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Synthesis of 3-Substituted 4-Aroylisoquinolines via Pd-Catalyzed Carbonylative Cyclization of 2-(1-Alkynyl)benzaldimines

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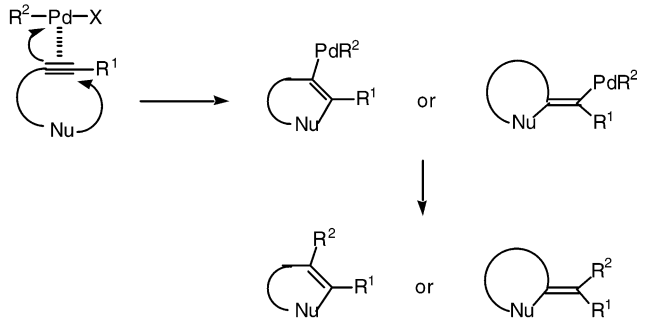
A number of 3-substituted 4-aroylisoquinolines have been prepared in good yields by treating *N*-*tert*-butyl-2-(1-alkynyl)benzaldimines with aryl halides in the presence of CO and a palladium catalyst. Synthetically the methodology provides a simple and convenient route to isoquinolines containing an aryl, alkyl, or vinylic group at C-3 and an aroyl group at C-4 of the isoquinoline ring. The reaction is believed to proceed via cyclization of the alkyne containing a proximate nucleophilic center promoted by an acylpalladium complex.

Introduction

Alkyne-based palladium-catalyzed reactions provide some of the most versatile and efficient routes to heterocyclic derivatives (Scheme 1).[1] A variety of heterocycles have been prepared through in situ hydroarylation (hydrovinylation)/cyclization reactions,[2] in situ coupling/cyclization reactions,[3] and annulation reactions promoted by σ-vinyl- and σ-arylpalladium complexes.[1,4] Heterocyclization promoted by σ-vinyl- and σ-arylpalladium complexes is extremely valuable, since generation of the heterocyclic skeleton accommodates functionalities amenable to further functional group manipulation and affords a rapid increase in molecular complexity. When such reactions are carried out in the presence of carbon monoxide, one carbon−heteroatom bond and two carbon−carbon bonds are generated in a single synthetic operation.

Since the acylpalladation of alkynes containing oxygen and nitrogen nucleophiles near the carbon−carbon triple bond has been employed in the synthesis of ketone-containing indoles[5] and benzo[*b*]furans, we thought that analogous chemistry might be used to generate the isoquinoline skeleton. We have recently reported convenient methods for the preparation of 3-monosubstituted[6] and 3,4-disubstituted isoquinolines,[7] disubstituted β- and γ-carbolines,[8] and monosubstituted β- and γ-carbolines[9] by the palladium-promoted cyclization of alkynylimines. Herein we report analogous acylpalladation chemistry of

SCHEME 1



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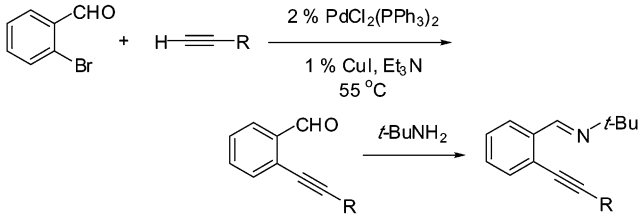
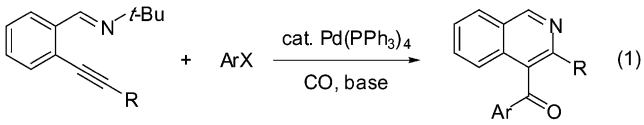
SCHEME 2



N-tert-butyl-2-(1-alkynyl)benzaldimines for the synthesis of 3-substituted 4-aroylisoquinolines (eq 1).[10]

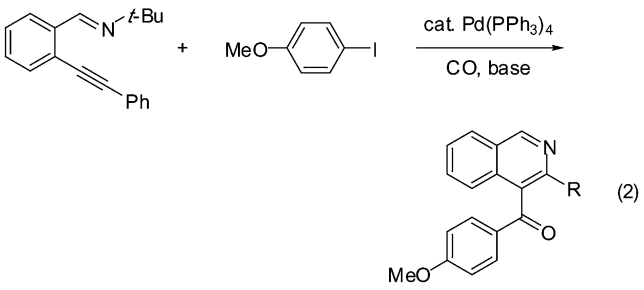


(1)

Starting Materials. The starting *N-tert*-butyl-2-(1-alkynyl)benzaldimines can be easily prepared by the Sonogashira coupling of a 2-bromoarenecarboxaldehyde and a terminal acetylene in the presence of 2 mol % $PdCl_2(PPh_3)_2$, 1 mol % CuI, and Et_3N at 55 °C,[11] followed by condensation with *tert*-butylamine (Scheme 2). Both steps proceed smoothly in high yields.

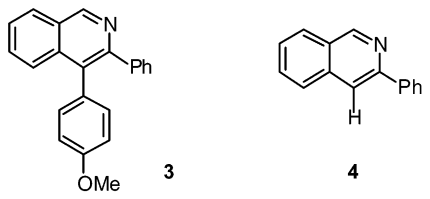
Results and Discussion

Optimization. Our first attempt to explore the reaction of *N-tert*-butyl-2-(phenylethynyl)benzaldimine (**1**) and 5 equiv of 4-iodoanisole under 1 atm of CO employed 5 mol % $Pd(PPh_3)_4$ and 5 equiv of K_2CO_3 in DMF at 100 °C (eq 2), reaction conditions that were used in our earlier



(2)

Pd-catalyzed synthesis of 3,4-disubstituted isoquinolines.[7c] The desired ketone product **2** was formed in only a 40% isolated yield. Two other isoquinoline products, **3** and **4**, were also isolated in 14% and 11% yields, respectively (Table 1, entry 1). 4-(4-Methoxybenzoyl)-3-phenyliso-



quinoline (**3**) is formed without incorporation of CO by a process reported previously by us.[7c] The formation of 3-phenylisoquinoline (**4**) is assumed to proceed by a thermal or Pd(II)-catalyzed cyclization of the 2-(1-alkynyl)-benzaldimines **1**.[6] Decreasing the amount of the aryl iodide from 5 to 3 equiv and thus increasing the ratio of CO to aryl iodide in the reaction did not improve the yield (entry 2). The use of KOAc failed to afford any of the desired ketone product (entry 3) presumably as a result of acetate attack on the acylpalladium intermediate (see the later mechanistic discussion).

TABLE 1. Optimization of the Pd-Catalyzed Cross-Coupling of *N-tert*-Butyl-2-(phenylethynyl)benzaldimine (1) and 4-Iodoanisole (eq 2)[a]

	base (equiv)	temp (°C)	time (h)	**2** (%)	**3** (%)	**4** (%)
1	K_2CO_3 (5)	100	20	40	14	11
2[b]	K_2CO_3 (5)	100	7	36	13	14
3[c]	KOAc (5)	100	11	0	0	5
4	Et_3N (5)	100	10	73	0	7
5	$(n\text{-}Bu)_3N$ (5)	100	12	74	0	5
6	$(i\text{-}Pr)_2NEt$ (5)	100	9	64	0	11
7	pyridine (5)	100	48	45	0	12
8	*N,N*-dimethylaniline (5)	100	48	52	0	27
9	$(n\text{-}Bu)_3N$ (1.5)	100	8	56	0	4
10	$(n\text{-}Bu)_3N$ (5)	80	40	74	0	3
11	$(n\text{-}Bu)_3N$ (5)	120	12	50	16	23

[a] All of the reactions were run employing **1** (0.0653 g, 0.25 mmol), 4-iodoanisole (0.2925 g, 1.25 mmol), $Pd(PPh_3)_4$ (14.4 mg, 0.0125 mmol), and the base (1.25 mmol) in the presence of 1 atm of CO in 5 mL of DMF. [b] Three equivalents of 4-iodoanisole was employed. [c] A 65% yield of 2-(phenylethynyl)benzaldehyde was also obtained.

Vastly improved yields were obtained by substitution of the inorganic base K_2CO_3 by the organic amine bases Et_3N and $(n\text{-}Bu)_3N$. Both of these bases led to cleaner reactions, affording the desired product **2** in greater than 70% yields with none of the side product **3** and very little of the side product **4** (entries 4 and 5). Lower yields were observed by using a more hindered amine, *N,N*-diisopropylethylamine, or the less basic organic amines pyridine and *N,N*-dimethylaniline (entries 6−8). Between Et_3N and $(n\text{-}Bu)_3N$, the two best amines for this reaction, we chose $(n\text{-}Bu)_3N$ over Et_3N because $(n\text{-}Bu)_3N$ has a higher boiling point than Et_3N and is less easily lost during the reaction at 100 °C.

The optimal amount of the organic amine base has been studied. While 5 equiv of $(n\text{-}Bu)_3N$ was initially employed, mechanistically only 1 equiv of the base is required. We therefore examined the reaction using less base. However, a significantly lower yield of **2** was observed when only 1.5 equiv of $(n\text{-}Bu)_3N$ was employed (entry 9).

The temperature of the reaction has also been investigated. At 80 °C, the reaction takes a longer time, 40 h, to complete, but the results are comparable to those obtained at 100 °C (compare entries 10 and 5). At the higher temperature of 120 °C, the reaction displays poorer selectivity between the three cyclization products **2**, **3**, and **4** (entry 11).

(7) For the annulation of internal alkynes by 2-iodobenzaldimines, see: (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. For the cyclization of alkynyl imines by carbopalladation, see: (c) Dai, G.; Larock, R. C. *Org. Lett.* **2001**, *3*, 4035. (d) Dai, G.; Larock, R. C. *Org. Lett.* **2002**, *4*, 193. For the electrophile-promoted cyclization of alkynyl imines, see: (e) Huang, Q.; Larock, R. C. *Org. Lett.* **2001**, *3*, 2973. (f) Huang, Q.; Hunter, J. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 3437.

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By optimization, the combination of *N*-*tert*-butyl-2-(phenylethynyl)benzaldimine (**1**, 0.25 mmol), 5 equiv of 4-iodoanisole, 5 mol % of $Pd(PPh_3)_4$, and 5 equiv of tri-*n*-butylamine in 5 mL of DMF at 100 °C under 1 atm of CO gave the best results. This procedure provided the three isoquinolines **2**, **3**, and **4** in 74%, 0%, and 5% yields, respectively (Table 1, entry 5).

Carbonylative Cross-Coupling of *N*-*tert*-Butyl-2-(1-alkynyl)benzaldimines with Aryl Halides. We next investigated the reaction scope by employing different aryl halides under the optimal reaction conditions reported above. Aryl iodides with a methoxy group in the *para*, *meta*, and *ortho* positions afforded the corresponding ketone products **2**, **5** and **6** in 74%, 76%, and 50% yields, respectively (Table 2, entries 1−3). Steric hindrance due to an *ortho* substituent thus appears to lower the yield significantly. Employing 4-bromoanisole generated none of the desired ketone product (entry 4). A pattern similar to that of the iodoanisoles has been observed for the isomeric iodotoluenes, although a smaller drop in yield was observed (entries 5−7). Phenyl iodide and 1-iodonaphthalene also afforded good yields (entries 8 and 9), as did two isomeric iodothiophenes (entries 10 and 11). In most of these reactions, only a very small amount of or no 4-aryl 3-substituted isoquinoline was isolated. Thus, these reactions exhibit good reaction selectivities.

The lower yield from 2-iodoanisole versus the *meta* and *para* isomers and the relatively long reaction time show the negative effect of the steric hindrance of the *o*-OMe on the reaction (entry 3). Since 2-iodotoluene gave a higher yield for the reaction (entry 7) than 2-iodoanisole it indicates that besides the steric effect of the *ortho* substituent, the possible chelation of the *ortho* methoxy substituent to the Pd(0) catalyst could also perhaps have a negative influence on the yield.

Because bromides do not react with the imine substrate under the optimal conditions, 4-bromoiodobenzene was employed (entry 12). The bromide product was cleanly produced in a 74% yield.

The reactions of **1** and aryl iodides with electron-withdrawing groups, such as CO_2Et and CF_3 groups in the *meta* or *para* positions, afforded the corresponding 4-aroyl 3-phenylisoquinolines in reasonable yields, although we did generally observe a slight decrease in the yields compared to aryl iodides with no electron-withdrawing groups (entries 13, 15, and 16). Aryl iodides containing a CO_2Me group in the *ortho* position afforded none of the desired ketone product (entry 14).

The reaction of **1** and 4-iodonitrobenzene afforded a low yield of the 4-(4-nitrobenzoyl)-3-phenylisoquinoline (**19**) and a slightly higher yield of the 4-(4-nitrophenyl)-3-phenylisoquinoline (**20**) (entry 17). Because the *p*-nitro group has a strong electron-withdrawing effect and 4-iodonitrobenzene gave the best result of any aryl iodide in the palladium-catalyzed cross-coupling of *N*-*tert*-butyl-2-(phenylethynyl)benzaldimine (**1**) and aryl halides without CO to form 4-(4-nitrophenyl)-3-phenylisoquinoline (**20**),[7c] this result was not unexpected. The low yield of 4-(4-nitrobenzoyl)-3-phenylisoquinoline (**19**) and the poor selectivity between **19** and **20** apparently result from the very similar reactivities of the ArPdI and ArCOPdI intermediates toward the *o*-alkynyl imine, both of which promote cyclization to isoquinolines. In an attempt to improve the selectivity of the reaction and the yield of the desired ketone, we carried out three further experiments in which we increased the CO pressure[12] and decreased the reaction temperature (entries 18−20). We were pleased to observe that these experiments provided higher yields of the desired product **19** and better selectivity between the two 3,4-disubstituted isoquinolines **19** and **20**. Using both a lower temperature and higher CO pressure improved the yield of the ketone product **19** to 66% and afforded an improved ratio of **19**/**20**/**4** (entry 20).

While 3-iodonitrobenzene gave a modest yield of ketone under our usual reaction conditions (entry 21), 2-iodonitrobenzene did not afford any of the desired ketone-containing isoquinoline (entry 22). Contrary to the electron-rich 4-bromoanisole, which failed to produce any of the CO-incorporated product **2**, 4-bromonitrobenzene gave a 28% of the corresponding 4-aroyl isoquinoline **19**, 22% of **20**, and 16% of **4** (entry 23).

The 2-(1-alkynyl)benzaldimines containing a 1-cyclohexenyl (**23**), *n*-butyl (**25**), 3-cyanopropyl (**27**), and MOM (**29**) group as R afforded good yields when allowed to react with ethyl 3-iodobenzoate or phenyl iodide (entries 24−27).

The electron-rich imine substrates **31** and **34** displayed good reactivities toward 4-iodoanisole, 3-iodobenzotrifluoride, and ethyl 3-iodobenzoate, affording high yields of the desired 4-aroyl isoquinolines (entries 28−31). However, the electron-deficient *N*-*tert*-butyl-2-phenylethynyl-3-pyridinecarboxaldimine (**37**) did not react with 4-iodoanisole under our "optimal" conditions to afford the desired ketone (entry 32).

Carbonylative Cross-Coupling of an *N*-*tert*-Butyl-*o*-(1-alkynyl)benzaldimine with Benzoyl Chloride. Acyl halides readily undergo oxidative addition to Pd(0) to form acylpalladium intermediates, RCOPdX, which subsequently undergo a wide range of useful transformations.[12] We have, therefore, studied the utility of benzoyl chloride in our chemistry. Under 1 atm of CO (Table 2, entry 33) and with no CO present (entry 36), neither reaction afforded any 3,4-diphenylisoquinoline (**3**) at all, indicating that the initially formed acylpalladium intermediate PhCOPdX does not undergo decarbonylation to the corresponding arylpalladium species very easily.[13] However, whether there is external CO or not does make a difference in the yields of the product **10** and the reaction rates. The reaction was complete after 48 h under 1 atm of CO and was not complete after the same amount of time without CO. Better results were obtained using 1 atm of CO, in which case a 62% yield of ketone **10** was obtained. With no CO present, only a 42% yield was obtained.

Attempts to react the 2-(1-alkynyl)benzaldimine **1** with diallyl carbonate, 3-bromocyclohexene, benzyl chloride, ethyl *cis*-3-iodoacrylate, 1-iodo-1-decyne, and *p*-tosyl chloride under 1 atm of CO failed to afford any recognizable ketone-containing products (entries 35−40).

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TABLE 2. Synthesis of 3-Substituted 4-Aroylisoquinolines by Pd-Catalyzed Carbonylative Cyclization of *N*-*tert*-Butyl-2-(1-alkynyl)benzaldimines and Aryl Halides (eq 2)[a]

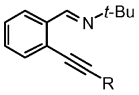
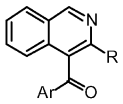
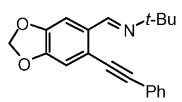
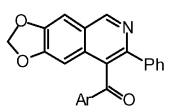
	alkynyl imine 	ArX /ArCOCl	time (h)	isoquinoline ketone 		% isolated yield[b]
1	R = C_6H_5 (**1**)	*p*-$MeOC_6H_4I$	12	Ar = *p*-$MeOC_6H_4$	(**2**)	74 (0, 5)
2	**1**	*m*-$MeOC_6H_4I$	48	Ar = *m*-$MeOC_6H_4$	(**5**)	76 (0, 5)
3	**1**	*o*-$MeOC_6H_4I$	48	Ar = *o*-$MeOC_6H_4$	(**6**)	50 (9, 6)
4	**1**	*p*-$MeOC_6H_4Br$	24	Ar = *p*-$MeOC_6H_4$	(**2**)	0 (0, 20)
5	**1**	*p*-MeC_6H_4I	24	Ar = *p*-MeC_6H_4	(**7**)	77 (9,6)
6	**1**	*m*-MeC_6H_4I	48	Ar = *m*-MeC_6H_4	(**8**)	83 (0,6)
7	**1**	*o*-MeC_6H_4I	72	Ar = *o*-MeC_6H_4	(**9**)	66 (0, 4)
8	**1**	C_6H_5I	24	Ar = C_6H_5	(**10**)	84 (9, 4)
9	**1**	1-iodonaphthalene	48	Ar = 1-naphthyl	(**11**)	73 (0, 0)
10	**1**	2-iodothiophene	24	Ar = 2-thienyl	(**12**)	61 (0, 0)
11	**1**	3-iodothiophene	24	Ar = 3-thienyl	(**13**)	69 (0, 0)
12	**1**	*p*-BrC_6H_4I	24	Ar = *p*-BrC_6H_4	(**14**)	74 (0, 7)
13	**1**	*m*-$EtO_2CC_6H_4I$	48	Ar = *m*-$EtO_2CC_6H_4$	(**15**)	68 (0, 7)
14	**1**	*o*-$MeO_2CC_6H_4I$	24	Ar = *o*-$EtO_2CC_6H_4$	(**16**)	0 (0, 42)
15	**1**	*m*-$F_3CC_6H_4I$	48	Ar = *m*-$F_3CC_6H_4$	(**17**)	63 (5, 5)
16	**1**	*p*-$F_3CC_6H_4I$	24	Ar = *p*-$F_3CC_6H_4$	(**18**)	52 (0, 11)
17	**1**	*p*-$O_2NC_6H_4I$	12	Ar = *p*-$O_2NC_6H_4$	(**19**)	31 (37, 7)
18[c]	**1**	*p*-$O_2NC_6H_4I$	12	Ar = *p*-$O_2NC_6H_4$	(**19**)	56 (11, 4)
19[d]	**1**	*p*-$O_2NC_6H_4I$	48	Ar = *p*-$O_2NC_6H_4$	(**19**)	52 (10, 5)
20[e]	**1**	*p*-$O_2NC_6H_4I$	24	Ar = *p*-$O_2NC_6H_4$	(**19**)	66 (7, 0)
21	**1**	*m*-$O_2NC_6H_4I$	72	Ar = *m*-$O_2NC_6H_4$	(**21**)	40 (13, 10)
22	**1**	*o*-$O_2NC_6H_4I$	24	Ar = *o*-$O_2NC_6H_4$	(**22**)	0 (0, 60)
23	**1**	*p*-$O_2NC_6H_4Br$	24	Ar = *p*-$O_2NC_6H_4$	(**19**)	28 (22, 16)
24	R = 1-cyclohexenyl (**23**)	*m*-$EtO_2CC_6H_4I$	24	Ar = *m*-$EtO_2CC_6H_4$	(**24**)	55 (0, 0)
25	R = *n*-butyl (**25**)	*m*-$EtO_2CC_6H_4I$	24	Ar = *m*-$EtO_2CC_6H_4$	(**26**)	64 (0, 0)
26	R = 3-cyanopropyl (**27**)	C_6H_5I	24	Ar = C_6H_5	(**28**)	62 (0, 0)
27	R = MOM (29) 	C_6H_5I	24	Ar = C_6H_5 	(**30**)	57 (0, 0)

Table 2 (Continued)

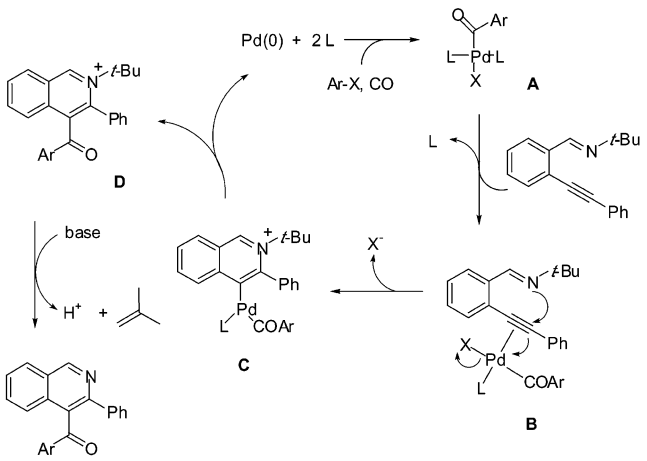
	alkynyl imine	ArX /ArCOCl	time (h)	isoquinoline ketone		% isolated yield[b]
28	(**31**)	*p*-$MeOC_6H_4I$	15	Ar = *p*-$MeOC_6H_4$	(**32**)	75 (0, 0)
29	**31**	*p*-$F_3CC_6H_4I$	24	Ar = *m*-$F_3CC_6H_4$	(**33**)	69 (0, 0)
30	(**34**)	*p*-$MeOC_6H_4I$	24	Ar = *p*-$MeOC_6H_4$	(**35**)	79 (0, 0)
31	**34**	*m*-$EtO_2CC_6H_4I$	48	Ar = *m*-$EtO_2CC_6H_4$	(**36**)	73 (8, 4)
32	(**37**)	*p*-$MeOC_6H_4I$	24	Ar = *p*-$MeOC_6H_4$	(**38**)	0 (0, 0)
33	**1**	PhCOCl	48	Ar = C_6H_5	(**10**)	62 (0, 13)
34[f]	**1**	PhCOCl	48	Ar = C_6H_5	(**10**)	42 (0, 20)
35	**1**	diallyl carbonate	24	R = allyl	(**39**)	0 (0, 50)
36	**1**	3-bromocyclohexene	24	R = 3-cyclohexenyl	(**40**)	0 (0, 52)
37	**1**	benzyl chloride	24	R = benzyl	(**41**)	0 (0, 55)
38	**1**	*cis*-ethyl 3-iodoacrylate	24	R = *cis*-ethyoxycarbonylvinyl	(**42**)	0 (14, 61)
39	**1**	1-iodo-1-decyne	24	R = 1-decynyl	(**43**)	0 (0, 57)
40	**1**	*p*-tosyl chloride	24	R = *p*-tosyl	(**44**)	0 (0, 75)

Mechanism. The mechanism shown in Scheme 3 is proposed for this process. It is similar to mechanisms proposed in previously reported Pd-catalyzed syntheses of furans,[14] benzofurans,[1] and indoles.[5b,c] It consists of the following key steps: (1) oxidative addition of the aryl halide to the Pd(0) catalyst, followed by CO insertion,[15] (2) coordination of the resulting acylpalladium intermediate **A** to the alkyne triple bond to form complex **B**, which activates the triple bond toward nucleophilic attack,[5b,c] (3) intramolecular nucleophilic attack of the nitrogen atom of the imine on the activated carbon−carbon triple bond to afford intermediate **C**,[5b,c,14,16] (4) reductive elimination to form a carbon−carbon bond between the carbonyl group and the isoquinoline ring in **D** and simultaneous regeneration of the Pd(0) catalyst,[5b,c,14,17] and (5) cleavage of the *tert*-butyl group from the nitrogen to release the strain between the *tert*-butyl group and the 3-phenyl group with simultaneous generation of the 3-substituted 4-aroylisoquinoline.[6,7]

Two competing processes are (1) cyclization of the starting material by a thermal or Pd(II)-catalyzed process to afford the 3-monosubstituted product,[6] and (2) cyclization of the imine starting material promoted by an arylpalladium intermediate to afford a 3-substituted 4-arylisoquinoline.[7c]

(14) Arcadi, A.; Cacchi, S.; Larock, R. C.; Marinelli, F. *Tetrahedron Lett.* **1993**, *34*, 2813.
(15) Stille, J. K.; Lau, K. S. Y. *Acc. Chem. Res.* **1977**, *10*, 434.
(16) 4Tsuda, T.; Ohashi, Y.; Nagahama, S.; Sumiya, S.; Saegusa, T. *J. Org. Chem.* **1988**, *53*, 2650.
(17) Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett.* **1965**, 4387.

SCHEME 3



The yields of ketones obtained by this process are less dependent on the nature of the substituents present in the aryl iodide than the yields of 4-arylisoquinolines obtained from arylation of these same alkynyl imines.[7c] This is easily understood when one considers that the key step in the present synthesis apparently involves attack of an electron-deficient acylpalladium species on the carbon−carbon triple bond. The nature of the substituents present in the aroylpalladium intermediate is not going to change their electronics as profoundly as they would the electronics of the corresponding arylpalladium species.

The presence of steric hindrance in the aryl iodide is also less likely to affect the yield in the carbonylative cyclization, because of the presence of the carbonyl group in the aroylpalladium intermediates. However, possible chelation of the *o*-substituent could prevent the reaction from proceeding as desired.

Conclusions

In summary, we have developed an efficient synthetic approach for the carbonylative cyclization of *N*-*tert*-butyl-2-(1-alkynyl)benzaldimines and aryl halides to the corresponding 3-substituted 4-aroylisoquinolines. The reaction utilizes readily available starting materials, employs mild reaction conditions, and tolerates a variety of functional groups. It also works with a wide variety of substituents on the remote end of the alkyne triple bond.

Experimental Section

General Methods. All ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz, respectively. Thin-layer chromatography (TLC) was performed using commercially prepared 60 mesh silica gel plates (Whatman K6F), and visualization was effected with short-wavelength UV light (254 nm) and a basic solution of $KMnO_4$ [3 g of $KMnO_4$ + 20 g of K_2CO_3 + 5 mL of NaOH (5%) + 300 mL of H_2O].

Reagents. The starting material **1** for the cyclization was prepared according to the previous literature.[7c,e] The preparation and characterization of the other 2-(1-alkynyl)benzaldimines are included in Supporting Information.

General Procedure for the Synthesis of 3-Substituted 4-Aroylisoquinolines. DMF (5 mL), $Pd(PPh_3)_4$ (14.4 mg, 0.0125 mmol), tri-*n*-butylamine (0.2317 g, 1.25 mmol), the *N*-*tert*-butyl-2-(1-alkynyl)benzaldimine (0.25 mmol), and the aryl halide (1.25 mmol) were stirred at room temperature for 5 min. The mixture was flushed with CO and fitted with a CO-filled balloon (caution!). The reaction mixture was heated to 100 °C with vigorous stirring for the specified time, then cooled to room temperature, diluted with diethyl ether (25 mL), and washed with brine (20 mL). The aqueous layer was reextracted with diethyl ether (15 mL). The organic layers were combined, dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on a silica gel column.

4-(4-Methylbenzoyl)-3-phenylisoquinoline (7). The reaction mixture was chromatographed using 4:1 hexanes/EtOAc to yield a yellow solid: mp 120−121 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3H), 7.07 (d, J = 8.0 Hz, 2H), 7.21−7.29 (m, 3H), 7.58 (d, J = 8.0 Hz, 2H), 7.63−7.68 (m, 4H), 7.72, (d, J = 7.2 Hz, 1H), 8.07−8.09 (m, 1H), 9.45 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.86, 124.76, 127.09, 127.72, 128.09, 128.43, 128.55, 129.08, 129.45, 129.67, 129.92, 131.57, 134.33, 135.17, 139.82, 144.87, 149.82, 153.43, 197.76; IR ($CHCl_3$) 3018, 1658 cm^{-1}; HRMS 323.1315 (calcd for $C_{23}H_{17}NO$ 323.1310).

The product characterization data for all other isoquinolines prepared appears in Supporting Information.

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Supporting Information Available: Product characterization data for the isoquinoline products and ^{1}H and ^{13}C NMR spectra for all new compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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