoarene (10.0 mmol) and terminal alkyne (12.0 mmol) in Et_3N (40 mL) was added $PdCl_2(PPh_3)_2$ (140 mg, 2 mol %). The mixture was then stirred for 5 min, and CuI (20 mg, 1 mol %) was added. The resulting mixture was heated under a nitrogen atmosphere at 50 °C. The reaction was monitored by TLC to establish completion. The reaction mixture was allowed to cool to room temperature, and the ammonium salt was removed by filtration. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel to afford the pure alkynes.

Alkynes Prepared. 1-Phenyl-3-methoxy-1-propyne. The acetylene was prepared by employing iodobenzene (2.04 g, 10 mmol) and methyl propargyl ether (0.84 g, 12 mmol). Column chromatography on silica gel using 20:1 hexanes/EtOAc afforded 1.39 g (95%) of the desired compound as a yellow oil with spectral properties identical to those previously reported.[24]

6-Phenyl-5-hexyn-1-ol. The acetylene was prepared by employing iodobenzene (2.04 g, 10 mmol) and 5-hexyn-1-ol (1.18 g, 12 mmol). Column chromatography on silica gel using 2:1 hexanes/EtOAc afforded 1.70 g (98%) of the desired compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.63−1.80 (m, 5H), 2.45 (t, J = 6.6 Hz, 2H), 3.70 (t, J = 6.3 Hz, 2H), 7.24−7.29 (m, 3H), 7.36−7.41 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 19.3, 25.1, 32.0, 62.5, 81.0, 90.0, 124.0, 127.7, 128.3, 131.6.

1-(3-Methylphenyl)-1-hexyne. The acetylene was prepared by employing 3-bromotoluene (1.71 g, 10.0 mmol) and 1-hexyne (0.99 g, 12.0 mmol) at 90 °C. Column chromatography on silica gel using hexanes afforded 1.70 g (99%) of the desired compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.96 (t, J = 7.2 Hz, 3H), 1.44−1.54 (m, 2H), 1.56−1.65 (m, 2H), 2.32 (s, 3H), 2.42 (t, J = 6.9 Hz, 2H), 7.08 (d, J = 7.2 Hz, 1H), 7.15−7.24 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 13.7, 19.2, 21.3, 22.1, 31.0, 80.7, 90.1, 124.0, 128.2, 128.4, 128.7, 132.3, 137.9.

1-(3-Methoxyphenyl)-1-hexyne. The acetylene was prepared by employing 3-iodoanisole (2.34 g, 10.0 mmol) and 1-hexyne (0.99 g, 12.0 mmol). Column chromatography on silica gel using 25:1 hexanes/EtOAc afforded 1.88 g (100%) of the desired compound as a yellow oil with spectral properties identical to those previously reported.[25]

1-(3-Trifluoromethylphenyl)-1-hexyne. The acetylene was prepared by employing 3-iodobenzotrifluoride (2.72 g, 10.0 mmol) and 1-hexyne (0.99 g, 12.0 mmol). Column chromatography on silica gel using hexanes afforded 2.26 g (100%) of the desired compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.96 (t, J = 7.2 Hz, 3H), 1.41−1.65 (m, 4H), 2.42 (t, J = 6.9 Hz, 2H), 7.39 (dd, J = 7.8, 7.8 Hz, 1H), 7.52 (d, J = 13.8 Hz, 1H), 7.54 (d, J = 13.5 Hz, 1H), 7.65 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7, 19.1, 22.1, 30.7, 79.3, 92.3, 123.9 (q, $^1J_{C-F}$ = 272.6 Hz), 124.1 (q, $^3J_{C-F}$ = 3.9 Hz), 125.1, 128.4 (q, $^4J_{C-F}$ = 3.8 Hz), 128.7, 130.8 (q, $^2J_{C-F}$ = 32.6 Hz), 134.7.

Ethyl 2-(1-hexynyl)benzoate. The acetylene was prepared by employing ethyl 3-iodobenzoate (2.76 g, 10.0 mmol) and 1-hexyne (0.99 g, 12.0 mmol). Column chromatography on silica gel using 20:1 hexanes/EtOAc afforded 2.16 g (94%) of the desired compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.93 (t, J = 7.2 Hz, 3H), 1.37 (t, J = 7.2 Hz, 3H), 1.42−150 (m, 2H), 1.53−1.63 (m, 2H) 2.39 (t, J = 6.9 Hz, 2H), 4.35 (q, J = 7.2 Hz, 2H), 7.32 (ddd, J = 0.3, 7.8, 7.8 Hz, 1H), 7.53 (ddd, J = 1.5, 1.5, 6.3 Hz, 1H), 7.91 (ddd, J = 1.2, 1.2, 7.8 Hz, 1H), 8.05 (dd, J = 1.5, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7, 14.4, 19.1, 22.1, 30.8, 61.1, 79.8, 91.5, 124.6, 128.3, 128.5, 130.7, 132.7, 135.7, 166.1.

1-(5-Pyrimidyl)-1-hexyne. The acetylene was prepared by employing 5-bromopyrimidine (1.59 g, 10 mmol) and 1-hexyne (0.99 g, 12 mmol). Column chromatography on silica gel using 15:1 hexanes/EtOAc afforded 1.53 g (96%) of the desired compound as a dark yellow oil with spectral properties identical to those previously reported.[26]

1-(2-Thienyl)-1-hexyne.[27] The acetylene was prepared by employing 2-iodothiophene (2.10 g, 10 mmol) and 1-hexyne (0.99 g, 12 mmol). Column chromatography on silica gel using 25:1 hexanes/EtOAc afforded 1.64 g (100%) of the desired compound as a dark yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.96 (t, J = 7.2 Hz, 3H), 1.41−1.65 (m, 4H), 2.44 (t, J = 7.2 Hz, 2H), 6.94 (dd, J = 3.6, 5.1 Hz, 1H), 7.12 (dd, J = 1.2, 3.6 Hz, 1H), 7.17 (dd, J = 1.2, 5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7, 19.5, 22.1, 30.7, 73.7, 94.6, 124.4, 125.9, 126.8, 130.9.

Imines Prepared. Benzylidene(2-iodophenyl)amine (1).[28] A mixture of 2-iodoaniline (2.19 g, 10 mmol), benzaldehyde (1.06 g, 10 mmol), and *p*-toluenesulfonic acid monohydrate (1 crystal) in benzene (40 mL) was refluxed with the aid of a Dean−Stark apparatus to remove the water produced. The reaction was monitored by TLC to establish completion. The reaction mixture was then cooled to room temperature, and the solvent was removed under reduced pressure. The oily residue was dissolved in a minimal amount of 100% ethanol and cooled. The resulting solid was collected to afford 2.15 g (70%) of the imine **21** as an off-white solid: mp 56−57 °C; ^{1}H NMR ($CDCl_3$) δ 6.94 (td, J = 1.5, 7.8 Hz, 1H), 7.02 (dd, J = 1.5, 8.1 Hz, 1H), 7.38 (td, J = 1.2, 7.5 Hz, 1H), 7.48−7.55 (m, 3H), 7.93 (dd, J = 1.2, 7.8 Hz, 1H), 7.99−8.02 (m, 2H), 8.31 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 95.0, 118.6, 127.2, 129.0, 129.3, 129.5,

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131.9, 135.9, 139.2, 153.1, 161.1; IR ($CHCl_3$, cm^{-1}) 3052, 3001, 1626, 1573; HRMS calcd for $C_{13}H_{10}IN$ 306.9858, found 306.9855.

4-Chlorobenzylidene(2-iodophenyl)amine (16). The imine was prepared by the same method used for imine **1** by employing 2-iodoaniline (2.19 g, 10 mmol) and 4-chlorobenzaldehyde (1.41 g, 10 mmol). Crystallization from 100% ethanol afforded 2.46 g (72%) of the imine **16** as a yellow solid: mp 44−45 °C; ^{1}H NMR ($CDCl_3$) δ 6.94 (td, J = 0.9, 5.7 Hz, 1H), 7.00 (dd, J = 1.2, 6.0 Hz, 1H), 7.37 (td, J = 0.9, 6.0 Hz, 1H), 7.47 (dt, J = 1.5, 6.6 Hz, 2H), 7.90−7.93 (m, 3H), 8.26 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 95.0, 118.3, 127.4, 129.2, 129.4, 130.3, 134.3, 137.9, 139.2, 152.7, 159.5; IR ($CHCl_3$, cm^{-1}) 3056, 2997, 1628, 1569; HRMS calcd for $C_{13}H_9ClIN$ 340.9468, found 340.9472.

Methyl 4-Benzylideneamino-3-iodobenzoate (18). The imine was prepared by the method used for imine **1** by employing methyl 3-iodo-4-aminobenzoate (4.27 g, 15.4 mmol) and benzaldehyde (2.45 g, 23.1 mmol). Crystallization from 100% ethanol afforded 1.46 g (40%) of the imine **18** as an off-white solid: mp 64−65 °C; ^{1}H NMR ($CDCl_3$) δ 3.93 (s, 3H), 7.00 (d, J = 8.1 Hz, 1H), 7.45−7.57 (m, 3H), 7.98 (dd, J = 1.5, 6.3 Hz, 2H), 8.04 (dd, J = 1.5, 8.1 Hz, 1H), 8.30 (s, 1H), 8.5 (d, J = 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 52.4, 93.6, 118.2, 128.5, 129.0, 129.4, 131.0, 132.3, 135.5, 140.5, 157.2, 162.0, 165.6; IR ($CHCl_3$, cm^{-1}) 3060, 2949, 1720, 1631, 1585; HRMS calcd for $C_{15}H_{12}INO_2$ 364.9913, found 364.9921.

General Procedure for the Palladium-Catalyzed Formation of Isoindolo[2,1-*a*]indoles. Procedure A: DMF (10 mL), $Pd(OAc)_2$ (6 mg, 0.027 mmol), LiCl (21 mg, 0.5 mmol), Na_2CO_3 (56 mg, 0.5 mmol), and the alkyne (1.0 mmol) were placed in a 4 dram vial. Procedure B: DMF (5 mL), $Pd(OAc)_2$ (6 mg, 0.027 mmol), *n*-Bu_4NCl (139 mg, 0.5 mmol), *i*-Pr_2NEt (130 mg, 1.0 mmol), and the alkyne (0.6 mmol) were placed in a 2 dram vial. Procedure C: DMF (10 mL), $Pd(OAc)_2$ (6 mg, 0.027 mmol), *n*-Bu_4NCl (139 mg, 0.5 mmol), *i*-Pr_2NEt (130 mg, 1.0 mmol), and the alkyne (1.2 mmol) were placed in a 4 dram vial. The chemicals for procedures A−C were mixed, and the appropriate imine (0.5 mmol) was added. The vial was flushed with nitrogen and heated in an oil bath at 100 °C for the indicated period of time. The reaction was monitored by TLC to establish completion. The reaction mixture was then cooled to room temperature, diluted with 30 mL of ether, washed with 45 mL (procedures A and C) or 30 mL (procedure B) of saturated aqueous NH_4Cl, dried (Na_2SO_4), and filtered. The solvent was evaporated under reduced pressure, and the product was isolated by chromatography on a silica gel column.

Compounds Prepared. 6,11-Diphenylisoindolo[2,1-*a*]-indole (Compound 3; Table 3, Entry 3). The reaction was run using procedure C and chromatographed using 25:1 hexanes/EtOAc to afford 168 mg (94%) of the indicated compound as a white solid: mp 168−169 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$) δ 6.20 (s, 1H), 7.02 (dt, J = 0.6, 8.1 Hz, 1H), 7.16 (dddd, J = 1.5, 7.2, 7.2, 22.2 Hz, 2H), 7.25−7.49 (m, 9H), 7.63 (t, J = 7.5 Hz, 2H), 7.87−7.94 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 64.5, 109.8, 110.3, 120.3, 120.5, 121.1, 122.4, 124.1, 126.5, 127.3, 127.7, 128.4, 128.6, 128.9, 129.3, 129.5, 131.9, 132.0, 133.7, 135.1, 138.9, 139.5, 147.5; IR ($CHCl_3$, cm^{-1}) 3065, 3028, 1602, 1450; MS *m*/*z* (rel intens) 358 (28, M + 1), 357 (100, M^+), 356 (26), 280 (78). Anal. Calcd for $C_{27}H_{19}N$: C, 90.72; H, 5.36; N, 3.92. Found: C, 90.39; H, 5.61; N, 3.94.

11-Ethyl-6-phenylisoindolo[2,1-*a*]indole (Compound 4; Table 3, Entry 5). The reaction was run using procedure B and chromatographed using 25:1 hexanes/EtOAc to afford 126 mg (81%) of the indicated compound as a white solid: mp 144−145 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.50 (t, J = 7.5 Hz, 3H), 3.18 (q, J = 7.5 Hz, 2H), 6.14 (s, 1H), 6.97 (dd, J = 1.8, 7.8 Hz, 1H), 7.06−7.16 (m, 2H), 7.22−7.26 (m, 4H), 7.35−7.47 (m, 4H), 7.75 (d, J = 8.1 Hz, 1H), 7.84 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 15.9, 18.1, 64.3, 109.9, 110.1, 119.1, 119.8, 120.9, 121.7, 124.1, 126.8, 127.2, 128.4, 128.5, 129.1, 132.5, 132.8, 133.6, 139.1, 139.4, 147.2; IR ($CHCl_3$, cm^{-1}) 3057, 2926, 1611, 1451; HRMS calcd for $C_{23}H_{19}N$ 309.1518, found 309.1516. Anal. Calcd for $C_{23}H_{19}N$: C, 89.28; H, 6.19; N, 4.53. Found: C, 88.95; H, 6.47; N, 4.66.

11-*n*-Butyl-6-phenylisoindolo[2,1-*a*]indole (5). The reaction was run using procedure B and chromatographed using 25:1 hexanes/EtOAc to afford 137 mg (81%) of the indicated compound as a white solid: mp 135−136 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.04 (t, J = 7.5 Hz, 3H), 1.56 (sextet, J = 7.5 Hz, 2H), 1.86 (quintet, J = 7.5 Hz, 2H), 3.14 (t, J = 7.5 Hz, 2H), 6.14 (s, 1H), 6.93 (dd, J = 0.9, 7.5 Hz, 1H), 7.09 (dddd, J = 1.2, 7.2, 7.2, 17.7 Hz, 2H), 7.18−7.24 (m, 4H), 7.33−7.44 (m, 4H), 7.71 (dd, J = 0.6, 8.1 Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3, 22.9, 24.5, 33.5, 64.3, 108.3, 110.0, 119.1, 119.9, 120.9, 121.6, 124.1, 126.8, 127.2, 128.3, 128.4, 129.1, 132.5, 133.1, 133.5, 139.4, 139.5, 147.2; IR ($CHCl_3$, cm^{-1}) 3046, 2922, 1610, 1450; HRMS calcd for $C_{25}H_{23}N$ 337.1831, found 337.1831. Anal. Calcd for $C_{25}H_{23}N$: C, 88.98; H, 6.87; N, 4.15. Found: C, 88.72; H, 7.00; N, 4.26.

Ethyl 6-Phenylisoindolo[2,1-*a*]indole-11-carboxylate (6). The reaction was run using procedure A and chromatographed using 7:1 hexanes/EtOAc to afford 141 mg (80%) of the indicated compound as a white solid: mp 181−182 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.57 (t, J = 7.2 Hz, 3H), 4.55 (q, J = 7.2 Hz, 2H), 6.02 (s, 1H), 6.90 (d, J = 8.1 Hz, 1H), 7.06−7.13 (m, 3H), 7.24 (dt, J = 0.9, 14.4 Hz, 2H), 7.30−7.37 (m, 4H), 7.49 (dt, J = 0.6, 14.7 Hz, 1H), 8.28 (d, J = 8.1 Hz, 1H), 8.78 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.9, 60.0, 64.9, 99.9, 110.4, 122.0, 122.9, 123.4, 125.7, 127.2, 128.8, 129.2, 129.3, 130.7, 131.2, 133.1, 137.5, 148.3, 148.6, 165.8 (two sp^2 carbons missing due to overlap); IR ($CHCl_3$, cm^{-1}) 3056, 2980, 1688, 1559; HRMS calcd for $C_{24}H_{19}NO_2$ 353.1416, found 353.1416.

11-Hydroxymethyl-6-phenylisoindolo[2,1-*a*]indole (7). The reaction was run using procedure A and chromatographed using 1:1 hexanes/EtOAc to afford 80 mg (51%) of the indicated compound as a white solid: mp 182−183 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.59 (br s, 1H), 5.20 (s, 2H), 6.12 (s, 1H), 6.92 (d, J = 7.8 Hz, 1H), 7.10 (dddd, J = 1.2, 6.9, 6.9, 19.5 Hz, 2H), 7.15−7.22 (m, 2H), 7.25, (dd, J = 0.9, 5.4 Hz, 2H), 7.28−7.35 (m, 3H), 7.41 (td, J = 1.8, 8.1 Hz, 1H), 7.76 (d, J = 7.5 Hz, 1H), 7.92 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 56.2, 64.6, 106.6, 110.2, 119.7, 120.0, 121.8, 122.1, 124.0, 127.2, 127.6, 128.5, 128.6, 129.2, 131.5, 132.1, 133.4, 138.7, 141.3, 147.3; IR ($CHCl_3$, cm^{-1}) 3382, 3047, 1614, 1450; HRMS calcd for $C_{22}H_{17}NO$ 311.1310, found 311.1307.

11-Methoxymethyl-6-phenylisoindolo[2,1-*a*]indole (8). The reaction was run using procedure B and chromatographed using 10:1 hexanes/EtOAc to afford 75 mg (46%) of the indicated compound as a white solid: mp 144−145 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$) δ 3.53 (s, 3H), 5.03 (s, 2H), 6.12 (s, 1H), 6.94 (dd, J = 0.3, 7.8 Hz, 1H), 7.11 (dddd, J = 1.2, 7.2, 7.2, 21.6 Hz, 2H), 7.19 (dd, J = 3.6, 7.5 Hz, 2H), 7.25−7.27 (m, 2H), 7.33−7.36 (m, 3H), 7.43 (td, J = 2.4, 8.1 Hz, 1H), 7.78 (dd, J = 0.6, 7.8 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 57.6, 64.5, 65.3, 103.8, 110.2, 119.90, 119.94, 121.9, 122.0, 124.0, 127.2, 127.5, 128.5, 128.6, 129.2, 131.8, 132.9, 133.4, 138.83, 141.9, 147.4; IR ($CHCl_3$, cm^{-1}) 3055, 2923, 1612, 1451; HRMS calcd for $C_{23}H_{19}NO$ 325.1467, found 325.1466. Anal. Calcd for $C_{23}H_{19}NO$: C, 84.89; H, 5.88; N, 4.30. Found: C, 84.82; H, 6.16; N, 4.36.

11-(4-Hydroxybutyl)-6-phenylisoindolo[2,1-*a*]indole (9). The reaction was run using procedure B and chromatographed using 1:1 hexanes/EtOAc to afford 127 mg (72%) of the indicated compound as a white solid: mp 136−137 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.61 (br s, 1H), 1.73−1.82 (m, 2H), 1.89−1.99 (m, 2H), 3.16 (t, J = 7.2 Hz, 2H), 3.71 (t, J = 6.6 Hz, 2H), 6.13 (s, 1H), 6.93 (dd, J = 1.2, 7.2 Hz, 1H), 7.08 (dddd, J = 1.2, 7.2, 7.2, 15.9 Hz, 2H), 7.17−7.26 (m, 4H), 7.31−7.43, (m, 4H), 7.68 (dd, J = 1.2, 6.9 Hz, 1H), 7.80 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 24.4, 27.3, 32.7, 63.1, 64.2, 107.6, 110.1, 119.2, 119.8, 120.8, 121.7, 124.1, 126.9, 127.2, 128.3, 128.4, 129.1, 132.4, 133.0, 133.5, 139.3, 139.6, 147.1; IR ($CHCl_3$, cm^{-1}) 3046, 2922, 1610, 1450; IR ($CHCl_3$, cm^{-1}) 3365, 3049, 2935, 1610, 1450; HRMS calcd for $C_{25}H_{23}NO$ 353.1780, found 353.1787.

11-*n*-Butyl-9-methyl-6-phenylisoindolo[2,1-*a*]indole (10). The reaction was run using procedure B and chromatographed using 50:1 hexanes/EtOAc to afford 142 mg (81%) of the

indicated compound as a yellow solid: mp 122−124 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.08 (t, J = 7.2 Hz, 3H), 1.61 (sextet, J = 7.5 Hz, 2H), 1.90 (quintet, J = 7.2 Hz, 2H), 2.51 (s, 3H), 3.18 (t, J = 7.5 Hz, 2H), 6.11 (s, 1H), 6.95 (dd, J = 1.2, 6.9 Hz, 1H), 7.05−7.17 (m, 4H), 7.20−7.25 (m, 2H), 7.32−7.40 (m, 3H), 7.65 (s, 1H), 7.74 (dd, J = 0.6, 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.4, 21.8, 22.9, 24.5, 33.5, 64.1, 108.2, 110.0, 119.0, 119.9, 121.5, 121.6, 123.8, 127.2, 127.7, 128.3, 129.1, 132.7, 133.2, 133.6, 138.2, 139.6, 139.7, 144.6; IR ($CDCl_3$, cm^{-1}) 3058, 2954, 1620, 1452; HRMS calcd for $C_{26}H_{25}N$ 351.1987, found 351.1987.

11-*n*-Butyl-7-methoxy-6-phenylisoindolo[2,1-*a*]indole (11). The reaction was run using procedure B and chromatographed using 25:1 hexanes/EtOAc to afford 144 mg (78%) of the indicated compound as a white solid: mp 153−154 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$) δ 0.99 (t, J = 7.5 Hz, 3H), 1.52 (sextet, J = 7.5 Hz, 2H), 1.81 (quintet, J = 7.5 Hz, 2H), 3.08 (t, J = 7.5 Hz, 2H), 3.88 (s, 3H), 6.08 (s, 1H), 6.75 (dd, J = 2.4, 8.4 Hz, 1H), 6.89 (dddd, J = 0.9, 0.9, 0.9, 8.1 Hz, 1H), 7.04 (dddd, J = 1.2, 6.9, 6.9, 22.2 Hz, 2H), 7.10 (d, J = 8.4 Hz, 1H), 7.14−7.20 (m, 2H), 7.28−7.36 (m, 4H), 7.65 (dddd, J = 0.9, 0.9, 0.9, 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.4, 22.9, 24.5, 33.5, 55.7, 63.8, 106.7, 108.5, 110.0, 112.3, 119.1, 120.0, 121.7, 124.7, 127.2, 128.3, 129.1, 133.1, 133.6, 133.8, 139.3, 139.6, 139.8, 160.2; IR ($CHCl_3$, cm^{-1}) 3043, 2925, 1626, 1456; HRMS calcd for $C_{26}H_{25}NO$ 367.1936, found 367.1936.

11-*n*-Butyl-9-trifluoromethyl-6-phenylisoindolo[2,1-*a*]indole (12). The reaction was run using procedure B and chromatographed using 25:1 hexanes/EtOAc to afford 193 mg (95%) of the indicated compound as a yellow solid: mp 139−140 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.01 (t, J = 7.2 Hz, 3H), 1.52 (sextet, J = 7.5 Hz, 2H), 1.83 (quintet, J = 7.5 Hz, 2H), 3.11 (t, J = 7.5 Hz, 2H), 6.23 (s, 1H), 6.90 (dd, J = 1.2, 6.3 Hz, 1H), 7.09 (dddd, J = 1.5, 7.2, 7.2, 14.1 Hz, 2H), 7.15 (d, J = 1.8 Hz, 1H), 7.17 (d, J = 4.2 Hz, 1H), 7.29−7.37 (m, 4H), 7.46 (dd, J = 0.6, 8.1 Hz, 1H), 7.70 (dd, J = 1.5, 6.9 Hz, 1H), 7.96 (s,1H); ^{13}C NMR ($CDCl_3$) δ 14.2, 22.8, 24.4, 33.3, 64.1, 109.7, 110.1, 117.4 (q, $^3J_{C-F}$ = 2.8 Hz), 119.4, 120.3, 122.3, 123.6 (q, $^4J_{C-F}$ = 2.7 Hz), 124.2 (q, $^1J_{C-F}$ = 204.1 Hz), 124.4, 127.1, 128.7, 129.3, 130.0 (q, $^2J_{C-F}$ = 24.2 Hz), 133.0, 133.2, 133.5, 137.9, 138.4, 150.3; IR ($CHCl_3$, cm^{-1}) 3049, 2926, 1455, 1438; HRMS calcd for $C_{26}H_{22}F_3N$ 405.1704, found 405.1705.

Ethyl 11-*n*-Butyl-6-phenylisoindolo[2,1-*a*]indole-7-carboxylate (13). The reaction was run using procedure B and chromatographed using 10:1 hexanes/EtOAc to afford 151 mg (74%) of the indicated compound as a yellow solid: mp 120−121 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.02 (t, J = 7.5 Hz, 3H), 1.44 (t, J = 7.2 Hz, 3H), 1.53 (sextet, J = 7.5 Hz, 2H), 1.84 (quintet, J = 7.5 Hz, 2H), 3.14 (t, J = 7.5 Hz, 2H), 4.44 (q, J = 7.2 Hz, 2H), 6.15 (s, 1H), 6.90 (ddd, J = 0.9, 0.9, 8.1 Hz, 1H), 7.07 (dddd, J = 1.2, 7.2, 7.2, 14.7 Hz, 2H), 7.15−7.18 (m, 2H), 7.26 (d, J = 8.1 Hz, 1H), 7.31−7.36 (m, 3H), 7.68 (ddd, J = 1.5, 6.6 Hz, 1H), 7.90 (dd, J = 1.5, 8.1 Hz, 1H), 8.41 (d, J = 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3, 14.5, 22.8, 24.4, 33.4, 61.3, 64.3, 109.3, 110.1, 119.4, 120.2, 121.8, 122.1, 123.9, 127.2, 128.2, 128.6, 129.2, 131.0, 132.9, 133.1, 133.5, 138.4, 138.7, 151.5, 166.4; IR ($CDCl_3$, cm^{-1}) 3056, 2967, 1720, 1437; HRMS calcd for $C_{26}H_{27}NO_2$ 409.2042, found 409.2048.

Compound 14 (Table 3, Entry 16). The reaction was run using procedure B and chromatographed using 1:1 hexanes/EtOAc to afford 158 mg (93%) of the indicated compound as an off-white solid: mp 200−201 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$) δ 0.99 (t, J = 7.2 Hz, 3H), 1.49 (sextet, J = 7.5 Hz, 2H), 1.82 (quintet, J = 7.5 Hz, 2H), 3.08 (t, J = 7.5 Hz, 2H), 6.17 (s, 1H), 6.96 (dddd, J = 3.6, 3.6, 7.8, 7.8 Hz, 1H), 7.13 (dddd, J = 1.2, 1.2, 8.1, 8.1 Hz, 2H), 7.19 (dd, J = 3.6, 7.5 Hz, 2H), 7.35−7.38 (m, 3H), 7.71 (dddd, J = 3.3, 3.3, 11.1, 11.1 Hz, 1H), 9.00 (s, 1H), 9.04 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.2, 22.8, 24.9, 33.2, 64.6, 110.7, 112.4, 120.0, 120.5, 123.2, 125.5, 127.2, 129.0, 129.3, 132.1, 133.5, 134.1, 135.9, 147.8, 156.0, 173.6; IR ($CHCl_3$, cm^{-1}) 3028, 2953, 1495, 1456; HRMS calcd for $C_{23}H_{21}N_3$ 339.1736, found 339.1738.

Compound 15 (Table 3, Entry 17). The reaction was run using procedure B and chromatographed using 25:1 hexanes/EtOAc to afford 144 mg (84%) of the indicated compound as an off-white solid: mp 104−105 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.01 (t, J = 7.2 Hz, 3H), 1.50 (sextet, J = 7.5 Hz, 2H), 1.85 (quintet, J = 7.2 Hz, 2H), 2.95 (t, J = 7.5 Hz, 2H), 6.07 (s, 1H), 6.86−6.89 (m, 2H), 7.04 (dddd, J = 1.5, 6.9, 6.9, 13.8 Hz, 2H), 7.20 (dddd, J = 4.2, 4.2, 4.2, 6.3 Hz, 2H), 7.27 (d, J = 4.8 Hz, 1H), 7.30−7.37 (m, 3H), 7.62 (dddd, J = 0.6, 0.6, 0.6, 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3, 22.9, 24.9, 32.8, 63.2, 105.8, 109.3, 118.9, 120.0, 121.5, 121.7, 127.1, 128.3, 128.4, 129.2, 132.5, 133.0, 134.5, 136.7, 138.6, 151.1; IR ($CHCl_3$, cm^{-1}) 3041, 2925, 1552, 1454; HRMS calcd for $C_{23}H_{21}NS$ 343.1395, found 343.1395.

11-Phenyl-6-(3-chlorophenyl)isoindolo[2,1-*a*]indole (17). The reaction was run using procedure C and chromatographed using 25:1 hexanes/EtOAc to afford 182 mg (93%) of the indicated compound as a white solid: mp 165−166 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$) δ 6.11 (s, 1H), 6.99 (dd, J = 1.2, 7.2 Hz, 1H), 7.13−7.39 (m, 9H), 7.47 (t, J = 7.5 Hz, 1H), 7.63 (t, J = 7.5 Hz, 2H), 7.86−7.93 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 63.7, 110.0, 110.2, 120.5, 120.6, 121.2, 122.5, 123.9, 126.6, 127.8, 128.6, 128.7, 129.0, 129.5, 129.5, 131.8, 132.0, 133.6, 134.4, 134.9, 137.5, 139.3, 147.0; IR ($CHCl_3$, cm^{-1}) 3051, 3016, 1602, 1489; HRMS calcd for $C_{27}H_{18}ClN$ 391.1128, found 391.1121.

Methyl 6,11-Diphenylisoindolo[2,1-*a*]indole-2-carboxylate (19). The reaction was run using procedure C and chromatographed using 15:1 hexanes/EtOAc to afford 172 mg (83%) of the indicated compound as a white solid: mp 170−171 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H), 6.22 (s, 1H), 6.95 (d, J = 8.7 Hz, 1H), 7.21−7.47 (m, 9H), 7.60 (t, J = 7.5 Hz, 2H), 7.77−7.88 (m, 4H), 8.55 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 51.9, 64.5, 109.8, 110.9, 121.3, 122.2, 123.3, 123.8, 124.1, 126.9, 127.2, 128.2, 128.5, 128.7, 129.1, 129.3, 129.5, 131.2, 131.6, 134.1, 136.0, 138.4, 140.7, 147.3, 168.2; IR ($CDCl_3$, cm^{-1}) 3063, 2947, 1711, 1621, 1437; HRMS calcd for $C_{29}H_{21}NO_2$ 415.1572, found 415.1574.

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Supporting Information Available: Copies of ^{1}H and ^{13}C spectra for compounds **1**, **7**, and **15**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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