Synthesis of Substituted Isoquinolines by Electrophilic Cyclization of Iminoalkynes

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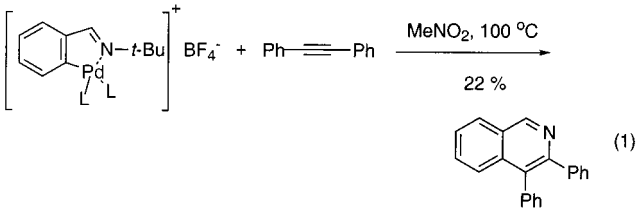
The *tert*-butylimines of *o*-(1-alkynyl)benzaldehydes and analogous pyridinecarbaldehydes have been cyclized under very mild reaction conditions in the presence of I_2, ICl, PhSeCl, PhSCl, and *p*-$O_2NC_6H_4SCl$ to give the corresponding halogen-, selenium-, and sulfur-containing disubstituted isoquinolines and naphthyridines, respectively. This methodology accommodates a variety of iminoalkynes and affords the anticipated heterocycles in moderate to excellent yields. Monosubstituted isoquinolines and naphthyridines have been synthesized by the metal-catalyzed ring closure of these same iminoalkynes. The silver-catalyzed ring closure is highly effective in cyclizing aryl-, alkenyl-, and alkyl-substituted iminoalkynes at 50 °C.

Introduction

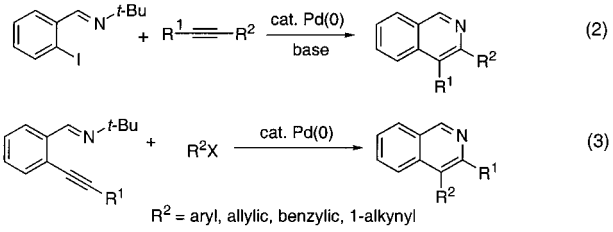
The isoquinoline backbone appears in numerous natural products. Thus, the synthesis of isoquinolines has received much recent attention.[1] Although classical methods have been frequently employed in the total synthesis of isoquinoline alkaloids, these approaches often have drawbacks. For example, the Bischler−Napieralski,[2] Pictet−Spengler,[3] and Pomeranz−Fritsh[4] protocols require relatively strong acids to cyclize *β*-phenethylamines. Also, the Bischler−Napieralski[2] and Pictet−Spengler[3] reactions afford dihydro- and tetrahydroisoquinolines, respectively. An additional step involving dehydrogenation is thus required to complete the synthesis of the isoquinoline.

Recently, substituted isoquinolines have been synthesized by employing palladium chemistry. Widdowson has published a synthesis of isoquinolines by the reaction of a cyclopalladated *N*-*tert*-butylarylaldimine and acrylonitrile.[5] His synthesis suffers from the use of stoichiometric amounts of palladium salts and high reaction temperatures (180−200 °C) for the final step. Heck has also reported the formation of 3,4-diphenylisoquinoline by the reaction of diphenylacetylene and a cyclopalladated *N*-*tert*-butylbenzaldimine tetrafluoroborate complex (eq 1).[6] This synthesis also utilizes a stoichiometric amount of palladium salts, which is not very practical in organic synthesis.



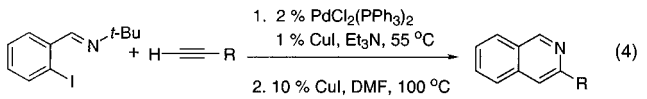
(1)

We have recently reported the formation of numerous 3,4-disubstituted isoquinolines by the palladium-catalyzed annulation of internal alkynes (eq 2)[7] and carbopalladation of the *tert*-butylimines of *o*-(1-alkynyl)benzaldehydes (eq 3).[8] 3-Substituted isoquinoline derivatives can be prepared by the palladium/copper-catalyzed cross coupling of terminal alkynes and subsequent ring closure by catalytic CuI (eq 4)[9] or by the reaction of *o*-(1-alkynyl)benzaldehydes with NH_3 (eq 5).[10]

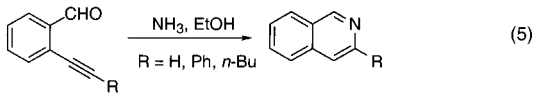


(2)

(3)



(4)



(5)

During the course of our isoquinoline annulation studies, we were encouraged to examine the electrophilic

(1) (a) Buske, A.; Busemann, S.; Mühlbacker, J.; Schmidt, J.; Porzel, A.; Bringmann, G.; Adam, G. *Tetrahedron* **1999**, *55*, 1079. (b) Bringmann, G.; Holenz, J.; Weirich, R.; Rübenacker, M.; Funke, C. *Tetrahedron* **1998**, *54*, 497. (c) Xu, X.-Y.; Qin, G.-W.; Xu, R.-S.; Zhu, X.-Z. *Tetrahedron* **1998**, *54*, 14179. (d) Brossi, A. *Heterocycles* **1988**, *12*, 2905. (e) Fitzgerald, J. J.; Michael, F. E.; Olofson, R. A. *Tetrahedron Lett.* **1994**, *49*, 9191. (f) Rozwadowska, M. D. *Heterocycles* **1994**, *39*, 903. (g) Kohno, H.; Yamada, K. *Heterocycles* **1999**, *51*, 103. (h) Flippin, L. A.; Muchowski, J. M. *J. Org. Chem.* **1993**, *58*, 2631. (i) Aubert, T.; Farnier, M.; Hanquet, B.; Guilard, R. *Synth. Commun.* **1987**, *17*, 1831. (j) Bobbitt, J. M.; Bourque, A. J. *Heterocycles* **1987**, *25*, 601. (k) Diederen, J. J. H.; Sinkeldam, R. W.; Frühauf, H.-W.; Hiemstra, H.; Vrieze, K. *Tetrahedron Lett.* **1999**, *40*, 4255.

(2) Whaley, W. M.; Govindachari, T. R. In *Organic Reactions*; Adams, R., Ed.; Wiley: New York, 1951; Vol. 6, pp 151−190.

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

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

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

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

(7) (a) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 5306. (b) Roesch, K. R.; Zhang, H.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 8042.

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Scheme 1

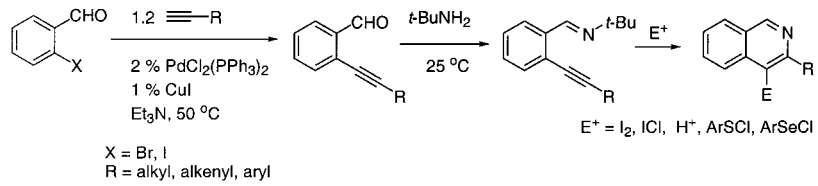
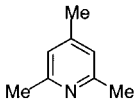
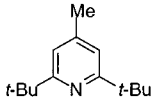
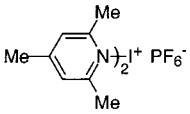


Table 1. Ring Closure of Iminoalkyne 1 by I_2 (eq 6)[a]

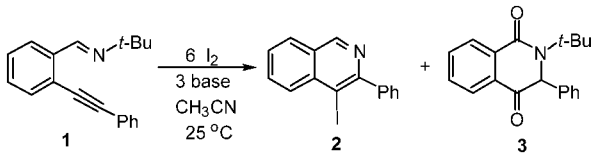
entry	base	time (h)	% yield of **2**[b]	% yield of **3**[b]
1	-	3	17	trace
2	$NaHCO_3$	3	36	24
3	Na_2CO_3	24	30	26
4	K_2CO_3	3	31	28
5	$NaOCO_2CH_3$	0.5	68	0
6	*t*-BuOK	3	17	0
7	*n*-$C_3H_7CO_2Na$	72	20	0
8	Et_3N	72	trace	0
9	pyridine[c]	72	20	0
10		72	32	trace
11		72	22	0
12[d]		72	30	0
13[e]		72	trace	0

[a] All reactions were run under the following conditions, unless otherwise described: 0.25 mmol of **1** and 0.75 mmol of the base in 7 mL of CH_3CN were stirred at room temperature under Ar for the specified period of time. [b] Isolated yields. [c] Pyridine (7 mL) was used as both the solvent and the base. [d] No I_2 was employed, and 7 mL of CH_2Cl_2 was used as the solvent. [e] No I_2 was employed.

cyclization of our iminoalkynes by electrophiles other than organopalladium compounds in order to obtain 3,4-disubstituted isoquinolines (Scheme 1). The requisite iminoalkynes can be easily prepared by the Sonogashira reaction of a 2-halobenzaldehyde and a terminal alkyne, followed by reaction with *tert*-butylamine. We now report that the electrophilic cyclization of the *tert*-butyl imines of *o*-(1-alkynyl)benzaldehydes and analogues provides a very efficient synthesis of a wide variety of substituted isoquinolines.

Results and Discussion

First, we studied the reaction of iminoalkyne **1** with I_2 in CH_3CN at room temperature in the presence of a variety of bases (eq 6). The results are summarized in Table 1, entries 1−11.



When no base was employed, this cyclization reaction only gave 17% of the desired isoquinoline product **2** (entry 1). The addition of carbonate bases such as $NaHCO_3$, Na_2CO_3, and K_2CO_3 increased the yields of **2** to 36, 30, and 31%, respectively (entries 2−4), while side product **3** was observed in 24−28% yields. The side product **3** probably arises from reaction of the intermediate isoquinolinium salt with water, hydroxide, or the carbonate base (see the later mechanistic discussion). Surprisingly, the use of $NaOCO_2CH_3$[11] as the base (entry 5) produced a 68% yield of **2** and none of the side product **3** was produced. This reaction was complete in 0.5 h. The very different results from the reaction of $NaOCO_2CH_3$ and the other carbonate bases can be explained by the fact that $NaOCO_2CH_3$ reacts with a proton to produce CO_2 and MeOH, while the reactions of a proton with the bases $NaHCO_3$, Na_2CO_3, or K_2CO_3 generate CO_2 and H_2O. The H_2O generated probably leads to the formation of side product **3** and thus results in low yields of **2**. When a stronger base, KO-*t*-Bu, was employed, only a 17% yield of **2** was observed (entry 6). The low yield may be a direct result of the fact that the imine appears to be unstable in the presence of this strong base. The reactions employ-

(8) Dai, G.; Larock, R. C. *Org. Lett.* **2001**, *3*, 4035.
(9) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 553.
(10) Unpublished work cited in: Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1988**, *27*, 2225.

ing the less basic salt n-$C_3H_7CO_2Na$ and the organic base Et_3N were quite slow (entries 7 and 8). These reactions are not complete even in 3 days and give only a 20% yield and a trace of **2**, respectively. Pyridine and hindered pyridine derivatives such as 2,4,6-trimethylpyridine and 2,6-di-*tert*-butyl-4-methylpyridine have also been employed (entries 9−11). Although no side product **3** was produced, all of these reactions were slow and suffered low yields ranging from 20 to 32%. The use of bis-(2,4,6-trimethylpyridine)iodine(I) hexafluorophosphate, which is both a source of iodine cation and a potential base, failed to improve the yield of **2**. A 30% yield of **2** was observed when the reaction was carried out in CH_2Cl_2 (entry 12), while only trace amounts of **2** were produced in CH_3CN (entry 13). We have found that using less than 3 equiv of the base and 6 equiv of I_2 results in a lower yield. So we have chosen the following conditions as optimal for all subsequent experiments: 0.25 mmol of the iminoalkyne, 6 equiv of I_2, and 3 equiv of $NaOCO_2CH_3$ in 7 mL of CH_3CN stirred at room temperature for an appropriate amount of time. Most of the reactions are complete in 0.5 h and afford good to excellent yields of the corresponding iodoisoquinolines and iodonaphthyridines. The results using I_2 are summarized in Table 2, entries 1, 3, 4, 6, 8, 10, 12, and 13.

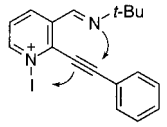
The stronger electrophilic reagent ICl has also been employed in these cyclizations, and the corresponding cyclization products have been observed in yields comparable to those obtained using I_2, except for iminoalkynes **10** (compare entries 8 and 9) and **16** (compare entries 13 and 14). The reasons for this are not obvious. The reaction times are also usually pretty similar to those of I_2. The results are summarized in Table 2, entries 2, 5, 7, 9, 11, and 14.

Of all of the electrophilic reagents examined, I_2 and ICl close the six-membered ring the fastest. Most of these reactions are complete in 0.5 h. The reactions of **1** with I_2 and ICl gave almost identical yields of 67 and 68%, respectively (entries 1 and 2). When the iminoalkyne **4** bearing a cyclohexenyl group was allowed to react with I_2 (entry 3), the yield was similar to that of **1**. This indicates that this electrophilic reaction can tolerate double bonds.

To further test the scope of this electrophilic ring closure, alkyl-substituted acetylenes such as iminoalkynes *o*-(*t*-BuN=CH)C_6H_4C≡CR [R = cyclohexyl (**38**) or CH_2CH_2OTHP (**40**)] have been allowed to react with I_2 and ICl. Cacchi has reported that alkyl-substituted *o*-(1-alkynyl)phenols react with I_2 to give substituted iodobenzofurans.[11] However, in our chemistry, I_2 and ICl do not react with either of the alkyl-substituted iminoalkynes to afford the desired products and neither do PhSeCl or PhSCl as will be discussed later. The coordination of iodine to the carbon−carbon triple bonds in these iminoalkynes should result in a partial postive charge on the carbon next to the aromatic ring, since an aryl group stabilizes a carbocation better than an alkyl group. Obviously, the formation of isoquinolines from such an intermediate is impossible.

While iminoalkyne **21**, *o*-(*t*-BuN=CH)C_6H_4C≡CC_6H_4-*p*-CF_3, bearing an electron-deficient arylethynyl group did not react with I_2 or ICl at all, the introduction of an electron-rich arylethynyl group, as found in iminoalkynes **6** (entries 4 and 5) and **8** (entries 6 and 7), rather surprisingly resulted in low yields of the desired heterocyclic iodides. Similarly, none of the desired product has been obtained when iminoalkyne **10** with a methylenedioxo substituent is allowed to react with I_2 (entry 8), although all of the starting material is gone in 0.5 h. However, a 52% yield of **11** was observed when ICl was employed as the electrophile (entry 9). This is possibly because ICl is a stronger electrophile than I_2.

From entries 10 and 11 in Table 2, one can see that the introduction of a pyridine ring into the starting material results in relatively high yields when either I_2 or ICl is employed as an electrophile. This might be explained by an intermediate such as **46**.



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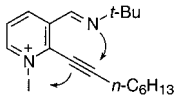
The pyridine nitrogen might first coordinate to the electrophile to form a pyridinium cation. Because of this coordination, electrophilic attack of the triple bond might then occur in an intramolecular fashion. The intramolecular assistance significantly increases the yields for the reactions of I_2 and ICl from 68 and 67% for iminoalkyne **1** (entries 1 and 2) to 90 and 92% for iminoalkyne **12** (entries 10 and 11), respectively.

Alternatively, the presence of the pyridine moiety in iminoalkyne **12** may simply be directing the cationic charge of the intermediate iodonium ion to the more remote carbon of the alkyne, which should favor formation of the six-membered ring isoquinoline. Whatever the reason, the result is very encouraging, since it broadens the potential applications of this cyclization and improves its efficiency.

As described above, iminoalkynes derived from *o*-iodobenzaldehyde and acetylenes bearing simple alkyl groups do not react with I_2. However, iminoalkyne **14** can be cyclized by I_2 giving naphthyridine **15** in a 76% yield (entry 12). Again, we believe that the key is the coordination of the electrophile to the pyridine nitrogen and formation of an intermediate like **47**.



47

In an attempt to try to confirm this intramolecular assistance, iminoalkyne **16** has been allowed to react with I_2, and only a 13% yield of **17** was obtained (entry 13). Compared to the reaction of **12** and I_2 (entry 10), the yield dropped from 90 to 13%. This may arise because **16** geometrically disfavors intramolecular assistance, or it may simply be that we have now further removed the more electron-withdrawing nitrogen from the vicinity of the carbon−carbon triple bond. However, iminoalkyne **16** reacts with ICl to give naphthyridine **17** in 72% yield, although this reaction requires 1 day to reach completion (entry 14). It is logical that ICl, a stronger electrophile than I_2, should work better in this reaction.

The next electrophilic reagent studied was PhSeCl. A variety of reaction conditions have been examined, and the results are summarized in Table 3. Very similar

(11) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L. *Synlett* **1999**, 1432.

Table 2. Synthesis of Isoquinolines and Naphthyridines by the Reaction of Iminoalkynes and Electrophiles[a]

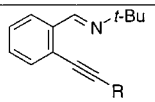
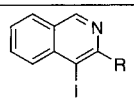
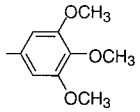
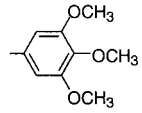
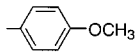
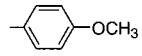
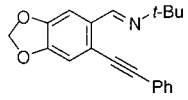
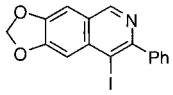
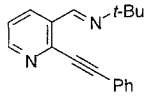
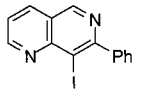
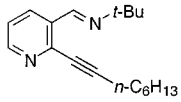
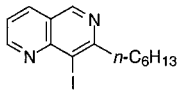
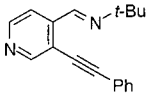
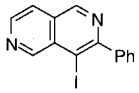
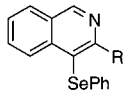
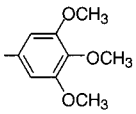
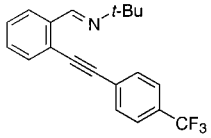
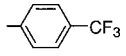
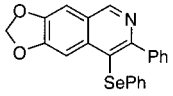
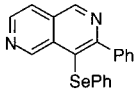
entry	iminoalkyne		electrophile	time (h)	product		% isolated yield
							
1	R = Ph	**(1)**	I_2[b]	0.5	R = Ph	**(2)**	68
2			ICl[c]	0.5		**(2)**	67
3	R = 	**(4)**	I_2[b]	0.5	R = 	**(5)**	67
4	R = 	**(6)**	I_2[b]	0.5	R = 	**(7)**	30
5			ICl[c]	0.5		**(7)**	24
6	R = 	**(8)**	I_2[b]	0.1	R = 	**(9)**	37
7			ICl[c]	0.5		**(9)**	40
8		**(10)**	I_2[b]	0.5		**(11)**	0
9			ICl[c]	0.5		**(11)**	52
10		**(12)**	I_2[b]	0.5		**(13)**	90
11			ICl[c]	0.5		**(13)**	92
12		**(14)**	I_2[b]	0.5		**(15)**	76
13		**(16)**	I_2[b]	0.2		**(17)**	13
14			ICl[c]	24		**(17)**	72
							
15	**1**		PhSeCl	24	R = Ph	**(18)**	76
16	**4**		PhSeCl	24	R = 	**(19)**	96
17	**6**		PhSeCl	48	R = 	**(20)**	95
18		**(21)**	PhSeCl	72	R = 	**(22)**	18
19	**10**		PhSeCl	72		**(23)**	60
20	**16**		PhSeCl	72		**(24)**	80

Table 2. (Continued)

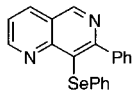
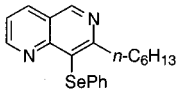
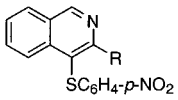
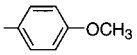
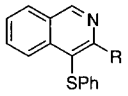
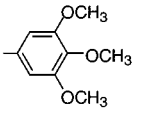
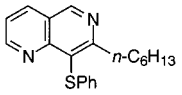
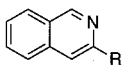
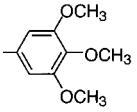
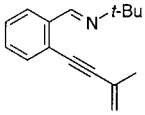
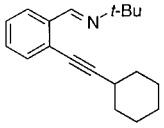
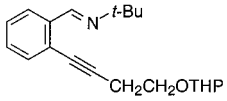
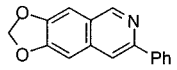
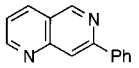
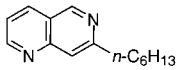
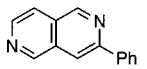
entry	iminoalkyne	electrophile	time (h)	product	% isolated yield
21	**12**	PhSeCl	24	 **(25)**	72
22	**14**	PhSeCl	72	 **(26)**	61
					
23	**1**	p-$O_2NC_6H_4SCl$	48	R = Ph **(27)**	46
24	**4**	p-$O_2NC_6H_4SCl$	48	R =  **(28)**	33
25	**8**	p-$O_2NC_6H_4SCl$	72	R =  **(29)**	25
					
26	**4**	PhSCl	24	R =  **(30)**	45
27	**6**	PhSCl	24	R =  **(31)**	43
28	**14**	PhSCl	24	 **(32)**	40
					
29	**1**	$AgNO_3$[d]	24	R = Ph **(33)**	82
30		CuI[e]	3	**(33)**	100
31	**4**	$AgNO_3$[d]	24	R =  **(34)**	78
32		CuI[e]	3	**(34)**	81
33	**6**	$AgNO_3$[d]	72	R =  **(35)**	71
34	 **(36)**	$AgNO_3$[d]	72	R =  **(37)**	54
35	 **(38)**	$AgNO_3$[d]	24	R =  **(39)**	75
36		CuI[e]	6	**(39)**	93
37	 **(40)**	$AgNO_3$[d]	24	R = CH_2CH_2OTHP **(41)**	62
38		CuI[e]	5	**(41)**	83

Table 2. (Continued)

entry	iminoalkyne	electrophile	time (h)	product		% isolated yield
39	**9**	$AgNO_3$[d]	24		**(42)**	56
40	**11**	$AgNO_3$[d]	24		**(43)**	92
41	**13**	$AgNO_3$[d]	72		**(44)**	45
42	**15**	$AgNO_3$[d]	72		**(45)**	80

[a] All reactions were run under the following conditions, unless otherwise specified: 0.25 mmol of the iminoalkyne and 2 equiv of the electrophile in 7 mL of CH_2Cl_2 at room temperature. [b] Iminoalkyne (0.25 mmol) , 6 equiv of I_2, and 3 equiv of $NaOCO_2CH_3$ in 7 mL of CH_3CN at room temperature. [c] ICl (4 equiv) has been used. [d] Iminoalkyne (0.25 mmol) and 5 mol % $AgNO_3$ in 7 mL of $CHCl_3$ at 50 °C. [e] Iminoalkyne (0.25 mmol) and 10 mol % CuI in 5 mL of DMF at 100 °C.

Table 3. Optimization of the Cyclization Reaction Employing Se and S Electrophiles[a]

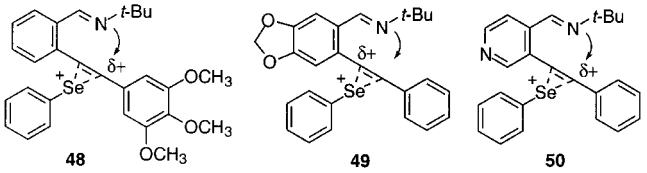
entry	electrophile	equiv of electrophile	temp (°C)	time (days)	% yield
1	PhSeCl	1	25 °C	1	74
2		2		1	78
3				1	70[b]
4	PhSeSePh			1	0
5	*p*-$NO_2C_6H_4SCl$			3	47
6				3	45[c]
7			60 °C	3	47

[a] All reactions were run using 0.25 mmol of **1** in 7 mL of CH_2Cl_2, unless otherwise specified. [b] CH_2Cl_2 (2 mL) was used. [c] $ZnCl_2$ (2 equiv) was added.

yields, 74 and 78%, of isoquinoline **18** have been obtained from iminoalkyne **1** using 1 and 2 equiv of PhSeCl, respectively (Table 3, entries 1 and 2). The concentration of the reactants seems to play a minor role in this reaction. From entry 3, one can see that a more concentrated reaction actually gave a slightly lower yield. The reagent PhSeSePh failed to yield any of the corresponding isoquinoline (entry 4). Thus, we chose 0.25 mmol of the iminoalkyne and 2 equiv of PhSeCl in 7 mL of CH_2Cl_2 at room temperature as our standard reaction conditions for the reaction of PhSeCl and our iminoalkynes. In general, the reaction of iminoalkynes and PhSeCl requires 1−3 days and good to excellent yields of selenium-containing isoquinolines and naphthyridines are obtained (Table 2, entries 15−22). The major exception was iminoalkyne **21**, which gave only an 18% yield after 3 days of reaction time (entry 18).

Cyclizations employing PhSeCl have generally proven to be quite successful. A 76% yield of the isoquinoline product **18** has been obtained when iminoalkyne **1** is allowed to react with PhSeCl (entry 15). When an iminoalkyne bearing a vinylic group on the triple bond is employed, a 96% yield of selenium-containing isoquinoline **19** has been observed (entry 16). In contrast to the reactions of I_2 and ICl, the introduction of an electron-rich arylethynyl group into the iminoalkyne increases the yield from 76% (entry 15) to 95% (entry 17). However, the reaction of PhSeCl and iminoalkyne **21** bearing an electron-deficient arylethynyl group results in only an 18% yield of isoquinoline (entry 18). Thus,

Scheme 2



electron-rich arylethynyl groups benefit the ring closure by PhSeCl, while an electron-deficient arylethynyl group disfavors cyclization. Obviously, the presence of an electron-rich arylethynyl group may be favoring the formation of the positive charge on the carbon necessary for formation of the six-membered ring. This supposition is confirmed by the reaction of **10** and PhSeCl, where the electron-rich methylenedioxy group presumably favors cation formation on the "wrong" carbon of the alkyne, which results in a lower yield of selenium-substituted naphthalene (entry 19). Only a 60% yield of **23** was obtained when **10** was allowed to react with PhSeCl. Although both iminoalkynes **6** (entry 17) and **10** (entry 19) have relatively electron-rich triple bonds, they afford quite different results. The lower yield of **23** can be explained as shown in Scheme 2. The positive charge on the alkyne carbon bearing the trimethoxyphenyl ring in intermediate **48** is better stabilized, and therefore closure to a six-membered ring and formation of the isoquinoline product **20** are favored (entry 17). In intermediate **49**, more of the partial positive charge is located on the alkyne carbon bearing the methylenedioxyphenyl ring, which disfavors the formation of a six-membered ring and results in a decrease in the yield from 95% (entry 17) to 60% (entry 19).

Although the electron density on both the triple bond and the imine nitrogen is decreased by the presence of a pyridine ring in compound **16**, we still obtain an 80% yield from the reaction of iminoalkyne **16** and PhSeCl (entry 20). This may be explained by the fact that the partial positive charge in intermediate **50** (Scheme 2) is delocalized better by the phenyl group. Subsequent endo-6-trig attack apparently proceeds smoothly to form a stable isoquinoline product.

Iminoalkynes **12** and **14** also react with PhSeCl to give decent yields (entries 21 and 22). The success of these

reactions may be the result of intramolecular assistance as described above. Alternatively, the presence of an electron-deficient pyridine ring may simply be favoring formation of an intermediate with a positive charge located on the carbon necessary to close the six-membered ring and disfavoring formation of the "wrong cation" on the carbon−carbon triple bond.

Unfortunately, when PhSeCl has been allowed to react with alkyl-substituted iminoalkynes such as iminoalkynes *o*-(*t*-BuN=CH)C_6H_4C≡CR [R = cyclohexyl (**38**) or CH_2-CH_2OTHP (**40**)], none of the desired product was observed. The results are similar to those from the reactions of I_2 and iminoalkynes **38** and **40**.

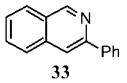
The electrophile *p*-$O_2NC_6H_4SCl$ has been examined under the optimal reaction conditions developed for PhSeCl. The isoquinoline product **27** expected from iminoalkyne **1** was obtained in a rather low yield of 47% (Table 3, entry 5). The addition of the Lewis acid $ZnCl_2$ (entry 6) or an increase in the reaction temperature (entry 7) in an attempt to induce cyclization had little effect on the product yield, so the optimal reaction conditions for PhSeCl have been used in the reactions of *p*-$O_2NC_6H_4SCl$ and PhSCl[12] (Table 2, entries 23−28). In general, the yields of sulfur-containing isoquinolines from *p*-$O_2NC_6H_4SCl$ and PhSCl fall in the range of 25−46%. The reactions producing nitro-containing products generally proceed in a slightly lower yield and require much longer reaction times.

The electrophile *p*-$O_2NC_6H_4SCl$ reacts with iminoalkynes **1**, **4**, and **8** to produce the corresponding 4-(*p*-nitrophenylsulfenyl)isoquinoline derivatives in modest yields (entries 23−25). These yields are lower than those of reactions with I_2, ICl, or PhSeCl. This is probably because this reagent is a weaker electrophile. Much better yields of the sulfur-containing isoquinolines were obtained when PhSCl was employed as the electrophile. As shown in entries 26−28, iminoalkynes **4**, **6**, and **14** were allowed to react with PhSCl and the corresponding sulfide products **30**−**32** were obtained in yields ranging from 40 to 45%. All of these reactions were complete in 24 h. However, the reactions of PhSCl and the alkyl-substituted iminoalkynes **38** and **40** afforded none of the desired product. Thus, rather surprisingly, the pyridine-containing iminoalkyne **32** actually gives better results than the corresponding alkyl-substituted phenyl analogues. This may be due to intramolecular assistance by the pyridine as described earlier.

To synthesize monosubstituted isoquinolines, 10 mol % CuI has been employed to close these same iminoalkynes to heterocycles with a hydrogen in the 4 position.[7] The results from these cyclizations are summarized in Table 2, entries 30, 32, 36, and 38. We now report that catalytic amounts of $AgNO_3$ will effect the same transformation and that the reaction occurs under milder reaction conditions, although the yields are often a bit lower. Thus, 0.25 mmol of iminoalkyne **1** have been allowed to react with 2 equiv of $AgNO_3$ in 7 mL of $CHCl_3$ at 50 °C (Table 4, entry 1). After 1 day, the monosubstituted isoquinoline **33** was obtained in a 90% isolated yield. Further study indicated that 5 mol % $AgNO_3$ is enough to close the six-membered ring in good yield (entries 2−4). The reaction failed when only 1% $AgNO_3$ was employed as the catalyst. Both $AgNO_3$ and AgOAc gave approximately the same yields for this ring closure

(12) Brillon, D.; Sauvé, G. *J. Org. Chem.* **1990**, *55*, 2246.

Table 4. Silver-Catalyzed Ring Closure of Iminoalkyne 1[a]

entry	silver salt (equivs)	solvent	product	% isolated yield
1	$AgNO_3$ (2.00)	$CHCl_3$	 **33**	90
2	(0.10)			80
3	(0.05)			82
4	(0.01)			0[b]
5	AgOAc (0.05)			80
6	$AgNO_3$ (2.00)	$CDCl_3$		69

[a] All reactions were run under the following conditions, unless otherwise specified: 0.25 mmol of iminoalkyne **1** and the indicated amount of silver salt in 7 mL of the solvent were stirred at 50 °C for 24 h. [b] After 24 h, there was only a minimal amount of the desired product present by TLC.

(compare entries 3 and 5). Thus, the following standard conditions have been employed in all subsequent experiments: 0.25 mmol of the iminoalkyne and 5 mol % $AgNO_3$ were stirred at 50 °C in 7 mL of $CHCl_3$ for the appropriate reaction time. The reaction takes 1−3 days at 50 °C and gives decent yields of the corresponding cyclization products (Table 2, entries 29, 31, 33−35, 37, and 39−42).

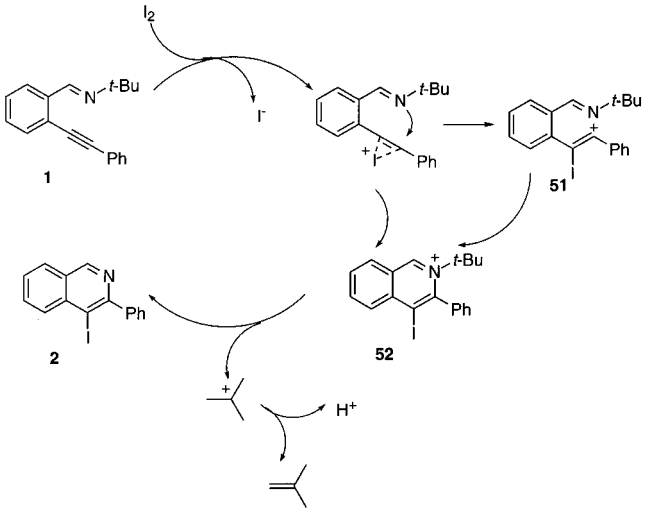
The source of the hydrogen atom ending up in the 4 position of the isoquinoline is not obvious. If the hydrogen atom comes from the solvent, the use of $DCCl_3$ would have resulted in a deuterated product (Table 4, entry 6). This was not the case as indicated by ^{1}H NMR spectroscopic analysis. Thus, we believe that the hydrogen is coming from the *tert*-butyl group of the imine or from small amounts of water present in the reaction.

As described above, alkyl-substituted *N*-(*o*-(1-alkynyl)-benzylidene)-*tert*-butylamines failed to afford any of the desired isoquinolines when allowed to react with I_2, ICl, PhSeCl, or *p*-$O_2NC_6H_4SCl$. However, iminoalkyne **38** and **40** do react with $AgNO_3$ or CuI to afford decent yields of the corresponding isoquinolines (Table 2, entries 35−38).

In general, the reactions of I_2 and ICl form the six-membered ring isoquinolines the fastest. In most cases, these reactions are complete in 0.5 h. However, the yields are less than those obtained from the reactions of PhSeCl, $AgNO_3$, or CuI. The reagents PhSCl and *p*-$O_2NC_6H_4SCl$ are the least efficient electrophilic reagents for this process, and their reactions require longer reaction times and result in lower yields.

For the reactions of I_2 or ICl and iminoalkyne **1**, we propose the mechanism shown in Scheme 3. First, the carbon−carbon triple bond of iminoalkyne **1** coordinates to the iodine cation generated from I_2 to generate an iodonium intermediate. This is followed by attack of the imine nitrogen on the activated triple bond to form intermediate **52**. Alternatively, the coordination of the iodine cation to the carbon−carbon triple bond may form a cationic intermediate like **51**, which cyclizes to intermediate **52**. The isoquinolinium salt **52** then presumably ionizes to produce the iodoisoquinoline **2** and a *tert*-butyl cation, which generates isobutylene.

Scheme 3



Conclusions

In conclusion, a procedure for the efficient synthesis of a wide variety of substituted isoquinolines has been developed that employs very mild reaction conditions. This methodology accommodates a variety of iminoalkynes and affords the anticipated substituted isoquinolines in moderate to excellent yields.

Experimental Section

General. The ^{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, 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 triple quadrupole mass spectrometer. High-resolution mass spectra were recorded on a double focusing magnetic sector mass spectrometer using EI at 70 eV. All reagents were used directly as obtained commercially unless otherwise noted. 2-Bromopyridine-3-carboxaldehyde,[13] 3-bromopyridine-4-carboxaldehyde,[13] and PhSCl[14] were prepared according to literature procedures. The preparation and characterization of the starting materials 2-(2-propenylethynyl)benzyl alcohol, 2-(2-propenylethynyl)benzaldehyde, 2-(phenylethynyl)benzaldehyde, 2-(2-cyclohex-1-enylethynyl)benzaldehyde, 2-(3,4,5-trimethoxyphenylethynyl)benzaldehyde, 2-(4-methoxyphenylethynyl)benzaldehyde, 4,5-methylenedioxy-2-(phenylethynyl)benzaldehyde, 2-(phenylethynyl)pyridine-3-carboxaldehyde, 2-(1-octyn-1-yl)pyridine-3- carboxaldehyde, 3-(phenylethynyl)pyridine-4-carboxaldehyde, 2-(4-trifluoromethylphenylethynyl)benzaldehyde, 2-(cyclohexylethynyl)benzaldehyde, and 2-(4-(tetrahydropyran-2-yloxy)but-1-ynyl)benzaldehyde can be found in Supporting Information.

Representative Procedure for Preparation of Imines: *N*-(2-Phenylethynylbenzylidene)-*tert*-butylamine (1). To a solution of 2-bromobenzaldehyde (1.86 g, 10.0 mmol) and phenylacetylene (1.22 g, 12.0 mmol) in Et_3N (40 mL) were added $PdCl_2(PPh_3)_2$ (140 mg, 2 mol %) and CuI (20 mg, 1 mol %). The resulting mixture was then heated under an Ar atmosphere at 50 °C. The reaction was monitored by TLC to establish completion. When the reaction was complete, the mixture was allowed to cool to room temperature, and the ammonium salt was removed by filtration. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography using 20:1 hexane/EtOAc to afford 1.94 g (94%) of 2-(2-phenylethynyl)benzaldehyde as a yellow oil with spectral properties identical to those previously reported.[9] To 2-(phenylethynyl)benzaldehyde (1.03 g, 5.0 mmol) in a 4 dram vial was added *t*-BuNH_2 (6 equiv). The mixture was then stirred under an Ar atmosphere at room temperature for 24 h. The resulting mixture was extracted with ether. The combined organic layers were dried (Na_2SO_4) and filtered. Removal of the solvent afforded 1.30 g of the desired compound in 100% yield as a yellow solid: mp 53−54 °C; ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 9H), 7.28−7.35 (m, 5H), 7.49−7.54 (m, 3H), 8.07−8.10 (m, 1H), 8.94 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 30.0, 58.0, 86.9, 95.1, 123.3, 124.1, 126.2, 128.7, 128.7, 128.8, 129.9, 131.6, 132.4, 138.8, 154.2; IR ($CHCl_3$, cm^{-1}) 3060, 2214, 1637; HRMS calcd for $C_{19}H_{19}N$ 261.1518, found 261.1518.

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

Typical Procedure for Cyclization Reactions: 4-Iodo-3-phenylisoquinoline (2). To a 2 dram vial were added 0.381 g of I_2 (1.50 mmol), 62 mg of $NaOCOCH_3$ (0.75 mmol), and 5 mL of CH_3CN. The iminoalkyne **1** (65 mg, 0.25 mmol) in 2 mL of CH_3CN was added dropwise to the vial. The vial was flushed with Ar, and the reaction mixture was stirred at room temperature for 0.5 h. The reaction mixture was then diluted with 25 mL of ether, washed with 25 mL of saturated $Na_2S_2O_3$, dried (Na_2SO_4), and filtered. The solvent was evaporated under reduced pressure, and the product was purified by flash chromatography (3:1 hexane/EtOAc) to afford 56 mg (68%) (Table 2, entry 1) of the product as a yellow solid: mp 84−85 °C; ^{1}H NMR ($CDCl_3$) δ 7.26−7.52 (m, 3H), 7.61−7.70 (m, 3H), 7.70−7.85 (m, 2H), 7.95 (d, J = 8.1 Hz, 1H), 8.22 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 98.3, 128.1, 128.2, 128.3, 128.5, 130.3, 132.4, 132.6, 138.8, 143.9, 152.2, 157.4 (one sp^2 carbon missing due to overlap); IR ($CHCl_3$, cm^{-1}) 3055, 1630, 1549; HRMS calcd for $C_{15}H_{10}IN$ 330.9858, found 330.9862.

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

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Supporting Information Available: Preparation and characterization of the starting materials; characterization data for compounds **2**, **3**, **5**, **7**, **9**, **11**, **13**, **15**, **17**−**20**, **22**−**32**, **34**, **35**, **37**, **39**, and **41**−**45**; and copies of ^{1}H and ^{13}C NMR spectra for compounds **1**−**32** and **34**−**45**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) (a) Numata, A.; Kondo, Y.; Sakamoto, T. *Synthesis* **1999**, *2*, 306. (b) Bjork, P.; Aakermann, T.; Hornfeldt, A.; Gronowitz, S. *J. Heterocycl. Chem.* **1995**, *32*, 751. (c) Melnyk, P.; Gasche, J.; Thal, C. *Synth. Commun.* **1993**, 2727.

(14) (a) Harpp, D. N.; Friedlander, B. T.; Smith, R. A. *Synthesis* **1979**, *3*, 181. (b) Mueller, W. H.; Butler, P. E. *J. Am. Chem. Soc.* **1968**, *90*, 2075.