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Synthesis of β- and γ-Carbolines by the Palladium-Catalyzed Iminoannulation of Alkynes

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A variety of substituted β- and γ-carbolines have been prepared in moderate to excellent yields by the palladium-catalyzed annulation of internal and terminal acetylenes by the *tert*-butylimines of *N*-substituted 3-iodoindole-2-carboxaldehydes and 2-haloindole-3-carboxaldehydes, respectively. This annulation chemistry is effective for a wide range of alkynes, including aryl-, alkyl-, hydroxymethyl-, ethoxycarbonyl-, and trimethylsilyl-substituted alkynes. When an unsymmetrical internal alkyne is employed, this method generally gives two regioisomers. When a terminal alkyne is employed, only one regioisomer has been isolated. This palladium-catalyzed annulation chemistry has also been successfully applied to the synthesis of two biologically interesting β-carboline alkaloids, ZK93423 and abecarnil (ZK112119).

Introduction

Pyrido[3,4-*b*]indoles[1] and pyrido[4,3-*b*]indoles,[2] commonly known as β- and γ-carbolines, respectively, are the key structural units for a variety of biologically important alkaloids. For example, numerous β-carbolines possess potent and varied central nervous system and anticancer activity,[1] and γ-carbolines have been studied extensively as antitumor agents.[3] The latter are condensed analogues of the ellipticine/olivacine anticancer agents, and some do indeed display potent activity.[3] The isolation and synthesis of naturally occurring carbolines and the synthesis of β- and γ-carboline derivatives have received considerable attention in the literature[1,2,4] due to their biological and pharmaceutical importance.

Carboline heterocycles have been synthesized by employing palladium methodology. For instance, a combination of palladium-catalyzed cross-coupling and base-promoted intramolecular nucleophilic aromatic substitution generates the α-, β-, γ-, and δ-carboline parent systems.[5] This strategy has been successfully applied to the synthesis of eudistomin T, a β-carboline alkaloid.[6] A combination of palladium-catalyzed amination and arylation reactions has also been developed to synthesize the carboline parent systems.[4a] A palladium-mediated intramolecular amination, which produces substituted β-carbolines as important intermediates for the total synthesis of lavendamycin methyl ester, has been reported by Boger.[7] This synthesis has the disadvantage of using more than 1 equiv of the palladium reagent. Recently, β- and γ-carbolines have also been synthesized by a combination of palladium-catalyzed coupling, imine/oxime formation, and cyclization.[4c,f−k] Employing this chemistry, Hibino has synthesized several naturally occurring β-carbolines.[4f,h]

Annulation processes have proven very useful in organic synthesis due to the ease with which a wide variety of complicated hetero- and carbocycles can be rapidly constructed. In our own laboratories, it has been demonstrated that palladium-catalyzed annulation methodology[8] can be effectively employed for the synthesis of indoles,[9] isoindolo[2,1-*a*]indoles,[10] benzofurans,[11] benzopyrans,[11] isocoumarins,[11,12] α-pyrones,[12,13] indenones,[14] and polycyclic aromatic hydrocarbons.[15]

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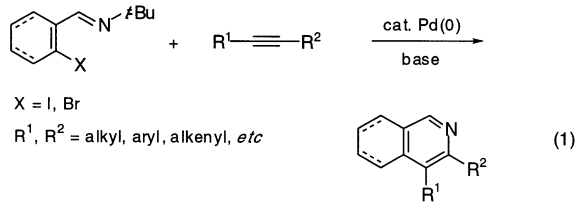
Recently, we have developed a general synthesis of isoquinolines and pyridines by the palladium-catalyzed iminoannulation of internal alkynes (eq 1).[16] Our own

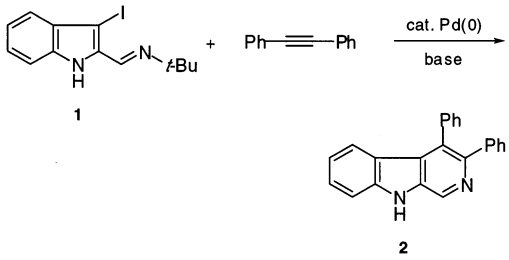


(1)

interest in extending this type of iminoannulation reaction prompted us to examine potential applications to the synthesis of a wide variety of β- and γ-carbolines. A brief communication on this work has been previously reported.[17] Herein, we wish to report the full details of this palladium-catalyzed annulation of internal alkynes for the synthesis of various β- and γ-carbolines, extension of this methodology to terminal alkynes, and applications to the synthesis of two biologically active β-carboline alkaloids, ZK93423[18] and abecarnil (ZK112119).[19]

Results and Discussion

Our initial studies focused on the palladium-catalyzed iminoannulation of internal alkynes employing the *tert*-butylimine of 3-iodo-1*H*-indole-2-carboxaldehyde (**1**). The reaction of diphenylacetylene and imine **1** was chosen as the model system for optimization (eq 2). In the early



(2)

stages of this work, the reaction conditions examined were similar to the conditions employed in our earlier isoquinoline synthesis.[16] For example, the reactions were run with 0.25 mmol of the *tert*-butylimine, 2 equiv of diphenylacetylene, 5 mol % of $Pd(OAc)_2$, 10 mol % of PPh_3, and 1 equiv of Na_2CO_3 as a base in 5 mL of DMF at 100 °C (Table 1, entry 1). However, these conditions failed to produce any of the desired β-carboline **2**. When the reaction temperature was raised to 130 °C, still no desired product was detected after 48 h (entry 2). We next examined different inorganic bases in the reaction, since the nature of the base often has a dramatic effect on these palladium-catalyzed annulation reactions.[8] All of the inorganic bases we tried, including K_2CO_3, Cs_2CO_3, NaOAc, and KOAc proved to be ineffective (entries 3−6). Two pyridine bases, namely pyridine and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), also failed to produce any of the desired product (entries 7 and 8). When the tertiary amine base triethylamine was employed, a 39% yield of the desired product was isolated (entry 9). Several other tertiary amine bases, including *N*,*N*-diisopropylethylamine (*i*-Pr_2NEt), *N*-ethyldicyclohexylamine (Cy_2-NEt), and tri-*n*-butylamine (*n*-Bu_3N), generated the desired product, but in relatively low yields (entries 10−12). Comparing entries 11 and 12, we noticed that the use of *n*-Bu_3N not only required shorter reaction times

TABLE 1. Optimization of the Palladium-Catalyzed Formation of 3,4-Diphenyl-β-carboline (eq 2)

entry	catalyst	% catal	% PPh_3	base (equiv)	temp, °C; time, h	isolated yield of 2, %
1	$Pd(OAc)_2$	5	10	Na_2CO_3 (1)	100; 48	0
2	$Pd(OAc)_2$	5	10	Na_2CO_3 (1)	130; 48	0
3	$Pd(OAc)_2$	5	10	K_2CO_3 (1)	100; 48	0
4	$Pd(OAc)_2$	5	10	Cs_2CO_3 (1)	100; 48	0
5	$Pd(OAc)_2$	5	10	NaOAc (1)	100; 48	0
6	$Pd(OAc)_2$	5	10	KOAc (1)	100; 48	0
7	$Pd(OAc)_2$	5	10	pyridine (1)	100; 48	0
8	$Pd(OAc)_2$	5	10	DTBMP[a] (1)	100; 48	0
9	$Pd(OAc)_2$	5	10	NEt_3 (1)	100; 24	39
10	$Pd(OAc)_2$	5	10	*i*-Pr_2NEt (1)	100; 24	40
11	$Pd(OAc)_2$	5	10	Cy_2NEt (1)	100; 50	48
12	$Pd(OAc)_2$	5	10	*n*-Bu_3N (1)	100; 24	48
13	$Pd(OAc)_2$	5	5	*n*-Bu_3N (1)	100; 10	54
14	$Pd(OAc)_2$	5	2.5	*n*-Bu_3N (1)	100; 10	45
15	$Pd(OAc)_2$	10	5	*n*-Bu_3N (1)	100; 8	51
16	$Pd(OAc)_2$	5	5	*n*-Bu_3N (2)	100; 10	52
17	$PdCl_2(PPh_3)_2$	5	5	*n*-Bu_3N (1)	100; 10	40
18	$PdCl_2(PhCN)_2$	5	5	*n*-Bu_3N (1)	100; 10	46
19	$Pd(PPh_3)_4$	5	5	*n*-Bu_3N (1)	100; 10	41
20	$Pd(dba)_2$	5	5	*n*-Bu_3N (1)	100; 10	41
21	$Pd(dppe)_2$	5	5	*n*-Bu_3N (1)	100; 10	51

[a] 2,6-Di-*tert*-butyl-4-methylpyridine.

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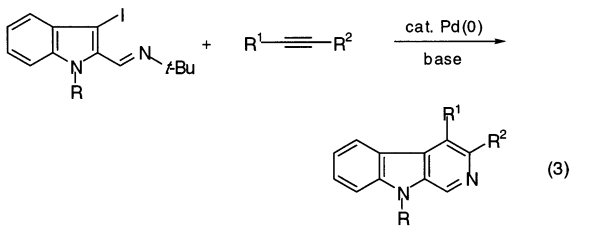
but also produced a cleaner reaction as monitored by TLC analysis than the use of Cy_2NEt. Therefore, we selected *n*-Bu_3N as the base of choice for the succeeding optimization work. We next changed the amount of PPh_3 ligand.

When 5 mol % of PPh_3 was employed in the reaction, a slight increase in the yield, as well as a reduction in the reaction time, was observed (entry 13). Further reduction in the amount of PPh_3 to 2.5 mol % was accompanied by a decrease in the product yield (entry 14). Additional attempts to optimize this annulation process employed 5 mol % of PPh_3 but varied either the amount of $Pd(OAc)_2$ (entry 15) or *n*-Bu_3N (entry 16). A slight decrease in the product yield was observed in both cases. Finally, 5 mol % of five different palladium catalysts other than $Pd(OAc)_2$ were employed, but none of these reactions gave a yield higher than 54% (entry 13, where 5 mol % of $Pd(OAc)_2$, 5 mol % of PPh_3, and 1 equiv of *n*-Bu_3N were employed).

It has been reported that aryl halides and indole can undergo palladium-catalyzed amination to produce *N*-arylindoles.[20] The low yields of carboline observed under various reaction conditions may be a result of the *N*-arylation of our N−H-containing indole by another molecule of starting material to form a dimer, which may subsequently form oligomers or polymers. However, no direct evidence has been obtained during the course of our study to support this hypothesis. The easiest way to solve this problem is to employ *N*-protected indole imines. 3-Iodo-1-methylindole-2-methylene-*tert*-butylamine (**3**) was, therefore, prepared and allowed to react with diphenylacetylene under the optimal reaction conditions for the annulation of diphenylacetylene by imine **1** (Table 1, entry 13; conditions A in Table 2). As we expected, a substantial 76% yield of the desired *β*-carboline **4** was observed (Table 2, entry 1). It is worth noting that when the conditions in our earlier isoquinoline synthesis[16] were employed, the same reaction afforded the desired product, but in a lower yield. When imine **3** and ethyl 3-phenylpropiolate are employed, the annulation reaction gives two isomers, **5** and **6**, in 58% and 42% isolated yields, respectively (Table 2, entry 3). Thus, we have chosen conditions A as our general reaction procedure for the synthesis of *β*-carbolines, instead of endlessly optimizing the reaction conditions. We then proceeded to determine the scope and limitations of this methodology by annulating a wide variety of acetylenes with imine **3** and other *N*-substituted indole imines (eq 3). The results of this study are summarized in Table 2.



(3)

The annulation of a variety of internal alkynes with imine **3** under conditions A has afforded the desired *β*-carbolines in moderate to excellent yields (entries 1, 2, 4, 6−8, 10−13, 15, and 16). When an unsymmetrical alkyne is employed, two regioisomers have generally been observed, usually with poor regioselectivity (entries 2, 4, 6−8, 10, 11, 13, and 15). These results are consistent with our isoquinoline synthesis in which two regioisomers were also observed when an electron-rich imine was employed.[16] Interestingly, the poor regioselectivity can often be improved by simply adding 1 equiv of *n*-Bu_4NCl (TBAC) (conditions B; also see the latter mechanistic discussion). For example, the annulation of imine **3** with ethyl 3-phenylpropiolate under conditions B gave predominantly a single isomer (entry 3). The regioselectivity of reactions of imine **3** with 1-phenylpropyne and ethyl 2-butynoate improved from around 1:1 to about 3:1 and 2:1, respectively (entries 5 and 9). However, the regioselectivity of the annulation of phenyl(trimethylsilyl)-acetylene by imine **3** under conditions B remained essentially unchanged (compare entries 13 and 14). Therefore, the use of TBAC is not generally applicable for increasing the regioselectivity of this chemistry, which is believed to be highly sensitive to the nature of the internal alkyne. The annulation results from the reactions of phenyl(trimethylsilyl)acetylene or 1-trimethylsilyl-1-propyne and imine **3** (entries 13 and 15) were quite interesting, since these alkynes produced unexpected carboline products bearing the more hindered trimethylsilyl group in the 4-position as the major isomers, while the same alkynes afforded desilylated monosubstituted products in our isoquinoline synthesis.[16] This annulation chemistry also works on an alkyne bearing a bulky *tert*-butyl group. For example, 3,3-dimethyl-1-phenyl-1-butyne, which failed to afford any of the desired product in our isoquinoline synthesis,[16] produces in a 32% yield only the unexpected isomer **22** (entry 16), whose regiochemistry has been confirmed by its NOESY spectrum. When another *tert*-butyl-bearing alkyne, 4,4-dimethyl-2-pentyne, was employed in this annulation chemistry, it produced only a trace of the carboline product (entry 17). Quite possibly, the low boiling point of 4,4-dimethyl-2-pentyne (82 °C) results in loss of the acetylene from the reaction vessel under the reaction conditions and thus lowers the yield significantly.

Three other *N*-substituted indole imines were also employed in this palladium-catalyzed iminoannulation chemistry. The annulation of diphenylacetylene by the *N*-methoxymethyl-, *N*-benzyl-, and *N*-tosyl-substituted imines **24**, **26**, and **28** under conditions A afforded 80%, 100%, and 32% yields of the desired products, respectively (entries 18−20). Finally, the annulation of diphenylacetylene by the 1-methoxymethyl-5-benzyloxy-substituted imine **30** under conditions A was carried out, which generated the desired *β*-carboline **31** in a 79% yield (entry 21).

Encouraged by our success with the synthesis of *β*-carbolines, we have also investigated the palladium-catalyzed iminoannulation of internal acetylenes using 2-haloindole-3-methylene-*tert*-butylamines in order to synthesize substituted *γ*- carbolines (eq 4). The results of this investigation are summarized in Table 3.

The annulation reaction of the *tert*-butylimine of 2-iodo-1-methylindole-3-carboxaldehyde (**32**) and diphenylacetylene under conditions A, which were quite successful in our *β*-carboline synthesis, was first examined. To our

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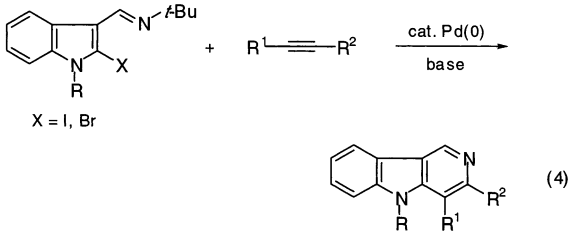


(4)

surprise, this reaction did not afford any of the desired product **33** (entry 1), but a 74% yield of the reduced product 1-methylindole-3-carboxaldehyde was obtained instead. This product apparently arises from the hydrolysis of 1-methylindole-3-methylene-*tert*-butylamine during the workup. When 4-octyne was employed under the same reaction conditions, none of the desired product was observed either. Instead, the same reduced product was isolated in a 76% yield (entry 3). When the standard reaction conditions in our isoquinoline synthesis,[16] conditions C, were employed in the annulation of diphenylacetylene by imine **32**, a messy reaction was observed and only a 24% yield of the desired product was obtained (entry 2). Surprisingly, the reaction of imine **32** with 4-octyne under conditions C afforded a 78% yield of the desired γ-carboline **34** (entry 4). Even more exciting was the observation that the annulation of ethyl 3-phenylpropiolate by imine **32** under conditions C gave a single regioisomer bearing the phenyl group in the 4-position in a 72% yield (entry 5). When ethyl 2-butynoate was employed, two regioisomers in a 69% total yield, as well as a small amount of the corresponding reduced indolecarboxaldehyde product, were observed (entry 6). Unfortunately, when the alkynes 1-phenylpropyne, 3-phenyl-2-propyn-1-ol, diethyl acetylenedicarboxylate, phenyl(trimethylsilyl)acetylene, and 3,3-dimethyl-1-phenyl-1-butyne were employed in this palladium-catalyzed iminoannulation with imine **32**, messy reactions and low yields were observed in all cases.

The annulation of diphenylacetylene by *N*-methoxymethyl-substituted imine **38** took 72 h at 100 °C and subsequently 24 h at 125 °C to reach completion, and only 40% of the desired product **39** was isolated. Neither the *N*-benzyl nor the *N*-tosyl-substituted 2-iodoimines afforded any of the desired products when allowed to react with diphenylacetylene under conditions C. Finally, the annulation reaction of the unsubstituted imine **40** and diphenylacetylene was examined under both conditions C and A. Surprisingly, conditions C did not afford any recognizable product, even after 96 h (entry 8). However, conditions A, which have usually only given the reduced product, afforded a 68% yield of the desired γ-carboline **41** after 96 h (entry 9).

Since the 2-iodoindole imines **32**, **38**, and **40** did not give very promising results with this palladium-catalyzed iminoannulation chemistry, the corresponding 2-bromoindole imines **42**, **43**, and **52** were prepared in order to examine their iminoannulation chemistry with internal alkynes. The annulation of diphenylacetylene by the unsubstituted 2-bromoindole imine **42** was first examined using conditions A. This reaction gave the desired γ-carboline **41** in a 41% yield (entry 10). When the same reaction was run using conditions C, none of the desired product was observed (entry 11). These results are consistent with the results from the annulation of diphenylacetylene by 2-iodoindole imine **40** (compare entries 8−11). Interestingly, the annulation of diphenylacetylene by 2-bromo-1-methylindole-3-methylene-*tert*-butylamine (**43**) under conditions A gave a 30% yield of γ-carboline **33** (entry 12). The same reaction using conditions C afforded a 58% yield of the desired product after 96 h (entry 13). When the temperature was increased to 125 °C, the reaction was complete in a much shorter time (18 h), producing a 70% yield of γ-carboline **33** (entry 14). Encouraged by this result, we examined the palladium-catalyzed iminoannulation of other internal alkynes by imine **43** under conditions C at the elevated temperature of 125 °C. Symmetrical alkynes, such as 4-octyne, 2-butyne-1,4-diol, and diethyl acetylenedicarboxylate, afforded the desired products in moderate to good yields (entries 15−17). However, when unsymmetrical alkynes were employed, this chemistry generally produced two regioisomers with poor regioselectivity (entries 18, 19, and 23). Ethyl 3-phenyl propiolate produced two regioisomers with the major isomer bearing the phenyl group in the 4-position (entry 18). 1-Phenyl-1-propyne afforded two regioisomers in approximately a 1:1 ratio (entry 19). We tried to improve the regioselectivity of the annulation of 1-phenyl-1-propyne by imine **43**, but none of our attempts gave any improved regioselectivity (entries 20−22). A screening of 88 different combinations of palladium catalysts and bases for this reaction using multiplexed capillary electrophoresis also failed to give reaction conditions that afford both good regioselectivity and a good yield.[21] The annulation of ethyl 2-butynoate by imine **43** produced a mixture of two regioisomers in an 84% combined yield, with the major isomer having the ester group in the 3-position (entry 23). The reactions of two alkynes bearing sterically bulky groups, phenyl(trimethylsilyl)acetylene and 3,3-dimethyl-1-phenyl-1-butyne, were then examined. The former alkyne gave a 1:5 mixture of γ-carboline **49** and its desilylated product **50** in a 38% combined yield (entry 24), and the latter did not give any of the desired carboline product.

Finally, the *N*-methoxymethyl-substituted 2-bromoindole imine **52** was employed in the annulation of diphenylacetylene. The reaction gave a 70% yield of the desired product **39** (entry 26). It is noteworthy that the reaction of the corresponding *N*-benzyl-substituted 2-bromoindole imine with diphenylacetylene did not give a significant yield of the desired product, presumably because of the extra steric hindrance introduced by the benzyl group.

We propose a mechanism for this palladium-catalyzed iminoannulation chemistry that is similar to our isoquinoline synthesis (Scheme 1).[16] Specifically, oxidative addition of the indole halide to Pd(0) produces an organopalladium intermediate **A**, which then undergoes alkyne insertion, producing a vinylic palladium intermediate, which then reacts with the neighboring imine substituent to form a seven-membered palladacyclic immonium salt **B**. Subsequent reductive elimination produces a *tert*-butylcarbolinium salt **C** and regenerates the catalyst Pd(0). As previously suggested by Heck,[22] the *tert*-butyl group of the *tert*-butylcarbolinium salt **C**

(21) Zhang, Y.; Gong, X.; Zhang, H.; Larock, R. C.; Yeung, E. S. *J. Comb. Chem.* **2000**, *2*, 450.

(22) (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.

TABLE 2. Synthesis of β-Carbolines by the Palladium-Catalyzed Annulation of Internal Alkynes (eq 3)[a]

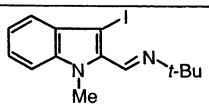
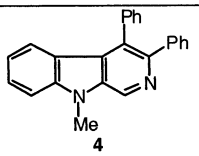
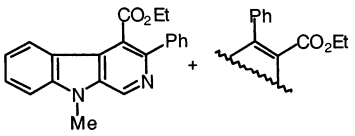
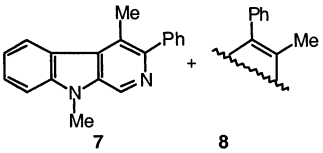
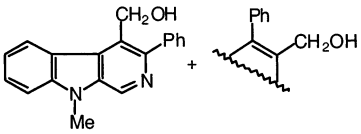
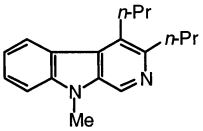
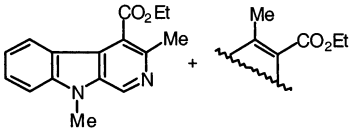
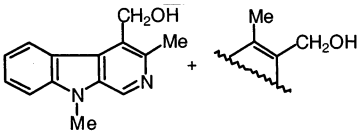
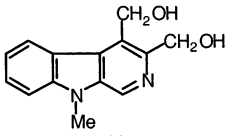
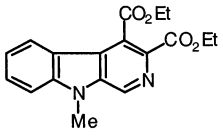
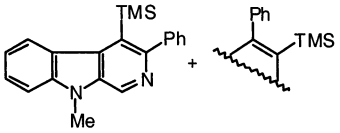
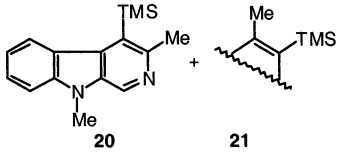
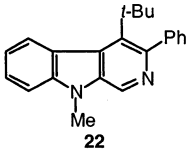
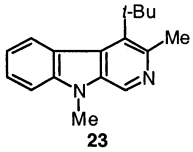
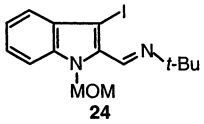
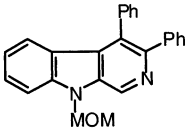
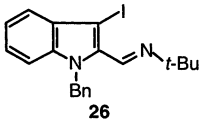
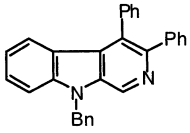
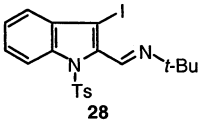
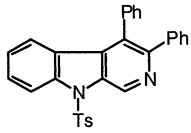
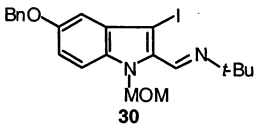
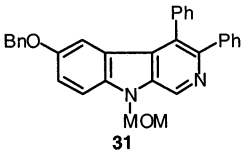
entry	imine	alkyne	cond.	time (h)	product(s)	% isolated yield
1	 **3**	Ph—≡—Ph	A	4	 **4**	76
2		Ph—≡—CO_2Et	A	5	 **5** **6**	58 + 42
3			B	17		99 + trace
4		Ph—≡—Me	A	5	 **7** **8**	49 + 42
5			B	6		64 + 22
6		Ph—≡—CH_2OH	A	2	 **9** **10**	43 + 36
7		*n*-Pr—≡—*n*-Pr	A	2	 **11**	72
8		Me—≡—CO_2Et	A	2	 **12** **13**	73 (1:1)[b]
9			B	22		62 (1:1.7)[b]
10		Me—≡—CH_2OH	A	2	 **14** **15**	100 (1:1)[b]
11		HOH_2C—≡—CH_2OH	A	2	 **16**	96
12		EtO_2C—≡—CO_2Et	A	9	 **17**	49

TABLE 2. (Continued)

entry	imine	alkyne	cond.	time (h)	product(s)	% isolated yield
13		Ph—≡—TMS	A	1.5	 **18** **19**	34 + 25
14			B	24		31 + 24
15		Me—≡—TMS	A	1.5	 **20** **21**	31 + 22
16		Ph—≡—*t*-Bu	A	1	 **22**	32
17		Me—≡—*t*-Bu	A	2	 **23**	trace
18	 **24**	Ph—≡—Ph	A	3	 **25**	80
19	 **26**	Ph—≡—Ph	A	5	 **27**	100
20	 **28**	Ph—≡—Ph	A	5	 **29**	32
21	 **30**	Ph—≡—Ph	A	1	 **31**	79

[a] Representative procedure for conditions A: 5 mol % $Pd(OAc)_2$, 5 mol % PPh_3, *n*-Bu_3N (0.25 mmol), the acetylene (0.5 mmol), the imine (0.25 mmol), and DMF (5 mL) were placed in a 4 dram vial and heated at 100 °C for the indicated time. Conditions B: TBAC (0.25 mmol) was added to conditions A. [b] The ratio was determined by ^1H NMR spectroscopic analysis.

apparently fragments to relieve the strain resulting from interaction with the substituent present in the 3-position.

As mentioned earlier, the poor regioselectivity in our β-carboline synthesis can often be improved by simply adding 1 equiv of TBAC (Table 2, entries 3, 5, and 9). Presumably, the chloride anion of the TBAC displaces the iodide in Pd(II) intermediate **A** and thus slows down the addition of intermediate **A** across the carbon−carbon triple bond of the alkyne, which was confirmed by the observation of prolonged reaction times (compare entries 2, 4, 8, and 13 with entries 3, 5, 9, and 14). Consequently, the reaction gives the more thermodynamically stable regioisomer as the major product.

It is now easy to understand why the annulation reaction of 3,3-dimethyl-1-phenyl-1-butyne with imine **3** produces only one isomer, **22**. As previously mentioned,

TABLE 3. Synthesis of γ-Carbolines by the Palladium-Catalyzed Annulation of Internal Alkynes (eq 4)[a]

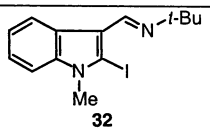
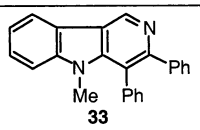
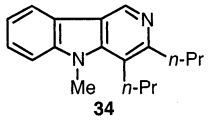
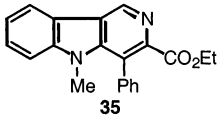
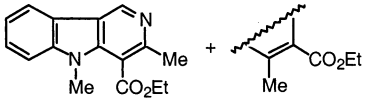
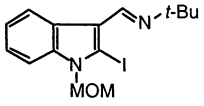
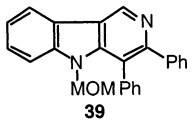
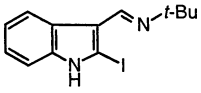
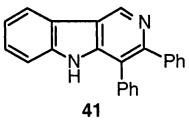
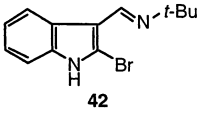
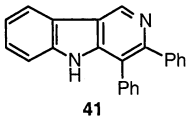
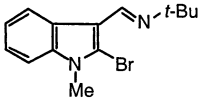
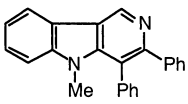
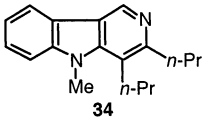
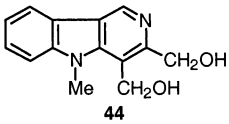
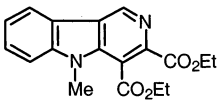
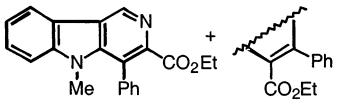
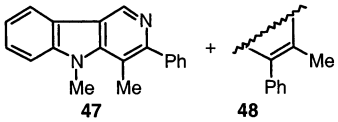
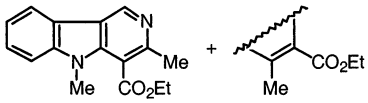
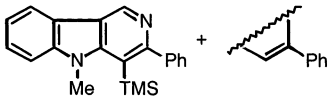
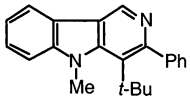
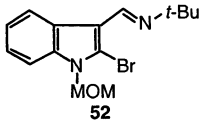
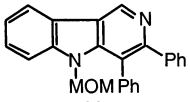
entry	imine	alkyne	cond.	time (h)	product(s)	% isolated yield
1	 **32**	Ph—≡—Ph	A	24	 **33**	0[b]
2			C	48		24
3		*n*-Pr—≡—*n*-Pr	A	12	 **34**	0[c]
4			C	50		78
5		Ph—≡—CO_2Et	C	28	 **35**	72
6		Me—≡—CO_2Et	C	24	 **36** **37**	69 (1:7.5)[d]
7	 **38**	Ph—≡—Ph	C	96[e]	 **39**	40
8	 **40**	Ph—≡—Ph	C	96	 **41**	0
9			A	96		68
10	 **42**	Ph—≡—Ph	A	50	 **41**	41
11			C	96		0
12	 **43**	Ph—≡—Ph	A	96	 **33**	30
13			C	96		58
14			C[f]	18		70
15		*n*-Pr—≡—*n*-Pr	C[f]	16	 **34**	67
16		HOH_2C—≡—CH_2OH	C[f]	20	 **44**	65

TABLE 3. (Continued)

entry	imine	alkyne	cond.	time (h)	product(s)	% isolated yield
17		$EtO_2C{-}{\equiv}{-}CO_2Et$	C[f]	24	 **45**	49
18		$Ph{-}{\equiv}{-}CO_2Et$	C[f]	20	 **35** **46**	63 + 37
19		$Ph{-}{\equiv}{-}Me$	C[f]	20	 **47** **48**	49 + 51
20			C	72		44 + 45
21			C[g]	240		50 + 45
22			C[h]	20		29 + 34
23		$Me{-}{\equiv}{-}CO_2Et$	C[f]	20	 **36** **37**	84 (1:2.4)[d]
24		$Ph{-}{\equiv}{-}TMS$	C[f]	20	 **49** **50**	38 (1:5)[d]
25		$Ph{-}{\equiv}{-}t\text{-}Bu$	C[f]	45	 **51**	trace
26	 **52**	$Ph{-}{\equiv}{-}Ph$	C[f]	72	 **39**	70

[a] Representative procedure for conditions A: 5 mol % $Pd(OAc)_2$, 5 mol % PPh_3, *n*-Bu_3N (0.25 mmol), the acetylene (0.5 mmol), the imine (0.25 mmol), and DMF (5 mL) were placed in a 4 dram vial and heated at 100 °C for the indicated time. Conditions C: 10 mol % PPh_3, Na_2CO_3 as the base (0.25 mmol); everything else is the same as in conditions A. [b] A 74% yield of the reduced product 1-methylindole-3-carboxaldehyde was isolated. [c] A 76% yield of the reduced product 1-methylindole-3-carboxaldehyde was isolated. [d] The ratio was determined by ^1H NMR spectroscopic analysis. [e] The reaction was run at 100 °C for 72 h and subsequently at 125 °C for 24 h. [f] The reaction was run at 125 °C. [g] The reaction was run at 85 °C. [h] 1 equiv of TBAC was added and the reaction was run at 125 °C.

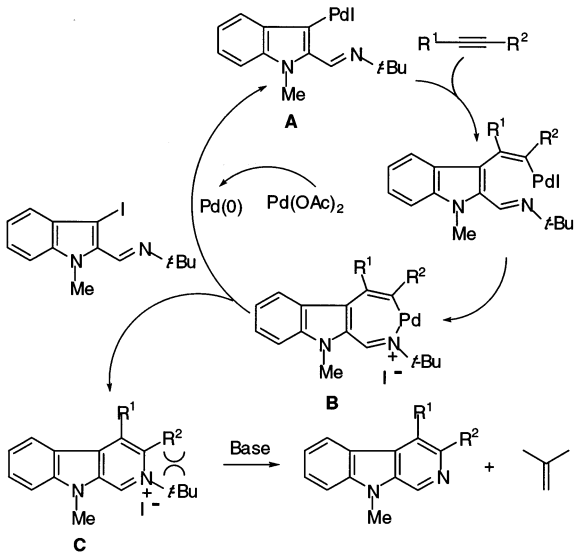
unsymmetrical alkynes usually give two regioisomers. However, in this case, this hindered alkyne is apparently unable to form the other regioisomer. To generate the other isomer, the corresponding vinylic Pd(II) intermediate has to undergo reductive elimination to generate a β-carbolinium salt having bulky *tert*-butyl groups in both the 2- and 3-positions. Apparently, the steric hindrance between these two *tert*-butyl groups disfavors formation of the anticipated β-carbolinium salt (see Figure 1).

It is also understandable why the reaction of 3,3-dimethyl-1-phenyl-1-butyne and imine **43** did not afford any γ-carboline product. Very likely, the steric hindrance between the 2-*tert*-butyl, 3-phenyl, 4-*tert*-butyl, and the 5-methyl groups prevents formation of the anticipated γ-carbolinium intermediate (see Figure 2).

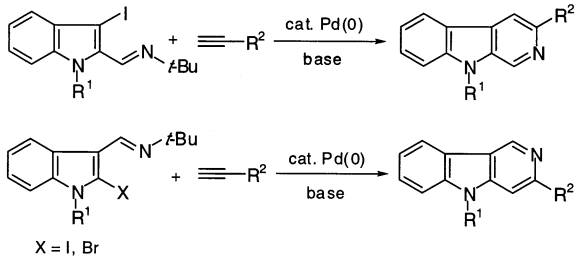
Thus far, our iminoannulation chemistry for the synthesis of β- and γ-carbolines has employed only internal alkynes. Although the palladium-catalyzed annulation of terminal alkynes has been rarely investigated,[23] we were determined to examine the palladium-catalyzed iminoannulation of terminal alkynes (Scheme 2) in order to broaden the scope and reduce the limitations of our iminoannulation chemistry. Previously, we have reported useful two-step approaches to the synthesis of β- and γ-carbolines involving the Sonogashira cross-coupling of terminal alkynes with the corresponding haloindolecar-

(23) (a) Kundo, N. G.; Pal, M.; Nandi, B. *J. Chem. Soc., Perkin Trans. 1* **1998**, 561. (b) Gevorgyan, V.; Radhakrishnan, U.; Takeda, A.; Rubina, M.; Rubin, M.; Yamamoto, Y. *J. Org. Chem.* **2001**, *66*, 2835. (c) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 86.

SCHEME 1



SCHEME 2



boxaldehydes, followed by imine formation with *t*-BuNH$_2$ and either CuI-catalyzed or thermal cyclization (Scheme 3).[4j,k] We hoped to be able to develop this approach into a more convenient one-step process. The results of this investigation are summarized in Table 4.

The annulation of imine **3** by phenylacetylene under our standard conditions for the synthesis of β-carbolines (conditions A) was first examined. We were excited to see that only one regioisomer, **53**, was isolated, although in only a moderate 43% yield (Table 4, entry 1). Unfortunately, either adding 2 mol % of CuI to conditions A or employing our standard conditions for the synthesis of γ-carbolines (conditions C) afforded even lower yields of β-carboline **53** (entries 2 and 3). The reactions of 1-octyne and ethyl propiolate generated a low yield (32%) of β-carboline **54** and only a trace amount of the desired β-carboline **56**, respectively (entries 4 and 6). However, 3-butyn-1-ol afforded an appreciable 60% yield of the desired β-carboline **55** (entry 5). The annulation of phenylacetylene by the *N*-methoxymethyl-protected imine **24** produced β-carboline **57** in a yield comparable to that of the methyl imine **3** (entry 7).

According to the mechanism we have proposed (Scheme 1), the annulation of imine **3** with a terminal acetylene, for example, phenylacetylene, should generate two isomeric *tert*-butylcarbolinium intermediates, $\mathbf{C_1}$ and $\mathbf{C_2}$ (Scheme 4). As mentioned previously, the *tert*-butyl group of the *tert*-butylcarbolinium salt $\mathbf{C_1}$ apparently fragments to relieve the strain resulting from interaction with the phenyl group present in the 3-position. However, the *tert*-butyl group of salt $\mathbf{C_2}$ fails to fragment, due to the lack

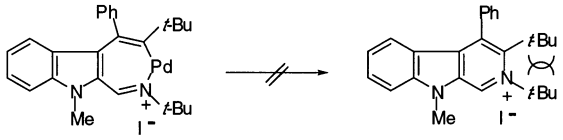


FIGURE 1. Formation of the β-carbolinium salt is disfavored due to steric hindrance.

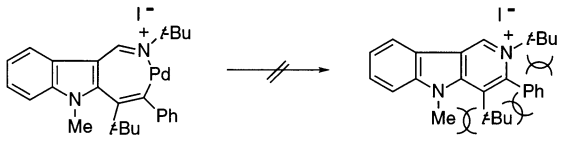
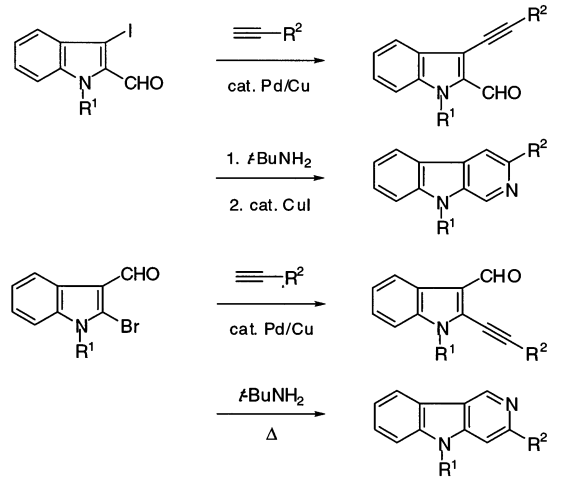


FIGURE 2. Formation of the γ-carbolinium salt is disfavored due to steric hindrance.

SCHEME 3

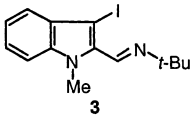
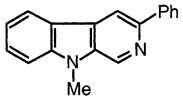
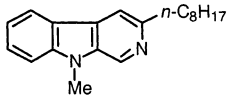
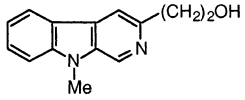
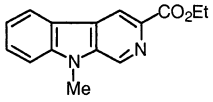
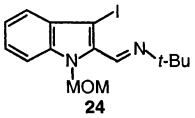
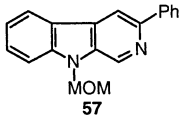
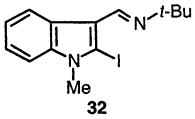
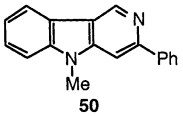
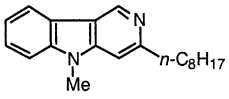
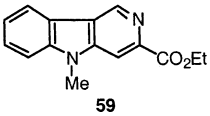
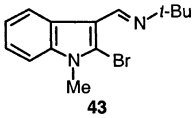
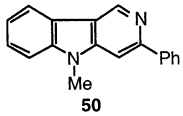
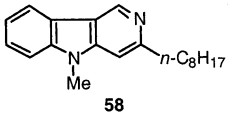
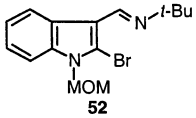
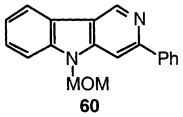
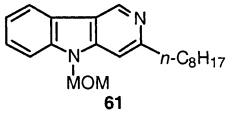


of steric interaction between the *tert*-butyl group and the neighboring small hydrogen. Indeed, we have observed extremely polar and highly fluorescent compounds by TLC analysis in essentially every reaction mixture of the annulation of terminal alkynes by 3-iodoimines. These compounds were easily transferred into the aqueous layer during aqueous workup. The evidence obtained from ^{1}H NMR spectra of the reaction mixture of imine **3** and diphenylacetylene and of the contents in the aqueous layer after workup also prove the existence of the corresponding *tert*-butylcarbolinium salt $\mathbf{C_2}$. That is probably why most of the reactions of 3-iodoimines with terminal alkynes only produce moderate yields of carbolines. Moreover, terminal alkynes can undergo palladium-catalyzed homocoupling,[24] which might also decrease the yields of the annulation products.

The annulation of two terminal alkynes, namely phenylacetylene and 1-octyne, by 2-iodoimine **32** only produced moderate yields of the γ-carboline products **50** and **58** under our standard γ-carboline conditions (conditions C) (entries 8 and 9). Interestingly, ethyl propiolate afforded a 71% yield of the desired γ-carboline **59** (entry 10). The relatively low yields might be a direct result of the 2-iodoimine **32** being reduced during the reaction, which has been observed in other reactions employing internal alkynes.

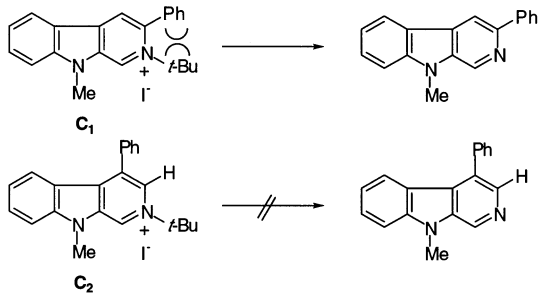
(24) (a) Lei, A.; Srivastava, M.; Zhang, X. *J. Org. Chem.* **2002**, *67*, 1969. (b) Lücking, U.; Pfaltz, A. *Synlett.* **2000**, *1261*. (c) Trost, B. M.; Chan, C.; Rühter, G. *J. Am. Chem. Soc.* **1987**, *109*, 3486.

TABLE 4. Synthesis of β- and γ-Carbolines by the Palladium-Catalyzed Annulation of Terminal Alkynes[a]

entry	imine	alkyne	cond.	time (h)	product	% isolated yield
1	 **3**	—Ph	A	24	 **53**	43
2			A	24		33[b]
3			C	5		34
4		—*n*-C_8H_{17}	A	6	 **54**	32
5		—$(CH_2)_2OH$	A	7	 **55**	60
6		—CO_2Et	A	7	 **56**	trace
7	 **24**	—Ph	A	8	 **57**	44
8	 **32**	—Ph	C	24	 **50**	56[c]
9		—*n*-C_8H_{17}	C	20	 **58**	42
10		—CO_2Et	C	20	 **59**	71
11	 **43**	—Ph	C[d]	24	 **50**	70
12		—*n*-C_8H_{17}	C[d]	18	 **58**	64
13	 **52**	—Ph	C[d]	24	 **60**	83
14		—*n*-C_8H_{17}	C[d]	16	 **61**	92

[a] Representative procedure for conditions A: 5 mol % $Pd(OAc)_2$, 5 mol % PPh_3, *n*-Bu_3N (0.25 mmol), the acetylene (0.5 mmol), the imine (0.25 mmol), and DMF (5 mL) were placed in a 4 dram vial and heated at 100 °C for the indicated time. Conditions C: Na_2CO_3 (0.25 mmol) was used as the base. [b] CuI (2 mol %) was added. [c] An inseparable mixture of carboline **50** and an unidentified byproduct was isolated. The yield was based on ^1H NMR spectroscopy. [d] The reaction was run at 125 °C.

SCHEME 4



Surprisingly, when 2-bromoimine **43** was employed in the annulation reactions with phenylacetylene and 1-octyne at 125 °C, both reactions afforded reasonably good yields of the desired γ-carbolines **50** and **58** (entries 11 and 12). To our delight, the annulation of phenylacetylene and 1-decyne by *N*-methoxymethyl-substituted bromo imine **52** generated an 83% yield of γ-carboline **60** and a 92% yield of γ-carboline **61**, respectively. It is worth mentioning that we did not observe significant amounts of extremely polar and highly fluorescent compounds presumably corresponding to the isomeric *tert*-butylcarbolinium intermediates **C** (Figure 3) in the reactions employing 2-halo imines and terminal alkynes.

As seen from the mechanism we have proposed (Scheme 1), the annulation of imine **43** and phenylacetylene should, for example, form two isomeric seven-membered palladacyclic immonium salts $\mathbf{B_1}$ and $\mathbf{B_2}$ as intermediates (Figure 4). However, salt $\mathbf{B_2}$ is more difficult to form due to steric interactions between the 4-phenyl and 5-methyl groups. Therefore, the energy difference between these two isomeric salts should be significant enough to result in the production of only one γ-carboline regioisomer. However, in the case of the annulation of imine **3** and phenylacetylene, because of the lack of steric interactions between the 4- and 5-positions, the energy difference between the two isomeric seven-membered palladacyclic immonium salts $\mathbf{B_3}$ and $\mathbf{B_4}$ should not be significant (Figure 4). Therefore, we are able to observe the *tert*-butyl-β-carbolinium salt $\mathbf{C_2}$ that arises from the reductive elimination of Pd(0) from immonium salt $\mathbf{B_4}$ by TLC and NMR analysis, as mentioned earlier.

Alternatively, since only the 3-substituted γ-carboline product was observed, other mechanisms might be operating in this system. The following alternative mechanism may be envisioned for this transformation (Scheme 5). Specifically, the Sonogashira coupling of 2-haloindole imine with a terminal alkyne produces an intermediate 2-(1-alkynyl)indole imine, which can then be cyclized thermally in the presence of spurious amount of water, producing a *tert*-butylcarbolinium salt, which apparently fragments, producing the γ-carboline.[4k] Although we have been unable to observe the 2-(1-alkynyl)indole imine intermediate when the reaction of imine **52** and phenylacetylene was stopped after only 1 h, the mechanism proposed in Scheme 5 is still possible for this process and cannot be excluded.

To demonstrate the versatility of this annulation chemistry, we have applied the palladium-catalyzed iminoannulation process to the synthesis of two biologically interesting β-carboline alkaloids, ZK93423 (**62**) and abecarnil (ZK112119, **63**). ZK93423 is a full agonist at

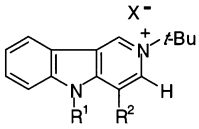


FIGURE 3. Isomeric *tert*-butyl-γ-carbolinium salts **C** were not observed.

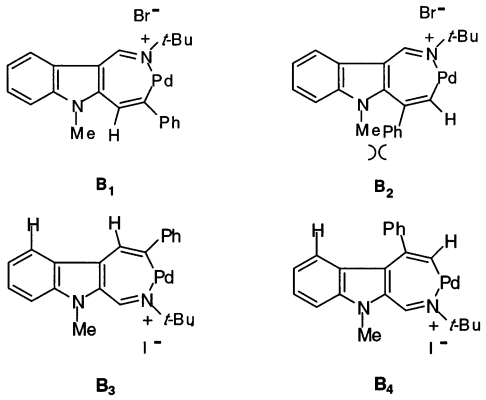
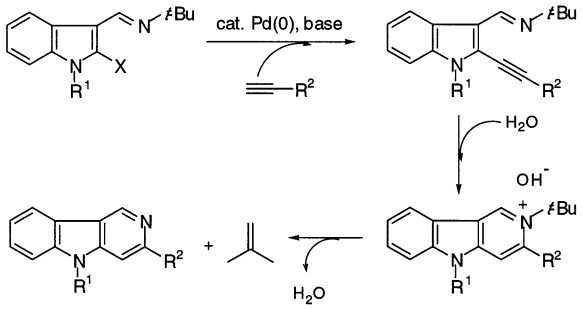


FIGURE 4. Salts $\mathbf{B_1}$ and $\mathbf{B_2}$ should have significantly different energy, but $\mathbf{B_3}$ and $\mathbf{B_4}$ should not.

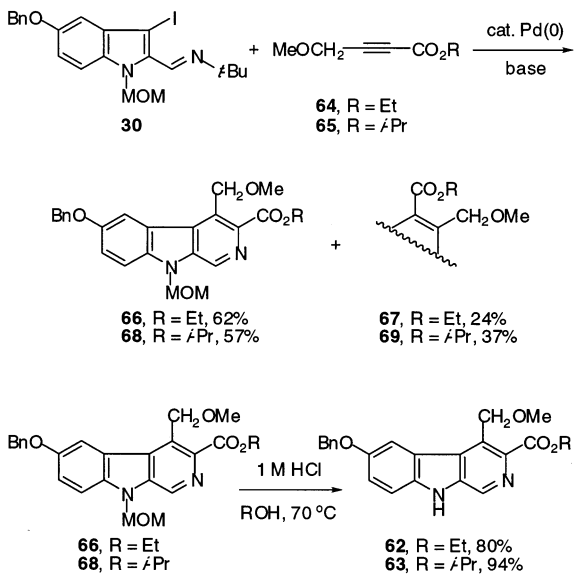
SCHEME 5



the wild type and recombinant $GABA_A$ receptor,[18] and abecarnil displays metabolically stable, anxioselective activity at benzodiazapine receptors and anticonvulsant properties.[19] Although the syntheses of ZK93423[18b,d] and abecarnil[19c] have been achieved previously, our approach may provide a useful alternative to existing methodology. Upon examination of the structures of ZK93423 and abecarnil, we felt that they could be synthesized by employing our palladium-catalyzed iminoannulation using 1-methoxymethyl-5-benzyloxy-substituted imine **30** and internal alkynes **64** and **65**, followed by acid-promoted deprotection of the *N*-methoxymethyl group (Scheme 6). Despite our concern that the annulation reactions might produce two regioisomers, we anticipated that the desired isomer would be the major one required for the synthesis of ZK93423 (**62**) and abecarnil (**63**).

By employing the standard reaction conditions for our β-carboline synthesis (conditions A), the annulation of ethyl 4-methoxy-2-butynoate (**64**) by imine **30** fortunately produced the desired β-carboline **66** in a 62% yield, along with a 24% yield of regioisomer **67**. It is noteworthy that when employing conditions B, which contains 1 equiv of *n*-Bu_4NCl (TBAC), the same reaction generated a similar combined yield, but with decreased regioselectivity, presumably due to coordination of the 4-methoxy group

SCHEME 6



to the palladium. Similarly, the annulation of isopropyl 4-methoxy-2-butynoate (**65**) by imine **30** under conditions A afforded a 57% yield of the desired isomer **68**, as well as a 37% yield of regioisomer **69**. To avoid hydrolysis of the ethyl and isopropyl esters in the 3-position during acid-promoted deprotection of the *N*-methoxymethyl group, EtOH and *i*-PrOH were chosen as the solvents for deprotection of the β-carbolines **66** and **68**, respectively. The acid-promoted deprotection proceeded smoothly at 70 °C, generating ZK93423 (**62**) in an 80% yield and abecarnil (**63**) in a 94% yield, respectively (Scheme 6).

Conclusions

An efficient, palladium-catalyzed synthesis of substituted β- and γ-carbolines from simple internal and terminal alkynes and the *tert*-butylimines of *N*-substituted 3-iodoindole-2-carboxaldehydes and 2-haloindole-3-carboxaldehydes has been developed. The best reaction conditions for the β-carboline synthesis employ 0.25 mmol of the *tert*-butylimine, 2 equiv of alkyne, 5 mol % of Pd(OAc)$_2$, 5 mol % of PPh_3, and 1 equiv of *n*-Bu_3N as the base in 5 mL of DMF at 100 °C. The preferred conditions for the γ-carboline synthesis employ 0.25 mmol of the *tert*-butylimine, 2 equiv of alkyne, 5 mol % of Pd(OAc)$_2$, 10 mol % of PPh_3, and 1 equiv of Na_2CO_3 as the base in 5 mL of DMF at 100 or 125 °C. A wide variety of aryl-, alkyl-, hydroxymethyl-, ethoxycarbonyl-, and trimethylsilyl-substituted acetylenes undergo this process in moderate to excellent yields. When unsymmetrical internal alkynes are employed, mixtures of regioisomers are observed in most cases. When terminal alkynes are employed, only one regioisomer has been isolated. This annulation chemistry has also been successfully applied to the synthesis of two biologically interesting β-carboline alkaloids, ZK93423 and abecarnil (ZK112119).

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates, and visualization was effected with short-wavelength UV light (254 nm). All melting points are uncorrected. All reagents were used directly as obtained commercially unless otherwise noted. 3-Iodo-1-methylindole-2-carboxaldehyde, 2-bromo-1-methylindole-3-carboxaldehyde, 2-bromo-1-methoxylmethylindole-3-carboxaldehyde, and compounds **1**−**6**, **11**, **16**, **24**, **25**, **32**−**35**, **39**, **43**, **44**, **46**, **50**, **52**, **53**−**55**, **57**, **58**, and **60** have been previously reported.[4k,17] 3-Iodo-1*H*-indole-2-carboxaldehyde,[25] 3-iodo-1-(methoxymethyl)indole-2-carboxaldehyde,[25] and 2-bromo-1*H*-indole-3-carboxaldehyde[26] were prepared according to previous literature procedures. The preparation and characterization of the starting materials 1-benzyl-3-iodoindole-2-carboxaldehyde, 3-iodo-1-tosylindole-2-carboxaldehyde, 5-benzyloxy-3-iodo-1-(methoxymethyl)indole-2-carboxaldehyde, 2-iodo-1*H*-indole-3-carboxaldehyde, 2-iodo-1-(methoxymethyl)indole-3-carboxaldehyde, ethyl 4-methoxy-2-butynoate (**64**), and isopropyl 4-methoxy-2-butynoate (**65**) can be found in the Supporting Information.

Preparation of Imines. The following procedures are representative of those used to prepare the imines.

1-Benzyl-3-iodoindole-2-methylene-*tert*-butylamine (26). The imine was prepared by the method used to prepare **1**,[17] only employing 1-benzyl-3-iodoindole-2-carboxaldehyde (180 mg, 0.5 mmol). Removal of the solvent afforded 210 mg (100%) of the imine as a yellow viscous oil: ^{1}H NMR ($CDCl_3$) δ 1.22 (s, 9H), 6.06 (s, 2H), 7.05 (d, J = 6.8 Hz, 2H), 7.15−7.22 (m, 4H), 7.27−7.31 (m, 2H), 7.51 (d, J = 8.0 Hz, 1H), 8.49 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.4, 47.0, 57.2, 67.4, 109.5, 119.8, 121.0, 124.0, 125.6, 125.8, 127.2, 129.0, 131.8, 137.6, 138.6, 147.7; IR (neat, cm^{-1}) 3061, 2967; HRMS calcd for $C_{20}H_{21}IN_2$ 416.0750, found 416.0757.

Characterization of all other imines prepared in this study can be found in the Supporting Information.

General Procedure for the Palladium-Catalyzed Formation of Carbolines. The following were placed in a 4-dram vial: for conditions A, DMF (5 mL), Pd(OAc)$_2$ (3.0 mg, 0.013 mmol), PPh_3 (3.3 mg, 0.013 mmol), *n*-Bu_3N (47 mg, 0.25 mmol), and the alkyne (0.5 mmol); for conditions B, *n*-Bu_4NCl (TBAC, 46 mg, 0.25 mmol) and everything else as in conditions A; or conditions C, PPh_3 (6.5 mg, 0.025 mmol), Na_2CO_3 instead of *n*-Bu_3N (26.5 mg, 0.25 mmol), and everything else as in conditions A. The contents were then stirred for 1 min and the appropriate imine (0.25 mmol) was added. The vial was flushed with Ar and heated in an oil bath at 100 or 125 °C for the indicated period of time. The completion of the reactions was established by the observation of palladium black. The reaction mixture (except entries 10 and 11 in Table 2 and entry 16 in Table 3, which afford fairly water soluble carbolines) was cooled, diluted with ether, washed with 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. The reaction mixtures of entries 10 and 11 in Table 1 and entry 16 in Table 3 were filtered, the solvent was removed directly under reduced pressure, and the residue was purified by chromatography. The following carbolines are representative of these prepared using this procedure.

Diethyl 9-Methyl-9*H*-pyrido[3,4-*b*]indole-3,4-dicarboxylate (17). The reaction was carried out under conditions A (Table 2, entry 12) and the mixture was chromatographed using 1:4 hexanes/EtOAc to afford 40 mg (49%) of the indicated compound as a white solid: mp 154−155 °C; ^{1}H NMR (acetone-d_6) δ 1.41 (t, J = 7.2 Hz, 3H), 1.43 (t, J = 7.2 Hz, 3H), 4.13 (s, 3H), 4.41 (q, J = 7.2 Hz, 2H), 4.59 (q, J = 7.2 Hz, 3H), 7.36 (t, J = 7.2 Hz, 1H), 7.69−7.77 (m, 2H), 8.12 (d, J = 8.0 Hz, 1H), 9.12 (s, 1H); ^{13}C NMR (acetone-d_6) δ 14.7, 15.0, 62.3, 62.9, 111.6, 120.7, 121.9, 124.1, 125.4, 126.0, 130.5, 133.6, 136.4,

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(26) Gilchrist, T. L.; Kemmitt, P. D.; Germain, A. L. *Tetrahedron* **1997**, *53*, 4447. We used ethyl acetate, instead of diethyl ether, as the extraction solvent, and were able to isolate 2-bromo-1*H*-indole-3-carboxaldehyde in 55% yield.

139.0, 143.7, 166.8, 168.5; IR (neat, cm^{-1}) 2987, 1734, 1718; HRMS calcd for $C_{18}H_{18}N_2O_4$ 326.1267, found 326.1273.

Diethyl 5-Methyl-5*H*-pyrido[4,3-*b*]indole-3,4-dicarboxylate (45). The reaction was carried out under conditions C (Table 3, entry 17) and the mixture was chromatographed using 1:1 hexanes/EtOAc to afford 40 mg (49%) of the indicated compound as a yellow solid: mp 118−119 °C; ^{1}H NMR ($CDCl_3$) δ 1.48 (q, J = 7.2 Hz, 6H), 3.90 (s, 3H), 4.53 (q, J = 7.2 Hz, 2H), 4.58 (q, J = 7.2 Hz, 2H), 7.39 (t, J = 7.6 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 8.20 (d, J = 8.0 Hz, 1H), 9.38 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 14.4, 30.5, 62.3, 62.5, 109.6, 116.1, 120.0, 121.2, 121.6, 122.4, 128.5, 140.5, 140.7, 142.2, 142.5, 165.7, 167.7; IR (neat, cm^{-1}) 2983, 1725; HRMS calcd for $C_{18}H_{18}N_2O_4$ 326.1267, found 326.1273.

Characterization of all other carbolines prepared in this study can be found in the Supporting Information.

Ethyl 6-Benzyloxy-4-methoxymethyl-9*H*-pyrido[3,4-*b*]-indole-3-carboxylate (62, ZK93423). To a 2-dram vial were added β-carboline **66** (50 mg), hydrochloric acid (1 M, 1 mL), and EtOH (2 mL). The mixture was then heated at 70 °C for 24 h, cooled, neutralized with saturated aqueous Na_2CO_3, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and filtered. The solvent was removed in a vacuum and the residue was purified by chromatography on a silica gel column using 10:1 $CHCl_3$/MeOH to afford 36 mg (80%) of ZK93423 (**62**) as a white solid: mp 167−168 (lit.[18b] mp 187 °C); ^{1}H NMR ($CDCl_3$) δ 1.41 (t, J = 7.2 Hz, 3H), 3.48 (s, 3H), 4.48 (q, J = 7.2 Hz, 2H), 5.20 (s, 2H), 5.34 (s, 2H), 7.28−7.45 (m, 5H), 7.50 (d, J = 7.2 Hz, 2H), 7.87 (d, J = 2.4 Hz, 1H), 8.79 (s, 1H), 9.55 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.4, 58.2, 61.8, 67.8, 71.0, 108.7, 112.6, 119.5, 121.8, 127.7, 128.0, 128.7, 128.9, 129.2, 133.0, 136.2, 137.2, 137.5, 137.7, 153.8, 167.2; IR (neat, cm^{-1}) 3234, 2981, 1712; HRMS calcd for $C_{23}H_{22}N_2O_4$ 390.1580, found 390.1585.

Isopropyl 6-Benzyloxy-4-methoxymethyl-9*H*-pyrido-[3,4-*b*]indole-3-carboxylate (63, Abecarnil). *i*-PrOH (2 mL) instead of EtOH was used as the solvent to deprotect the *N*-methoxymethyl group of β-carboline **68** (60 mg). Everything else is the same as in the case of β-carboline **66**. The mixture was chromatographed using 10:1 $CHCl_3$/MeOH to afford 51 mg (94%) of abecarnil (**63**) as a white solid: mp 148−149 °C (lit.[27] mp 150−151 °C); ^{1}H NMR ($CDCl_3$) δ 1.40 (d, J = 6.3 Hz, 6H), 3.47 (s, 3H), 5.20 (s, 2H), 5.30 (s, 2H), 5.37 (m, 1H), 7.28−7.52 (m, 7H), 7.86 (d, J = 2.4 Hz, 1H), 8.76 (s, 1H), 9.72 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.1, 58.3, 68.1, 69.6, 71.2, 108.8, 112.8, 119.6, 122.0, 127.9, 128.2, 128.7, 128.8 (2), 129.0, 133.3, 136.4, 137.4, 137.6, 153.9, 167.2; IR (neat, cm^{-1}) 3290, 2981, 1706; HRMS calcd for $C_{24}H_{24}N_2O_4$ 404.1736, found 404.1742.

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Supporting Information Available: Preparation and characterization of the starting materials; characterization data for compounds **7**−**10**, **12**−**15**, **18**−**22**, **27**−**31**, **36**−**38**, **40**−**42**, **47**, **48**, **59**, **61**−**63**, and **66**−**69**; ^{1}H and ^{13}C NMR spectra for compounds **7**−**10**, **12**−**15**, **17**−**22**, **26**−**31**, **36**−**38**, **40**−**42**, **45**, **47**, **48**, **59**, **61**−**63,** and **66**−**69**; and NOESY spectra for compounds **12** and **13**, **21**, **22**, **36**, **37**, **47**, **66**, and **68**. This material is available free of charge via the Internet at http://pubs.acs.org.

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