Synthesis of Isoquinolines and Pyridines by the Palladium/Copper-Catalyzed Coupling and Cyclization of Terminal Acetylenes and Unsaturated Imines: The Total Synthesis of Decumbenine B

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Monosubstituted isoquinolines and pyridines have been prepared in good to excellent yields via coupling of terminal acetylenes with the *tert*-butylimines of *o*-iodobenzaldehydes and 3-halo-2-alkenals in the presence of a palladium catalyst and subsequent copper-catalyzed cyclization of the intermediate iminoalkynes. In addition, isoquinoline heterocycles have been prepared in excellent yields via copper-catalyzed cyclization of iminoalkynes. The choice of cyclization conditions is dependent upon the nature of the terminal acetylene that is employed, as only aryl and alkenyl acetylenes cyclize under the palladium-catalyzed reaction conditions that have been developed. However, aryl-, vinylic-, and alkyl-substituted acetylenes undergo palladium-catalyzed coupling and subsequent copper-catalyzed cyclization in excellent yields. The total synthesis of the isoquinoline natural product decumbenine B has been accomplished in seven steps and 20% overall yield by employing this palladium-catalyzed coupling and cyclization methodology.

Introduction

The palladium-catalyzed annulation of alkynes has recently proven to be a powerful method for the construction of a variety of carbo- and heterocycles. For example, we have employed the annulation of internal alkynes for the synthesis of indoles,[1] isoindolo[2,1-*a*]indoles,[2] benzofurans,[3] benzopyrans,[3] isocoumarins,[3,4] indenones,[5] isoquinolines,[6] α-pyrones,[4,7] and polycyclic aromatic hydrocarbons.[8] In addition, the transition metal-catalyzed cyclization of alkynes, which possess a nucleophile in proximity to the triple bond, by in situ coupling/cyclization reactions,[9] and reactions promoted by *σ*-vinyl-, *σ*-aryl-, and *σ*-alkynylpalladium complexes[10] have also been shown to be extremely effective for the synthesis of a wide variety of carbo- and heterocycles.

Isoquinoline derivatives have been synthesized via base-catalyzed cyclization of terminal and disubstituted alkynes. For example, Sharp has reported the synthesis of *N*-sulfonylimine isoquinolines in modest yields (40−77%) from the base-induced cyclization of *o*-ethynyl hydrazones.[11] The synthesis of these heterocycles is not general, however, as only terminal acetylenes could be cyclized under the reaction conditions employed. The reaction of *o*-alkynyl oximes and K_2CO_3 affords modest yields (39−78%) of isoquinoline *N*-oxides.[12] Finally, 3-substituted isoquinolines are formed by the reaction of *o*-ethynylbenzaldehydes and ammonia in modest to excellent yields (45−95%).[13] Since few examples of the latter two processes have been reported, the true synthetic utility of this chemistry cannot be fully determined at this time.

During the course of our earlier investigation of the palladium-catalyzed iminoannulation of internal alkynes, we observed an interesting new isoquinoline synthesis (eq 1).[6] To our surprise, 3-phenylisoquinoline, and not

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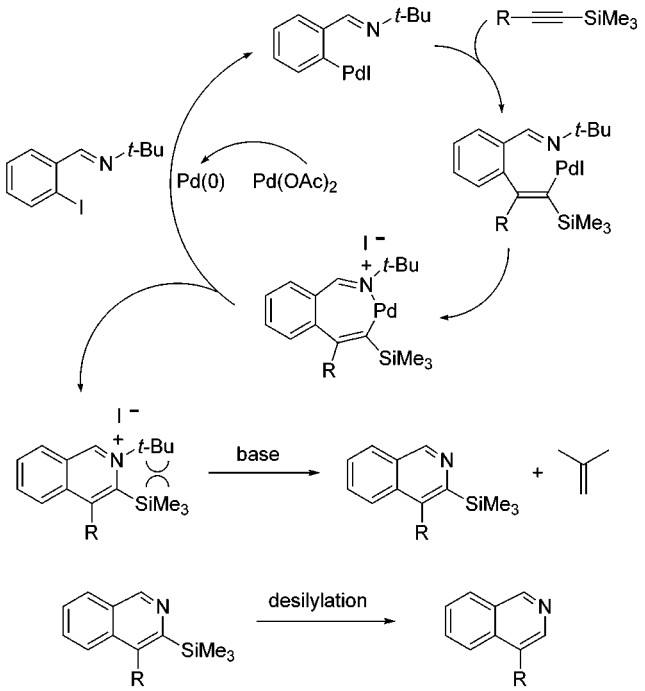
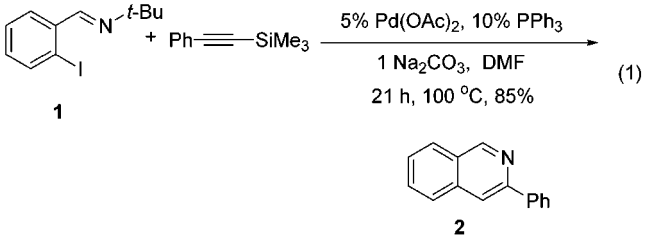
Scheme 1



the expected disubstituted heterocycle, 4-phenyl-3-(trimethylsilyl)isoquinoline, was isolated in 85% yield from the palladium-catalyzed reaction of *N*-(2-iodobenzylidene)-*tert*-butylamine (**1**) and 1-phenyl-2-(trimethylsilyl)acetylene. Herein, we report a full investigation of this intriguing reaction, the development of a new isoquinoline synthesis by the heteroannulation of terminal alkynes, and the application of this methodology to the synthesis of the naturally occurring isoquinoline alkaloid decumbenine B (**38**).[14]

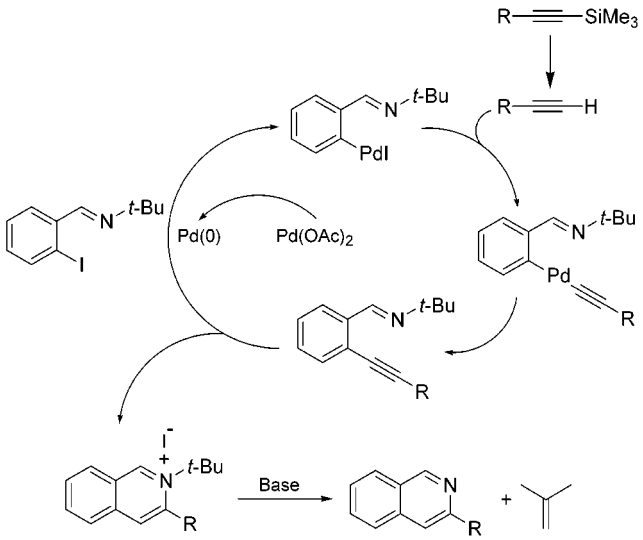


Results and Discussion

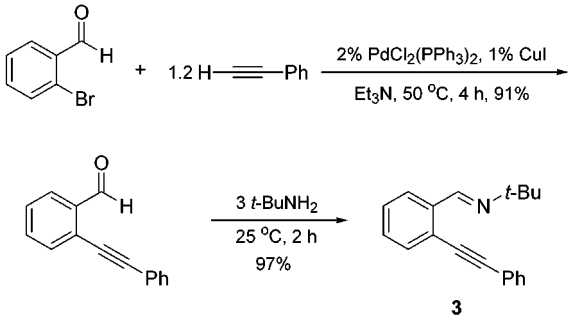
The surprising results obtained from silyl acetylenes (eq 1) encouraged us to examine the mechanism of this interesting transformation and to define the scope and limitations of this new isoquinoline synthesis. On the basis of the regiochemical outcome of much of our other alkyne annulation chemistry, in which the palladium adds to the more hindered end of the alkyne (Scheme 1), the expected products from the reaction with trimethylsilyl-substituted alkynes were either the 3,4-disubstituted products retaining the silyl group or the corresponding 4-substituted isoquinoline arising from desilylation of the 3,4-disubstituted isoquinoline.

However, since a product was isolated from this reaction in which the trimethylsilyl substituent was not incorporated and the phenyl substituent was in the 3-position of the isoquinoline, other mechanisms must be operating in this system. This was confirmed by the observation that 2-(2-phenylethynyl)benzaldehyde could be isolated if the reactions were not allowed to proceed to completion. Therefore, an alternative mechanistic picture was envisioned for this transformation (Scheme 2). Specifically, oxidative addition of the aryl halide to Pd(0) produces an organopalladium intermediate, which then couples with a terminal acetylene or acetylide that is formed in situ. The disubstituted alkyne that is subsequently produced must then be cyclized by palladium catalysis, producing a *tert*-butylisoquinolinium salt. As in our internal alkyne annulation chemistry, the *tert*-butyl group apparently fragments to relieve the strain resulting from interaction with the substituent present in the 3-position.[6]

Scheme 2



Scheme 3



To gain additional insight into this process, iminoalkyne **3** was independently synthesized by a palladium-catalyzed coupling of 2-bromobenzaldehyde and phenylacetylene, followed by imine formation (Scheme 3). Imine **3** was then subjected to a variety of reaction conditions in order to effect its cyclization to 3-phenylisoquinoline (**2**) (eq 2, Table 1). Under the standard palladium reaction conditions that were developed for our internal alkyne isoquinoline synthesis [5 mol % $Pd(OAc)_2$, 10 mol % PPh_3, and 1 equiv of Na_2CO_3 in 10 mL of DMF at 100 °C], isoquinoline **2** was isolated in 75% yield after a 39 h reaction time (entry 1). Thus, our assumptions about the mechanism of this process appeared to be correct. We then were interested in optimizing the yield

(14) For a preliminary communication, see: Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 553.

Table 1. Synthesis of 3-Phenylisoquinoline (2) (eq 2)[a]

entry	5 mol % Pd catalyst	1 equiv Na_2CO_3	10 mol % PPh_3	temp (°C), time (h)	% yield of **2**
1	$Pd(OAc)_2$	+	+	100 (39)	75
2	$Pd(OAc)_2$	−	−	100 (14)	78
3	$PdCl_2$	−	−	100 (15)	65
4	$PdCl_2$	+	−	100 (36)	69
5	$PdCl_2(PhCN)_2$	+	−	100 (48)	88
6	$PdCl_2(PhCN)_2$	−	−	100 (42)	58
7	−	−	−	100 (6)	100[b]
8	−	−	−	100 (6)	77[c]
9	−	−	−	130 (45)	57
10	−	+	−	130 (45)	63

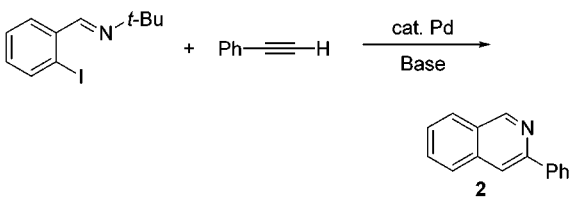
[a] All reactions were run with 0.25 mmol of the imine in 5 mL of DMF. [b] A 10 mol % quantity of CuI was added. [c] A 5 mol % quantity of CuI was added.

and reaction time for this process.

(2)

Upon removal of the base and the phosphine from the reaction, the desired product was isolated in 78% yield in a shorter reaction time (cf. entries 1 and 2). $PdCl_2$ was also observed to promote the cyclization, although a decrease in yield was observed (entries 3 and 4). Employing $PdCl_2(PhCN)_2$ as the palladium catalyst and Na_2CO_3 allowed the desired product to be isolated in 88% yield after a 48 h reaction time (entry 5). Removal of the base from the $PdCl_2(PhCN)_2$-catalyzed reaction, however, resulted in a lower isolated yield of the desired product (entry 6). Interestingly, employing only CuI as a catalyst allowed the desired product to be obtained in quantitative yield in a short reaction time (entry 7). In an effort to reduce the amount of catalyst that was employed in the reaction, 5 mol % of CuI was added, but a decrease in the yield was observed (entry 8). Finally, this iminoalkyne can also be cyclized thermally, although the yields are lower than either of the palladium- or copper-catalyzed cyclizations and higher temperatures and longer reactions times are required (entries 9 and 10).

On the basis of the mechanistic picture that has emerged for this process, it was expected that terminal acetylenes would also undergo this annulation. Indeed, phenylacetylene was subsequently observed to participate in this palladium-catalyzed annulation (eq 3). However, under the standard internal alkyne annulation conditions, 3-phenylisoquinoline could only be obtained in 62% isolated yield. Thus, we again were interested in optimizing the yield and reaction time for this process. The results of this investigation are shown in Table 2. After optimization of the reaction conditions, we found that employing 1 equiv of **1**, 1.1 equiv of phenylacetylene, 5 mol % $PdCl_2(PhCN)_2$, and 1 equiv of Na_2CO_3 in DMF at 100 °C allowed isoquinoline **2** to be isolated in 85% yield after a 14 h reaction time (entry 10). It is interesting to note that CuI was not required as a cocatalyst for this annulation.



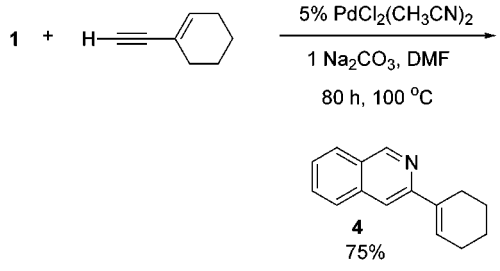
(3)

Table 2. Synthesis of 3-Phenylisoquinoline (2) by Pd-Catalyzed Coupling and Cyclization (eq 3)[a]

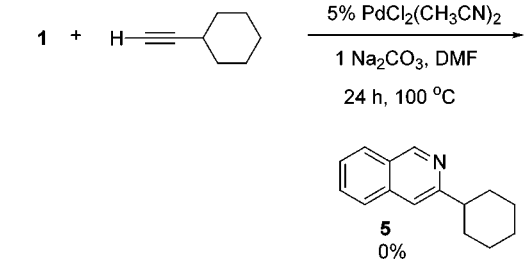
entry	base (equiv)	5 mol % Pd catalyst	5 mol % CuI	10 mol % PPh_3	temp (°C), time (h)	% yield
1	Na_2CO_3 (1)	$Pd(OAc)_2$	−	+	100 (58)	62
2	Na_2CO_3 (1)	$Pd(OAc)_2$	+	+	rt (12), 100 (75)	68
3	NEt_3 (2)	$Pd(OAc)_2$	+	+	rt (12), 100 (22)	60
4	*i*-Pr_2NEt (2)	$Pd(OAc)_2$	+	+	rt (1), 100 (14)	50
5	Na_2CO_3 (1)	$Pd(OAc)_2$	−	−	100 (11)	83[b]
6	NEt_3 (2)	$PdCl_2(PPh_3)_2$	+	−	rt (3), 100 (15)	59
7	Na_2CO_3 (1)	$PdCl_2(PPh_3)_2$	−	−	100 (12)	77[b,c]
8	Na_2CO_3 (1)	$PdCl_2(PhCN)_2$	−	+	100 (72)	78
9	Na_2CO_3 (1)	$PdCl_2(PhCN)_2$	−	−	100 (30)	60
10	Na_2CO_3 (1)	$PdCl_2(PhCN)_2$	−	−	100 (14)	85[b]
11	Na_2CO_3 (1)	$PdCl_2(PhCN)_2$	+	−	100 (12)	75[b]
12	Na_2CO_3 (1)	$PdCl_2(PhCN)_2$	−	+	100 (23)	85[b]

[a] All reactions were run with 0.5 mmol of the imine and 1.0 mmol of phenylacetylene in 10 mL of DMF unless otherwise noted. [b] A 1.1 equiv quantity of phenylacetylene was used. [c] A 10 mol % quantity of CuI was added.

After optimization of the reaction conditions with phenylacetylene, we then proceeded to define the scope and limitations of the terminal acetylene annulation. The reaction in which 1-ethynylcyclohexene was employed also afforded the desired isoquinoline **4** in good yield (eq 4). Unfortunately, when cyclohexyl acetylene was employed under the same conditions, none of the desired isoquinoline **5** was obtained (eq 5). In addition, the standard isoquinoline internal alkyne annulation conditions also afforded none of the desired heterocycle. Therefore, it again became necessary to find reaction conditions that would increase the generality of this annulation process.



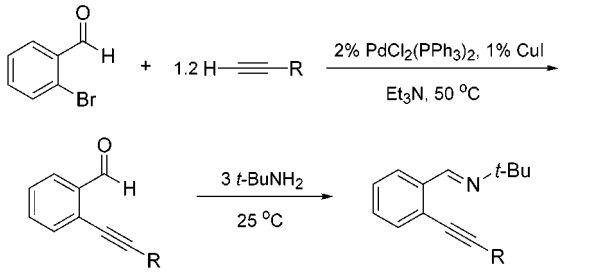
(4)



(5)

Due to the success of the copper-catalyzed cyclization of iminoalkyne **3** (Table 1, entry 7), the cyclization of iminoalkynes with differing functionality was investigated. All of the iminoalkynes employed in this cyclization process were synthesized in excellent yields by the

Scheme 4



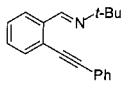
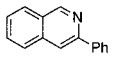
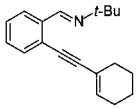
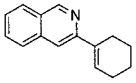
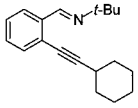
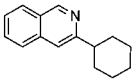
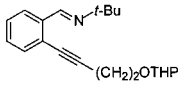
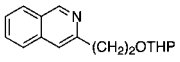
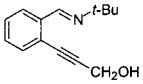
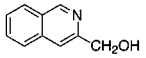
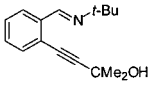
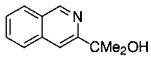
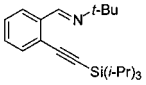
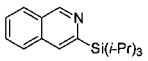
	R	% yield		% yield
6		95	12	96
7		95	13	95
8	$(CH_2)_2OTHP$	99	14	94
9	CH_2OH	89	15	96
10	CMe_2OH	96	16	97
11	$Si(i\text{-}Pr)_3$	92	17	97

same sequence of transformations used for the preparation of alkyne **3** (Scheme 4). Although limited success was obtained from the terminal acetylene coupling/cyclization chemistry discussed previously, the copper-catalyzed cyclization proved to be more general with respect to the functionality that can be introduced into the products (Table 3). For example, iminoalkynes containing aryl, alkenyl, and alkyl substituents afford excellent yields of the desired monosubstituted isoquinoline heterocycles (Table 3, entries 1−4). However, free propargylic hydroxy groups are not tolerated in these cyclization reactions (entries 5 and 6), nor were highly hindered iminoalkynes (entry 7). The failure of the hydroxy alkynes is surprising since our later synthesis of decumbenine B (see eq 8) involves a successful coupling and cyclization of an alkyne bearing a free hydroxy group, although the hydroxy group in that alkyne is further removed from the carbon−carbon triple bond and the cyclization there involves palladium, not copper.

Although the copper-catalyzed synthesis was more general than the palladium-catalyzed terminal acetylene coupling/cyclization reactions with respect to the types of functionality that could be incorporated into the isoquinoline, this synthesis was still not as efficient as the one-pot reaction discussed previously (eqs 3 and 4), since three transformations (coupling, imine formation, and copper-catalyzed cyclization) were required. Consequently, we more closely examined the reaction of imine **1** and cyclohexyl acetylene with different bases and palladium catalysts (Table 4). Employing Et_3N, instead of Na_2CO_3, as a base in the presence of 5 mol % $Pd(OAc)_2$ and 2.5 mol % CuI, allowed 3-cyclohexylisoquinoline (**5**) to be isolated in low yield (entry 3). Increasing the amount of CuI to 10 mol % led to a slight increase in yield (entry 4). All additional attempts to increase the yield by changing bases and palladium catalysts in this reaction, however, proved to be futile (entries 5−11).

On the basis of our work up to this point, we felt that a reasonable mechanism had been formulated for this annulation process (Scheme 2). Specifically, coupling of the aryl halide and terminal acetylene must first occur to produce the intermediate iminoalkyne, followed by a cyclization step to produce the isoquinoline. Therefore, the reaction conditions employed for a one-pot synthesis must be compatible with both steps in the catalytic cycle.

Table 3. Synthesis of Isoquinoline Heterocycles by the Cu-Catalyzed Cyclization of Iminoalkynes[a]

entry	imine	time (h)	product	% yield
1	 **3**	3	 **2**	100
2	 **12**	3	 **4**	81
3	 **13**	6	 **5**	93
4	 **14**	5	 **18**	83
5	 **15**	12	 **19**	0
6	 **16**	12	 **20**	0
7	 **17**	24	 **21**	0[b]

[a] Representative procedure for the cyclization of iminoalkynes: 10 mol % CuI, the imine (0.25 mmol), and DMF (5 mL) were placed in a 2 dram vial and heated at 100 °C for the indicated time. [b] The amount of starting material recovered was 100%.

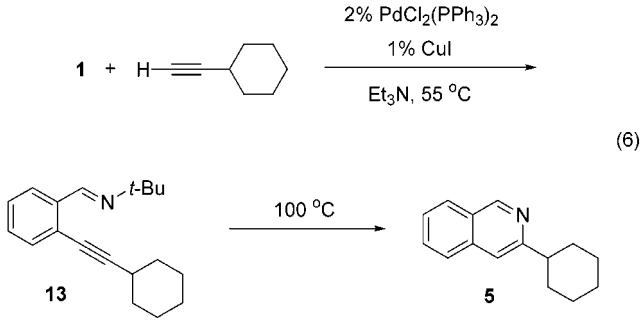
Table 4. Synthesis of Compound 5 by the Pd-Catalyzed Coupling and Cyclization of Imine 1 and Cyclohexyl Acetylene[a]

entry	base (equiv)	5 mol % Pd catalyst	CuI (mol %)	temp (°C), time (h)	% yield of **5**
1	Na_2CO_3 (1)	$Pd(OAc)_2$	0	100 (24)	0
2	Na_2CO_3 (1)	$Pd(OAc)_2$	10	100 (24)	0
3	Et_3N (1)	$Pd(OAc)_2$	2.5	100 (12)	20
4	Et_3N (1)	$Pd(OAc)_2$	10	100 (12)	26
5	Et_3N (1)	$Pd(OAc)_2$	10	100 (12)	19[b]
6	Et_3N (0.15)	$Pd(OAc)_2$	10	100 (12)	18
7	$i\text{-}Pr_2NEt$ (1)	$Pd(OAc)_2$	10	100 (11)	15
8	pyridine (1)	$Pd(OAc)_2$	10	100 (11)	10
9	Et_3N (1)	$Pd(dba)_2$	10	100 (10)	14
10	Et_3N (1)	$PdCl_2(CH_3CN)_2$	10	100 (10)	12
11	Et_3N (1)	$PdCl_2(PPh_3)_2$	10	100 (10)	13

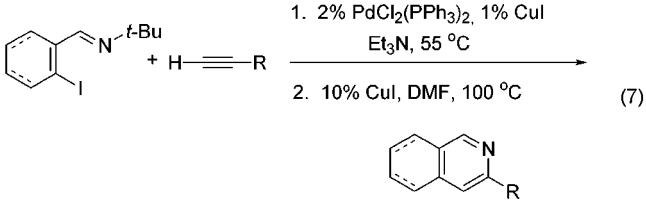
[a] All reactions were run with 0.25 mmol of the imine and 1.1 mmol of cyclohexyl acetylene in 5 mL of DMF unless otherwise noted. [b] Quantities of 1.1 mmol of the imine and 1.0 mmol of cyclohexyl acetylene were employed.

Since we had considerable success with the palladium-catalyzed coupling of *o*-bromobenzaldehyde and terminal acetylenes (Scheme 4), and also with the copper-catalyzed cyclization of iminoalkynes (Table 3), we felt that by an appropriate choice of reaction conditions, it should be possible to efficiently synthesize the desired isoquinolines.

We therefore investigated the use of the coupling conditions employed in Scheme 4 for both the coupling and cyclization steps (eq 6), since triethylamine was employed for the coupling reactions and afforded the best yield of isoquinoline **5** (Table 4, entry 4). These reactions were run with 0.5 mmol of the haloimine **1** and 0.6 mmol of cyclohexyl acetylene with 2 mol % $PdCl_2(PPh_3)_2$ and 1 mol % CuI in 2 mL of Et_3N at 50 °C for 1 h to effect the coupling, and then at 100 °C for 48 h to promote the cyclization of the intermediate iminoalkyne **13**. Although only a trace of isoquinoline product was observed under these reaction conditions, it was possible to recover 95% of the intermediate coupled product, thus indicating that an efficient coupling step had occurred. On the basis of this result, an additional 10 mol % of CuI was added to the reaction mixture after the coupling step had gone to completion in hopes of promoting the cyclization step. Unfortunately, this also was quite inefficient, although a 22% yield of the product was observed. Finally, two reactions were run in which an additional 10 mol % of CuI and 3 mL of either Et_3N or DMF were added after the coupling was complete. Unfortunately, this also afforded only trace amounts of the desired isoquinoline.



On the basis of these results, it appeared that the coupling of imine **1** and cyclohexyl acetylene was proceeding in high yield to produce iminoalkyne **13**. However, under the reaction conditions employed, **13** was not efficiently cyclized to isoquinoline **5**. Since the coupling reaction proceeded in high yield in Et_3N, which serves as both the solvent and the base, and we have had considerable success with the copper-catalyzed cyclization in DMF, modified reaction conditions were developed to incorporate both of these transformations into a single reaction sequence (eq 7).



We thus employed the following reaction conditions for the isoquinoline synthesis: the imine (0.5 mmol), the terminal acetylene (0.6 mmol), 2 mol % of $PdCl_2(PPh_3)_2$, and 1 mol % of CuI in 2 mL of Et_3N were heated at 55 °C until the coupling was judged to be complete by thin-layer chromatography. The solvent and the precipitates were subsequently removed, and DMF (5 mL) and 10 mol % of CuI were added to the residue. The resulting mixture was then heated at 100 °C until the cyclization was judged to be complete by thin-layer chromatography. Employing this reaction sequence allowed a variety of isoquinolines to be synthesized in good to excellent yields (Table 5).

A variety of functionalized terminal acetylenes have been employed in this palladium/copper-catalyzed process. For example, the reaction of imine **1** with aryl-, alkenyl-, and alkyl-substituted acetylenes affords the desired isoquinolines in good to excellent yields (Table 5, entries 1−7). As in our copper-catalyzed cyclization of iminoalkynes, free hydroxy groups are not tolerated, as the reaction of **1** with 3-butyn-1-ol afforded none of the desired heterocycle. Protection of the free hydroxy group as the tetrahydropyranyl ether, however, afforded the desired isoquinoline **18** in 95% yield (entry 4). Acetal and nitrile functional groups were also tolerated (entries 5 and 6). Using 1,6-heptadiyne as the terminal acetylene afforded bis-isoquinoline **24** in 56% yield. Unfortunately, when the highly hindered terminal alkyne 3,3-dimethyl-1-butyne was employed, 2-(3,3-dimethylbut-1-ynyl)benzaldehyde (imine hydrolysis occurred during purification) was isolated in 95% yield after a 24 h cyclization time. Thus, this isoquinoline synthesis appears to be limited to the use of relatively unhindered acetylenes. Finally, isoquinolines **26** and **27** and naphthyridines **29** and **30** have also been synthesized in good yields from imines **25** and **28**, respectively (entries 8−11).

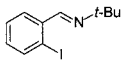
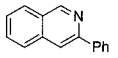
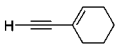
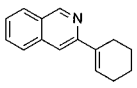
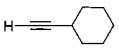
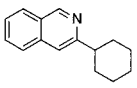
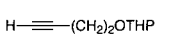
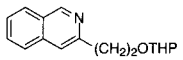
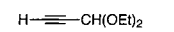
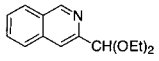
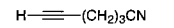
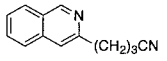
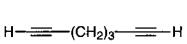
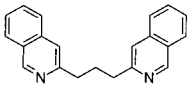
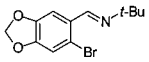
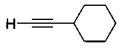
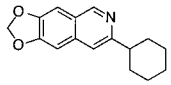
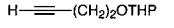
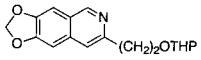
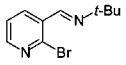
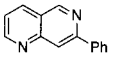
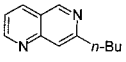
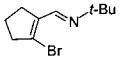
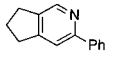
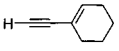
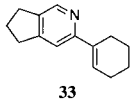
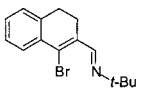
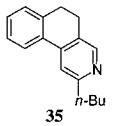
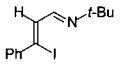
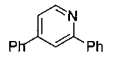
As in our isoquinoline synthesis from internal alkynes, pyridines can be synthesized by employing vinylic imines. Pyridines **32** and **33** have been synthesized from cyclic imine **31**. This pyridine synthesis provides best results using aryl- and alkenyl-substituted acetylenes. The reaction of imine **31** and *N*-(2-bromocyclohex-1-enylmethylene)-*tert*-butylamine with various alkyl-substituted acetylenes afforded only low yields of the desired pyridines (∼10%). Interestingly, the reaction of 1-hexyne and imine **34** did afford pyridine **35** in 46% yield. Finally, pyridine **37** has been synthesized from the acyclic imine **36** in 57% yield.

To demonstrate the utility of this annulation methodology, we have applied this coupling/cyclization process to the synthesis of the naturally occurring isoquinoline alkaloid decumbenine B (**38**). Decumbenine B has recently been isolated in small amounts from the plant tubers of *Corydalis decumbens*, which have been used in Chinese folk herbal medicine for the treatment of paralytic stroke and rheumatic arthritis.[15] One total synthesis of this alkaloid has recently appeared.[16] However, the reported synthesis was accomplished in a low overall yield and in 18 steps. We felt that decumbenine B could be efficiently synthesized by employing the palladium-catalyzed coupling and cyclization methodology developed here.

A retrosynthetic analysis for the synthesis of **38** is shown in Scheme 5. It was envisioned that decumbenine B could be synthesized by the palladium-catalyzed coupling of imine **39** and alkyne **40** and subsequent cycliza-

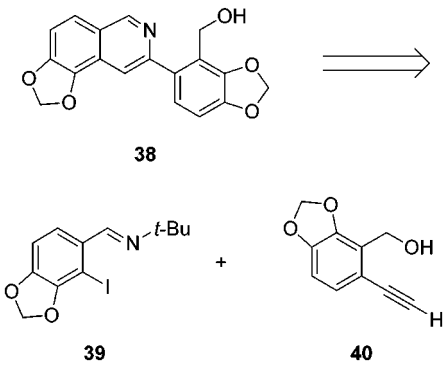
(15) Zhang, J.; Zhu, D.; Hong, S. *Phytochemistry* **1995**, *39*, 435.
(16) Xu, X.; Qin, G.; Xu, R.; Zhu, X. *Tetrahedron* **1998**, *54*, 14179.

Table 5. Synthesis of Isoquinolines and Pyridines by the Pd-Catalyzed Coupling and Cu-Catalyzed Cyclization of Terminal Acetylenes (eq 7)[a]

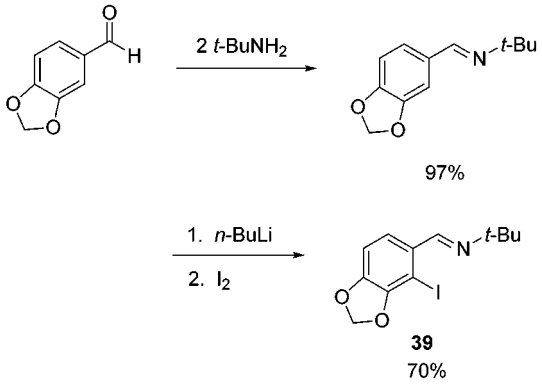
entry	imine	alkyne	coupling time (h)	cyclization time (h)	product	% yield
1	 **1**		2	1	 **2**	91
2			1	5	 **4**	81
3			1	2	 **5**	88
4			6	2	 **18**	95
5			1	2	 **22**	84
6			1	3	 **23**	87
7			7	8	 **24**	56
8	 **25**		2	12	 **26**	76
9			8	12	 **27**	81
10	 **28**		2	15	 **29**	85
11			2	15	 **30**	72
12	 **31**		1	24	 **32**	69
13			1	60	 **33**	55
14	 **34**		1	48	 **35**	46
15	 **36**		1	36	 **37**	57

[a] All reactions were run using 2 mol % of $PdCl_2(PPh_3)_2$ and 1 mol % of CuI in 2 mL of Et_3N to effect the coupling step, and 10 mol % of CuI in 5 mL of DMF to effect cyclization to the nitrogen heterocycle.

Scheme 5



Scheme 6



tion of the intermediate iminoalkyne. The starting materials required for the synthesis of decumbenine B were easily prepared in a minimal number of synthetic transformations from the commercially available aldehydes piperonal and 2,3-(methylenedioxy)benzaldehyde.

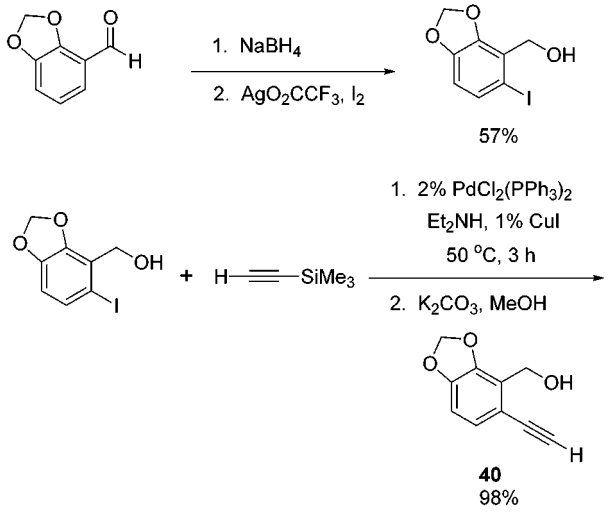
The synthesis of imine **39** was accomplished in two steps as shown in Scheme 6. The *tert*-butyl imine of piperonal was synthesized in high yield and was subjected to reaction conditions previously reported for the metalation of cyclohexylimines derived from piperonal.[17] Treatment of the imine with *n*-BuLi and subsequent quenching with iodine afforded the desired iodoimine in 70% yield. It is interesting to note that the *tert*-butyl imine served as an excellent directing group for the lithiation reaction, with no addition products of *n*-BuLi to the imine being observed. In addition, employing the *tert*-butyl imine, rather than the cyclohexylimine as was reported, allowed several steps involving imine formation and hydrolysis to be avoided.

The synthesis of alkyne **40** was accomplished in four steps by the synthetic route shown in Scheme 7. Reduction of 3,4-(methylenedioxy)benzaldehyde to the benzyl alcohol and subsequent iodination afforded the intermediate iodide in 57% overall yield. Alkyne **40** was then synthesized in 98% overall yield by a palladium-catalyzed coupling of the aryl iodide with trimethylsilylacetylene and subsequent desilylation with potassium carbonate.

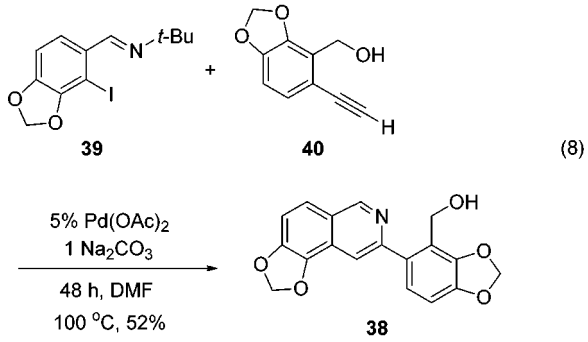
With imine **39** and alkyne **40** in hand, we completed the synthesis of decumbenine B in 52% yield by employing our palladium-catalyzed methodology (eq 8). Despite the low yield for the key palladium-catalyzed reaction, this synthesis of decumbenine B was completed in seven steps and 20% overall yield, which demonstrates the

(17) Ziegler, F. E.; Fowler, K. W. *J. Org. Chem.* **1976**, *41*, 1564.

Scheme 7



effectiveness of this methodology and its ability to tolerate functionality.



Conclusion

Efficient palladium- and copper-catalyzed syntheses of isoquinolines and pyridines have been developed. Only aryl- and alkenyl-substituted alkynes cyclize when employing the palladium-catalyzed reaction conditions that have been developed. However, a wide variety of functionalized terminal acetylenes participate in a palladium-catalyzed coupling and copper-catalyzed cyclization process to afford the desired nitrogen heterocycles in moderate to excellent yields. The effectiveness of the palladium-catalyzed terminal acetylene annulation methodology has been demonstrated by the total synthesis of the isoquinoline alkaloid decumbenine B in seven steps and 20% overall yield.

Experimental Section

General. ^{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 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. Low-resolution mass spectra were recorded on a Finnigan TSQ700 triple quadrupole mass spectrometer (Finnigan MAT, San Jose, CA). High-resolution mass spectra were recorded on a Kratos MS50TC double-focusing magnetic sector mass spectrometer using EI at 70 eV. Elemental analyses were performed at Iowa State University on a Perkin-Elmer 2400 CHNS/O Series II Analyzer. All reagents were used directly as obtained commercially unless otherwise noted. Anhydrous forms of Na_2CO_3,

DMF, methanol, 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 **4**, **5**, **22**, **26**, **30**, and **33** have been previously reported.[14] 2-Iodobenzaldehyde,[5] 2-bromopiperonal,[18] 2-bromocyclopentene-1-carboxaldehyde,[19] 1-bromo-3,4-dihydronaphthalene-2-carboxaldehyde,[20] (*Z*)-3-iodo-3-phenyl-2-propenal,[21] and 2-bromo-3-formylpyridine[22] were prepared according to previous literature procedures. The following starting materials were prepared as indicated.

General Procedure for the Preparation of 2-(1-Alkynyl)benzaldehydes: 2-(2-Phenylethynyl)benzaldehyde. To a solution of 2-bromobenzaldehyde (1.85 g, 10.0 mmol) and phenylacetylene (1.23 g, 12.0 mmol) in Et_3N (40 mL) was added $PdCl_2(PPh_3)_2$ (140 mg, 2 mol %). The mixture was stirred for 5 min, and CuI (20 mg, 1 mol %) was added. The resulting mixture was then heated under a nitrogen atmosphere at 50 °C for 4 h. 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 using 20:1 hexanes/EtOAc to afford 1.88 g (91%) of the compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.35−7.44 (m, 4H), 7.52−7.64 (m, 4H), 7.94 (dd, J = 0.3, 7.8 Hz, 1H), 10.65 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 85.1, 96.5, 122.4, 126.9, 127.3, 128.6, 128.7, 129.2, 131.8, 133.3, 133.9, 135.9, 191.7. Aldehydes **6**−**11** have been prepared using the same procedure. Details and spectral identification are reported in Supporting Information.

General Preparation of Imines: *N*-(2-Iodobenzylidene)-*tert*-butylamine (1). To a mixture of 2-iodobenzaldehyde (1.00 g, 4.3 mmol) and H_2O (0.25 mL/mmol) was added *tert*-butylamine (12.9 mmol, 3 equiv). The mixture was stirred under a nitrogen atmosphere at room temperature for 12 h. The excess *tert*-butylamine was removed under reduced pressure, and the resulting mixture was extracted with ether. The combined organic layers were dried (Na_2SO_4) and filtered. Removal of the solvent afforded 1.18 g (95%) of the imine as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 9H), 7.07 (td, J = 1.5, 7.2 Hz, 1H), 7.36 (tt, J = 0.6, 7.2 Hz, 1H), 7.83 (dd, J = 0.9, 7.8 Hz, 1H), 7.94 (dd, J = 1.8, 7.8 Hz, 1H), 8.41 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 29.8, 58.0, 100.4, 128.5, 128.7, 131.6, 137.9, 139.4, 159.2; IR (neat, cm^{-1}) 3059, 2966, 1633; HRMS calcd for $C_{11}H_{14}IN$ 287.0170, found 287.0173. Imines **3**, **12**−**17**, **25**, **28**, **31**, **34**, and **36** have been prepared using the same procedure. Details are provided in Supporting Information.

General Procedure for the Copper-Catalyzed Cyclization of Iminoalkynes: 3-Phenylisoquinoline (2). DMF (5 mL), the imine (0.25 mmol), and CuI (5 mg, 0.025 mmol) were placed in a 2 dram vial. 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 cooled, diluted with 25 mL of ether, washed with 30 mL of saturated NH_4Cl, dried (Na_2SO_4), and filtered. The solvent was evaporated under reduced pressure, and the reaction mixture was chromatographed using 15:1 hexanes/EtOAc to afford 51 mg (100%) of the indicated compound with spectral properties identical to those previously reported:[23] mp 102−103 °C (lit.[23] 101−102 °C). Isoquinolines **16**−**18** were prepared in an identical manner. Experimental details and spectral characterization are provided in Supporting Information.

General Procedure for the Palladium/Copper-Catalyzed Formation of Isoquinolines and Pyridines from Terminal Acetylenes: 3-Phenylisoquinoline (2). Et_3N (2 mL), $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol), the imine (0.5 mmol), the terminal acetylene (0.6 mmol), and CuI (1 mg, 0.005 mmol) were placed in a 2 dram vial. The vial was flushed with nitrogen and heated in an oil bath at 55 °C for the indicated period of time. The reaction was monitored by TLC to establish completion. For the reactions with imine **7**, the reaction mixture was cooled, the precipitates were filtered off and washed with ether, and the solvent was removed under reduced pressure. For the reactions with imines **32**, **35**, **37**, and **39**, the reaction mixture was cooled, the solvent was removed under reduced pressure, the precipitates were filtered off and washed with ether, and the solvent was removed under reduced pressure. The residue obtained was transferred to a 2 dram vial, and DMF (5 mL) and CuI (10 mg, 0.05 mmol) were added. The vial was flushed with nitrogen and heated in an oil bath at 100 °C for the indicated period of time. The reaction mixture was cooled, diluted with 25 mL of ether, washed with 30 mL of saturated aqueous NH_4Cl, dried (Na_2SO_4), and filtered. The solvent was evaporated under reduced pressure, and the reaction mixture was chromatographed using 15:1 hexanes/EtOAc to afford 94 mg (91%) of the indicated compound **2**, whose spectral data were identical with that reported above.

Total Synthesis of Decumbenine B. *N*-(Benzo[1,3]-dioxol-5-ylmethylene)-*tert*-butylamine. To a mixture of piperonal (2.00 g, 13.3 mmol) and H_2O (2 mL) was added *tert*-butylamine (26.6 mmol, 2 equiv). The mixture was then stirred under a nitrogen atmosphere at room temperature for 12 h. The excess *tert*-butylamine was removed under reduced pressure, and the resulting mixture was extracted with ether. The combined organic layers were dried (Na_2SO_4) and filtered. Removal of the solvent afforded 2.65 g (97%) of the imine as a white solid: mp 44−45 °C; ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 9H), 5.97 (s, 2H), 6.81 (d, J = 8.4 Hz, 1H), 7.10 (dd, J = 1.5, 8.1 Hz, 1H), 7.38 (d, J = 1.5 Hz, 1H), 8.15 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 29.9, 57.0, 101.4, 106.6, 108.0, 123.9, 132.2, 148.3, 149.5, 154.3; IR ($CHCl_3$, cm^{-1}) 3060, 2214, 1637; HRMS calcd for $C_{12}H_{15}NO_2$ 205.1100, found 205.1103.

***N*-(4-Iodobenzo[1,3]dioxol-5-ylmethylene)-*tert*-butylamine (39).** *N*-(4-Iodo-benzo[1,3]dioxol-5-ylmethylene)-*tert*-butylamine was prepared according to a modified literature procedure.[17] To a solution of *N*-(benzo[1,3]dioxol-5-ylmethylene)-*tert*-butylamine (1.03 g, 5.00 mmol) in 40 mL of THF at −78 °C was added 5.25 mmol of *n*-BuLi (2.5 M in hexanes) dropwise over a five minute period. The solution was stirred for 30 min at −78 °C, and a solution of I_2 (2.68 g, 7.5 mmol) in 15 mL of THF was added dropwise. The resulting solution was warmed to room temperature and stirred for 2 h. The reaction was quenched with water, and the mixture was extracted with ether, washed with saturated aqueous $Na_2S_2O_3$, dried ($MgSO_4$), and filtered; the solvent was removed under reduced pressure. Recrystallization from hexanes/EtOAc afforded 0.77 g (70%) of the desired compound as an off-white solid: mp 126−127 °C; ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 9H), 6.05 (s, 2H), 6.61 (d, J = 8.1 Hz, 1H), 7.53 (d, J = 8.1 Hz, 1H), 8.32 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 29.9, 57.8, 77.1, 100.9, 108.6, 122.7, 131.2, 147.6, 149.4, 157.4; IR ($CHCl_3$, cm^{-1}) 3062, 2965, 1596; HRMS calcd for $C_{12}H_{14}INO_2$ 331.0069, found 331.0064.

(5-Iodobenzo[1,3]dioxol-4-yl)methanol. To a solution of 2,3-(methylenedioxy)benzaldehyde (1.50 g, 10.0 mmol) in 5 mL CH_2Cl_2 was added $NaBH_4$ (0.47 g, 12.5 mmol) in MeOH (5 mL). The reaction mixture was stirred for 2 h at room temperature, and the reaction was quenched with water. The mixture was then extracted with CH_2Cl_2, dried (Na_2SO_4), and filtered, and the solvent was removed under reduced pressure to afford 1.52 g of the desired alcohol as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.36 (br s, 1H), 4.64 (s, 2H), 5.93 (s, 2H), 6.73−6.85 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 60.0, 101.1, 108.2, 121.2, 121.8, 122.4, 145.1, 147.4. To a mixture of this alcohol and AgO_2CCF_3 (2.21 g, 10.0 mmol) in 15 mL of $CHCl_3$ was added a solution of iodine (2.54 g, 10.0 mmol) in 80 mL of $CHCl_3$. The reaction mixture was stirred for 24 h and then filtered. The filtrate was washed

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with saturated aqueous $NaHCO_3$, brine, dried ($MgSO_4$), and filtered. Removal of the solvent afforded a yellow oil, which was dissolved in ether. Addition of hexanes precipitated 1.58 g (57%) of the desired alcohol as a yellow solid: mp 96−97 °C; ^{1}H NMR ($CDCl_3$) δ 2.20 (br s, 1H), 4.69 (s, 2H), 5.99 (s, 2H), 6.53 (d, J = 8.1 Hz, 1H), 7.28 (d, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 63.4, 88.3, 101.8, 110.2, 124.3, 132.1, 146.6, 148.2; IR ($CHCl_3$, cm^{-1}) 3358, 2891, 1460; HRMS calcd for $C_8H_7IO_3$ 277.9444, found 277.9442.

(5-Ethynylbenzo[1,3]dioxol-4-yl)methanol (40). To a solution of (5-iodobenzo[1,3]dioxol-4-yl)methanol (0.56 g, 2.0 mmol) and (trimethylsilyl)acetylene (0.24 g, 2.4 mmol) in Et_2-NH (10 mL) was added $PdCl_2(PPh_3)_2$ (28 mg, 2 mol %). The mixture was stirred for 5 min, and CuI (4 mg, 1 mol %) was added. The resulting mixture was then heated under a nitrogen atmosphere at 50 °C for 4 h. 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 crude silyl acetylene was dissolved in 30 mL of MeOH, and K_2CO_3 (0.55 g, 4 mmol) was added. The mixture was then stirred for 1 h at room temperature. The mixture was washed with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, dried (Na_2SO_4), and filtered. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel using 2:1 hexanes/EtOAc to afford 0.30 g (98%) of the desired compound as a brown solid: mp 64−65 °C; ^{1}H NMR ($CDCl_3$) δ 2.50 (br t, J = 5.7 Hz, 1H), 3.20 (s, 1H), 4.77 (d, J = 5.4 Hz, 2H), 5.98 (s, 2H), 6.68 (d, J = 8.1 Hz, 1H), 7.03 (d, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 58.1, 79.9, 81.4, 101.7, 108.0, 114.7, 124.1, 127.6, 146.0, 148.3; IR ($CHCl_3$, cm^{-1}) 3401, 3286, 2099, 1466; HRMS calcd for $C_{10}H_8O_3$ 176.0474, found 176.0474.

Decumbenine B (38). DMF (5 mL), $Pd(OAc)_2$ (3 mg, 0.013 mmol), Na_2CO_3 (26 mg, 0.25 mmol), and *N*-(4-iodobenzo[1,3]-dioxol-5-ylmethylene)-*tert*-butylamine (0.083 g, 0.25 mmol) were placed in a 2 dram vial. The contents were then stirred for 1 min, and (5-ethynylbenzo[1,3]dioxol-4-yl)methanol (42 mg, 0.28 mmol) was added. The vial was flushed with nitrogen and heated in an oil bath at 100 °C for 48 h. The reaction was monitored by TLC to establish completion. The reaction mixture was cooled, diluted with 25 mL of ether, washed with 30 mL 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 using 1:1 hexanes/EtOAc to afford 42 mg (52%) of the indicated compound with spectral properties identical to those previously reported:[15,16] mp 221−222 °C (lit.[15,16] 222−224 °C).

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Supporting Information Available: Experimental details for the preparation of aldehydes **6**−**11**; imines **3**, **12**−**17**, **25**, **28**, **31**, **34**, and **36**; isoquinolines **4**, **5**, **18**, **22**−**24**, **26**, **27**, **29**, **30**, **32**, **33**, and **35**; and pyridine **37**; and spectral characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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