Synthesis of Isoquinolines and Pyridines by the Palladium-Catalyzed Iminoannulation of Internal Alkynes

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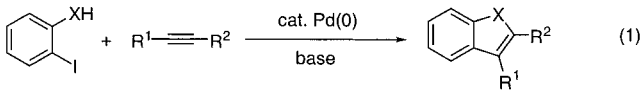
A wide variety of substituted isoquinoline, tetrahydroisoquinoline, 5,6-dihydrobenz[*f*]isoquinoline, pyrindine, and pyridine heterocycles have been prepared in good to excellent yields via annulation of internal acetylenes with the *tert*-butylimines of *o*-iodobenzaldehydes and 3-halo-2-alkenals in the presence of a palladium catalyst. The best results are obtained by employing 5 mol % of $Pd(OAc)_2$, an excess of the alkyne, 1 equiv of Na_2CO_3 as a base, and 10 mol % of PPh_3 in DMF as the solvent. This annulation methodology is particularly effective for aryl- or alkenyl-substituted alkynes. When electron-rich imines are employed, this chemistry can be extended to alkyl-substituted alkynes. Trimethylsilyl-substituted alkynes also undergo this annulation process to afford monosubstituted heterocyclic products absent the silyl group.

Introduction

Annulation processes have found numerous applications in organic synthesis, primarily due to the ease with which a wide variety of complicated hetero- and carbocycles can be rapidly constructed.[1] In our own laboratories, it has been demonstrated that palladium-catalyzed annulation methodology[2] can be effectively employed for the synthesis of indoles,[3] isoindolo[2,1-*a*]indoles,[4] benzofurans,[5] benzopyrans,[6] isocoumarins,[5,6] α-pyrones,[6,7] indenones,[8] and polycyclic aromatic hydrocarbons[9] (eq 1).



(1)

X = NR, O, CR_2O, CO, CO_2

R^1, R^2 = alkyl, aryl, silyl, alkenyl

The synthesis of isoquinoline heterocycles has received considerable attention in the literature due to the fact that the isoquinoline ring system is present in numerous naturally occurring alkaloids. Although the classical methods for the synthesis of this important ring system, the Bischler−Napieralski reaction,[10] the Pomeranz−Fritsch reaction,[10a,11] and the Pictet−Spengler reaction[10a,12] have been frequently employed in the total synthesis of isoquinoline alkaloids, they are all quite limited synthetically. For example, all of these methods are based on electrophilic cyclizations of a β-phenylethylamine to form the nitrogen-containing ring and therefore suffer the disadvantages of employing strong acids in their ring closure steps. The synthesis of appropriate starting materials is also often difficult. Furthermore, all of these reactions exhibit poor regioselectivity during ring closure. Finally, the Bischler−Napieralski and Pictet−Spengler reactions require dehydrogenations of dihydro- and tetrahydroisoquinolines, respectively.

Substituted isoquinoline heterocycles have also been synthesized by employing palladium methodology. For instance, Widdowson reported the synthesis of isoquinoline derivatives from cyclopalladated *N*-*tert*-butylarylaldimines in yields from 10 to 56%.[13] However, this synthesis suffers from the disadvantages that stoichiometric amounts of palladium salts are required for the preparation of the intermediate iminoalkenes, and the final step involves pyrolysis at 180−200 °C.

Pfeffer has reported the formation of an isoquinolinium salt in 14% yield, as well as a disubstituted isoquinoline derivative in 60% yield from a cyclopalladated *N*,*N*-dimethylbenzylamine complex.[14] An entirely different heterocycle was obtained by the thermal depalladation of a cationic tetrafluoroborate palladium complex. These

(1) (a) Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081. (b) Pfeffer, M. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 567. (c) Negishi, E.; Copéret, C.; Ma, S.; Liou, S.; Liu, F. *Chem. Rev.* **1996**, *96*, 365. (d) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635.

(2) For reviews, see: (a) Larock, R. C. *J. Organomet. Chem.* **1999**, *576*, 111. (b) Larock, R. C. Palladium-Catalyzed Annulation. In *Perspectives in Organopalladium Chemistry for the XXI Century*, Tsuji, J., Ed.; Elsevier Press: Lausanne, Switzerland, 1999; pp 111−124. (c) Larock, R. C. *Pure Appl. Chem.* **1999**, *71*, 1435.

(3) (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652.

(4) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 1551.

(5) Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270.

(6) Larock, R. C.; Doty, M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770.

(7) Larock, R. C.; Han, X.; Doty, M. J. *Tetrahedron Lett.* **1998**, *39*, 5713.

(8) Larock, R. C.; Doty, M. J.; Cacchi, S. J. *J. Org. Chem.* **1993**, *58*, 4579.

(9) (a) Larock, R. C.; Doty, M. J.; Tian, Q.; Zenner, J. M. *J. Org. Chem.* **1997**, *62*, 7536. (b) Larock, R. C.; Tian, Q. *J. Org. Chem.* **1998**, *63*, 2002.

(10) (a) Kametani, T.; Fukumoto, K. In *The Chemistry of Heterocyclic Compounds, Isoquinolines*; Grethe, G., Ed.; Wiley: New York, 1981; Vol. 38, Part 1, Chapter 2, pp 139−274. (b) Whaley, W. M.; Govindachari, T. R. In *Organic Reactions*; Adams, R., Ed.; Wiley: New York, 1951; Vol. 6, pp 151−190.

(11) Gensler, W. J. In *Organic Reactions*; Adams, R., Ed.; Wiley: New York, 1951; Vol. 6, pp 191−206.

(12) Whaley, W. M.; Govindachari, T. R. In *Organic Reactions*; Adams, R., Ed.; Wiley: New York, 1951; Vol. 6, pp 74−150.

(13) Girling, I. R.; Widdowson, D. A. *Tetrahedron Lett.* **1982**, *23*, 4281.

(14) Maassarani, F.; Pfeffer, M.; Le Borgne, G. *J. Chem. Soc., Chem. Commun.* **1987**, 565.

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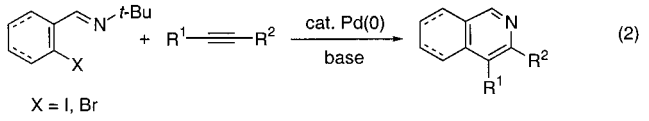
syntheses also have the disadvantage that they use stoichiometric amounts of palladium salts for the preparation of the starting cyclopalladated complexes.

Heck has also reported the synthesis of isoquinolinium tetrafluoroborate salts in moderate yields from the reaction of cyclopalladated arylaldimine tetrafluoroborates and internal alkynes.[15] In one instance, Heck observed the formation of 3,4-diphenylisoquinoline in 22% yield from the reaction of a cationic, tetrafluoroborate *N*-*tert*-butylbenzaldimine palladium complex and diphenylacetylene. These two syntheses, however, also suffer from the use of stoichiometric amounts of palladium salts.

Our own interest in this type of annulation reaction has prompted us to investigate a catalytic version of these isoquinoline syntheses and we have previously reported that excellent yields of isoquinolines and pyridines can be obtained from the palladium-catalyzed annulation of internal alkynes by the *tert*-butylimines of *o*-iodobenzaldehydes and 3-halo-2-alkenals.[16] Herein, we report the full details of this catalytic annulation chemistry for the synthesis of a wide variety of nitrogen heterocycles, including isoquinolines, tetrahydroisoquinolines, 5,6-dihydrobenz[*f*]isoquinolines, pyrindines, and pyridines.

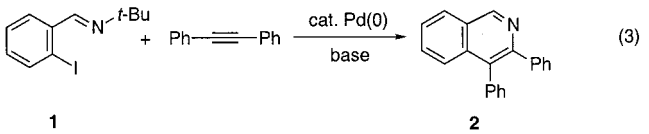
Results and Discussion

Our initial studies focused on the palladium-catalyzed iminoannulation of internal alkynes employing the methyl imine of *o*-iodobenzaldehyde. However, this substrate failed to produce any of the desired isoquinoline even at elevated temperatures. Furthermore, use of the corresponding isopropyl, allyl, and benzyl imines also failed to produce the desired heterocyclic products. The reaction of the α-methylbenzyl imine with diphenylacetylene did produce the desired product, 3,4-diphenylisoquinoline, albeit in low yields (6−11%). By employing the *tert*-butylimine, however, we were able to obtain substantially improved results with a variety of alkynes after optimization of the reaction conditions (eq 2).



(2)

The reaction of diphenylacetylene and the *tert*-butylimine of *o*-iodobenzaldehyde (**1**) was chosen as the model system for optimization of this annulation process (eq 3).



(3)

1 **2**

In the early stages of this work, the reaction conditions that were chosen were similar to the conditions employed in our other alkyne annulation chemistry (Table 1).[2−9] For example, 0.5 mmol of the *tert*-butylimine, 1.0 mmol of diphenylacetylene, 1 equiv of LiCl, with 1 equiv of Na_2CO_3 as a base in 10 mL of DMF at 100 °C afforded 3,4-diphenylisoquinoline in 76% yield after a 53 h reaction time (entry 1). By increasing the temperature to 110 °C, the reaction time was reduced, while the yield was comparable to that of entry 1 (entry 2). It was also observed that chloride salts significantly increased the reaction times when employing Na_2CO_3 as a base (compare entries 1−4 and entry 5). Upon removal of the chloride salts from the reaction mixture, we were able to isolate the desired product in a relatively short reaction time, and in yields comparable to the reactions in which chloride salts were employed (entry 5).

Table 1. Optimization of the Palladium-Catalyzed Formation of 3,4-Diphenylisoquinoline (eq 3)

entry	Cl^- source (equiv)	base	10 mol % of PPh_3	temp (°C), time (h)	% isolated yield of **2**
1	LiCl (1)	Na_2CO_3	−	100, 53	76
2	LiCl (1)	Na_2CO_3	−	110, 25	71
3	LiCl (2)	Na_2CO_3	−	100, 115	69
4	*n*-Bu_4NCl (1)	Na_2CO_3	−	100, 86	81
5	−	Na_2CO_3	−	100, 23	80
6	−	Na_2CO_3	+	100, 25	96
7	−	$NaHCO_3$	+	100, 32	77
8	−	NaOAc	+	100, 25	87
9	−	K_2CO_3	+	110, 88	69
10	−	*i*-Pr_2NEt	+	100, 9	68
11	−	Et_3N	+	100, 8	76
12	−	Na_2CO_3	+	80, 115	70
13	−	Et_3N	+	80, 21	63
14	−	Na_2CO_3	+	100, 96	77[a]

[a] Two mol % of $Pd(OAc)_2$ and 4 mol % of PPh_3 were used.

The effect of PPh_3 on the reaction was then investigated. The yield of 3,4-diphenylisoquinoline was observed to increase upon addition of a catalytic amount of PPh_3 (10 mol %) to the reaction mixture (compare entries 5 and 6). Presumably, the added phosphine disrupts coordination of the neighboring imine substituent to the palladium atom in the arylpalladium intermediate (see the latter mechanistic discussion). Other inorganic bases were also employed in the reaction with PPh_3. However, lower yields were observed with other bases, and in the case of K_2CO_3, a significant increase in the reaction time was observed (compare entries 7−9 with entry 6). When tertiary organic amine bases were employed, a reduction in the reaction time and yield of product was observed (entries 10 and 11).

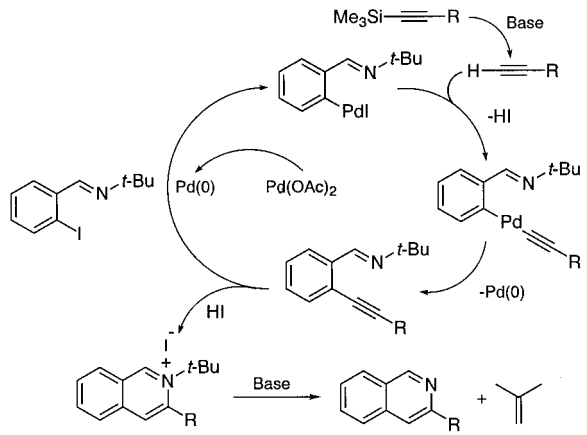
Additional attempts to optimize this annulation process included an investigation of two more reaction variables. First of all, based on the success with Na_2CO_3 and PPh_3 (entry 6), the reaction temperature was lowered to 80 °C in order to determine the effect on the reaction rate and yield (entry 12). Unfortunately, the reduction in the temperature of the reaction was accompanied by an increase in the reaction time, and a decrease in the product yield. Furthermore, since the reaction times were relatively short with the organic amine bases employed, a reaction was run with Et_3N at 80 °C (entry 13). Although the reaction time with this base was relatively short, the yield was significantly less than that of Na_2CO_3 at 100 °C (compare entries 6 and 13).

Finally, in an effort to reduce the amount of the palladium catalyst, one reaction was run in which the amount of $Pd(OAc)_2$ was reduced from 5 mol % to 2 mol % (entry 14). However, a decrease in the reaction rate, as well as the yield, was observed. These results have led to the development of the following general reaction procedure for our heterocycle synthesis: 1 equiv of the *tert*-butylimine, 2 equiv of the acetylene, 5 mol % of $Pd(OAc)_2$, 10 mol % of PPh_3, 1 equiv of Na_2CO_3 in DMF as the solvent at 100 °C. We then wanted to determine

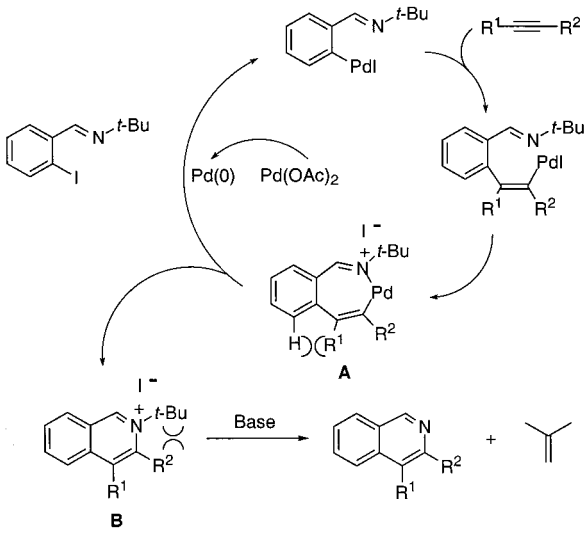
(15) (a) Wu, G.; Rheingold, A. L.; Geib, S. J.; Heck, R. F. *Organometallics* **1987**, *6*, 1941. (b) Wu, G.; Geib, S. J.; Rheingold, A. L.; Heck, R. F. *J. Org. Chem.* **1988**, *53*, 3238.

(16) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 5306.

Scheme 1



Scheme 2



the scope and limitations of this methodology by annulating a wide variety of acetylenes with a number of aryl and vinylic imines. The results of this study are summarized in Table 2.

The annulation of a variety of aryl-substituted alkynes by the *tert*-butylimine of *o*-iodobenzaldehyde (**1**) has afforded the desired disubstituted isoquinolines in moderate to excellent yields with high regioselectivity (Table 2, entries 1−6). The regiochemistry of the products is based on analogy with our previous alkyne annulation chemistry[2−9] and comparison of the spectral and physical data for compounds **3**[14] and **4**[17] with those already in the literature.

The annulation of a relatively unhindered diyne and enyne by imine **1** also afforded the anticipated isoquinoline products in good yields, although mixtures of regioisomers were obtained (entries 7−9). The annulation of 1,4-diphenylbutadiyne by imine **1** is observed to give an unexpected major product bearing the more hindered phenyl group in the 4-position (entry 7). This is in contrast to the regiochemical outcome of much of our other alkyne annulation chemistry in which the palladium adds to the more hindered end of the alkyne.[2−9] The regiochemistry of the products from this annulation has been confirmed by comparison of the ^{1}H NMR spectral properties of compounds **8** and **9** with the spectral properties of 3-phenyl-4-(phenylethynyl)isoquinoline, which has been isolated as a minor product from the annulation of imine **1** by phenylacetylene. This annulation methodology has also been extended to trimethylsilyl-substituted alkynes. To our surprise, 3-monosubstituted isoquinolines were isolated in moderate yields from these reactions (entries 10 and 11). These are rather surprising results, since the expected products were either the 3,4-disubstituted products retaining the silyl group, or the corresponding 4-substituted isoquinolines arising from desilylation of the former. On the basis of the results from an extensive investigation of this reaction, it appears that the trimethylsilyl acetylenes are being desilylated by the base in the reaction (see Scheme 1). The terminal alkynes, which are thus produced, are apparently undergoing palladium-catalyzed coupling and subsequent cyclization. A preliminary account of this investigation has been reported.[18]

In the case of the imine **16** bearing an electron-withdrawing group and an unsymmetrical alkyne, only a single regioisomer was obtained (entry 13), with hydrolysis of the unreacted imine presumably occurring during the workup of the reaction.

The attempted annulation of other alkyl-substituted alkynes, namely 4-octyne, 3-hexyne, 4,4-dimethyl-2-pentyne, and 3,3-dimethyl-1-phenyl-1-butyne by imine **1** failed to produce any of the desired heterocycles. Based on the observations of Heck,[15] it is presumed that multiple alkyne insertion products are being formed with these alkynes, although none of these products have been identified. Moreover, the use of alkynes bearing bulky groups might inhibit the formation of intermediates **A** or **B** due to the increased steric hindrance (see Scheme 2 and the latter mechanistic discussion). With simple alkynes such as 4-octyne and 3-hexyne, the presumed vinylpalladium intermediate (see the latter mechanistic discussion) may be undergoing palladium beta hydride elimination to an allene or oxidative addition of the C−H bond of the imine moiety to the palladium to form an indenone upon reductive elimination and hydrolysis.[8]

However, electron-rich imines afford good yields of isoquinolines from a wide variety of alkynes (entries 14−37). 4-Octyne produces the desired isoquinoline products in good yields when an electron-rich imine is employed (entries 17, 24, and 36). Even a very electron-deficient alkyne, diethyl acetylenedicarboxylate, afforded the desired heterocycles in moderate yields (entries 19, 34, and 37). The relatively low yields obtained when using this alkyne can be rationalized by the fact that it can form palladacyclopentadiene complexes with Pd(0) and the resulting palladacyclopentadiene complex can further react with another molecule of acetylenedicarboxylate to generate the corresponding benzene hexacarboxylate.[19] Surprisingly, when an electron-rich imine, such as **19** or **32**, is employed in reactions that previously gave only single regioisomers, mixtures of regioisomers have been observed (compare entries 15, 16, and 23 with entries 2 and 3). Thus, the annulation of electron-rich imines gives

(17) Brooks, J. R.; Harcourt, D. N.; Waigh, R. D. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2588.

(18) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 553.

(19) (a) Moseley, K.; Maitlis, P. M. *J. Chem. Soc., Chem. Commun.* **1971**, 1604. (b) Moseley, K.; Maitlis, P. M. *J. Chem. Soc., Dalton Trans.* **1974**, 169. (c) Brown, L. D.; Itoh, K.; Suzuki, H.; Hirai, K.; Ibers, J. A. *J. Am. Chem. Soc.* **1978**, *100*, 8232. (d) Dieck, H. T.; Munz, C.; Müller, C. *J. Organomet. Chem.* **1990**, *384*, 243. (e) Stephan, C.; Munz, C.; Dieck, H. T. *J. Organomet. Chem.* **1993**, *452*, 223. (f) Pena, D.; Pérez, D.; Guitián, E.; Castedo, L. *J. Org. Chem.* **2000**, *65*, 6944.

Table 2. Synthesis of Isoquinolines and Pyridines by the Palladium-Catalyzed Annulation of Internal Alkynes (eq 2)[a]

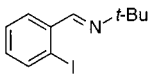
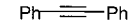
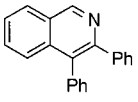
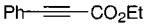
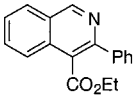
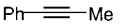
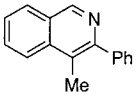
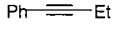
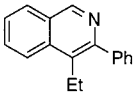
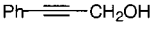
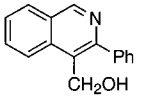
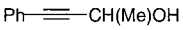
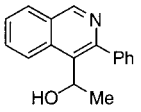
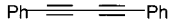
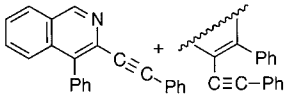
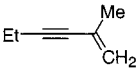
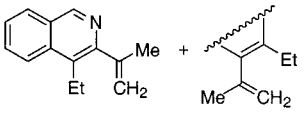
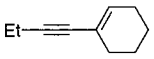
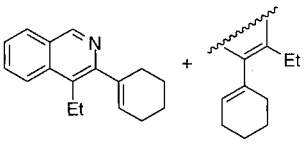
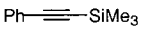
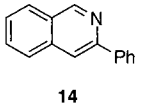
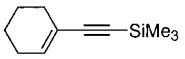
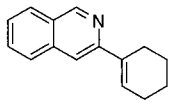
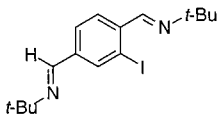
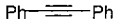
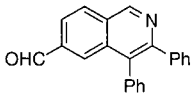
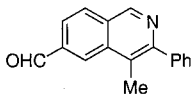
entry	imine	alkyne	time (h)	product(s)	% yield
1	 **1**		24	 **2**	96
2			5	 **3**	99
3			21	 **4**	84
4			16	 **5**	93
5			7	 **6**	100
6			4	 **7**	65
7			25	 **8** **9**	72 + 13
8			21	 **10** **11**	69[b]
9			10	 **12** **13**	69[c]
10			21	 **14**	85
11			78	 **15**	77
12	 **16**		36	 **17**	87
13			36	 **18**	69

Table 2. (Continued)

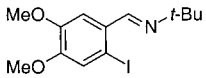
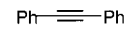
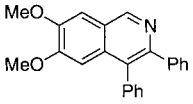
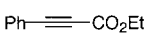
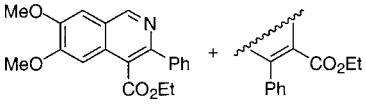
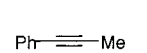
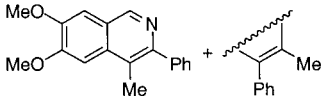
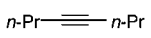
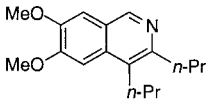
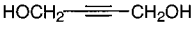
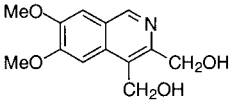
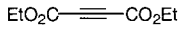
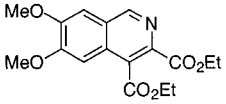
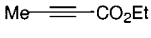
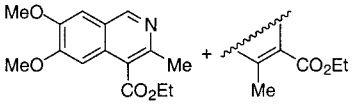
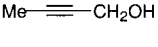
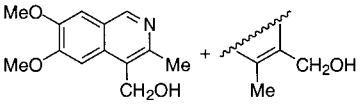
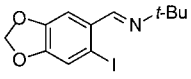
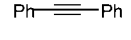
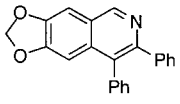
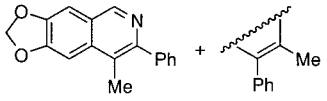
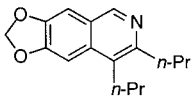
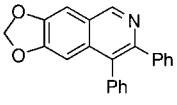
entry	imine	alkyne	time (h)	product(s)	% yield
14	 **19**		24	 **20**	82
15			29	 **21** **22**	95 + 5
16			29	 **23** **24**	67 + 17
17			24	 **25**	67
18			7	 **26**	61
19			68	 **27**	45
20			16	 **28** **29**	76[a]
21			21	 **30** **31**	50 + 50
22	 **32**		44	 **33**	83
23			44	 **34** **35**	77 + 14
24			42	 **36**	69
25	 **37**		72	 **33**	20

Table 2. (Continued)

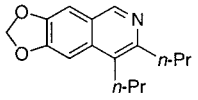
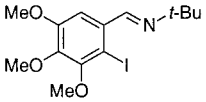
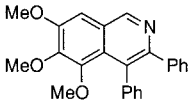
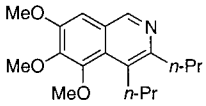
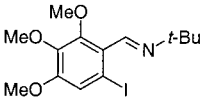
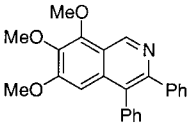
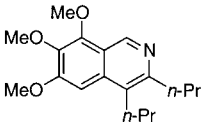
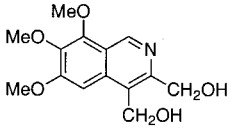
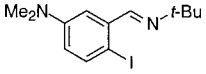
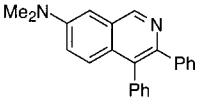
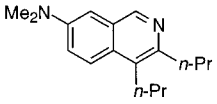
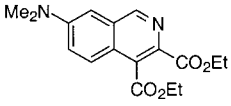
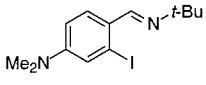
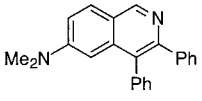
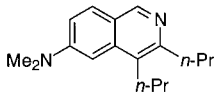
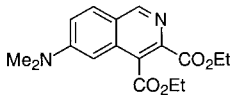
entry	imine	alkyne	time (h)	product(s)	% yield
26		*n*-Pr—≡—*n*-Pr	72	 **36**	11
27	 **38**	Ph—≡—Ph	46	 **39**	24
28		*n*-Pr—≡—*n*-Pr	44	 **40**	15
29	 **41**	Ph—≡—Ph	38	 **42**	32
30		*n*-Pr—≡—*n*-Pr	24	 **43**	27
31		$HOCH_2$—≡—CH_2OH	8	 **44**	40
32	 **45**	Ph—≡—Ph	22	 **46**	87
33		*n*-Pr—≡—*n*-Pr	12	 **47**	0[e]
34		EtO_2C—≡—CO_2Et	24	 **48**	31
35	 **49**	Ph—≡—Ph	20	 **50**	88
36		*n*-Pr—≡—*n*-Pr	20	 **51**	72
37		EtO_2C—≡—CO_2Et	90	 **52**	27

Table 2. (Continued)

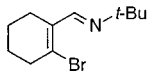
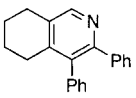
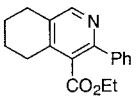
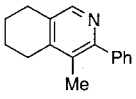
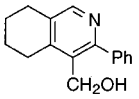
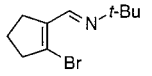
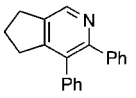
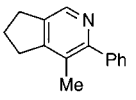
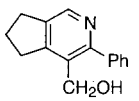
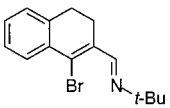
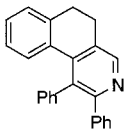
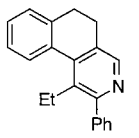
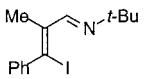
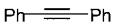
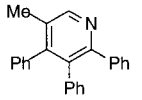
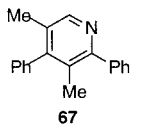
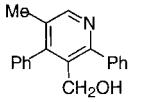
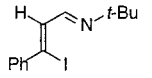
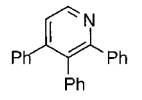
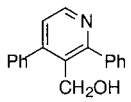
entry	imine	alkyne	time (h)	product(s)	% yield
38	 **53**		16	 **54**	72
39			14	 **55**	99
40			14	 **56**	74
41			3	 **57**	100
42	 **58**		4	 **59**	71
43			3	 **60**	96
44			2	 **61**	72
45	 **62**		11	 **63**	85
46			3	 **64**	94
47	 **65**		17	 **66**	68
48			15	 **67**	65
49			2	 **68**	95
50	 **69**		4	 **70**	52

Table 2. (Continued)

Entry	imine	alkyne	time (h)	Product(s)	% yield
51		Ph—≡—CH_2OH	2	 **71**	79

[a] A representative procedure for the annulation of internal acetylenes: 5 mol % of $Pd(OAc)_2$, 10 mol % of PPh_3, Na_2CO_3 (0.5 mmol), the acetylene (1.0 mmol), the imine (0.5 mmol), and DMF (10 mL) were placed in a 4 dram vial and were heated at 100 °C for the indicated time. [b] Isolated in an 85:15 ratio of **10** to **11** as an inseparable mixture of isomers. [c] Isolated in a 95:5 ratio of **12** to **13** as an inseparable mixture of isomers. [d] Isolated as a 1:3 inseparable mixture of isomers **28** to **29**. [e] A byproduct 6-(dimethylamino)-2,3-dipropylindenone was isolated in a 10% yield.

relatively poor regiochemistry when unsymmetrical alkynes are employed (entries 15, 16, 20, 21, and 23). Interestingly, the electron-rich *o*-bromoimine **37** also affords isoquinolines when allowed to react with diphenylacetylene and 4-octyne, but in relatively low yields compared to the corresponding *o*-iodoimine (entries 25 and 26). In the case of imines **38** and **41** bearing three methoxy groups, the annulation chemistry proceeds with 4-octyne (entries 28 and 30) and even 2-butyne-1,4-diol (entry 31), as expected, but in low yields. Even the reactions of these imines with diphenylacetylene afford low yields (entries 27 and 29). This may be due to the extra steric hindrance expected in the intermediate palladacycles (Figure 1).

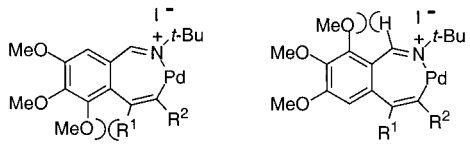


Figure 1. Steric hindrance in the intermediate palladacycles derived from imines **38** and **41**.

Finally, the dimethylamino-substituted imines **45** and **49** have also been prepared and employed in this annulation process (entries 32−37). The desired isoquinoline products are obtained in good yields (entries 32, 35 and 36) in some cases, but not all cases. It is interesting to note that the annulation of imine **45** with 4-octyne did not afford the desired isoquinoline. Instead, the reaction was quite messy and about a 10% yield of 6-(dimethylamino)-2,3-di-*n*-propylindenone was isolated. It is possible that the anticipated palladium intermediate might be a zwitterionic palladium carbene species,[20] which undergoes a series of side reactions (Figure 2). The

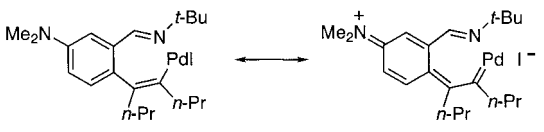


Figure 2. A possible zwitterionic palladium carbene species.

by-product 6-(dimethylamino)-2,3-di-*n*-propylindenone could be the product of a typical carbene C−H insertion into the imine moiety, followed by hydrolysis during the workup. Alternatively, the imine may simply be hydrolyzing to the benzaldehyde, which forms the indenone as expected from prior work.[8]

When diphenylacetylene and diethyl acetylenedicarboxylate are employed in annulations involving imine **45**, the desired isoquinolines are obtained (entries 32 and 34). This may be due to the fact that the electron density is now delocalized into the phenyl ring or the ester group. Therefore, no palladium carbene species is formed, and the reaction smoothly affords the desired isoquinolines (Figure 3).

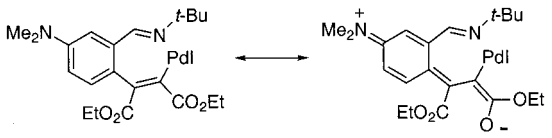


Figure 3. Delocalization into the ester group of the reaction intermediate.

It is worth noting that electronically, the electron-donating groups on the phenyl ring increase the electron density on the nitrogen atom of the imine and thus increase the ability of the nitrogen to coordinate to palladium and stabilize the reaction intermediate. This apparently facilitates the annulation reactions of electron-rich imines with internal alkynes.

This annulation chemistry has also been extended to vinylic imines. For example, the tetrahydroisoquinoline derivatives **54**−**57** have been synthesized by annulation with the cyclic vinylic imine **53** (entries 38−41). In addition, the pyrindine derivatives **59**−**61** and the dihydrobenzoisoquinoline derivatives **63** and **64** have been synthesized from vinylic imines **58** and **62**, respectively (entries 42−46). Finally, the acyclic vinylic imines **65** and **69** have also been successfully employed in this annulation process to produce highly substituted pyridine derivatives (entries 47−51). It is interesting to note that the compounds derived from the vinylic imines were all isolated as single regioisomers. Surprisingly, the imine **69** works quite well in this pyridine synthesis, whereas the corresponding ethyl ester (*Z*-PhCI=$CHCO_2Et$) fails to undergo annulation of this same alkyne to produce the corresponding α-pyrone, a process with which we have recently had considerable success.[7]

We propose a mechanism for this process which is similar to our other alkyne annulation chemistry (Scheme 2). Specifically, oxidative addition of the aryl or vinylic halide to Pd(0) produces an organopalladium intermediate, which then inserts the acetylene, producing a vinylic palladium intermediate, which then reacts with the neighboring imine substituent to form a seven-membered palladacyclic ammonium salt **A**. Subsequent reductive

(20) For palladium carbene intermediates, see: (a) Tsuji, J.; Watanabe, H.; Minami, I.; Shimizu, I. *J. Am. Chem. Soc.* **1985**, *107*, 2196. (b) Trost, B. M.; Hashmi, A. S. K. *J. Am. Chem. Soc.* **1994**, *116*, 2183. (c) Sierra, M. A.; Mancheno, M. J.; Saez, E.; del Amo, J. C. *J. Am. Chem. Soc.* **1998**, *120*, 6812. (d) Balme, G.; Monteiro N. *J. Org. Chem.* **2000**, *65*, 3223.

elimination produces a *tert*-butylisoquinolinium salt **B** and regenerates Pd(0). As previously suggested by Heck,[15] the *tert*-butyl group apparently fragments to relieve the strain resulting from interaction with the substituent present in the 3-position. It is also easy to understand why when an extremely bulky alkyne like 3,3-dimethyl-1-phenyl-1-butyne is employed in this annulation process, none of the desired heterocyclic product is produced. In this case, the reaction intermediate **A** might form either **A** with R^1 = *t*-Bu and R^2 = Ph or **A** with R^1 = Ph and R^2 = *t*-Bu. Generally, an intermediate, such as the former is difficult to generate due to the steric hindrance between the bulky *tert*-butyl group and the neighboring arene. Although the latter might be formed as an intermediate, it is unable to undergo palladium reductive elimination to generate **B**, because of steric hindrance between the two bulky *tert*-butyl groups in the 2 and 3 positions of **B**.

Conclusion

An efficient, palladium-catalyzed synthesis of nitrogen heterocycles, including isoquinolines, tetrahydroisoquinolines, 5,6-dihydrobenz[*f*]isoquinolines, pyrindines, and pyridines has been developed. A wide variety of acetylenes undergo this process in moderate to excellent yields, with high regioselectivity being observed in most cases. When a relatively unhindered diyne and enyne or an electron-rich imine are employed, mixtures of regioisomers are observed. By employing trimethylsilyl-containing acetylenes, we have been able to synthesize monosubstituted heterocyclic products.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz or 400 and 100 MHz, respectively. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm) and basic $KMnO_4$ solution [3 g of $KMnO_4$ + 20 g of K_2CO_3 + 5 mL of NaOH (5%) + 300 mL of H_2O]. All melting points are uncorrected. Low resolution mass spectra were recorded on a Finnigan TSQ700 triple quadrupole mass spectrometer (Finnigan MAT, San Jose, CA). High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. Elemental analyses were performed at Iowa State University on a Perkin-Elmer 2400 CHNS/O Series II Analyzer. All reagents were used directly as obtained commercially unless otherwise noted. Anhydrous forms of Na_2CO_3, K_2CO_3, NaOAc, $NaHCO_3$, LiCl, DMF, THF, ethyl ether, hexanes, and ethyl acetate were purchased from Fisher Scientific Co. All palladium salts were donated by Johnson Matthey Inc. and Kawaken Fine Chemicals Co. Ltd. PPh_3 was donated by Kawaken Fine Chemicals Co. Ltd. Compounds **2**, **3**, **4**, **7**, **8**, **9**, **10**, **11**, **18**, **34**, **35**, **54**, **60**, **68**, and **71** have been previously reported.[16] 2-Iodobenzaldehyde,[8] 2-bromopiperonal,[21] 2-bromocyclohexene-1-carboxaldehyde,[22] 2-bromocyclopentene-1-carboxaldehyde,[23] 1-bromo-3,4-dihydronaphthalene-2-carboxaldehyde,[24] (*Z*)-3-iodo-2-methyl-3-phenyl-2-propenal,[25] (*Z*)-3-iodo-3-phenyl-2-propenal,[25] 2-iodo-3,4,5-trimethoxybenzaldehyde,[26] 2-iodo-4,5,6-trimethoxybenzaldehyde,[27] and 2-iodo-4-dimethylaminobenzaldehyde[28] were prepared according to previous literature procedures. The preparation and characterization of the starting materials 1-(1-butynyl)cyclohexene, 2-iodopiperonal, 2-iodobenzene-1,4-dicarbaldehyde, and 2-iodo-5-(dimethylamino)benzaldehyde can be found in the Supporting Information.

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

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

***N*-(2-Iodo-3,4,5-trimethoxybenzylidene)-*tert*-butyl amine (38).** To 2-iodo-3,4,5-trimethoxybenzaldehyde (0.966 g, 3.0 mmol) was added *tert*-butylamine (6 mL, 2 mL/mmol). The tube was carefully sealed, and the mixture was then stirred under a nitrogen atmosphere at 100 °C for 24 h. The mixture was then cooled, diluted with ether, and dried with Na_2SO_4. The excess *tert*-butylamine was removed to afford 1.13 g (99%) of the imine **38** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 9H), 3.88 (s, 1H), 3.90 (s, 1H), 3.94 (s, 1H), 7.41 (s, 1H), 8.44 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 30.1, 56.4, 58.0, 61.1, 61.3, 89.5, 107.5, 133.7, 144.2, 152.9, 154.1, 159.2; IR (neat, cm^{-1}) 3011, 2968, 1475; HRMS Calcd for $C_{14}H_{20}INO_3$: 377.0488. Found: 377.0494.

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

General Procedure for the Palladium-Catalyzed Formation of Isoquinolines and Pyridines. DMF (10 mL), $Pd(OAc)_2$ (6.0 mg, 0.027 mmol), PPh_3 (13 mg, 0.05 mmol), Na_2CO_3 (53 mg, 0.5 mmol), and the alkyne (1.0 mmol) were placed in a 4 dram vial. The contents were then stirred for 1 min, and the appropriate imine (0.5 mmol) was added. The vial was flushed with nitrogen and heated in an oil bath at 100 °C for the indicated period of time. The reaction was monitored by TLC to establish completion. The reaction mixture (except entries 18, 21 and 31 in Table 2, which afford fairly water soluble isoquinoline derivatives) was cooled, diluted with 30 mL of ether, washed with 45 mL of saturated 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 18, 21, and 31 in Table 2 were filtered, the solvent was removed directly under reduced pressure, and the residue was purified by chromatography on a silica gel column.

4-Ethyl-3-phenylisoquinoline (5). The reaction mixture was chromatographed using 5:1 hexanes/EtOAc to afford 109 mg (93%) of the indicated compound as a white solid: mp 117−118 °C; ^{1}H NMR ($CDCl_3$) δ 1.30 (t, J = 7.5 Hz, 3H), 3.07 (q, J = 7.5 Hz, 2H), 7.39−7.56 (m, 5H), 7.62 (ddd J = 1.2, 6.9, 8.4 Hz, 1H), 7.77 (ddd, J = 1.2, 6.9, 8.1 Hz, 1H), 8.02 (d, J = 8.1 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 9.19 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.7, 21.9, 123.7, 126.6, 127.6, 127.9, 128.2, 128.5, 129.3, 130.4, 130.5, 135.3, 141.6, 150.2, 151.9; IR ($CHCl_3$, cm^{-1}) 3027, 2976, 1653, 1559; MS *m*/*z* (rel intensity) 233 (76, M^+), 232 (100), 217 (44). Anal. Calcd for $C_{17}H_{15}N$: C, 87.52; H, 6.48; N, 6.00. Found: C, 87.48; H, 6.68; N, 5.91.

(21) Conrad, P. C.; Kwiatkowski, P. L.; Fuchs, P. L. *J. Org. Chem.* **1987**, *52*, 586.
(22) Coates, R. M.; Senter, P. D.; Baker, W. R. *J. Org. Chem.* **1982**, *47*, 3597.
(23) Gilchrist, T. L.; Kemmitt, P. D. *Tetrahedron* **1995**, *51*, 9119.
(24) Gilchrist, T. L.; Summersell, R. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2595.
(25) Han, X. Ph.D. Dissertation, Iowa State University, 1998.
(26) Bradley, A.; Motherwell, W. B.; Ujjainwalla, F. *J. Chem. Soc., Chem. Commun.* **1999**, 917.
(27) Cherkaoui, M. Z.; Scherowsky, G. *New J. Chem.* **1997**, *21*, 1203.
(28) Raeppel, S.; Toussaint, D.; Suffert, J. *Synlett* **1998**, 537.

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

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Supporting Information Available: Preparation and characterization of the starting materials; characterization data for compounds **6**, **12**−**17**, **19**−**33**, **36**, **37**, **39**−**46**, **48**−**53**, **55**−**67**, **69**, and **70**, copies of ^{1}H and ^{13}C spectra for compounds **1**, **12**, **13**, **16**, **19**, **21**, **24**−**27**, **30**−**33**, **36**, **38**, **41**−**46**, **48**−**53**, **57**, **58**, **62**−**67**, and **69**. This material is available free of charge via the Internet at http://pubs.acs.org.

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