JOC Article

Synthesis of Annulated γ-Carbolines and Heteropolycycles by the Palladium-Catalyzed Intramolecular Annulation of Alkynes

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A variety of *N*-substituted 2-bromo-1*H*-indole-3-carboxaldehydes incorporating an alkyne-containing tether on the indole nitrogen have been converted to the corresponding *tert*-butylimines, which have been subjected to palladium-catalyzed intramolecular iminoannulation, affording various γ-carboline derivatives with an additional ring fused across the 4- and 5-positions in good to excellent yields. When the tethered carbon−carbon triple bond is terminal or substituted with a triethylsilyl group, the iminoannulation generates a *tert*-butyl-γ-carbolinium salt as the major product. The palladium-catalyzed intramolecular annulations of *N*-substituted 2-bromo-1*H*-indole-3-carboxaldehyde, methyl 2-iodo-1*H*-indole-3-carboxylate, and 2-iodo-3-phenyl-1*H*-indole containing a phenylpentynyl tether produce the corresponding heteropolycycles in moderate to good yields.

Introduction

Annulation processes have proven to be very useful in organic synthesis due to the ease with which a wide variety of complex carbocycles and heterocycles can be rapidly constructed. In our own laboratories, it has been demonstrated that palladium-catalyzed annulation methodology[1] can be effectively employed for the synthesis of indoles,[2] isoindolo[2,1-*a*]indoles,[3] benzofurans,[4] benzopyrans,[4] isocoumarins,[4,5] α-pyrones,[5,6] indenones,[7] pyridines,[8] isoquinolines,[8] naphthalenes,[9] and polycyclic aromatic hydrocarbons.[10] However, intramolecular palladium-catalyzed annulation has not been well-explored mainly because of the difficulty of assembling a halide, a carbon−carbon triple bond, and other necessary elements into the appropriate positions into a single starting material.[11]

Pyrido[4,3-*b*]-5*H*-indoles, commonly known as γ-carbolines, which are condensed analogues of the ellipticine/olivacine anticancer agents, have been studied extensively because of their potential pharmaceutical importance.[12] However, there are relatively few synthetic studies of γ-carboline derivatives having wide scope and generality,[12,13] and the synthesis of new alkaloid derivatives of γ-carboline with an additional ring fused across the 4- and 5-positions is rare.[14] Two closely related examples of this type of heteropolycyclic system having interesting biological activity are the pentacyclic γ-carboline **1**, which is a cardiovascular agent,[15] and the

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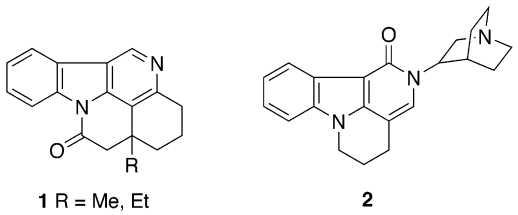
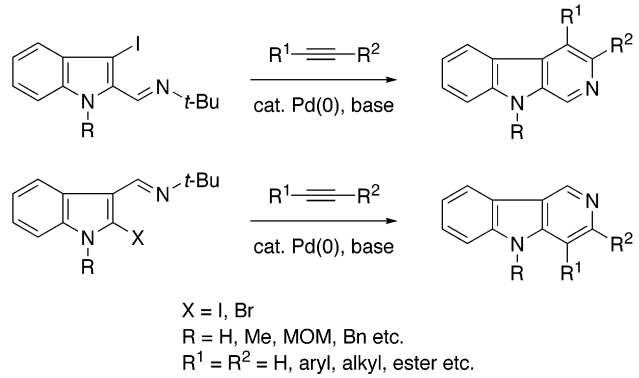
indolonaphthyridone **2**, which acts as a conformationally restricted 5-HT_3 receptor antagonist.[16]



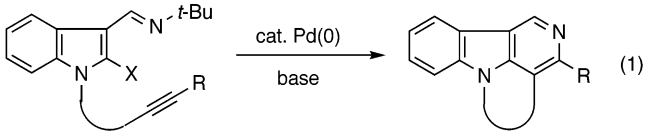
1 R = Me, Et **2**

Syntheses of annulated γ-carboline alkaloids have typically employed electrocyclic ring closures of 1-azatrienes,[14c,d] or intramolecular Diels−Alder reactions.[14a,b,e] However, both methods afford the desired γ-carbolines in relatively low yields. Recently, we have developed a general synthesis of 3,4-disubstituted β- and γ-carbolines by the palladium-catalyzed iminoannulation of acetylenes (Scheme 1).[17] While certain β- and γ-carbolines could be

SCHEME 1

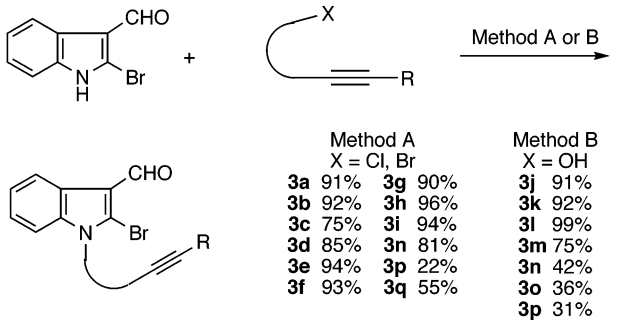


prepared in good to excellent yields, the regioselectivity of the reaction was too sensitive to the nature of the alkynes to be of broad applicability.[17] Alternatively, by readily incorporating an alkyne-containing tether onto the indole nitrogen, subsequent palladium-catalyzed intramolecular iminoannulation would enable regioselective construction of two rings in a single step, and provide a well-recognized entropic advantage (eq 1). Our



own interest in carboline synthesis therefore prompted us to examine the synthesis of a variety of annulated γ-carbolines. A brief communication of this study has been reported previously.[18] Herein, we wish to report the full details of the palladium-catalyzed intramolecular iminoannulation to synthesize annulated γ-carbolines, and extension of this "intramolecular" concept to other

SCHEME 2

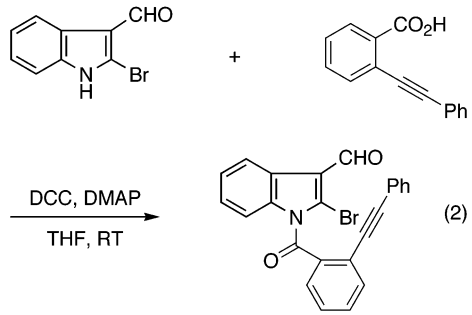


Method A X = Cl, Br				Method B X = OH	
3a	91%	**3g**	90%	**3j**	91%
3b	92%	**3h**	96%	**3k**	92%
3c	75%	**3i**	94%	**3l**	99%
3d	85%	**3n**	81%	**3m**	75%
3e	94%	**3p**	22%	**3n**	42%
3f	93%	**3q**	55%	**3o**	36%
				3p	31%

palladium-catalyzed annulations to synthesize various complex heteropolycycles.

Results and Discussion

In the early stage of our investigation, we were focused on finding a general, high-yielding method to prepare *N*-substituted 2-bromo-1*H*-indole-3-carboxaldehydes bearing a tether with a carbon−carbon triple bond for the palladium-catalyzed intramolecular iminoannulation. The alkylation and acylation of 1*H*-indole-3-carboxaldehyde to prepare alkyne-tethered indole-3-carboxaldehydes have been reported previously.[14a,b] We anticipated that 2-bromo-1*H*-indole-3-carboxaldehyde[17] would undergo a similar process and were delighted to observe that 2-bromo-1*H*-indole-3-carboxaldehyde reacts readily with the appropriate chlorides or bromides bearing a carbon−carbon triple bond in the presence of NaI and K_2CO_3 in acetone, affording the desired tethered indoles **3** in excellent yields in most cases (Method A in Scheme 2, see Table 1 and the Supporting Information for details). Relatively low yields were obtained only when the halide contains a conjugated enyne, which might be unstable under the reaction conditions (compare **3c**, **3p**, and **3q** with others). An alternative method employing the Mitsunobu reaction[19] of 2-bromo-1*H*-indole-3-carboxaldehyde with sterically unhindered alcohols containing a carbon−carbon triple bond has also generated good to excellent yields of the corresponding tethered indoles (Method B in Scheme 2, also see Table 1 and the Supporting Information for details). However, when relatively sterically hindered alcohols were employed, the corresponding Mitsunobu reaction only produced moderate yields of the desired tethered indoles (compare **3n**−**p** with the others). The acylation of 2-bromo-1*H*-indole-3-carboxaldehyde has proven more difficult. After several unsuccessful attempts, we finally managed to couple 2-bromo-1*H*-indole-3-carboxaldehyde with 2-(phenylethynyl)benzoic acid in



3r 50%

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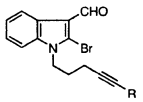
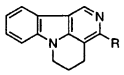
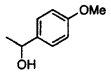
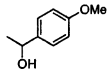
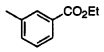
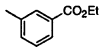
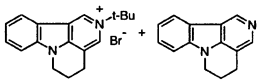
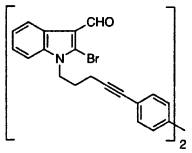
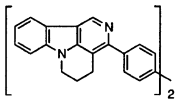
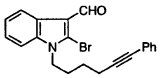
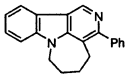
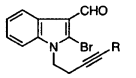
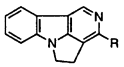
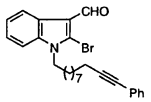
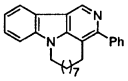
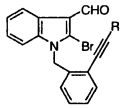
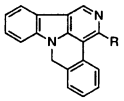
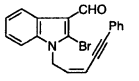
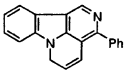
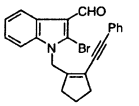
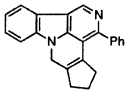
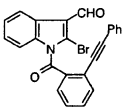
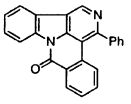
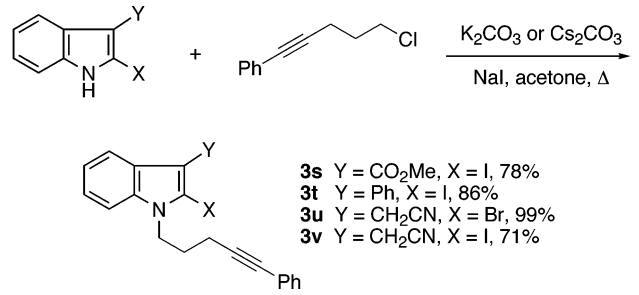
TABLE 1. Synthesis of Annulated γ-Carbolines by Palladium-Catalyzed Intramolecular Iminoannulation (eq 3)[a]

entry	aldehyde		annulation time (h)	product		% yield
						
	R			R		
1	Ph	**3a**	10	Ph	**4a**	93
2	n-C_6H_{13}	**3b**	24	n-C_6H_{13}	**4b**	95
3	(E)-CH=CHPh	**3c**	10	(E)-CH=CHPh	**4c**	94
4		**3d**	18		**4d**	95
5		**3e**	12		**4e**	93
6		**3f**	40		**4f**	99
7[b]	$SiEt_3$	**3g**	18		**4g + 4h**	53 + 40
8	H	**3h**	40		**4g + 4h**	72 + 10
9		**3i**	10		**4i**	91
10		**3j**	10		**4j**	90
						
	R			R		
11	Ph	**3k**	24	Ph	**4k**	84
12	n-C_6H_{13}	**3l**	12	n-C_6H_{13}	**4l**	91
13		**3m**	48		**4m**	trace
						
	R			R		
14	Ph	**3n**	24	Ph	**4n**	88
15	n-Bu	**3o**	20	n-Bu	**4o**	75
16		**3p**	18		**4p**	57
17		**3q**	14		**4q**	94
18[c]		**3r**	-		**4r**	-

[a] Representative procedure: the aldehyde (0.25 mmol) and *tert*-butylamine (1 mL) were placed in a 2-dram vial. The vial was flushed with Ar and carefully sealed, and the mixture was heated at 100 °C for 8 h. The mixture was cooled, diluted with ether, and dried over anhydrous Na_2SO_4 and the solvent was evaporated. The residue was dissolved in 5 mL of DMF and transferred to a 4-dram vial containing 5 mol % of $Pd(OAc)_2$, 10 mol % of PPh_3, and Na_2CO_3 (0.25 mmol). The mixture was then flushed with Ar and heated at 100 °C for the indicated time. [b] *n*-Bu_3N (0.25 mmol) instead of Na_2CO_3 was used as the base. [c] The amide bond was dissociated during the imine preparation.

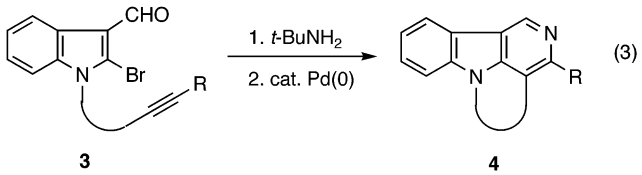
SCHEME 3



the presence of DCC and DMAP,[20] which only afforded a 50% yield of the desired product **3r** (eq 2). Unfortunately, 2-(1-octynyl)benzoic acid and 5-phenylpent-4-ynoic acid failed to give any significant amount of the products under the same reaction conditions.

Similarly, a phenylpentynyl tether has also been successfully incorporated onto the nitrogen of methyl 2-iodo-1*H*-indole-3-carboxylate, 2-iodo-3-phenyl-1*H*-indole,[21] 2-bromo-1*H*-indole-3-acetonitrile,[22] and 2-iodo-1*H*-indole-3-acetonitrile by employing the corresponding 2-haloindoles and 5-chloro-1-phenyl-1-pentyne in the presence of NaI and K_2CO_3 or Cs_2CO_3 in acetone (Scheme 3).

The *tert*-butylimine of indole **3a** was first prepared and employed in the intramolecular palladium-catalyzed iminoannulation under the reaction conditions used in our earlier intermolecular γ-carboline synthesis.[17] Considering that an intramolecular reaction might provide an entropic advantage, we lowered the reaction temperature from 125 °C to 100 °C. We were pleased to see that under these reaction conditions, the palladium-catalyzed intramolecular iminoannulation produced a 93% yield of the desired γ-carboline **4a** in only 10 h (Table 1, entry 1). It is noteworthy that the preparation of the *tert*-butylimines from the corresponding aldehydes is essentially quantitative, requiring no further purification and characterization of the starting imines used for the subsequent palladium-catalyzed annulation, as we have observed in our previous work.[17,23] Thus, by employing a two-step protocol, namely imine formation, followed by palladium-catalyzed intramolecular iminoannulation without isolation of the intermediate imine, we have been able to prepare a variety of annulated γ-carbolines and investigate the scope and limitations of this process (eq 3). The results of this investigation are summarized in Table 1.



(3)

As seen from Table 1, by employing *N*-substituted 2-bromo-1*H*-indole-3-carboxaldehydes with a trimethylene tether from the indole nitrogen to the carbon−carbon triple bond, the parent isocanthine skeleton[14a] can be readily constructed (entries 1−6). This route allows easy access to a variety of substituted isocanthine derivatives and tolerates various functional groups. For example, tethered indoles **3a**−**f** containing aryl, alkyl, alkenyl, hydroxy, ester, and pyrimidyl functionalities all afforded the desired annulation products **4a**−**f** in excellent yields (entries 1−6). Unfortunately, indole **3g** containing a triethylsilyl group did not generate the desired silyl-substituted isocanthine derivative. Instead, a desilylated γ-carbolinium salt with a *tert*-butyl group on the nitrogen (**4g**) was isolated in a 53% yield, along with a 40% yield of the desilylated isocanthine **4h** (entry 7). Tethered indole **3h** with a terminal carbon−carbon triple bond also afforded the same γ-carbolinium salt **4g** as in the silyl case in a 72% yield, as well as a 10% yield of isocanthine (**4h**) as the minor product (entry 8, also see the later discussion). As we expected, tethered indole **3i** readily underwent a double intramolecular iminoannulation, generating a complex isocanthine derivative **4i** in an excellent 91% yield (entry 9).

Interestingly, by employing indole **3j** with a tetramethylene tether, we have been able to isolate an annulated γ-carboline **4j** with a seven-membered ring fused to the 4- and 5-positions in a 90% yield (entry 10). We have also been able to obtain annulated γ-carbolines **4k** and **4l** with a five-membered ring fused across the 4- and 5-positions in 84% and 91% yields, by employing indoles **3k** and **3l** with a dimethylene tether, respectively (entries 11 and 12). It is worth noting that ring systems similar to carbolines **4j**,**k**,**l** have never been efficiently prepared by either an intramolecular Diels−Alder reaction[24] or the electrocyclization of a 1-azatriene,[14c] since those reactions require significant strain of the tether to achieve the necessary transition-state geometry, especially for the case of a five−five ring juncture. Unfortunately, our attempt to achieve a 12-membered ring fused γ-carboline by employing tethered indole **4m** failed to give any significant amount of the desired product (entry 13). A messy reaction with inseparable multiple products occurred. Presumably because of the entropic disadvantage of forming a 12-membered ring, the competitive intermolecular annulation in this case is significant enough to produce multiple byproducts.

Other types of tethers have also proven to be successful in this intramolecular annulation chemistry. For example, indoles **3n** and **3o** with a tether containing an aryl moiety afforded the desired annulated γ-carbolines **4n** and **4o** in 88% and 75% yields, respectively (entries 14 and 15). Indoles **3p** and **3q** with a tether incorporating an alkene moiety also afforded the desired annulated γ-carbolines **4p** and **4q** in 57% and 94% yields, respectively. The relatively low yield of γ-carboline **4p** may be attributable to the fact that the (*Z*)-enyne moiety in

(19) For recent reviews of the Mitsunobu reaction, see: (a) Dodge, J. A.; Jones, S. A. *Recent Res. Dev. Org. Chem.* **1997**, *1*, 273. (b) Simon, C.; Hosztafi, S.; Makleit, S. *J. Heterocycl. Chem.* **1997**, *34*, 349. (c) Hughes, D. L. *Org. Prep. Proced. Inter.* **1996**, *28*, 127. (d) Hughes, D. L. *Org. React.* **1992**, *42*, 335.

(20) For a similar acylation of 1*H*-indole-3-carboxaldehyde, see: Kraus, G. A.; Kim. H. *Synth. Commun.* **1993**, *23*, 55.

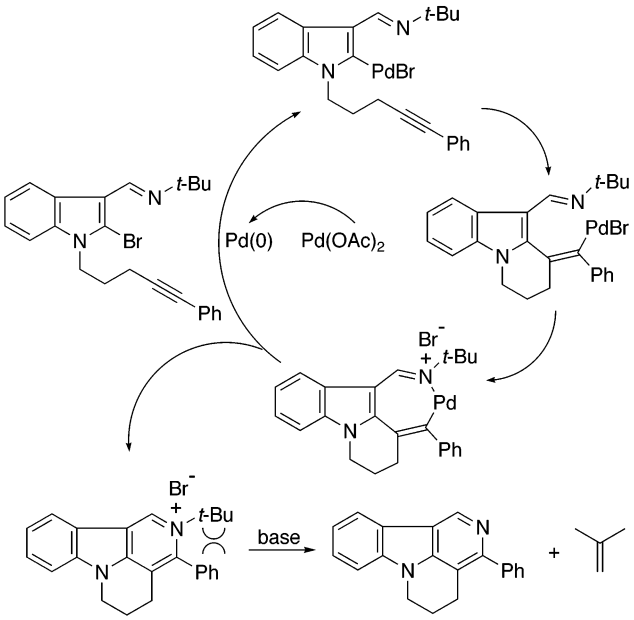
(21) Campo, M. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 5616.

(22) Mistry, A. G.; Smith, K.; Bye, M. R. *Tetrahedron Lett.* **1986**, *27*, 1051.

(23) (a) Zhang, H.; Larock, R. C. *Tetrahedron Lett.* **2002**, *43*, 1359. (b) Zhang, H.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 7048.

(24) Benson, S. C.; Li, J.-H.; Snyder, J. K. *J. Org. Chem.* **1992**, *57*, 5285.

SCHEME 4



indole **3p** can isomerize[25] or undergo side reactions[11a−c] in the presence of a palladium catalyst. Consistent with this hypothesis is the fact that the more highly substituted enyne **3q** gives an excellent yield.

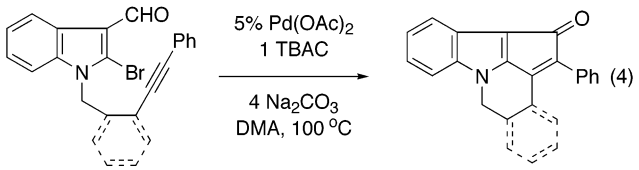
Unfortunately, indole **3r** having an amide linkage underwent transamidation during imine preparation. Therefore, this palladium-catalyzed intramolecular iminoannulation methodology is limited to those tethered indoles with a CH_2−N bond linkage. Our attempts to oxidize isocanthine **4a** to the corresponding isocanthin-6-one using benzyltriethylammonium permanganate[26] (BTAP), which has been used to oxidize amines to amides[26] and employed to oxidize canthine derivatives to their corresponding canthin-6-ones,[27] also failed to give any significant amount of the desired product.

We propose a mechanism for this palladium-catalyzed intramolecular iminoannulation chemistry, which is similar to our earlier intermolecular annulation (Scheme 4).[8,17] Specifically, oxidative addition of the indole bromide to Pd(0) produces an organopalladium intermediate, which then intramolecularly adds across the tethered carbon−carbon triple bond through an exo-dig addition, producing a vinylic palladium intermediate, which then reacts with the neighboring imine substituent to form a seven-membered palladacyclic immonium ion salt. Subsequent reductive elimination produces a *tert*-butylcarbolinium salt and regenerates Pd(0). As previously suggested by Heck,[28] the *tert*-butyl group apparently fragments to relieve the strain resulting from the interaction with the substituent present on the neighboring carbon.

Now it is easy to understand why tethered indole **3h** containing a terminal carbon−carbon produced the *tert*-butylcarbolinium salt **4g** as the major product. In this case, the *tert*-butylcarbolinium salt is unable to fragment the *tert*-butyl group due to the lack of strain between the *tert*-butyl group and the neighboring hydrogen. The observed small amount (10%) of product **4h,** absent of a *tert*-butyl group, presumably arises from thermal fragmentation of the *tert*-butyl group.

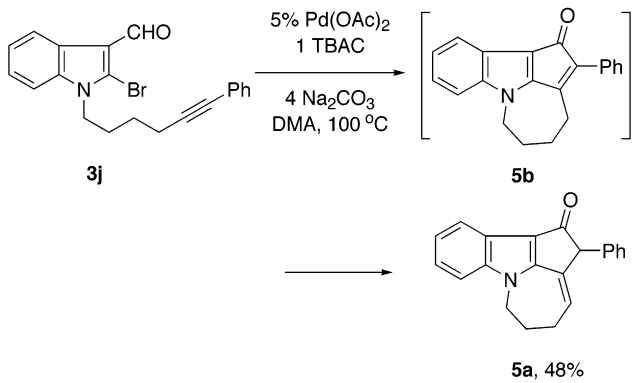
It is also understandable that tethered indole **3g** bearing a triethylsilyl-substituted carbon−carbon triple bond generated a mixture of the desilylated *tert*-butylcarbolinium salt and isocanthine **4h**. In this case, the *tert*-butylcarbolinium intermediate with a *tert*-butyl and a triethylsilyl group on adjacent atoms might undergo either protodesilylation to give the *tert*-butylcarbolinium salt **4g** (53%) without the silyl group or fragmentation of the *tert*-butyl group to give a silyl-substituted isocanthine derivative, which finally protodesilylates under the reaction conditions to give isocanthine **4h** (40%).

Encouraged by the success of our palladium-catalyzed intramolecular iminoannulation, we have also examined several other types of palladium-catalyzed intramolecular annulation. To our disappointment, the intramolecular annulation of aldehydes **3a** and **3n** under the conditions of our earlier indenone synthesis[7] did not generate significant amounts of the desired heterocycles (eq 4),



presumably because the desired products having a five−five−six ring juncture are too strained to form or too unstable under the reaction conditions. Interestingly, by simply increasing the length of the linkage, the palladium-catalyzed intramolecular annulation of aldehyde **3j** has generated a 48% yield of heterocycle **5a** with a five−five−seven ring juncture, which apparently arises from tautomerization of the anticipated less stable heterocycle **5b** (Scheme 5). Similar tautomerization has also been previously observed in our indenone synthesis.[7] Unfortunately, the palladium-catalyzed intramolecular annulation of aldehyde **3j** under the conditions of Yama-

SCHEME 5



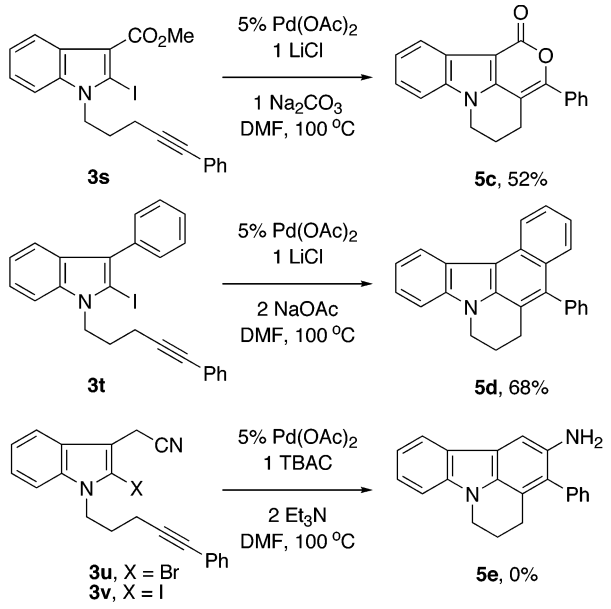
(25) For a recent review on the palladium-catalyzed isomerization of double bonds, see: Negishi, E.-I. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; John Wiley & Sons: New York, 2002; Vol. 2, pp 2783−2788.

(26) (a) Schmidt, H.-J.; Schaefer, H. J. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 68. (b) Schmidt, H.-J.; Schaefer, H. J. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 109.

(27) Li, J.-H.; Snyder, J. K. *Tetrahedron Lett.* **1994**, *35*, 1485.

(28) (a) Wu, G.; Rheingold, A. L.; Geib, S. J.; Heck, R. F. *Organometallics* **1987**, *6*, 1941. (b) Wu, G.; Geib, S. J.; Rheingold, A. L.; Heck, R. F. *J. Org. Chem.* **1988**, *53*, 3238.

SCHEME 6



moto's indenol synthesis[29] did not afford any significant yield of the desired alcohol or the tautomeric ketone.

To our great satisfaction, the intramolecular annulation of alkyne-tethered methyl 2-iodo-1*H*-indole-3-carboxylate **3s** under the conditions of our earlier isocoumarin synthesis[4,5] smoothly produced a 52% yield of the desired heterocycle **5c** (Scheme 6). Equally exciting was the fact that the intramolecular annulation of indole **3t** under the conditions of our earlier phenanthrene synthesis[10] also generated the desired annulation product **5d** in a 68% yield (Scheme 6). However, neither the 2-bromoindole **3u** nor 2-iodoindole **3v** containing acetonitrile functionality generated any of the desired carbazole **5e** under the conditions of our earlier palladium-catalyzed aminonaphthalene synthesis (Scheme 6).[9b] Messy reactions were observed in both cases. One possible reason is that the 2-haloindoles might be reduced to the corresponding indoles under the reaction conditions, as previously observed in our own laboratory.[30]

Conclusions

In conclusion, a number of *N*-substituted 2-bromo-1*H*-indole-3-carboxaldehydes bearing a tether with a carbon−carbon triple bond have been prepared, and an efficient synthesis of various annulated γ-carbolines by imination of these aldehydes, followed by palladium-catalyzed intramolecular iminoannulation has been developed. A wide variety of functionalized 2-bromo-1*H*-indole-3-carboxaldehydes participate in this process to afford the desired γ-carbolines in good to excellent yields. When the tethered carbon−carbon triple bond is terminal or substituted with a silyl group, the iminoannulation generates a *tert*-butyl-γ-carbolinium salt as the major product. This chemistry has also been extended to other palladium-catalyzed intramolecular annulations. An *N*-substituted 2-bromo-1*H*-indole-3-carboxaldehyde, 2-iodo-1*H*-indole-3-carboxylate, and 2-iodo-3-phenyl-1*H*-indole containing an alkyne tether have undergone palladium-catalyzed intramolecular annulation, producing the corresponding heteropolycycles in moderate to good yields. However, none of the desired products were observed in the palladium-catalyzed intramolecular annulation of an alkyne-tethered 2-bromo-1*H*-indole-3-acetonitrile or 2-iodo-1*H*-indole-3-acetonitrile.

Experimental Section

Compounds **3a**,**b**,**d**-**f**,**j**,**l**,**n**,**q**, **4a**,**b**,**d**−**f**,**j**,**l**,**n**,**q**, and **5a** have been previously reported.[18] 2-Iodo-3-phenyl-1*H*-indole was prepared according to a literature procedure.[21] The preparation and characterization of the starting materials and methyl 2-iodo-1*H*-indole-3-carboxylate and 2-iodo-1*H*-indole-3-acetonitrile can be found in the Supporting Information.

General Procedure for the Synthesis of *N*-Substituted 2-Bromo-1*H*-indole-3-carboxaldehydes. Method A: 2-Bromo-1*H*-indole-3-carboxaldehyde[17] (0.5 mmol), the alkynyl halide (0.6 mmol), NaI (0.75 mmol), and K_2CO_3 (0.75 mmol) were placed in a 4-dram vial and acetone (3 mL) was added. The vial was flushed with Ar and heated in an oil bath at 75 °C for 24 h. The mixture was cooled and diluted with ether (5 mL). The precipitate was removed by filtration and the solvent was evaporated. The residue was purified by chromatography on a silica gel column. **Method B:** To a mixture of 2-bromo-1*H*-indole-3-carboxaldehyde (0.5 mmol), the alkynyl alcohol (0.6 mmol), and PPh_3 (0.75 mmol) in CH_2Cl_2 (8 mL) was added diethyl azodicarboxylate (0.75 mmol) at 0 °C. The resulting mixture was flushed with Ar and stirred at room temperature for 24 h. The mixture was concentrated and the residue was purified by chromatography on a silica gel column.

Preparation of *N*-Substituted 2-Bromo-1*H*-indole-3-carboxaldehydes: 2-Bromo-1-[(*E*)-7-phenylhept-6-en-4-ynyl]-1*H*-indole-3-carboxaldehyde (3c). This compound was prepared with use of (*E*)-7-chloro-1-phenylhept-1-en-3-yne according to Method A. The product was purified with 4:1 hexanes/EtOAc to afford 147 mg (75%) of the indicated compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.09 (quintet, J = 7.2 Hz, 2H), 2.48 (dt, J = 2.1, 7.2 Hz, 2H), 4.42 (t, J = 7.2 Hz, 2H), 6.16 (dt, J = 16.2, 2.1 Hz, 1H), 6.90 (d, J = 16.2 Hz, 1H), 7.25−7.46 (m, 8H), 8.33 (m, 1H), 10.04 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 17.4, 28.7, 44.5, 81.5, 90.5, 108.4, 110.1, 115.7, 121.5, 123.6, 124.4, 125.6, 125.8, 126.4, 128.8, 129.0, 136.5, 137.1, 141.2, 185.6; IR (neat, cm^{-1}) 3017, 2926, 1654; HRMS calcd for $C_{22}H_{18}BrNO$ 391.0572, found 391.0579.

2-Bromo-1-(4-phenylbut-3-ynyl)-1*H*-indole-3-carboxaldehyde (3k). This compound was prepared with use of 4-phenylbut-3-yn-1-ol according to method B. The product was purified with 3:1 hexanes/EtOAc to afford 161 mg (92%) of the indicated compound as a yellow solid: mp 104−105 °C; ^{1}H NMR ($CDCl_3$) δ 2.95 (t, J = 7.2 Hz, 2H), 4.53 (t, J = 7.2 Hz, 2H), 7.24−7.33 (m, 7H), 7.46 (m, 1H), 8.34 (m, 1H), 10.05 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.6, 44.0, 83.6, 84.8, 110.0, 115.7, 121.4, 122.8, 123.5, 124.2, 125.4, 125.6, 128.2, 128.3, 131.5, 136.8, 185.6; IR (neat, cm^{-1}) 3055, 3017, 2807, 2237, 1652; HRMS calcd for $C_{19}H_{14}BrNO$ 351.0259, found 351.0265.

The preparation and characterization of all other tethered indoles can be found in the Supporting Information.

General Procedure for the Synthesis of Annulated γ-Carbolines by Palladium-Catalyzed Intramolecular Iminoannulation. The *N*-substituted 2-bromo-1*H*-indole-3-carboxaldehyde (0.25 mmol) was placed in a 2-dram vial and *tert*-butylamine (1 mL) was added. The vial was flushed with Ar and carefully sealed. The mixture was heated at 100 °C for 8 h and cooled, diluted with ether, dried over anhydrous Na_2SO_4, and filtered. The solvent was evaporated and the residue was dissolved in DMF (5 mL) and transferred to a 4-dram vial containing $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), and Na_2CO_3 (0.25 mmol). The mixture was flushed with Ar

(29) Gevorgyan, V.; Quan, L. G.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 4089.

(30) (a) Pletnev, A. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9428. (b) Pletnev, A. A.; Tian, Q.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9276.

and heated at 100 °C for the indicated time. The completion of the reaction was established by the observation of palladium black. The mixture (except for entries 4 and 6−8 in Table 1, which produce reasonably water soluble products) was diluted with EtOAc, washed with satd aq NH_4Cl, and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by chromatography on a silica gel column. The solvent from the reaction mixtures of entries 4 and 6−8 was directly evaporated and the residue was purified by chromatography on a silica gel column.

Preparation of Annulated γ-Carbolines: 3-[(*E*)-β-Styryl]-5,6-dihydro-4*H*-indolo[3,2,1-*ij*]-1,6-naphthyridine (4c). The mixture was chromatographed with 12:1 $CHCl_3$/MeOH to afford 73 mg (94%) of the indicated compound as a yellow solid: mp 131−132 °C; ^{1}H NMR ($CDCl_3$) δ 2.35 (quintet, J = 7.2 Hz, 2H), 3.15 (t, J = 7.2 Hz, 2H), 4.16 (t, J = 7.2 Hz, 2H), 7.24−7.31 (m, 2H), 7.34−7.50 (m, 5H), 7.63 (d, J = 8.0 Hz, 2H), 7.86 (d, J = 15.6 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H), 9.14 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.3, 22.2, 40.5, 108.8, 114.0, 116.6, 120.4, 121.2, 121.7, 123.9, 126.2, 127.1, 127.9, 128.7, 132.2, 137.5, 140.3, 140.4, 142.9, 146.0; IR (neat, cm^{-1}) 3054, 2947, 2865; HRMS calcd for $C_{22}H_{18}N_2$ 310.1470, found 310.1476.

2-*tert*-Butyl-5,6-dihydro-4*H*-indolo[3,2,1-*ij*]-1,6-naphthyridinium Bromide (4g). The mixture was chromatographed with 4:1 $CHCl_3$/MeOH to afford 46 mg (53%) of the indicated compound as a yellow solid: mp >300 °C; ^{1}H NMR ($CDCl_3$) δ 2.01 (s, 9H), 2.42 (quintet, J = 6.0 Hz, 2H), 3.44 (t, J = 6.0 Hz, 2H), 4.38 (t, J = 6.0 Hz, 2H), 7.44 (t, J = 7.8 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.64 (t, J = 7.8 Hz, 1H), 8.78 (d, J = 8.0 Hz, 1H), 9.15 (s, 1H), 10.06 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.2, 22.2, 31.1, 41.6, 68.0, 110.2, 118.1, 119.8, 120.9, 123.3, 124.4, 129.4, 132.3, 134.1, 141.7, 143.6; IR (neat, cm^{-1}) 3016, 2980; MS m/z (rel intensity) 345 (21, M^+), 209 (100, MH^+ − t-Bu − Br). Anal. Calcd for $C_{18}H_{21}BrN_2$: C, 62.62; H, 6.13; N, 8.11. Found: C, 62.16; H, 6.22; N, 8.01.

The preparation and characterization of all other annulated γ-carbolines can be found in the Supporting Information.

3-Phenyl-5,6-dihydro-1*H*,4*H*-benzo[*b*]pyrano[3,4,5-*hi*]-indolizin-1-one (5c). To a 4-dram vial were added methyl 2-iodo-1-(5-phenylpent-4-ynyl)-1*H*-indole-3-carboxylate (**3s**, 0.25 mmol), $Pd(OAc)_2$ (5 mol %), Na_2CO_3 (0.25 mmol), LiCl (0.25 mmol), and DMF (5 mL). The mixture was flushed with Ar and heated at 100 °C for 24 h. The mixture was diluted with EtOAc, washed with satd aq NH_4Cl, and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by chromatography on a silica gel column with 1:1 hexanes/EtOAc to afford 39 mg (52%) of the indicated compound as a white solid: mp 209−210 °C; ^{1}H NMR ($CDCl_3$) δ 2.16 (m, 2H), 2.95 (t, J = 6.0 Hz, 2H), 4.10 (t, J = 6.0 Hz, 2H), 7.27−7.31 (m, 3H), 7.31−7.46 (m, 3H), 7.65 (m, 2H), 8.15 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 22.1, 22.8, 40.9, 98.2, 103.8, 109.1, 121.4, 122.4, 124.0, 124.3, 128.3 (2), 129.4, 132.3, 138.2, 144.7, 153.4, 159.4; IR (neat, cm^{-1}) 3056, 2923, 1702; HRMS calcd for $C_{20}H_{15}NO_2$ 301.1103, found 301.1108. Anal. Calcd for $C_{20}H_{15}NO_2$: C, 79.73; H, 5.02; N, 4.65. Found: C, 79.43; H, 4.81; N, 4.41.

9-Phenyl-7,8-dihydro-6*H*-benzo[*c*]pyrido[1,2,3-*lm*]carbazole (5d). To a 4-dram vial were added 2-iodo-3-phenyl-1-(5-phenylpent-4-ynyl)-1*H*-indole (**3t**, 0.25 mmol), $Pd(OAc)_2$ (5 mol %), NaOAc (0.50 mmol), LiCl (0.25 mmol), and DMF (5 mL). The mixture was flushed with Ar and heated at 100 °C for 8 h. The mixture was diluted with EtOAc, washed with satd aq NH_4Cl, and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by chromatography on a silica gel column with 10:1 hexanes/EtOAc to afford 56 mg (68%) of the indicated compound as a yellow solid: mp 239−241 °C; ^{1}H NMR ($CDCl_3$) δ 2.27 (quintet, J = 6.0 Hz, 2H), 2.89 (t, J = 6.0 Hz, 2H), 4.34 (t, J = 6.0 Hz, 2H), 7.31 (m, 1H), 7.39 (m, 3H), 7.44−7.56 (m, 5H), 7.64 (m, 2H), 8.58 (d, J = 8.0 Hz, 1H), 8.76 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.6, 24.6, 41.1, 108.9, 112.2, 119.7, 120.9, 122.1, 122.4, 123.0, 123.5, 123.7, 125.7, 127.1, 127.7, 128.3, 128.9, 129.0, 130.6, 135.1, 135.5, 138.9, 139.0; IR (neat, cm^{-1}) 3050, 2944; HRMS calcd for $C_{25}H_{18}N$ 333.1518, found 333.1523. Anal. Calcd for $C_{25}H_{19}N$: C, 90.06; H, 5.74; N, 4.20. Found: C, 90.27; H, 5.44; N, 4.17.

Acknowledgment. We gratefully acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research and Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. for donations of palladium acetate.

Supporting Information Available: Preparation and characterization of starting materials; characterization data for compounds **3g**−**i**,**m**,**o**,**p**,**r**−**v** and **4h**,**i**,**k**,**o**,**p**; ^{1}H and ^{13}C NMR spectra for compounds **3c**,**g**−**i**,**k**,**m**,**o**,**p**,**r**−**v** and **4c**,**g**,**k**,**o**,**p**, and **5c**,**d**, and ^{1}H NMR spectrum for compound **4i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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