Synthesis of 2,3-Disubstituted Indoles via Palladium-Catalyzed Annulation of Internal Alkynes

R. C. Larock,* E. K. Yum, and M. D. Refvik

Department of Chemistry, Iowa State University, Ames, Iowa 50011

Received February 20, 1998

The palladium-catalyzed coupling of 2-iodoaniline and the corresponding *N*-methyl, -acetyl, and -tosyl derivatives with a wide variety of internal alkynes provides 2,3-disubstituted indoles in good-to-excellent yields. The best results are obtained by employing an excess of the alkyne and a sodium or potassium acetate or carbonate base plus 1 equiv of either LiCl or *n*-Bu_4NCl, occasionally adding 5 mol % PPh_3. The yields with LiCl appear to be higher and more reproducible than those obtained with *n*-Bu_4NCl. The process is quite general as far as the types of substituents which can be accommodated on the nitrogen of the aniline and the two ends of the alkyne triple bond. The reaction is quite regioselective, placing the aryl group of the aniline on the less sterically hindered end of the triple bond and the nitrogen moiety on the more sterically hindered end. This methodology readily affords 2-silylindoles, which can be easily protodesilylated, halogenated, or reacted with alkenes and $Pd(OAc)_2$ to produce 3-substituted indoles, 2-haloindoles, or 2-(1-alkenyl)-indoles, respectively. The presence of alcohol groups in the alkyne seems to have a particularly strong directing effect, perhaps due to coordination with palladium. This catalytic process apparently involves arylpalladium formation, regioselective addition to the C−C triple bond of the alkyne, and subsequent intramolecular palladium displacement.

Introduction

The palladium-catalyzed, carbo- and heteroannulation of 1,2-dienes,[1] 1,3-dienes,[2] 1,4-dienes,[3] and vinylic cyclopropanes or cyclobutanes[4] by aromatic halides bearing functional groups in the *ortho* position has recently proven to be an extremely versatile method for the synthesis of a wide variety of heterocycles and carbocycles. All of these processes are believed to proceed by π-allylpalladium intermediates. Although the addition of arylpalladium compounds to alkynes and subsequent intramolecular cyclization has been previously observed, such processes have generally involved stoichiometric amounts of arylpalladium compounds formed by *ortho*-palladation and insertion of more than 1 equiv of alkyne, followed in many cases by cyclization back onto the preexisting aromatic ring.[5,6] One exception is the synthesis of *N*-methylbenzo[*d*,*e*]quinolines by the palladium-catalyzed annulation of internal alkynes by 1-iodo-8-(dimethylamino)naphthalene.[7] In attempting to extend our annulation chemistry to alkynes,[8] we observed and previously communicated that excellent yields of 2,3-disubstituted indoles could be obtained from the palladium-catalyzed coupling of 2-iodoaniline and derivatives with internal alkynes.[9] That chemistry has subsequently been employed by others for the synthesis of potential migraine headache drugs and other heterocycles.[10] We wish at this time to report full details on this very useful new synthetic approach to indoles.[11]

(1) Larock, R. C.; Berrios-Peña, N. G.; Fried, C. A. *J. Org. Chem.* **1991**, *56*, 2615.

(2) (a) Larock, R. C.; Berrios-Peña, N.; Narayanan, K. *J. Org. Chem.* **1990**, *55*, 3447. (b) Larock, R. C.; Fried, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 5882. (c) O'Connor, J. M.; Stallman, B. J.; Clark, W. G.; Shu, A. Y. L.; Spada, R. E.; Stevenson, T. M.; Dieck, H. A. *J. Org. Chem.* **1983**, *48*, 807. (d) Larock, R. C.; Guo, L. *Synlett* **1995**, 465.

(3) Larock, R. C.; Berrios-Peña, N. G.; Fried, C. A.; Yum, E. K.; Tu, C.; Leong, W. *J. Org. Chem.* **1993**, *58*, 4509.

(4) Larock, R. C.; Yum, E. K. *Synlett* **1990**, 529.

(5) For general reviews, see: (a) Maitlis, P. M. *J. Organomet. Chem.* **1980**, *200*, 161. (b) Pfeffer, M. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 567.

(6) For the cascade carbopalladation of alkynes, see: (a) Wu, G.; Lamaty, F.; Negishi, E. *J. Org. Chem.* **1989**, *54*, 2507. (b) Negishi, E. *Pure Appl. Chem.* **1992**, *64*, 323. (c) Zhang, Y.; Negishi, E. *J. Am. Chem. Soc.* **1989**, *111*, 3454. (d) Negishi, E.; Harring, L. S.; Owczarczyk, Z.; Mohamud, M. M.; Ay, M. *Tetrahedron Lett.* **1992**, *33*, 3253. (e) Negishi, E.; Noda, Y.; Lamaty, F.; Vawter, E. J. *Tetrahedron Lett.* **1990**, *31*, 4393. (f) Torii, S.; Okumoto, H.; Nishimura, A. *Tetrahedron Lett.* **1991**, *32*, 4167. (g) Owczarczyk, Z.; Lamaty, F.; Vawter, E. J.; Negishi, E. *J. Am. Chem. Soc.* **1992**, *114*, 10091. (h) Negishi, E.; Ay, M.; Sugihara, T. *Tetrahedron* **1993**, *49*, 5471. (i) Coperet, C.; Sugihara, T.; Negishi, E. *Tetrahedron Lett.* **1995**, *36*, 1771. (j) Meyer, F. E.; Henniges, H.; de Meijere, A. *Tetrahedron Lett.* **1992**, *33*, 8039. (k) Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1992**, *114*, 791. (l) Meyer, F. E.; Brandenburg, J.; Parsons, P. J.; de Meijere, A. *J. Chem. Soc., Chem. Commun.* **1992**, 390. (m) Meyer, F. E.; de Meijere, A. *Synlett* **1991**, 777. (n) Meyer, F. E.; Parsons, P. J.; de Meijere, A. *J. Org. Chem.* **1991**, *56*, 6487. (o) Zhang, Y.; Wu, G.; Agnel, G.; Negishi, E. *J. Am. Chem. Soc.* **1990**, *112*, 8590. (p) Coperet, C.; Sugihara, T.; Negishi, E. *Tetrahedron Lett.* **1995**, *36*, 1771. (q) Ihle, N. C.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 560. (r) Sugihara, T.; Coperet, C.; Owczarczyk, Z.; Harring, L. S.; Negishi, E. *J. Am. Chem. Soc.* **1994**, *116*, 7923.

(7) Beydoun, N.; Pfeffer, M. *Synthesis* **1990**, 729.

(8) For some of our recent alkyne annulation chemistry, see: (a) Larock, R. C.; Doty, M. J.; Cacchi, S. *J. Org. Chem.* **1993**, *58*, 4579. (b) Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270. (c) Larock, R. C.; Doty, M. J.; Tian, Q.; Zenner, J. M. *J. Org. Chem.* **1997**, *62*, 7536. (d) Larock, R. C.; Tian, Q. *J. Org. Chem.* **1998**, *63*, 2002. (e) Larock; R. C.; Doty, M. J.; Han, X. *Tetrahedron Lett.* **1998**, *39*, 5143. (f). Larock, R. C.; Han, X.; Doty, M. J. *Tetrahedron Lett.* **1998**, *39*, 5713. (g) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 5306.

(9) (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. For subsequent intramolecular versions of this reaction, see: (b) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1992**, *33*, 3915. (c) Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L.; Pace, P. *Synlett* **1997**, 1363.

(10) (a) Wensbo, D.; Eriksson, A.; Jeschke, T.; Annby, U.; Gronowitz, S.; Cohen, L. A. *Tetrahedron Lett.* **1993**, *34*, 2823. (b) Chen, C.; Lieberman, D. R.; Larsen, R. D.; Reamer, R. A.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron. Lett.* **1994**, *35*, 6981. (c) Jeschke, T.; Wensbo, D.; Annby, U.; Gronowitz, S.; Cohen, L. A. *Tetrahedron Lett.* **1993**, *34*, 6471. (d) Smith, D. W.; Youcca, F. D.; Yevich, J. P.; Mattson, R. J.; Williams, A.; Ruediger, E. H.; Combrink, K. D.; Pearce, B. C. European Patent 0 548 813 A1, 1993. (e) Chen, C.-y.; Lieberman, D. R.; Street, L. J.; Guiblin, A. R.; Larsen, R. D.; Verhoeven, T. R. *Synth. Commun.* **1996**, *26*, 1977. (f) Zhang, H.-C.; Brumfield, K. K.; Maryanoff, B. E. *Tetrahedron Lett.* **1997**, *38*, 2439. (g) Park, S. S.; Choi, J. K.; Yum, E. K.; Ha, D.-C. *Tetrahedron Lett.* **1998**, *39*, 627.

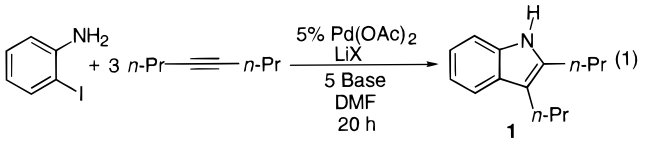
10.1021/jo9803277 CCC: $15.00
Published on Web 10/03/1998

Table 1. Palladium-Catalyzed Annulation of 4-Octyne 2-Iodoaniline (Eq 1)

entry	base	X	LiX (equiv)	PPh_3 (5 mol %)	temp (°C)	% isoltd yield of **1**
1	KOAc				120	36
2	KOAc	Cl	1		120	80
3	KOAc	Br	1		120	0
4	KOAc	I	1		120	26
5	KOAc	Cl	2		120	56
6	KOAc	Cl	3−5		120	0
7	KOAc	Cl	1	+	120	40
8	KOAc	Cl	2	+	120	36
9	KOAc	Cl	1		100	0
10	KOAc	Cl	1	+	100	0
11	K_2CO_3				120	46
12	K_2CO_3	Cl	1		120	60
13	K_2CO_3	Br	1		120	60
14	K_2CO_3	I	1		120	70
15	K_2CO_3	Cl	2		120	68
16	K_2CO_3	Cl	1	+	120	60
17	K_2CO_3	Cl	2	+	120	0
18	K_2CO_3	Cl	1		100	80
19	K_2CO_3	Cl	1	+	100	0
20	Na_2CO_3	Cl	1		120	46
21	Na_2CO_3	Br	1		120	0
22	Na_2CO_3	I	1		120	20
23	Na_2CO_3	Cl	2		120	50
24	Na_2CO_3	Cl	2	+	120	44
25	NaOAc	Cl	1		120	38
26	NaOAc	Br	1		120	0
27	NaOAc	Cl	1	+	120	42
28	NaOAc	Cl	1		100	0

Results and Discussion

Initial studies were directed toward finding a general set of reaction conditions that could be applied to a wide variety of 2-iodoaniline derivatives and alkynes. Since it appeared that reactions such as that of 2-iodoaniline itself with relatively unhindered alkynes, such as 4-octyne, were likely to prove the most difficult, we turned our attention to optimizing that particular process (eq 1). The following variables were closely examined: the



base, the added lithium halide and its stoichiometry, the presence or absence of PPh_3, and the reaction temperature. All reactions were run on a 0.25-mmol scale, using 5 mol % of $Pd(OAc)_2$ as catalyst, 3 equiv of alkyne, 5 equiv of base in 10 mL of DMF as solvent for 20 h. Some results from that study are summarized in Table 1.

KOAc was the first base examined (Table 1, entries 1−10). In the absence of any lithium halide or PPh_3 at 120 °C, a 36% yield of 2,3-di-*n*-propylindole (**1**) was obtained (entry 1). The addition of 1 equiv of LiCl, LiBr, or LiI afforded yields of 80%, 0%, and 26%, respectively (entries 2−4). The latter two salts appeared to give high molecular weight products assumed to be multiple insertion products. The use of LiCl is clearly superior and appears to give more reproducible results than *n*-Bu_4NCl, although many early results using the latter salt, reported later in Table 3, were obtained prior to this particular study. Further addition of LiCl resulted in substantially slower reactions and lower yields plus the apparent concomitant formation of multi-insertion products (entries 5 and 6). The addition of 5 mol % of PPh_3 also dramatically lowered the yield of indole and increased the amount of apparent multi-insertion products (entries 7 and 8). Whether PPh_3 was present or not, no indole was formed when the temperature was lowered to 100 °C (entries 9 and 10).

K_2CO_3 was the next base examined. Although it gave superior results to KOAc in the absence of other reagents (compare entries 1 and 11), when 1 equiv of LiCl was added, the results were inferior to those of KOAc (compare entries 2 and 12). Unlike reactions with KOAc, however, reactions with K_2CO_3 and LiBr or LiI (entries 13 and 14) or an additional equivalent of LiCl (entry 15) actually gave higher yields of indole. The addition of 5 mol % of PPh_3 to the reaction employing 1 equiv of LiCl gave exactly the same yield as the reaction without any PPh_3 (entry 16), but the addition of an additional 1 equiv of LiCl greatly slowed the reaction and none of the indole product was observed (entry 17). When the temperature of the reaction with 1 equiv of LiCl was lowered to 100 °C, an improved yield of 80% was actually obtained (entry 18), but the addition of PPh_3 resulted in much of the aryl iodide being recovered and none of the indole being obtained (entry 19).

When Na_2CO_3 was employed as the base, the results were generally inferior to those of KOAc or K_2CO_3 (entries 20−24). The addition of LiBr or LiI gave lower yields than LiCl (entries 21 and 22). Only a slight improvement in yield was observed by adding a second equivalent of LiCl (entry 23), and this improvement was negated by the addition of PPh_3 (entry 24).

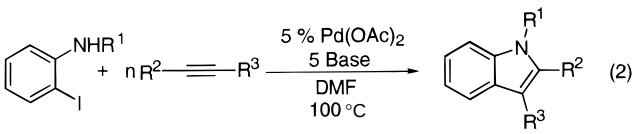
Poor results were also obtained when NaOAc was employed as the base (entries 25−28). Again, LiBr proved inferior to LiCl, and the addition of PPh_3 had little effect. Lowering the temperature to 100 °C failed to provide any of the desired indole product.

From these studies, at least with 2-iodoaniline itself, it appears that the best bases for this annulation process are KOAc and K_2CO_3 and that it is highly desireable to add 1 equiv of LiCl to the reaction. The stoichiometry of the LiCl salt is also very important. More than one equiv generally slows down the rate of reaction and sharply lowers the yield. With KOAc, a temperature of 120 °C is necessary for the reaction to reach completion in a reasonable amount of time, whereas K_2CO_3 can be employed at a slightly lower temperature of 100 °C. The addition of PPh_3 is generally unnecessary. In studies with other aryl iodides and alkynes, variations of these apparently "optimal" conditions have continued to be explored, because our previous work on this type of annulation chemistry has shown us that the optimal reaction conditions can often be highly dependent on the substrates employed. Many quite satisfactory results reported later using *n*-Bu_4NCl as the halide salt had been obtained prior to this optimization study.

Since the annulation of internal alkynes appeared to be very sensitive to the concentration of the alkyne, we have also explored the effect of varying the number of alkyne equivalents used in the reaction. Some of those results are summarized in Table 2. These reactions were run using 1 equiv of LiCl in DMF (10 mL per 0.25 mmol of ArI) at 100 °C for 1 day. In all reactions, reasonable yields of indole product were obtained using just 1 equiv of the alkyne, but better yields were possible when 2−5 equiv of alkyne was employed. In subsequent studies, an excess of alkyne was therefore commonly utilized.

(11) For a review of other palladium-based approaches to indoles, see: Hegedus, L. S. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1113.

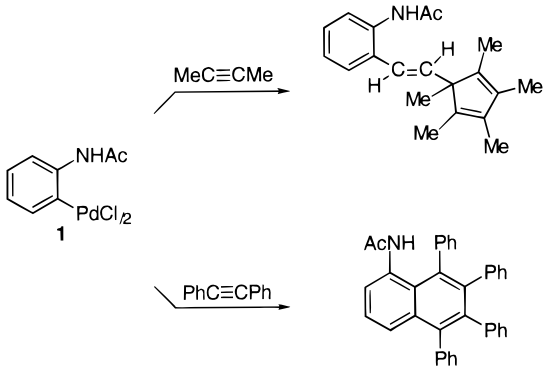
Having gained an understanding of the factors that were influencing the heteroannulation process, we subjected 2-iodoaniline and several derivatives, plus a wide range of internal alkynes, to this process to determine its scope and limitations (eq 2). All of the work was



(2)

carried out using 5 mol % of $Pd(OAc)_2$ and 1 equiv of LiCl or *n*-Bu_4NCl at 100 °C. Only after considerable work had been carried out was the superiority of LiCl discovered; therefore, not all reactions were necessarily run under optimal conditions. The significant variation in yields obtained in previous annulation work using different substrates and bases encouraged us to continue to try a number of different acetate and carbonate bases and to occasionally add 5 mol % of PPh_3. The effect of added PPh_3 also was not appreciated during much of our early work. The more volatile the alkyne, the greater the number of equivalents of alkyne that were employed. The best results obtained during this study are summarized in Table 3.

As indicated in Table 3, this approach to 2,3-disubstituted indoles is very versatile. 2-Iodoanilines with a wide variety of substitutents on the nitrogen moiety have been reacted successfully. We have been able to obtain high yields using 2-iodoaniline, *N*-methyl-2-iodoaniline, 2-iodoacetanilide, and *N*-tosyl-2-iodoaniline. It is particularly noteworthy that 2-iodoacetanilide undergoes this annulation process with a variety of alkyl and aryl acetylenes to afford indoles in high yields, because previous work on the reaction of the *ortho*-palladation complex **1** and alkynes demonstrated the exclusive formation of multi-insertion products (eq 3).[12] It is not



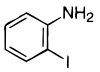
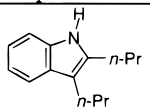
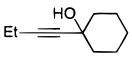
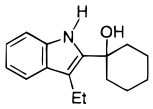
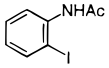
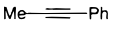
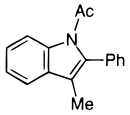
(3)

clear at present if this apparent difference in reactivity is due to the different halides present in the two reactions (only Cl versus I and Cl) or some other variable. It is known that the nature of the halide can have a pronounced effect on the nature of the products in these alkyne insertion processes.[13] 2-Bromoaniline and derivatives thereof are unreactive under our reaction conditions, but one might expect that the introduction of electron-withdrawing groups on the aromatic ring would increase their reactivity.

(12) Dupont, J.; Pfeffer, M.; Daran, J.-C.; Gouteron, J. *J. Chem. Soc., Dalton Trans.* **1988**, 2421.

(13) (a) Maassarani, F.; Pfeffer, M.; Le Borgne, G. *J. Chem. Soc., Chem. Commun.* **1987**, 565. (b) Maassarani, F.; Pfeffer, M.; Le Borgne, G. *Organometallics* **1987**, *6*, 2029.

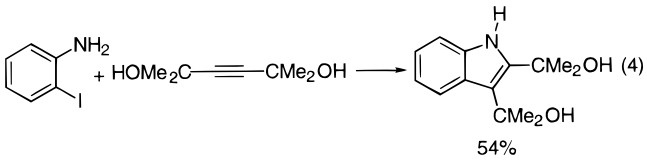
Table 2. Effect of Alkyne Stoichiometry

entry	aryl iodide	alkyne (equiv)	product	% isolated yield
1[a]		(1)		50
2[a]		(2)		64
3[a]		(3)		80
4[a]		(5)		80
5[b]		 (1)		51
6[b]		(2)		85
7[b]		 (1)		70
8[b]		(2)		75

[a] K_2CO_3 was employed as the base. [b] KOAc was employed as the base.

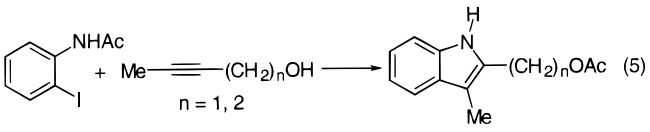
A wide variety of alkynes have been successfully employed in this indole synthesis. Simple unhindered alkyl-substituted alkynes, such as 4-octyne, afford high yields of the corresponding indoles. This is quite remarkable, because this type of unhindered aliphatic alkyne has failed in much of our other alkyne annulation chemistry in which functional groups other than nitrogen have been employed.[8] These relatively unhindered alkynes appear to be particularly reactive toward insertion[6h] and apparently readily undergo multi-insertion processes.

Alkynes bearing a variety of hindered and unhindered hydroxyalkyl groups can also be utilized (eq 4).[14–16]



(4)

However, migration of the *N*-acetyl group from nitrogen to the alcohol group has been observed in some reactions in which 2-iodoacetanilide was employed as the starting material (eq 5; Table 3, entries 20 and 23). This obvi-



(5)

(14) For one example of the synthesis of a cinnolinium salt by the stoichiometric, palladium-promoted heteroannulation of this particular alkynediol, see: Wu, G.; Rheingold, A. L.; Heck, R. F. *Organometallics* **1987**, *6*, 2386.

(15) For the palladium-catalyzed hydroarylation of alkynols, see: (a) Cacchi, S. *Pure Appl. Chem.* **1990**, *62*, 713. (b) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron* **1985**, *41*, 5121. (c) Arcadi, A.; Cacchi, S.; Ianelli, S.; Marinelli, F.; Nardelli, M. *Gazz. Chim. Ital.* **1986**, *116*, 725. (d) Arcadi, A.; Bernocchi, E.; Burini, A.; Cacchi, S.; Marinelli, F.; Pietroni, B. *Tetrahedron* **1988**, *44*, 481.

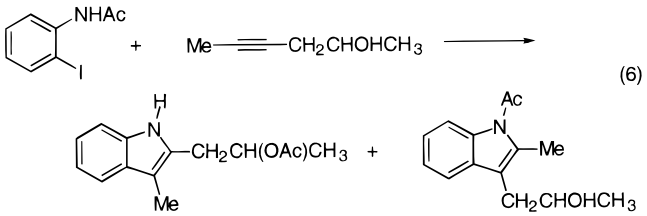
(16) For the palladium-catalyzed hydrovinylation of alkynols, see: Arcadi, A.; Bernocchi, E.; Burini, A.; Cacchi, S.; Marinelli, F.; Pietroni, B. *Tetrahedron Lett.* **1989**, *30*, 3465.

Table 3. Annulation of Internal Alkynes by 2-Iodoaniline and Derivatives (Eq 2)

entry	R^1	R^2	R^3	n	chloride	base	PPh_3 (5 mol %)	reactn time (h)	% isoltd yield
1	H	*n*-Pr	*n*-Pr	5	LiCl	K_2CO_3		20	80
2		*t*-Bu	Me	5	*n*-Bu_4NCl	Na_2CO_3	+	24	82
3		C_6H_{11}	Me	5	*n*-Bu_4NCl	KOAc		24	57
4		*i*-Pr	Me	5	*n*-Bu_4NCl	K_2CO_3	+	24	62, 25[a]
5		Et	Me	5	*n*-Bu_4NCl	K_2CO_3	+	24	62 (60:40)[b]
6		CMe_2OH	CMe_2OH	2	*n*-Bu_4NCl	Na_2CO_3	+	72	54
7		CMe_2OH	Me	2	*n*-Bu_4NCl	Na_2CO_3	+	12	52
8			$C(Me)=CH_2$	2	*n*-Bu_4NCl	KOAc		24	70
9			Et	2	LiCl	KOAc		24	85
10		Me_3Si	Me	5	*n*-Bu_4NCl	Na_2CO_3	+	24	98
11		Me_3Si	*n*-Bu	5	*n*-Bu_4NCl	NaOAc		12	81
12		Me_3Si	Ph	5	*n*-Bu_4NCl	NaOAc		16	68
13		Me_3Si	CH_2OH	2	*n*-Bu_4NCl	Na_2CO_3	+	24	60
14		Me_3Si	Me_3Si	2	*n*-Bu_4NCl	NaOAc		20	54[c]
15	Me	*n*-Pr	*n*-Pr	3	*n*-Bu_4NCl	K_2CO_3	+	24	71
16	Ac	*n*-Pr	*n*-Pr	3	*n*-Bu_4NCl	KOAc		24	91
17		*i*-Pr	Me	2	*n*-Bu_4NCl	Na_2CO_3		24	67, 26[a]
18		Et	Me	5	LiCl	K_2CO_3		24	30, 28[a]
19		Ph	Me	2	LiCl	KOAc		24	75
20		CH_2OH	Me	2	*n*-Bu_4NCl	K_2CO_3	+	24	60[d]
21		CH_2OH	$C(Me)=CH_2$	2	*n*-Bu_4NCl	NaOAc		24	27
22		CH_2CH_2OH	Me	2	*n*-Bu_4NCl	KOAc		24	43[e]
23		$CH_3CH(OH)CH_2$	Me	2	*n*-Bu_4NCl	Na_2CO_3	+	12	60, 16[f]
24		Me_3Si	Me	5	LiCl	K_2CO_3		12	70
25	Ts	*n*-Pr	*n*-Pr	3	*n*-Bu_4NCl	KOAc		24	86
26		*t*-Bu	Me	5	*n*-Bu_4NCl	KOAc		24	86
27		Et	Me	2	LiCl	K_2CO_3		36	60 (50:50)[b]
28		$CH(OEt)_2$	Me	5	*n*-Bu_4NCl	NaOAc		24	28, 28[a]
29		CMe_2OH	$C(Me)=CH_2$	2	*n*-Bu_4NCl	KOAc		24	45
30		Ph	Ph	2	LiCl	K_2CO_3		48	60

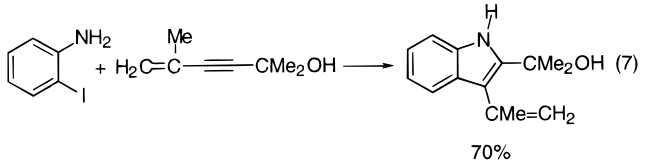
[a] Actual isolated yields of two regioisomers. [b] Ratio of regioisomers determined by GC and ^1H NMR spectroscopy. [c] The product is 3-(trimethylsilyl)indole. [d] The product is 2-acetoxymethyl-3-methylindole. [e] The product is 2-(2-acetoxyethyl)-3-methylindole. [f] The two products are 2-(2-acetoxypropyl)-3-methylindole and 1-acetyl-3-(2-hydroxypropyl)-2-methylindole, respectively.

ously involves a base-catalyzed, intramolecular transfer of the acetyl group from nitrogen to oxygen in the anticipated product; the annulation of 4-hexyn-2-ol is observed to give a mixture of regioisomers in which acetyl migration is observed in the product with the hydroxyalkyl group in the 2-position, but no migration is seen in the other regioisomer (eq 6; Table 3, entry 23). It is not


(6)

obvious why the product of the reaction of 2-iodoacetanilide and 4-methyl-4-penten-2-yn-1-ol (entry 21) apparently fails to undergo acetyl migration (unless we misassigned the regiochemistry of this product), although the product is only obtained in low yield.

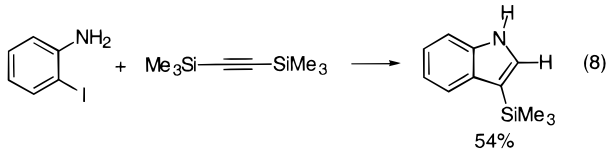
The chemoselectivity of this annulation process is apparently very high, because we have been able to annulate 4-methyl-4-penten-2-yn-1-ol (Table 3, entry 21) and 2,5-dimethyl-5-hexen-3-yn-2-ol (Table 3, entries 8 and 29) without any evidence for the corresponding products of alkene substitution (eq 7). It should be noted,


(7)

70%

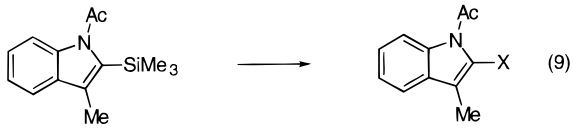
however, that although the yields are not always high, the reactions may not always have been run under optimal conditions.

It is especially noteworthy that a wide variety of silyl-substituted alkynes have been successfully employed in this annulation process.[17] The reaction conditions are sufficiently mild that desilylation is not usually a problem. However, when the hindered acetylene bis(trimethylsilyl)acetylene is annulated, the sole product observed is 3-(trimethylsilyl)indole (eq 8; Table 3, entry 14).


(8)

54%

The silyl-substituted indoles are versatile intermediates for the synthesis of a variety of other substituted indoles (eq 9). For example, protonolysis could be ac-


(9)

X = H (1. $AlCl_3$, 2. H_2O; 87%); Br (NBS, 70%);
E- CH=CHCOCH$_3$ (H_2C=CHCOCH$_3$, $Pd(OAc)_2$; 50%);
E- CH=CHCO$_2$Et (H_2C=CHCO$_2$Et, $Pd(OAc)_2$; 75%)

complished in 87% isolated yield by reacting 1-acetyl-3-

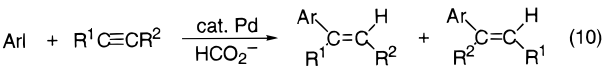
(17) For the palladium-catalyzed hydroarylation of silylalkynes, see ref 15a and Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1986**, *27*, 6397.

methyl-2-(trimethylsilyl)indole with $AlCl_3$ in CH_2Cl_2 for 1 h at 0 °C, followed by an aqueous workup. Protonolysis could also be effected in 80% isolated yield using aqueous HF in CH_3CN. Refluxing with *n*-Bu_4NF in 9:1 THF/MeOH failed to provide the hydrogen-substituted product. Although 3-monosubstituted indoles can be synthesized from 2-iodoanilines by *N*-allylation and subsequent intramolecular palladium-catalyzed cyclization,[18] this approach provides a useful, expeditious alternative and has proven valuable in establishing the regiochemistry of the annulation process.

The 2-silylindoles also undergo a variety of other synthetically useful substitution processes (eq 9). Thus, halogenation provides a convenient route to 2-halo-3-substituted indoles. The 2-silylindoles can also be reacted with $Pd(OAc)_2$ and alkenes, such as methyl vinyl ketone or ethyl acrylate, to afford the corresponding 2-(1-alkenyl)indoles. This appears to be one of the few successful applications of arylsilanes in the Heck reaction and the only one to use a heterocyclic silane and $Pd(OAc)_2$.[19]

It was a bit surprising that the annulation of the aryl-substituted alkynes 1-phenylpropyne and diphenylacetylene by 2-iodoaniline afforded only messy reactions exhibiting a multitude of products. Numerous single- and multi-insertion products of these alkynes and *ortho*-palladation compounds have been reported,[20−22] and both alkynes have provided high yields of a single product in many of our other alkyne annulation processes.[8] However, the reactions of 2-iodoacetanilide and 1-phenylpropyne (Table 3, entry 19) and *N*-tosyl-2-iodoaniline and diphenylacetylene (Table 3, entry 30) both afforded the anticipated indoles in fair-to-good yields.

This annulation process is quite regioselective, generally significantly more so than the related palladium-catalyzed hydroarylation process, which often produces mixtures of regioisomers (eq 10).[15−17,22] This is perhaps



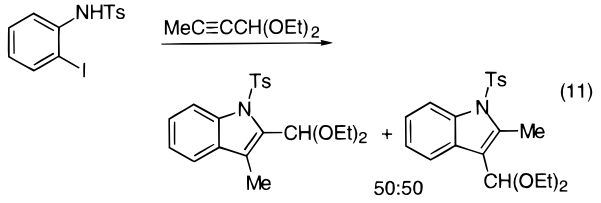
(10)

due to chelation of the palladium in our arylpalladium intermediates by the neighboring nitrogen, which reduces the overall reactivity and increases the steric hindrance of these intermediates toward alkyne insertion. As noted elsewhere,[6h] the rates and regiochemistry of these alkyne insertion processes appear to be controlled primarily by steric effects. Not too surprisingly, the annulation of 4,4-dimethyl-2-pentyne (*t*-Bu vs Me) by either 2-iodoaniline (Table 3, entry 2) or *N*-tosyl-2-iodoaniline (Table 3, entry 26) affords a single product, the 2-*tert*-butyl-3-methylindole, in excellent yields of 82% and 86%, respectively. Complete regioselectivity is also observed when annulating 1-cyclohexylpropyne (Cy vs Me; Table 3, entry 3). However, 4-methyl-2-pentyne (*i*-Pr vs Me) afforded two regioisomeric products in a 71:29 ratio for 2-iodoaniline (Table 3, entry 4) and 72:28 for 2-iodoacetanilide (Table 3, entry 17). The regioselectivity is somewhat dependent on the nature of the substituent on the nitrogen and the precise reaction conditions. 2-Pentyne (Et vs Me) gave a mixture of regioisomers in ratios of approximately 50:50 to 60:40 for 2-iodoaniline (Table 3, entry 5), 2-iodoacetanilide (entry 18), and *N*-tosyl-2-iodoaniline (Table 3, entry 27). The structures of the isomers in these latter mixtures could be easily assigned by the chemical shift of the methyl group.

Alcohol-containing alkynes exhibited a very interesting regiochemistry. In view of the substantial difference in steric effects at the two ends of the C−C triple bond, it was not too surprising that complete regioselectivity was observed in the annulation of the tertiary alkynols 2-methyl-3-pentyn-2-ol (CMe_2OH vs Me; Table 3, entry 7), 2,5-dimethyl-5-hexen-3-yn-2-ol (CMe_2OH vs isopropenyl; Table 3, entries 8 and 29), and 1-(1-butynyl)-cyclohexanol (1-hydroxycyclohexyl vs Et; Table 3, entry 9). However, even the primary alcohols 2-butyn-1-ol (CH_2OH vs Me; Table 3, entry 20), 3-pentyn-1-ol (CH_2CH_2OH vs Me; Table 3, entry 22), and 4-methyl-4-penten-2-yn-1-ol (CH_2OH vs isopropenyl; Table 3, entry 21) gave exclusively one product, although the yield was not always very high. It appears that there is either an electronic effect or, probably more likely, a chelation effect of the hydroxyl group which results in that substituent ending up in the 2-position of the resulting indole. An analogous directing effect of hydroxyl groups has been observed in the palladium-catalyzed hydroarylation of propargylic alcohols.[15b−d]

In contrast, while the less hindered primary alcohol 3-pentyn-1-ol (CH_2CH_2OH vs Me; Table 3, entry 22) gives a single product, the more highly branched secondary alcohol 4-hexyn-2-ol ($CH_2CHOHCH_3$ vs Me; Table 3, entry 23), which might therefore be expected to be even more regioselective, afforded a 79:21 mixture of regioisomers when allowed to react with 2-iodoacetanilide. This suggests that the latter alkyne, possessing a more hindered alcohol group, is less able to coordinate to palladium during the alkyne insertion step and therefore gives a mixture of regioisomers more reminiscent of 4-methyl-2-pentyne or other simple aliphatic alkynes with little steric difference between the two ends of the alkyne.

The failure of the diethyl acetal of 2-butynal to exhibit any regioselectivity at all would seem to argue against electronic effects playing any major role in this annulation process (eq 11; Table 3, entry 28). Apparently, steric



(11)

effects in this alkyne are not very important either.

(18) (a) Larock, R. C.; Babu, S. *Tetrahedron Lett.* **1987**, *28*, 5291. (b) Odle, R.; Blevins, B.: Ratcliff, M.; Hegedus, L. S. *J. Org. Chem.* **1980**, *45*, 2709.

(19) For prior Heck chemistry with $PhSiMe_3$, see: Akhrem, I. S.; Chistovalova, N. M.; Mysov, E. I.; Vol'pin, M. E. *J. Organomet. Chem.* **1974**, *72*, 163.

(20) For insertion products of 1-phenylpropyne, see refs 7 and 13b and (a) Bahsoun, A.; Dehand, J.; Pfeffer, M.; Zinsius, M.; Bouaoud, S.-E.; Le Borgne, G. *J. Chem. Soc., Dalton Trans.* **1979**, 547. (b) Maassarani, F.; Pfeffer, M.; Le Borgne, G. *Organometallics* **1987**, *6*, 2043.

(21) For insertion products of diphenylacetylene, see refs 5, 7, 12, 13b, 14 and (a) Kalinin, V. N.; Usatov, A. V.; Zakharkin, L. I. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1984**, 1646. (b) Dupont, J.; Pfeffer, M. *J. Organomet. Chem.* **1987**, *321*, C13. (c) Wu, G.; Geib, S. J.; Rheingold, A. L.; Heck, R. F. *J. Org. Chem.* **1988**, *53*, 3238. (d) Wu, G.; Rheingold, A. L.; Geib, S. J.; Heck, R. F. *Organometallics* **1987**, *6*, 1941. (e) Wu, G.; Rheingold, A. L.; Heck, R. F. *Organometallics* **1986**, *5*, 1922. (f) Maassarani, F.; Pfeffer, M. *J. Chem. Soc., Chem. Commun.* **1986**, 488.

(22) For the palladium-catalyzed hydroarylation and hydrovinylation of diphenylacetylene, see ref 16 and Cacchi, S.; Felici, M.; Pietroni, B. *Tetrahedron Lett.* **1984**, *25*, 3137.

The aryl group in 1-phenylpropyne (Ph vs Me) was observed to have a pronounced directing effect. The annulation of this alkyne by 2-iodoacetanilide afforded a good yield of a single product, which matched the literature characterization of 1-acetyl-3-methyl-2-phenylindole[23] (Table 3, entry 19). This result is consistent with the high regioselectivity generally observed in alkyne insertion processes of this alkyne[7,13b,20a,b] and the directive effect of aryl groups in general in the palladium-catalyzed hydroarylation process.[15b,c,16]

The annulation of 1-(trimethylsilyl)alkynes was found to be completely regioselective. In all cases examined, even for 3-trimethylsilyl-2-propyn-1-ol (Me_3Si vs CH_2OH; Table 3, entry 13) and 1-(trimethylsilyl)-2-phenylethyne (Me_3Si vs Ph; Table 3, entry 12), the sole product observed was the 2-(trimethylsilyl)indole. This is not surprising considering the importance of steric effects observed earlier in our studies using simple aliphatic alkynes, such as 4-methyl-2-pentyne, and the high regioselectivity observed previously in the palladium-catalyzed hydroarylation of these same trimethylsilylalkynes.[17]

The regiochemical assignments of the products obtained from the annulation of unsymmetrical alkynes are based on the following arguments. The annulation of 4,4-dimethyl-2-pentyne by 2-iodoaniline and 2-iodobenzaldehyde affords the corresponding known indole[24] and indenone,[8a] respectively, in which the *tert*-butyl group resides in the 2-position. The major product from the annulation of 2-pentyne by 2-iodoaniline matched the ^1H and ^{13}C NMR spectra previously reported for 2-ethyl-3-methylindole.[25] It is also known that a methyl group in the 3-position of an indole occurs in the ^1H NMR spectrum at approximately δ 2.3, which is upfield from a methyl group in the 2-position. On the basis of these observations, it is therefore concluded that the exclusive or predominant indole obtained from the annulation of simple, unsymmetrical aliphatic alkynes always has the more hindered alkyl group in the 2-position.

The annulation of 1-phenylpropyne by 2-iodoacetanilide afforded a single product known to have the phenyl group in the 2-position and the methyl group in the 3-position.[23] In the annulation of this same alkyne by 2-iodophenol,[8b] a mixture of benzofurans is obtained in which the minor regioisomer is the known 2-methyl-3-phenylbenzofuran.[26] Thus, 1-phenylpropyne consistently gives annulation products in which the aryl group resides in the 2-position. Analogous regiochemistry has been observed previously in the insertion of this alkyne into cyclopalladation adducts.[7,13b,20a,b]

The regiochemistry of the alkynol annulation products has been assigned as follows. The annulation of 2-butyn-1-ol by 2-iodoacetanilide (Table 3, entry 20) affords a known compound[27] in which the acetyl group has migrated to the alcohol, thus establishing the powerful directing effect of the hydroxyl group. It is assumed that the hydroxyl group in 4-methyl-4-penten-2-yn-1-ol is having a similar powerful directing effect, because only one product is formed, albeit in low yield (Table 3, entry 21).

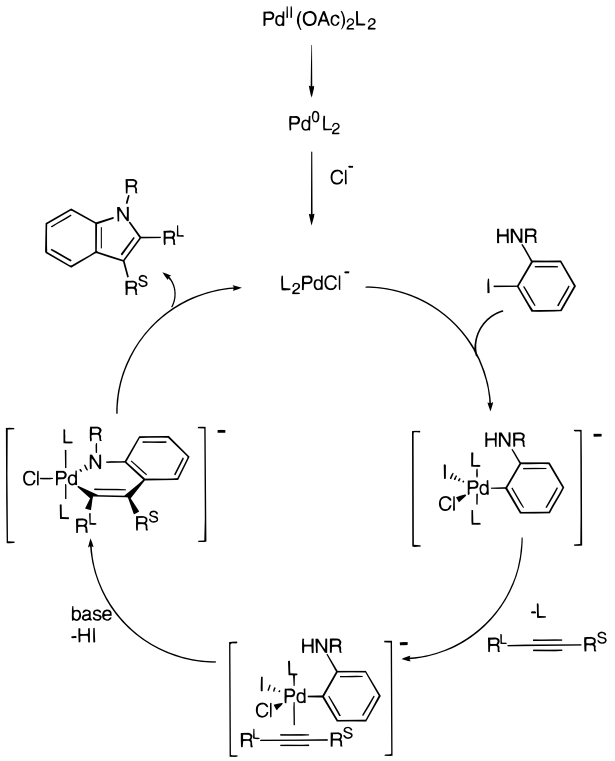
The reaction of 2-iodoacetanilide and 4-hexyn-2-ol gave two isomeric products (Table 3, entry 23). In the major product, according to the IR and ^1H NMR spectra, the OH has disappeared and has been replaced by an acetate ester and an NH [^1H NMR δ 2.28 (CH_3), 8.10 (NH)]. This product is believed to be 2-(2-acetoxypropyl)-3-methylindole on the basis of the chemical shift of the methyl group and the assumption that acetyl migration is more likely to occur when the alcohol group is located on a side chain in the 2-position rather than the 3-position. The minor product retains the hydroxyl group and possesses a methyl group further upfield in the ^1H NMR spectrum [^1H NMR δ 1.75 (OH), 2.60 (CH_3)]. It is known that the methyl in the ^1H NMR spectrum of 3-methylindole is further upfield than the methyl in 2-methylindole. Thus, this isomer appears to be 1-acetyl-3-(2-hydroxypropyl)-2-methylindole. The GCMS fragmentation patterns for these two isomers are consistent with these assignments; the major product has a base peak at M − 59 (loss of OAc), while the minor isomer has a base peak at M − 43 (loss of Ac).

The reaction of 3-pentyn-1-ol and 2-iodoacetanilide produces a single product in which the acetyl group has again migrated (Table 3, entry 22). The ^1H NMR spectrum indicates the presence of the indole NH and the absence of an OH group. The position of the methyl group is more consistent with a 3-methylindole. This product is assigned the structure 2-(2-acetoxyethyl)-3-methylindole, which is consistent with the strong preference for hydroxyalkyl groups to locate in the 2-position and the tendency of such groups to migrate an acetyl group. It is logical that the tertiary hydroxyalkyl-substituted acetylenes frequently employed in this study would provide indoles in which this more hindered group resides exclusively in the 2-position. All of these assignments are consistent with the strong directing effect of the hydroxyl group observed in the palladium-catalyzed hydroarylation of these same alcohol-containing alkynes.[15b−d,17]

Trimethylsilyl-substituted alkynes always afford a single indole product in which the silyl group resides in the 2-position. This is true whether the other end of the alkyne bears a Me (Table 3, entries 10 and 24), an *n*-Bu (entry 11), a Ph (entry 12), or a CH_2OH (entry 13). This regiochemistry is consistent with previous work on the palladium-catalyzed hydroarylation of silylalkynes[17] and more recent applications of our heteroannulation chemistry by others.[10a−c] The most convincing proof of this regiochemistry is found in the many compounds that have been desilylated to known products. For example, the protodesilylation of 3-methyl-2-(trimethylsilyl)indole[28] (entry 10), 3-phenyl-2-(trimethylsilyl)indole[29] (entry 12), and 1-acetyl-3-methyl-2-(trimethylsilyl)indole[30] (entry 24) all afford the corresponding known indoles. Bromination of the latter silylindole also provided a known bromoindole.[31] Desilylation of the 2-trimethylsilyl

(23) Itahara, T. *J. Org. Chem.* **1985**, *50*, 5272.
(24) Ito, Y.; Kobayashi, K.; Seko, N.; Saegusa, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 73.
(25) Naruse, Y.; Ito, Y.; Inagaki, S. *J. Org. Chem.* **1991**, *56*, 2256.
(26) Cardillo, G.; Cricchio, R.; Merlini, L. *Tetrahedron* **1971**, *27*, 1875.
(27) Gassman, P. G.; Campbell, G. A.; Mehta, G. *Tetrahedron* **1972**, *28*, 2749.
(28) Pouchert, C. *Aldrich Library of NMR Spectra*, Edition II, Vol. 2, Compound 519-D.
(29) Russell, G. A.; Yao, C.-F.; Tashtoush, H. I.; Russell, J. E.; Dedolph, D. F. *J. Org. Chem.* **1991**, *56*, 663.
(30) Pindur, U.; Flo, C.; Akgün, E.; Tunali, M. *Liebigs Ann. Chem.* **1986**, 1621.
(31) Hino, T.; Nakamura, T.; Nakagawa, M. *Chem. Pharm. Bull.* **1975**, *23*, 2990.

Scheme 1



group during the annulation of bis(trimethylsilyl)acetylene by 2-iodoaniline is observed to give the known compound 3-(trimethylsilyl)indole[24] (entry 14). Previous annulations of 1-(trimethylsilyl)propyne by 2-iodobenzaldehyde,[8a] methyl 2-iodobenzoate,[8b] and methyl 2-(trifluoromethanesulfonyloxy)cyclopentenecarboxylate[32] have all afforded silyl-substituted products in which the silyl group resides next to the functional group present in the starting material, as proven by desilylation to known compounds. The annulation of 4-trimethylsilyl-3-butyn-1-ol by a 4-substituted 2-iodoaniline has also recently been shown to produce 2-silylindoles, indicating that the steric hindrance of the silyl group exerts a more powerful directing effect than the alcohol group.[10b] We assume that this is also true for 3-trimethylsilyl-2-propyn-1-ol, for which a single silylindole is obtained in good yield (entry 13). Analogous regiochemistry has recently been reported in the heteroannulation of this same alkyne by 2-iodoheteroaromatic amines.[10a]

This indole synthesis presumably proceeds via (1) reduction of the $Pd(OAc)_2$ to Pd(0), (2) coordination of the chloride[33] to form a chloride-ligated zerovalent palladium species, (3) oxidative addition of the aryl iodide to Pd(0), (4) coordination of the alkyne to the palladium atom of the resulting arylpalladium intermediate and subsequent regioselective *syn*-insertion into the arylpalladium bond, (5) nitrogen displacement of the halide in the resulting vinylic palladium intermediate to form a six-membered, heteroatom-containing palladacycle, and (6) reductive elimination to form the indole and regenerate Pd(0) (Scheme 1). The chloride ligation step has been proposed by Amatore to explain various kinetic phenomena associated with the oxidative addition of aryl iodides to Pd(0) species.[33] The subsequent stabilized Pd(0) species and

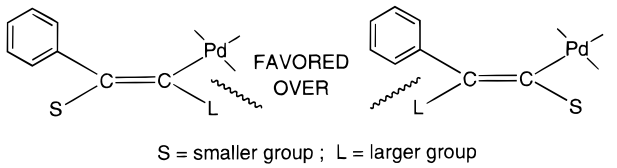
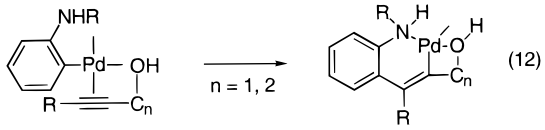


Figure 1. Steric effects on the regiochemistry of alkyne insertion.

the aryl iodide are expected to undergo relatively rapid oxidative addition. These first and third steps are well known and integral to a wide variety of Pd(0)-catalyzed processes. Whereas alkene coordination to palladium species has been well studied, analogous alkyne chemistry has received little attention and can only be surmised as a necessary prerequisite to alkyne insertion. Less hindered alkynes are known to insert more readily than more hindered alkynes.[6h] *syn*-Addition of the arylpalladium compound to the alkyne has been established for the analogous palladium-catalyzed hydroarylation process[15c] and assumed in many other alkyne insertion processes.[5−8]

Although it has been stated that the insertion of unsymmetrical alkynes into an arylpalladium bond proceeds to place the less hindered group next to palladium,[5b] this has not been our observation or that of Cacchi in the palladium-catalyzed hydroarylation and hydrovinylation of unsymmetrical alkynes.[15a] Indeed, all of our results are quite the contrary. It appears to us that the controlling factor in these insertion processes may be the steric hindrance present in the developing carbon−carbon bond or the orientation of the alkyne immediately prior to *syn*-insertion of the alkyne into the aryl palladium bond. Alkyne insertion occurs so as to generate the least steric strain in the vicinity of the shorter, developing carbon−carbon bond rather than the longer carbon−palladium bond (Figure 1). It may also be important that the alkyne adopts the orientation indicated in the pentacoordinate complex illustrated in Scheme 1. The arylpalladium bond and the alkyne must be parallel and *cis*-coordinated in order for the *syn*-addition to occur. Consequently, the alkyne may adopt an orientation in which the more sterically demanding group is situated away from the sterically encumbered aryl group. Analogous regiochemistry is observed in the insertion of alkynes into the carbon−manganese bond.[34] Some evidence apparently exists for the reversibility of such insertion processes,[35] although we think this is unlikely in our system.

The pronounced directive effect of neighboring alcohol groups on the regiochemistry of alkyne insertion would appear to be the result of coordination of the alcohol to the palladium during the insertion step (eq 12). An



analogous directive effect of hydroxyl groups has been observed in the palladium-catalyzed hydroarylation of propargylic alcohols.[15b−d,17]

(32) Larock, R. C.; Doty, M. J., work in progress.
(33) Amatore, C.; Jutand, A.; Suarez, A. *J. Am. Chem. Soc.* **1993**, *115*, 9531.
(34) Liebeskind, L. S.; Gasdaska, J. R.; McCallum, J. S.; Tremont, S. J. *J. Org. Chem.* **1989**, *54*, 669.
(35) See ref 41 in ref 5b above.

By the proper choice of reaction conditions, we are apparently able to minimize the amount of multiple alkyne insertion. The overall concentration of the reactants, the presence and/or absence of chloride, bromide and iodide ions, as well as PPh_3; the nature and steric effects of the substituents on the alkyne termini, and perhaps the solvent polarity all appear to play a significant role in this process. We note again the remarkable difference between our results using 2-iodoacetanilide and 1-phenylpropyne (Table 3, entry 19) and simple aliphatic alkynes (Table 3, entries 16−18) versus those reported previously using 2-butyne and diphenylacetylene in which multiple insertion predominated (eq 3).[12]

The final steps of this process are presumed to be palladacycle formation and subsequent reductive elimination. Although we have no actual proof for the intermediacy of such palladacycles, a closely related heterocyclic arylpalladium amide has been recently reported and shown to undergo analogous thermal reductive elimination to form the corresponding aromatic nitrogen heterocycle.[36] The presence of iodide (from the starting aryl halide) may be critical to the reductive elimination step. Pfeffer points out that the presence of an iodide ligand in such palladium complexes promotes formation of the carbon−nitrogen bond, perhaps due to its poorer σ-donor properties compared to those of chloride, a feature that has been shown to be crucial to reductive elimination processes involving palladium.[5b,13a] As noted previously, one equivalent of chloride appears to dramatically favor indole formation, whereas additional equivalents of chloride significantly slow the process and appear to favor multiple alkyne insertion. The latter process becomes an increasing problem when LiBr, LiI, and/or PPh_3 are added.

Experimental Section

General. All proton and carbon nuclear magnetic resonance spectra were recorded at 300 and 75.5 MHz, respectively. Flash chromatography was carried out on 230−400 mesh silica gel. Gas chromatographic analyses were carried out on an OV-101 packed column. All melting points are uncorrected.

Reagents. All chemicals were used directly as obtained from commercial sources unless otherwise noted. $Pd(OAc)_2$ was donated by Kawaken Fine Chemicals Co., Ltd., and Johnson Matthey, Inc. Anhydrous *n*-Bu_4NCl (Lancaster Synthesis Inc.), DMF and LiCl (Fisher Scientific Co.), 2-iodoaniline and PPh_3 (Aldrich Chemical Co. Inc.), and most alkynes (Farchan Scientific Co.) were purchased from commercial sources. The other aryl iodides and alkynes were prepared as follows.

2-Iodoacetanilide. 2-Iodoacetanilide was prepared by a procedure reported by Berrios-Peña.[37] 2-Iodoaniline (5.48 g, 25 mmol) was dissolved in 150 mL of Et_2O. Et_3N (3.51 mL) was added, and the solution was cooled to 0 °C. AcCl (2.55 g, 25.2 mmol) dissolved in 15 mL of Et_2O was added dropwise. After 1 hr of stirring at 0 °C, the reaction mixture was allowed to reach rt and then stirred overnight. Filtration (to remove Et_3N•HCl), followed by concentration of the filtrate, afforded 5.25 g (80%) of a white solid. Recrystallization from Et_2O afforded 4.9 g (75%) of colorless needles: mp 109−111 °C; IR ($CDCl_3$) 3407 (NH), 3026 (ArH), 1697 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.24 (s, 3 H), 6.48 (dd, 1 H, J = 7.5, 1.5 Hz), 7.34 (m, 1 H), 7.41 (br s, 1 H), 7.78 (d, 1 H, J = 7.5 Hz), 8.21 (d, 1 H, J = 8.3 Hz).

***N*-Methyl-2-iodoaniline.** *N*-Methyl-2-iodoaniline was prepared by a procedure reported by Harrison.[38] In a flame-dried 100-mL round-bottom flask, 2-iodoaniline (2.25 g, 10.3 mmol) was dissolved in 30 mL of dry THF. The resulting solution was cooled to −78 °C under N_2, 1.6 M MeLi (6.25 mL, 10 mmol) was added dropwise, and the resulting solution was stirred at −78 °C for 30 min. To the solution was added Me_2SO_4 (1.90 g, 15.1 mmol), and stirring was continued for 10 min at −78 °C. The solution was then warmed to rt and stirred for 2 h, followed by acidification with 10% HCl. The reaction mixture was diluted with ether, and the aqueous layer was removed. The ether extract was stirred with 30 mL of concd NH_4OH for 30 min. The aqueous layer was removed, and the organic phase was washed with 20 mL of water and 30 mL of brine, dried with $MgSO_4$, and concentrated. Distillation at 101−105 °C (2.0 mmHg) yielded 2.03 g (8.7 mmol, 87%) of *N*-methyl-2-iodoaniline: IR (neat) 3410 (NH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.80 (s, 3 H), 4.0 (br s, 1 H), 6.20−6.80 (m, 4 H); HRMS calcd for C_7H_8IN 232.9702, found: 232.9702.

1-(Trimethylsilyl)-2-phenylethyne. Under N_2, *n*-BuLi (1.5 M in hexane, 10.5 mL, 15.8 mmol) was added to a solution of PhC≡CH (1.45 g, 14.3 mmol) in dried THF (10 mL) at 0 °C over 10 min. The mixture was stirred for 1.5 h, and HMPA (2.8 mL) containing Me_3SiCl (3.0 g, 28 mmol) was slowly added. The mixture was stirred overnight at rt. The reaction mixture was poured into a mixture of ice and pentane (20 mL). The organic layer was separated, and the aqueous layer was extracted with pentane (20 mL). The combined organic layer was washed with brine (10 mL), dried, and concentrated. The crude product was distilled in a vacuum to give 1.9 g (65%) of 1-(trimethylsilyl)-2-phenylethyne: bp 63 °C, 2 mmHg; ^1H NMR ($CDCl_3$) δ 0.22 (s, 9 H), 7.27 (m, 3 H), 7.45 (m, 2 H). This material is now available from the Aldrich Chemical Co.

1-(Trimethylsilyl)-1-hexyne. This compound was prepared by the same procedure used for the synthesis of 1-(trimethylsilyl)-2-phenylethyne. A 70% yield of the desired product was obtained: ^1H NMR ($CDCl_3$) δ 0.11 (s, 9 H), 0.85 (t, 3 H, J = 5.1 Hz), 1.46 (m, 4 H), 2.18 (t, 2 H, J = 6.3 Hz). This material is now available from the Aldrich Chemical Co.

General Procedure for the Palladium-Catalyzed Heteroannulation of Alkynes. $Pd(OAc)_2$ (0.0125 mmol), LiCl (0.5 mmol) or *n*-Bu_4NCl (0.5 mmol), the appropriate base (2.50 mmol), the aryl iodide (0.50 mmol), the alkyne (0.50−2.50 mmol), DMF (10 mL), and where indicated PPh_3 (0.025 mmol) were added to a 4-dram vial equipped with a stirring bar and Teflon-lined screwcap. After being heated for the appropriate time at 100 °C, the reaction mixture was diluted with ether and washed with saturated aqueous NH_4Cl and H_2O. The organic layer was dried over $MgSO_4$. The reaction mixture was filtered and concentrated, and the product was purified by flash column chromatography using hexanes−ethyl acetate. The following compounds were prepared using the above general procedure.

2,3-Di-*n*-propylindole (Table 3, entry 1): slightly yellow oil; IR (neat) 3412 (NH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (m, 6 H), 1.72 (m, 4 H), 2.73 (m, 4 H), 7.15 (m, 2 H), 7.29 (m, 1 H), 7.56 (m, 1 H), 7.70 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.2, 14.5, 23.4, 24.3, 26.5, 28.3, 110.4, 112.2, 118.5, 119.0, 120.9, 129.0, 135.3, 135.4; HRMS calcd for $C_{14}H_{19}N$ 201.1518, found 201.1512. Anal. Calcd for $C_{14}H_{19}N$: C, 83.58; H, 9.45. Found: C, 83.44; H, 9.11.

2-*tert*-Butyl-3-methylindole[24] (Table 3, entry 2): slightly yellow oil; ^{13}C NMR ($CDCl_3$) δ 10.2, 29.3, 32.1, 105.2, 110.1, 117.7, 118.9, 120.8, 130.4, 133.7, 141.6; HRMS calcd for $C_{13}H_{17}N$ 187.1361, found 187.1361. IR and ^1H NMR data are consistent with previously reported data.[24]

2-Cyclohexyl-3-methylindole (Table 3, entry 3): slightly yellow oil; IR (neat) 3425 (NH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0−

(36) (a) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 4708. (b) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609. (c) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 8232. (d) Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451.

(37) Berrios-Peña, N. G. Ph.D. Dissertation, Iowa State University, Ames, IA, 1989.

(38) Harrison, L. W. Ph.D. Dissertation, Iowa State University, Ames, IA, 1984.

2.0 (m, 10 H), 2.30 (s, 3 H), 2.95 (m, 1 H), 7.10 (m, 2 H), 7.25 (m, 1 H), 7.50 (m, 1 H), 7.80 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 8.4, 26.1, 26.7, 32.8, 35.8, 105.3, 110.2, 118.0, 118.9, 120.7, 129.3, 134.8, 139.7. This compound decomposes fairly rapidly; so no further data was obtained.

2-Isopropyl-3-methylindole and 3-Isopropyl-2-methylindole (Table 3, entry 4). 2-Isopropyl-3-methylindole: colorless oil; R_f = 0.70 (6:1 hexanes/ethyl acetate); IR (neat) 3422 (NH), 3057 (ArH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35 (d, 6 H, J = 6.9 Hz), 2.29 (s, 3 H), 3.40 (m, 1 H), 7.14 (m, 2 H), 7.30 (m, 1 H), 7.51 (m, 1 H), 7.75 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.5, 22.6, 25.9, 105.4, 110.4, 118.2, 119.1, 121.0, 129.6, 135.0, 140.4; HRMS calcd for $C_{12}H_{15}N$ 173.1205, found 173.1207. **3-Isopropyl-2-methylindole:** slightly yellow oil; R_f = 0.55 (6:1 hexanes/ethyl acetate); IR (neat) 3406 (NH), 3059 (ArH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.40 (d, 6 H, J = 6.9 Hz), 2.36 (s, 3 H), 3.16 (m, 1 H), 7.06 (m, 2 H), 7.22 (m, 1 H), 7.55 (br s, 1 H), 7.64 (d, 1 H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 12.1, 23.0, 25.9, 110.2, 114.7, 118.6, 119.9, 120.4, 129.5, 135.3, 138.9; HRMS calcd for $C_{12}H_{15}N$ 173.1205, found 173.1206.

2-Ethyl-3-methylindole and 3-Ethyl-2-methylindole (Table 3, entry 5): slightly yellow oil; IR (neat, 1.5:1 mixture) 3401 (NH), 3057 (ArH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 1.5:1 mixture) δ 1.30 (m, 6 H), 2.32 (s, 3 H), 2.39 (s, 3 H), 2.80 (q, 4 H), 7.15 (m, 4 H), 7.28 (m, 2 H), 7.55 (m, 2 H), 7.60−7.70 (br s, 2 H); ^{13}C NMR ($CDCl_3$, 60:40 mixture) δ 8.3, 11.3, 14.0, 15.4, 15.5, 17.3, 19.3, 105.9, 110.1, 113.6, 117.9, 118.8, 120.6, 120.7, 124.1, 128.3, 129.3, 129.3, 129.5, 134.1, 135.1, 136.5; HRMS calcd for $C_{11}H_{13}N$ 159.1048, found 159.1051.

2,3-Bis(1-hydroxy-1-methylethyl)indole (Table 3, entry 6): slightly yellow oil; IR (neat) 3450 (OH), 3416 (NH), 3061 (ArH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.83 (s, 12 H), 2.03 (br s, 2 H), 7.30 (m, 2 H), 7.49 (d, 1 H, J = 8.1 Hz), 7.74 (d, 1 H, J = 7.5 Hz), 8.80 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 30.7 (overlapped), 69.7 (overlapped), 97.2, 111.1, 119.8, 120.5, 121.8, 128.4, 135.8, 145.8; HRMS calcd for $C_{14}H_{19}NO$ 233.1417, found 233.1417.

2-(1-Hydroxy-1-methylethyl)-3-methylindole (Table 3, entry 7): slightly yellow oil; IR (neat) 3431 (OH), 3352 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.67 (s, 6 H), 2.03 (br s, 1 H), 2.33 (s, 3 H), 7.10 (m, 2 H), 7.38 (d, 1 H, J = 6.0 Hz), 7.49 (d, 1 H, J = 7.5 Hz), 8.45 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 9.5, 30.0, 70.7, 103.7, 110.6, 118.9, 121.2, 127.1, 130.0, 133.5, 140.0; HRMS calcd for $C_{12}H_{15}NO$ 189.1154, found 189.1153.

2-(1-Hydroxy-1-methylethyl)-3-isopropenylindole (Table 3, entry 8): pale yellow solid; mp 122−123 °C; IR ($CDCl_3$) 3543 (OH), 3362 (NH), 1641 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.56 (s, 6 H), 2.03 (s, 3 H), 2.35 (br s, 1 H), 4.90 (d, 1 H, J = 1.2 Hz), 5.25 (d, 1 H, J = 1.2 Hz), 7.02 (m, 2 H), 7.16 (d, 1 H, J = 8.1 Hz), 7.36 (d, 1 H, J = 7.8 Hz), 8.45 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 25.6, 31.2, 71.3, 110.8, 113.7, 117.4, 119.2, 119.6, 121.8, 128.9, 133.8, 139.3, 140.5; HRMS calcd for $C_{14}H_{17}NO$ 215.1310, found 215.1310.

3-Ethyl-2-(1-hydroxycyclohexyl)indole (Table 3, entry 9): white solid; mp 89−90 °C; IR (neat) 3487 (OH), 3315 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3 H, J = 7.5 Hz), 1.65−1.86 (m, 6 H), 2.27 (m, 2 H), 2.45 (m, 2 H), 2.85 (q, 2 H, J = 7.5 Hz), 6.05 (br s, 1 H), 7.14 (m, 2 H), 7.28 (t, 1 H, J = 8.1 Hz), 7.59 (d, 1 H, J = 6.9 Hz), 7.77 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 16.2, 21.7, 21.9, 24.5, 38.0, 72.2, 110.8, 111.2, 118.6, 119.0, 121.3, 129.6, 133.9, 140.1; HRMS calcd for $C_{14}H_{15}NO_2$ 243.1623, found 243.1620.

3-Methyl-2-(trimethylsilyl)indole (Table 3, entry 10): slightly yellow oil; IR (neat) 3439 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.27 (s, 9 H), 2.32 (s, 3 H), 7.05 (m, 2 H), 7.23 (d, 1 H, J = 7.8 Hz), 7.48 (d, 1 H, J = 7.8 Hz), 7.76 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ −0.7, 10.7, 110.9, 118.8, 119.2, 120.4, 122.4, 130.7, 133.0, 138.2; HRMS calcd for $C_{12}H_{17}NSi$ 203.1130, found 203.1125.

3-*n*-Butyl-2-(trimethylsilyl)indole (Table 3, entry 11): pale yellow oil; IR ($CDCl_3$) 3439 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.26 (s, 9 H), 0.87 (t, 3 H, J = 7.2 Hz), 1.36 (m, 2 H), 1.53 (m, 2 H), 2.72 (t, 2 H, J = 7.8 Hz), 6.96 (t, 1 H, J = 5.1 Hz), 7.05 (t, 1 H, J = 4.2 Hz), 7.19 (d, 1 H, J = 8.1 Hz), 7.50 (d, 1 H, J = 7.5 Hz), 7.69 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ −0.3, 14.3, 28.3, 29.4, 34.6, 111.0, 119.1, 119.2, 122.3, 126.3, 129.0, 132.7, 138.4; HRMS calcd for $C_{15}H_{23}NSi$ 245.1600, found 245.1596.

3-Phenyl-2-(trimethylsilyl)indole (Table 3, entry 12): pale yellow oil; IR ($CDCl_3$) 3472 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.27 (s, 9 H), 7.15 (t, 1 H, J = 6.6 Hz), 7.27 (t, 2 H, J = 7.2 Hz), 7.45 (m, 5 H), 7.62 (d, 1 H, J = 7.8 Hz), 8.19 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ −0.2, 110.9, 114.6, 119.7, 120.0, 122.8, 126.7, 128.0, 128.2, 128.6, 128.7, 136.7, 138.0; HRMS calcd for $C_{17}H_{19}NSi$ 265.1289, found 265.1288.

3-(Hydroxymethyl)-2-(trimethylsilyl)indole (Table 3, entry 13): white solid; mp 156−158 °C; IR ($CDCl_3$) 3474 (OH), 3382 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.44 (s, 9 H), 1.50 (br s, 1 H), 4.95 (s, 2 H), 7.15 (m, 2 H), 7.40 (d, 1 H, J = 7.8 Hz), 7.76 (d, 1 H, J = 8.1 Hz), 8.20 (br s, 1 H); ^{13}C NMR (DMSO-d_6) δ −0.2, 55.1, 111.2, 118.3, 118.8, 121.3, 124.3, 128.1, 134.9, 138.4; HRMS calcd for $C_{12}H_{17}NOSi$ 219.1079, found 219.1081.

3-(Trimethylsilyl)indole[24] (Table 3, entry 14): yellow oil; ^{13}C NMR ($CDCl_3$) δ −0.8, 115.6, 118.1, 119.9, 120.8, 122.5, 128.9, 138.5, 138.9; HRMS calcd for $C_{11}H_{15}NSi$ 189.0974, found 189.0971. IR and ^{1}H NMR data are consistent with previously reported data.[24]

1-Methyl-2,3-di-*n*-propylindole (Table 3, entry 15): slightly yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.19 (m, 6 H), 1.85 (m, 4 H), 2.92 (m, 4 H), 3.86 (s, 3 H), 7.35 (m, 3 H), 7.74 (d, 1 H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 14.3, 14.6, 23.7, 24.7, 26.8, 26.9, 29.7, 108.7, 111.8, 118.5, 118.6, 120.6, 128.0, 136.8, 137.0; HRMS calcd for $C_{15}H_{21}N$ 215.1674, found 215.1674. Anal. Calcd for $C_{15}H_{21}N$: C, 83.72; H, 9.77. Found: C, 83.75; H, 9.83.

1-Acetyl-2,3-di-*n*-propylindole (Table 3, entry 16): slightly yellow oil; IR (neat) 1703 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.04 (m, 6 H), 1.67 (m, 4 H), 2.68 (t, 2 H, J = 7.5 Hz), 2.78 (s, 3 H), 3.01 (t, 2 H, J = 7.8 Hz), 7.23 (m, 2 H), 7.52 (m, 1 H), 7.78 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.3, 14.5, 23.3, 23.8, 26.2, 27.8, 29.1, 114.6, 118.9, 120.2, 122.7, 128.5, 131.0, 135.7, 138.3, 170.1; HRMS calcd for $C_{16}H_{21}N$ 243.1623, found 243.1619.

1-Acetyl-2-isopropyl-3-methylindole and 1-Acetyl-3-isopropyl-2-methylindole (Table 3, entry 17). 1-Acetyl-2-isopropyl-3-methylindole: pale yellow oil; R_f = 0.75 (4:1 hexanes/ethyl acetate); IR (neat) 3059 (ArH), 1701 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.42 (d, 6 H, J = 7.2 Hz), 2.29 (s, 3 H), 2.73 (s, 3 H), 3.75 (m, 1 H), 7.25 (m, 2 H), 7.47 (m, 1 H), 7.67 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 9.7, 21.4, 27.0, 27.9, 113.6, 114.7, 118.0, 122.3, 123.3, 131.6, 134.8, 142.8, 170.7; HRMS calcd for $C_{14}H_{17}N$ 215.1310, found: 215.1310. **1-Acetyl-3-isopropyl-2-methylindole:** pale yellow oil; R_f = 0.65 (4:1 hexanes/ethyl acetate); IR (neat) 3060 (ArH), 1700 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.42 (d, 6 H, J = 7.2 Hz), 2.57 (s, 3 H), 2.73 (s, 3 H), 3.12 (m, 1 H), 7.23 (m, 2 H), 7.67 (m, 1 H), 7.95 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.3, 21.9, 25.3, 27.7, 114.9, 119.7, 122.3, 123.1, 125.0, 129.0, 131.1, 137.0, 170.3; HRMS calcd for $C_{14}H_{17}N$ 215.1310, found: 215.1309.

1-Acetyl-2-ethyl-3-methylindole and 1-acetyl-3-ethyl-2-methylindole (Table 3, entry 18). 1-Acetyl-2-ethyl-3-methylindole: yellow oil; IR (neat) 1696 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.24 (t, 3 H, J = 7.2 Hz), 2.33 (s, 3 H), 2.79 (s, 3 H), 3.07 (q, 2 H, J = 7.2 Hz), 7.28 (m, 2 H), 7.49 (m, 1 H), 7.79 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 8.3, 14.4, 21.9, 27.6, 114.4, 118.4, 120.7, 122.6, 123.4, 131.4, 135.3, 139.5, 169.8; HRMS calcd for $C_{13}H_{15}NO$ 201.1154, found 201.1159. **1-Acetyl-3-ethyl-2-methylindole:** yellow oil; IR (neat) 1695 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.17 (t, 3 H, J = 7.8 Hz), 2.53 (s, 3 H), 2.67 (q, 2 H, J = 7.8 Hz), 2.69 (s, 3 H), 7.23 (m, 2 H), 7.45 (m, 1 H), 7.95 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.2, 14.5, 17.1, 27.5, 115.1, 118.1, 120.7, 122.7, 123.5, 130.2, 132.9, 135.9, 170.2; HRMS calcd for $C_{13}H_{15}NO$ 201.1159, found 201.1157.

1-Acetyl-3-methyl-2-phenylindole[23] (Table 3, entry 19): pale yellow crystals; mp 81−82 °C (lit.[23] mp 80.5−81.5 °C); IR ($CDCl_3$) 3063 (ArH), 1687 (C=O) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 9.4, 27.8, 116.4, 118.3, 118.9, 123.6, 125.4, 128.6, 128.8 (2 C), 130.3, 133.7, 135.0, 136.9, 171.1; HRMS calcd for $C_{17}H_{15}NO$ 249.1154, found 249.1154. Anal. Calcd for $C_{17}H_{15}NO$: C, 81.92; H, 6.17. Found: C, 82.35; H, 6.35. ^{1}H NMR data is consistent with previously reported data.[23]

2-(Acetoxymethyl)-3-methylindole[27] **(Table 3, entry 20):** pale yellow solid; mp 88−89 °C (lit.[27] mp 90−92 °C); IR ($CDCl_3$) 3398 (NH), 3059 (ArH), 1717 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.07 (s, 3 H), 2.37 (s, 3 H), 5.22 (s, 2 H), 7.20 (m, 3 H), 7.53 (d, 1 H, J = 7.8 Hz), 8.40 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 8.6, 21.5, 57.8, 111.1, 111.8, 119.4, 119.5, 123.0, 128.3, 129.0, 135.9, 172.4; HRMS calcd for $C_{12}H_{13}NO_2$ 203.0946, found 203.0943.

1-Acetyl-2-(hydroxymethyl)-3-isopropenylindole (Table 3, entry 21): pale yellow oil; IR (neat) 3383 (OH), 1701 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50 (br s, 1 H), 2.10 (s, 3 H), 2.68 (s, 3 H), 4.77 (s, 2 H), 5.27 (d, 1 H, J = 1.5 Hz), 5.53 (d, 1 H, J = 1.5 Hz), 7.32 (m, 2 H), 7.71 (m, 1 H), 8.21 (d, 1 H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 24.6, 26.4, 55.9, 116.0, 119.4, 119.8, 120.0, 123.7, 125.4, 129.0, 136.5, 136.9, 139.3, 170.6; HRMS calcd for $C_{14}H_{15}NO_2$ 229.1103, found 229.1101.

2-(2-Acetoxyethyl)-3-methylindole (Table 3, entry 22): pale yellow oil; IR ($CDCl_3$) 3398 (NH), 3059 (ArH), 1717 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10 (s, 3 H), 2.27 (s, 3 H), 3.06 (t, 2 H, J = 6.9 Hz), 4.31 (t, 2 H, J = 6.9 Hz), 7.13 (m, 2 H), 7.27 (m, 1 H), 7.51 (m, 1 H), 7.97 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 8.6, 21.2, 26.1, 63.8, 108.5, 110.5, 118.5, 119.3, 121.2, 129.2, 130.9, 135.6, 171.1; HRMS calcd for $C_{13}H_{15}NO_2$ 217.1103, found 217.1102.

2-(2-Acetoxypropyl)-3-methylindole and 1-Acetyl-3-(2-hydroxypropyl)-2-methylindole (Table 3, entry 23). 2-(2-Acetoxypropyl)-3-methylindole: yellow oil; IR (neat) 3401 (NH), 3059 (ArH), 1718 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (d, 3 H, J = 6.3 Hz), 2.09 (s, 3 H), 2.28 (s, 3 H), 3.00 (m, 2 H), 5.18 (m, 1 H), 7.13 (m, 2 H), 7.28 (t, 1 H, J = 7.2 Hz), 7.52 (d, 1 H, J = 7.5 Hz), 8.10 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 8.8, 19.5, 21.6, 32.8, 70.9, 108.9, 110.5, 118.4, 119.1, 121.5, 129.1, 130.6, 135.6, 170.2; HRMS calcd for $C_{14}H_{17}NO_2$ 231.1260, found 231.1262. **1-Acetyl-3-(2-hydroxypropyl)-2-methylindole:** yellow oil; IR ($CDCl_3$) 3383 (OH), 1701 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (d, 3 H, J = 6.3 Hz), 1.75 (br s, 1 H), 2.60 (s, 3 H), 2.72 (s, 3 H), 2.83 (d, 2 H, J = 6.6 Hz), 3.10 (m, 1 H), 7.30 (m, 2 H), 7.50 (m, 1 H), 7.90 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.0, 23.3, 27.8, 34.1, 68.1, 115.1, 115.2, 118.7, 122.1, 123.2, 124.1, 130.8, 134.6, 170.4; HRMS calcd for $C_{14}H_{17}NO_2$ 231.1260, found 231.1263.

1-Acetyl-3-methyl-2-(trimethylsilyl)indole (Table 3, entry 24): yellow solid; mp 65−67 °C; IR ($CDCl_3$) 1693 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.35 (s, 9 H), 2.35 (s, 3 H), 2.77 (s, 3 H), 7.20−7.33 (m, 2 H), 7.52 (d, 1 H, J = 7.5 Hz), 7.62 (d, 1 H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 2.8, 11.3, 26.5, 113.6, 119.5, 122.5, 124.8, 129.4, 134.0, 136.6, 137.1, 169.0; HRMS calcd for $C_{14}H_{19}NOSi$ 245.1236, found 245.1237.

2,3-Di-*n*-propyl-1-tosylindole (Table 3, entry 25): pale yellow oil; IR (neat) 1366 (SO_2), 1186 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, 3 H, J = 7.5 Hz), 1.00 (t, 3 H, J = 7.2 Hz), 1.57 (m, 2 H), 1.76 (m, 2 H), 2.29 (s, 3 H), 2.59 (t, 2 H, J = 7.8 Hz), 2.95 (t, 2 H, J = 7.5 Hz), 7.11 (d, 2 H, J = 7.8 Hz), 7.23 (m, 2 H), 7.38 (d, 1 H, J = 6.9 Hz), 7.53 (d, 2 H, J = 8.4 Hz), 8.17 (d, 1 H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 13.2, 14.9, 22.3, 23.0, 24.3, 26.2, 26.7, 114.2, 117.6, 119.6, 122.7, 124.4, 125.0, 127.2, 128.4, 130.5, 131.1, 136.8, 144.2; HRMS calcd for $C_{21}H_{25}NSO_2$ 355.1606, found 355.1600.

2-*tert*-Butyl-3-methyl-1-tosylindole (Table 3, entry 26): pale yellow oil; IR (neat) 1399 (SO_2), 1177 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.85 (s, 9 H), 2.38 (s, 3 H), 2.40 (s, 3 H), 7.09 (d, 2 H, J = 8.7 Hz), 7.28 (d, 2 H, J = 4.2 Hz), 7.34 (m, 1 H), 7.42 (d, 2 H, J = 8.4 Hz), 8.18 (d, 1 H, J = 4.8 Hz); ^{13}C NMR ($CDCl_3$) δ 12.6, 21.4, 31.8, 35.9, 117.9, 118.9, 124.3, 124.4, 124.6, 126.7, 128.3, 132.4, 135.0, 139.6, 143.6, 147.2; HRMS calcd for $C_{20}H_{23}NSO_2$ 341.1450, found 341.1446.

2-Ethyl-3-methyl-1-tosylindole and 3-Ethyl-2-methyl-1-tosylindole (Table 3, entry 27): pale yellow oil; IR (neat, 50:50 mixture) 3068 (ArH), 1371 (SO_2), 1188 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 1:1 mixture) δ 1.13 (t, 3 H, J = 7.5 Hz), 1.27 (t, 3 H, J = 7.2 Hz), 2.14 (s, 3 H), 2.31 (s, 3 H), 2.33 (s, 3 H), 2.53 (s, 3 H), 2.60 (q, 2 H, J = 7.5 Hz), 3.01 (q, 2 H, J = 7.2 Hz), 7.23 (m, 8 H), 7.38 (m, 2 H), 7.60 (q, 4 H, J = 8.4 Hz), 8.18 (d, 2 H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 50:50 mixture) δ 8.7, 12.5, 14.4, 15.0, 17.4, 19.8, 21.5, 114.6, 115.0, 116.0, 118.2, 118.2, 122.2, 123.1, 123.3, 123.7, 123.9, 129.6, 129.7, 131.5, 131.8, 136.1, 136.3, 136.4, 138.8, 144.3, 144.4.

2-Formyl-3-methyl-1-tosylindole Diethyl Acetal and 3-Formyl-2-methyl-1-tosylindole Diethyl Acetal (Table 3, entry 28). 2-Formyl-3-methyl-1-tosylindole diethyl acetal: yellow oil; IR (neat) 1369 (SO_2), 1202 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (t, 6 H, J = 6.9 Hz), 2.45 (s, 3 H), 2.58 (s, 3 H), 3.80 (m, 4 H), 6.84 (s, 1 H), 7.29 (d, 2 H, J = 7.8 Hz), 7.41 (m, 2 H), 7.59 (d, 1 H, J = 7.5 Hz), 7.92 (d, 2 H, J = 8.1 Hz), 8.29 (d, 1 H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 10.1, 15.4, 21.7, 68.2, 98.4, 115.4, 119.3, 120.9, 123.6, 125.3, 127.0, 129.5, 131.7, 133.5, 135.7, 136.5, 144.5; HRMS calcd for $C_{21}H_{25}NSO_4$ 387.1504, found: 387.1494. **3-Formyl-2-methyl-1-tosylindole diethyl acetal:** yellow oil; IR (neat) 1391 (SO_2), 1199 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (t, 6 H, J = 6.9 Hz), 2.50 (s, 3 H), 2.81 (s, 3 H), 3.70 (m, 4 H), 5.85 (s, 1 H), 7.36 (m, 4 H), 7.81 (d, 2 H, J = 9.6 Hz), 8.01 (d, 1 H, J = 7.8 Hz), 8.34 (d, 1 H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 13.3, 15.4, 21.7, 61.5, 98.7, 114.4, 118.0, 121.0, 123.7, 124.1, 126.5, 128.8, 129.8, 130.0, 135.3, 136.4, 144.8; HRMS calcd for $C_{21}H_{25}NSO_4$ 387.1504, found 387.1508.

3-Isopropenyl-2-(1-hydroxy-1-methylethyl)-1-tosylindole (Table 3, entry 29): slightly yellow oil; IR (neat) 3479 (OH), 1366 (SO_2), 1188 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.62 (s, 3 H), 1.66 (s, 3 H), 2.28 (s, 3 H), 2.32 (s, 3 H), 2.66 (br s, 1 H), 4.79 (s, 1 H), 5.24 (s, 1 H), 6.8−7.4 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 21.7, 26.0, 31.0, 32.0, 71.9, 115.1, 120.6, 122.4, 123.2, 124.5, 126.8, 127.1, 128.7, 129.6, 135.4, 136.4, 136.7, 140.9, 144.7; HRMS calcd for $C_{21}H_{23}NO_2$ 369.1399, found 369.1396.

2,3-Diphenyl-1-tosylindole (Table 3, entry 30): white solid; mp 173−174 °C; IR (neat) 3070 (ArH), 3040 (ArH), 1387 (SO_2), 1180 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.26 (s, 3 H), 7.0−7.5 (m, 17 H), 8.41 (d, 1 H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 21.4, 116.1, 119.9, 124.1, 124.7, 124.7, 125.0, 126.8, 127.1, 128.1, 128.3, 129.2, 129.7, 130.3, 130.8, 132.0, 132.5, 135.2, 136.7, 137.2, 144.5. Anal. Calcd for $C_{27}H_{21}NO_2S$: C, 76.57; H, 5.00. Found: C, 76.57; H, 5.05.

1-Acetyl-3-methylindole.[30] 1-Acetyl-3-methyl-2-(trimethylsilyl)indole (51 mg, 0.25 mmol) and $AlCl_3$ (33 mg, 0.25 mmol) were added to 5 mL of CH_2Cl_2, and the reaction mixture was stirred for 30 min at 0 °C. Water was added, and the reaction mixture was extracted with ether, dried over $MgSO_4$ and concentrated. Flash column chromatography using 4:1 hexane/ethyl acetate afforded 38 mg of crystalline product (87% yield): mp 66−67 °C (lit.[30] mp 66 °C); ^{13}C NMR ($CDCl_3$) δ 9.6, 23.8, 116.4, 118.2, 118.7, 122.1, 123.2, 125.0, 131.3, 135.7, 168.1; HRMS calcd for $C_{11}H_{11}NO$ 173.0841, found 173.0842. IR and ^1H NMR data are consistent with previously reported data.[30]

1-Acetyl-2-bromo-3-methylindole. 1-Acetyl-3-methyl-2-(trimethylsilyl)indole (51 mg, 0.25 mmol) and NBS (89 mg, 0.50 mmol) were dissolved in 5 mL of CH_2Cl_2 and refluxed for 30 min. The reaction mixture was concentrated and purified by flash chromatography using 4:1 hexane/ethyl acetate to give 44 mg (70%) of crystalline product: mp 61−62 °C (lit.[31] mp 49−50.5 °C); IR ($CDCl_3$) 1699 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.26 (s, 3 H), 2.83 (s, 3 H), 7.27 (m, 2 H), 7.43 (d, 1 H, J = 7.8 Hz), 8.20 (d, 1 H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 10.5, 28.1, 107.5, 118.1, 118.1, 120.8, 123.5, 125.2, 129.4, 137.0, 169.8. This compound rapidly decomposed, so no mass spectrum or elemental analysis could be obtained.

Ethyl(*E*)-3-(1-Acetyl-3-methyl-2-indolyl)acrylate. 1-Acetyl-3-methyl-2-(trimethylsilyl)indole (102 mg, 0.50 mmol), ethyl acrylate (100 mg, 1.0 mmol), palladium acetate (112 mg, 0.50 mmol), and 10 mL of DMF were added to a 4-dram vial equipped with a stirring bar and Teflon-lined screwcap. After being heated for 2 d at 100 °C, the reaction mixture was diluted with ether, washed with saturated aqueous NH_4Cl and H_2O, dried over $MgSO_4$, filtered, concentrated, and purified by flash column chromatography using 4:1 hexane/ethyl acetate to afford 102 mg (75%) of a crystalline solid: mp 70−71 °C; IR ($CDCl_3$) 3022 (C=CH), 1705 (C=O), 1630 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (t, 3 H, J = 7.2 Hz), 2.37 (s, 3 H), 2.67 (s, 3 H), 4.31 (q, 2 H, J = 7.2 Hz), 6.10 (d, 1 H, J = 15.9 Hz), 7.25−7.42

(m, 2 H), 7.54 (d, 1 H, J = 7.8 Hz), 7.89 (d, 1 H, J = 15.9 Hz), 8.07 (d, 1 H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 10.4, 14.4, 27.4, 60.7, 115.2, 119.7, 121.3, 121.9, 123.4, 126.4, 130.6, 131.3, 135.5, 136.5, 166.4, 169.9; HRMS calcd for $C_{14}H_{17}NO_3$ 271.1208, found 271.1206.

(*E*)-4-(1-Acetyl-3-methyl-2-indolyl)-3-buten-2-one. This compound was obtained as a yellow oil in 50% isolated yield from the reaction of 1-acetyl-3-methyl-2-(trimethylsilyl)indole and methyl vinyl ketone using the same method reported above for the synthesis of ethyl (*E*)-3-(1-acetyl-3-methyl-2-indolyl)acrylate: IR (neat) 1695 (C=O), 1653 (C=O), 1603 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3 H), 2.42 (s, 3 H), 2.72 (s, 3 H), 6.36 (d, 1 H, J = 16.2 Hz), 7.34 (m, 2 H), 7.57 (d, 1 H, J = 9.0 Hz), 7.83 (d, 1 H, J = 16.2 Hz), 7.94 (d, 1 H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 10.5, 27.4, 27.5, 114.8, 119.9, 122.2, 123.5, 126.4, 129.7, 130.9, 131.8, 134.9, 136.4, 170.0, 198.0; HRMS calcd for $C_{15}H_{15}NO_2$ 241.1103, found 241.1105.

Acknowledgment. We gratefully acknowledge the National Institutes of Health for their generous financial support and Johnson Matthey, Inc., and Kawaken Fine Chemicals Co., Ltd., for the palladium acetate.

Supporting Information Available: Copies of ^{1}H or ^{13}C NMR spectra (59 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9803277