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Synthesis of 3,4-Disubstituted Isoquinolines via Palladium-Catalyzed Cross-Coupling of 2-(1-Alkynyl)benzaldimines and Organic Halides

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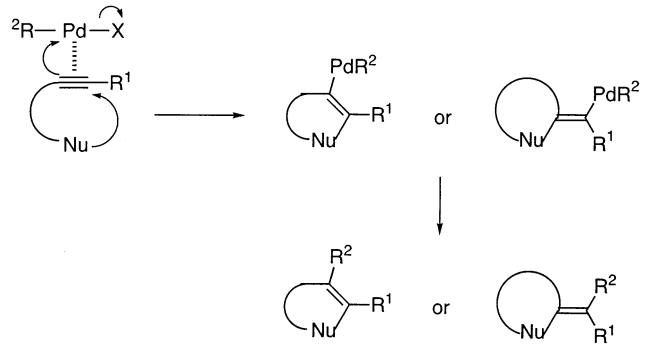
The palladium-catalyzed cross-coupling of readily available *N*-*tert*-butyl-2-(1-alkynyl)benzaldimines and aryl, allylic, benzylic, alkynyl halides, as well as a vinylic halide, provides a valuable new route to 3,4-disubstituted isoquinolines with aryl, allylic, benzylic, 1-alkynyl, and vinylic substituents, respectively, in the 4-position. The reaction appears to require an aryl group on the end of the acetylene furthest from the imine functionality. The reaction conditions have been optimized, and reasonably good yields have been obtained.

Introduction

The cyclization of alkynes containing proximate nucleophilic centers promoted by organopalladium complexes is currently of great interest and developing into a most effective strategy for heterocyclic ring construction.[1] This chemistry provides a straightforward approach to the synthesis of functionalized carbo- and heterocycles through the regio- and stereoselective addition of a nucleophile and an unsaturated carbon unit across the carbon−carbon triple bond (Scheme 1). Successful examples of this process have been reported for the synthesis of 2,3-disubstituted indoles,[2] 2,3-disubstituted benzofurans,[3] and other cyclic compounds.[4] However, no one has thus far employed this chemistry to synthesize isoquinolines.

SCHEME 1



The isoquinoline ring system is present in many natural alkaloids,[5] encouraging the development of a variety of classical approaches for isoquinoline synthesis, including the Bischler−Napieralski, Pictet−Spengler, and Pomeranz−Fritsch reactions.[6] However, these meth-

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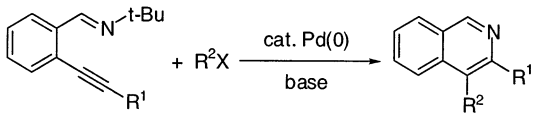
ods employ either strong acidic conditions for the ring closure (Bischler−Napieralski and Pomeranz−Fritsch) or tedious preparation of appropriately substituted phenethylamines as starting materials (Pictet−Spengler).

Palladium-catalyzed methodology has been employed more and more for the synthesis of substituted isoquinolines in recent years. For instance, Pfeffer and co-workers reported the formation of a disubstituted isoquinoline derivative from a cyclopalladated *N*,*N*-dimethylbenzylamine complex.[7] Heck and co-workers observed the formation of 3,4-diphenylisoquinoline in a 22% yield from the reaction of cyclopalladated *N*-*tert*-butylbenzaldimine tetrafluoroborate with diphenylacetylene.[8] Widdowson has also reported an isoquinoline synthesis based on cyclopalladated *N*-*tert*-butylarylaldimines.[9] These approaches to isoquinolines, however, suffer the major disadvantage that they are stoichiometric with respect to palladium, and a final pyrolysis step greatly limits the synthetic utility. In our own laboratories, we have developed the copper-catalyzed cyclization of 2-(1-alkynyl)arylaldimines to 3-substituted isoquinolines,[10] the palladium-catalyzed iminoannulation of internal alkynes,[11] and the electrophile-promoted cyclization of 2-(1-alkynyl)-arylaldimines[12] as simple approaches to 3,4-disubstituted isoquinolines, which proceed in excellent yields. Despite the broad applicability of these processes, there are still many 3,4-disubstituted isoquinolines that cannot be prepared by these approaches.

Therefore, we have examined the possibility of preparing 3,4-disubstituted isoquinolines by a more general process involving the palladium-catalyzed cross-coupling of *N*-*tert*-butyl-2-(1-alkynyl)benzaldimines and organic halides (eq 1). Hopefully, this approach might avoid the problem of regioselectivity that exists in the synthesis of isoquinolines by the iminoannulation of internal alkynes[11] and may offer a new way to construct the isoquinoline ring. We previously communicated this methodology for the synthesis of 3,4-disubstituted isoquinolines[13] and now report more recent developments.



(1)

Results and Discussion

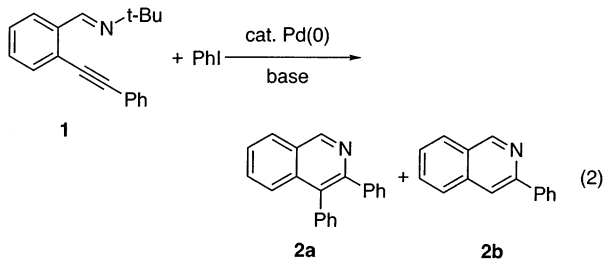
Starting Materials. The preparation of the starting materials for this chemistry is quite simple and straightforward. The appropriate imines are readily available in two steps from 2-bromoarenecarboxaldehydes and terminal alkynes. The first step is the Sonogashira coupling[14] of the aryl halide and a terminal alkyne catalyzed by 2 mol % $PdCl_2(PPh_3)_2$ and 1 mol % CuI in Et_3N at 55 °C. This step generally gives yields of the coupled product above 90%. The second step of the sequence involves reaction of the 2-(1-alkynyl)arenecarboxaldehyde and excess *tert*-butylamine at room temperature and proceeds in almost quantitative yields.

TABLE 1. Optimization of the Reaction of *N*-*tert*-Butyl-2-(phenylethynyl)-benzaldimine (1) and PhI (eq 2)[a]

entry	Pd catalyst	PhI (equiv)	base (equiv)	temp (°C)	time (h)[b]	% yield[c] **2a**:**2b**
1	$Pd(dba)_2$/2 PPh_3	3	Na_2CO_3 (3)	80	9	26:21
2	$Pd(dba)_2$/2 PPh_3	5	Na_2CO_3 (3)	80	9	20:23
3	$Pd(dba)_2$/2 PPh_3	3	Na_2CO_3 (3)	100	9	49:25
4	$Pd(dba)_2$/2 PPh_3	5	Na_2CO_3 (3)	100	9	61:10
5	$Pd(dba)_2$/2 PPh_3	5	Na_2CO_3 (3)	120	9	62:9
6	$Pd(PPh_3)_4$	5	KOAc (5)	50	10	36:<2
7	$Pd(PPh_3)_4$	5	KOAc (5)	75	10	27:5
8	$Pd(PPh_3)_4$	5	KOAc (5)	100	10	29:49
9	$Pd(PPh_3)_4$	5	K_2CO_3 (5)	50	12	17:0
10	$Pd(PPh_3)_4$	5	K_2CO_3 (5)	100	12	49:<2
11	$Pd(PPh_3)_4$	5	Na_2CO_3 (5)	100	12	48:<2
12	$Pd(PPh_3)_4$	5	Cs_2CO_3 (5)	100	24	22:0
13	$Pd(PPh_3)_4$	5	Li_2CO_3 (5)	100	24	28:36
14[d]	$Pd(PPh_3)_4$	5	K_2CO_3 (5)	100	24	36:12
15[e]	$Pd(PPh_3)_4$	5	K_2CO_3 (5)	100	24	24:45

[a] All reactions were carried out in 5 mL of DMF as the solvent, using 0.25 mmol of imine **1** and 5 mol % palladium catalyst unless otherwise specified. [b] In all cases, monitoring by TLC showed that the reaction had reached completion in less time than the time specified. [c] Yields are given for isolated products and refer to single runs. [d] Reaction was run in 5 mL of CH_3CN. [e] Reaction was run in 5 mL of DMSO.

Optimization. Our first attempt to explore the reaction of *N*-*tert*-butyl-2-(phenylethynyl)benzaldimine (**1**) and 3 equiv of phenyl iodide employed 5 mol % $Pd(dba)_2$, 10 mol % PPh_3, and 3 equiv of Na_2CO_3 in 5 mL of DMF at 100 °C (eq 2). Although the desired product 3,4-diphenylisoquinoline (**2a**) was formed, the generation of another product, 3-phenylisoquinoline (**2b**), was also observed. The 3-phenylisoquinoline (**2b**) is believed to be formed by either the thermal or Pd(II)-catalyzed cyclization of imine **1**.[10]



(2)

We have thus attempted to optimize the formation of the disubstituted isoquinoline **2a** (Table 1). Using $Pd(dba)_2$ as the catalyst plus 2 equiv of Ph_3P per palladium as the ligand and raising the temperature from 80 to 100 °C significantly increased the yields of 3,4-diphenylisoquinoline (**2a**) and the selectivity for **2a** over **2b** (Table 1, entries 1−4). Further raising the temperature from 100 to 120 °C did not help much (entry 5). Increasing the amount of the PhI from 3 to 5 equiv favored formation

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of the desired product **2a** at 100 °C (compare entries 3 and 4). The best result obtained was a 61% yield of **2a** and 10% yield of **2b** acquired using 5 equiv of PhI, 5 mol % $Pd(dba)_2$, 10 mol % PPh_3, and 3 equiv of Na_2CO_3 in 5 mL of DMF at 100 °C (entry 4).

The replacement of $Pd(dba)_2$ plus Ph_3P by $Pd(PPh_3)_4$ and 3 equiv of Na_2CO_3 by 5 equiv of KOAc at 50 °C (entry 6) reduced the amount of side product **2b** to only a trace, but the yield of **2a** was not sufficiently high to be synthetically useful. Increasing the temperature from 50 to 75 to 100 °C only reduced the selectivity between **2a** and **2b** and did not significantly improve the yield of **2a** (entries 6−8). Side product isoquinoline **2b** was not observed using K_2CO_3 as the base at 50 °C (entry 9), and a higher yield of **2a** and relatively low yield of **2b** were obtained when the temperature was further raised to 100 °C (entry 10). Using lithium, sodium, and cesium carbonate as bases failed to improve the yield of **2a** (entries 11−13). Changing the solvent from DMF to acetonitrile or DMSO did not enhance the yield of **2a** or the selectivity between the two isoquinoline products (entries 14 and 15).

The procedure summarized in Table 1, entry 10, is thought to give the best result because of the distribution of the two products and the ease with which one can isolate pure product, although the yield of the desired product **2a** suffers compared to the results described in Table 1, entry 4.

Cross-Coupling of *N*-*tert*-Butyl-2-(1-alkynyl)arylaldimines with Aryl Halides and Triflates. When the optimized reaction conditions reported above in entry 10 were applied to the reaction of *N*-*tert*-butyl-2-(phenylethynyl)benzaldimine (**1**) and phenyl triflate, which is assumed to form the corresponding PhPdOTf intermediate, no desired product, 3,4-diphenylisoquinoline (**2a**), was observed even after 48 h. A 40% yield of monosubstituted isoquinoline **2b** was obtained as the only product.

Under the optimized reaction conditions above, the reactions of imine **1** with a variety of aryl iodides afforded reasonable yields of the corresponding 3,4-disubstituted isoquinolines (eq 1; Table 2, entries 1−14). Aryl halides bearing an electron-withdrawing group in the *para* or *meta* positions usually lead to good to high yields of the 3,4-disubstituted isoquinoline products and low yields of side product 3-phenylisoquinoline (**2b**) (entries 2, 4, 6, 7, and 9−11). Aryl iodides with an *ortho* electron-withdrawing group, such as ethyl 2-iodobenzoate and 2-iodonitrobenzene, do not react well with imine **1** (entries 5 and 8). These two reactions afforded only the monosubstituted isoquinoline **2b**. This is apparently the result of a steric problem with the ArPdX intermediate, since electron-withdrawing groups elsewhere in the aryl halides generally give good results. Reactions with aryl halides containing electron-donating groups, like *o*- and *p*-iodotoluene and 4-iodoanisole, only afford low yields of the corresponding 3,4-disubstituted products and poor ratios of di- to monosubstituted isoquinoline products (entries 12−14). The best yield obtained with imine **1** was 75%, which was afforded by 4-iodonitrobenzene (entry 2). The corresponding aryl bromide 4-bromonitrobenzene affords 3,4-disubstituted isoquinoline product **3** in a 48% yield (entry 3). The relatively low yield indicates that the lower reactivity of an aryl bromide toward formation of the organopalladium ArPdX intermediate does affect the outcome of the reaction.

A variety of imines have also been tested using 4-iodonitrobenzene. According to the results in Table 2, the R^1 group of the imine (eq 1) also plays an important role in the reaction. When R^1 is an aryl group, the reactions work well with electron-deficient aryl halides. However, when R^1 is an alkyl or vinylic group, the yields drop significantly (entries 15−17), even when using 4-iodonitrobenzene. It is important to note, however, that the monosubsituted isoquinolines are not observed in these reactions.

In addition to the strong dependence of the reaction on the aryl halides employed, the electronic nature of the substituents attached to the aromatic rings of the imine significantly affects the outcome of the reactions with aryl halides. The electron-rich imine *N*-*tert*-butyl-2-[(4-methoxyphenyl)ethynyl]benzaldimine (**20**) affords slightly higher yields of 3,4-disubstituted isoquinoline products than imine **1** when allowed to react with 4-iodonitrobenzene and 4-iodoanisole (entries 18 and 19). However, placing a methylenedioxy moiety on the imine-bearing aryl ring (**23**) leads to a somewhat lower yield (entry 20). Using an electron-deficient pyridine-containing imine **25** and 4-iodonitrobenzene leads to the 3,4-disubstituted product **26** in only a 23% yield, and the 3-monosubstituted product was isolated in an 11% yield (entry 21).

Cross-Coupling of *N*-*tert*-Butyl-2-(1-alkynyl)arylaldimines with Allylic Halides and Esters. Allylpalladium complexes have been used to promote the cyclization of alkynes containing proximate nucleophiles (N and O) to afford 3-allylic indoles,[2c,g,h] 3-allylic benzo[*b*]furans,[3a,b] and 3-allylic furans.[4a,b] We here report that π-allylpalladium complexes can be successfully employed in the synthesis of 4-allylic 3-substituted isoquinolines.

First, we have investigated the reaction of our model imine **1** with allyl bromide under our optimized cross-coupling conditions. We were pleased to observe a 65% yield of the 4-allyl-3-phenylisoquinoline (**27**) and none of 3-phenylisoquinoline (**2b**) (entry 22). This reaction took 18 h to complete, showing the lower reactivity of the allylpalladium complex compared to the arylpalladium complex. When allyl chloride was used in the reaction (entry 23), it afforded a slightly higher yield, 69%, of product **27** and no side product **2b** at all. Although allylic bromides usually possess higher reactivities than allylic chlorides in π-allylpalladium chemistry, the stability of the halides must be taken into account in this case where there are 5 equiv of K_2CO_3 present in the reaction mixture.

We were also interested in investigating diallyl carbonate in this reaction (entry 24). In this case, only 2.5 equiv of K_2CO_3 was employed, because 1 equiv of base is formed when both allyl groups are released from each equivalent of carbonate. This reaction proceeded well and afforded a 68% yield of **27** after 18 h.

Then we turned to allyl acetate, another important source of π-allylpalladium intermediates. After 120 h, only 28% of the desired product **27** and 13% of side product **2b** were isolated, and 17% of starting material **1** was recovered (entry 25). Considering the fact that allyl acetate might not be very stable with so much base present in the reaction, we carried out another reaction in which only a stoichiometric amount of K_2CO_3 was

TABLE 2. Synthesis of 3,4-Disubstituted Isoquinolines by Pd-Catalyzed Cross-Coupling of *N*-*tert*-Butyl-2-(1-alkynyl)benzaldimines and Organic Halides (eq 1)[a]

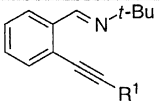
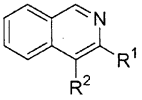
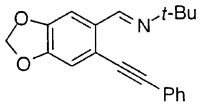
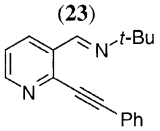
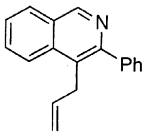
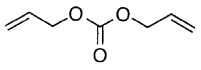
	alkynyl imine	R^2X	time (h)	isoquinoline		yield (%)[b]
						
1	$R^1 = C_6H_5$ (**1**)	C_6H_5I	12	$R^2 = C_6H_5$	(**2a**)	49 (<2)
2	**1**	*p*-$O_2NC_6H_4I$	12	R^2 = *p*-$O_2NC_6H_4$	(**3**)	75 (0)
3	**1**	*p*-$O_2NC_6H_4Br$	24		**3**	48 (0)
4	**1**	*m*-$O_2NC_6H_4I$	8	R^2 = *m*-$O_2NC_6H_4$	(**4**)	49 (0)
5	**1**	*o*-$O_2NC_6H_4I$	48	R^2 = *o*-$O_2NC_6H_4$	(**5**)	0 (42)
6	**1**	*p*-$EtO_2CC_6H_4I$	7	R^2 = *p*-$EtO_2CC_6H_4$	(**6**)	67 (<2)
7	**1**	*m*-$EtO_2CC_6H_4I$	11	R^2 = *m*-$EtO_2CC_6H_4$	(**7**)	55 (<2)
8	**1**	*o*-$EtO_2CC_6H_4I$	11	R^2 = *o*-$EtO_2CC_6H_4$	(**8**)	0 (48)
9	**1**	*p*-$F_3CC_6H_4I$	8	R^2 = *p*-$F_3CC_6H_4$	(**9**)	65 (0)
10	**1**	*m*-$F_3CC_6H_4I$	10	R^2 = *m*-$F_3CC_6H_4$	(**10**)	51 (<2)
11	**1**	3-iodopyridine	12	R^2 = 3-pyridyl	(**11**)	48 (0)
12	**1**	*p*-$H_3CC_6H_4I$	10	R^2 = *p*-$CH_3C_6H_4$	(**12**)	48 (1)
13	**1**	*o*-$H_3CC_6H_4I$	24	R^2 = *o*-$CH_3C_6H_4$	(**13**)	29 (16)
14	**1**	*p*-$H_3COC_6H_4I$	24	R^2 = *p*-$CH_3OC_6H_4$	(**14**)	13 (14)
15	R^1 = *n*-Bu (**15**)	*p*-$O_2NC_6H_4I$	6	R^2 = *p*-$O_2NC_6H_4$	(**16**)	35 (0)
16	R^1 = 1-cyclohexenyl (**17**)	*p*-$O_2NC_6H_4I$	12	R^2 = *p*-$O_2NC_6H_4$	(**18**)	60 (0)
17	**17**	*p*-$EtO_2CC_6H_4I$	12	R^2 = *p*-$EtO_2CC_6H_4$	(**19**)	61 (0)
18	R^1 = *p*-$MeOC_6H_4$ (**20**)	*p*-$O_2NC_6H_4I$	10	R^2 = *p*-$O_2NC_6H_4$	(**21**)	80 (0)
19	**20**	*p*-$CH_3OC_6H_4I$	48	R^2 = *p*-$CH_3OC_6H_4$	(**22**)	30 (19)
20	 (**23**)	*p*-$O_2NC_6H_4I$	10	R^2 = *p*-$O_2NC_6H_4$	(**24**)	59 (0)
21	 (**25**)	*p*-$O_2NC_6H_4I$	10	R^2 = *p*-$O_2NC_6H_4$	(**26**)	23 (11)
22	$R^1 = C_6H_5$ (**1**)		18		(**27**)	65 (0)
23	**1**		18		**27**	69 (0)
24	**1**		19		**27**	68 (0)[c]

Table 2 (Continued)

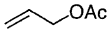
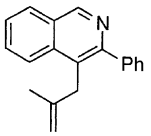
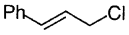
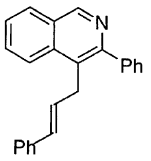
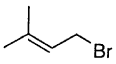
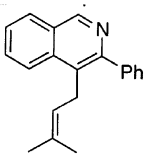
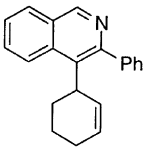
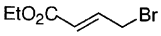
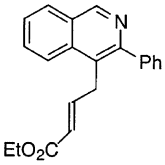
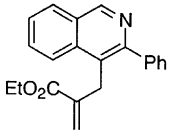
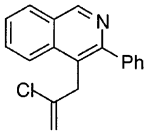
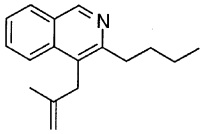
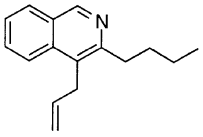
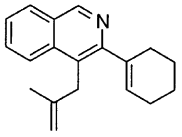
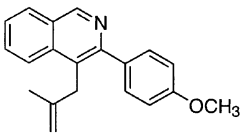
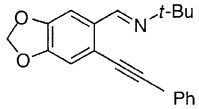
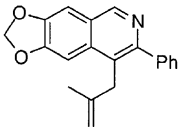
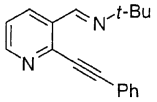
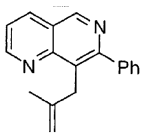
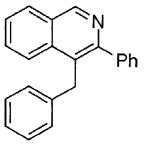
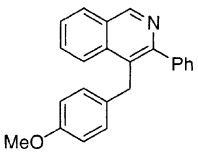
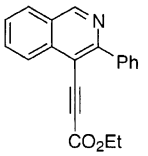
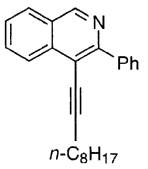
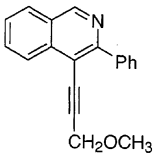
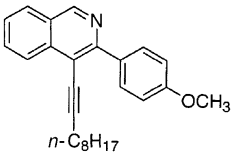
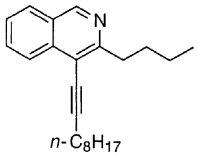
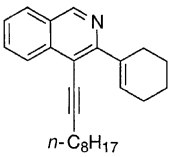
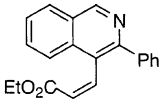
	alkynyl imine	R^2X	time (h)	isoquinoline		yield (%)[b]
25	**1**		120		**27**	28 (13)
26	**1**		24		(**28**)	71 (0)
27	**1**		20		(**29**)	48 (1)
28	**1**		42		(**30**)	0 (49)
29	**1**		72		(**31**)	0
30	**1**		24		(**32**)	0 (51)
31	**1**		48		(**33**)	59 (18)
32	**1**		21		(**34**)	0 (39)
33	R^1 = *n*-Bu (**15**)		48		(**35**)	62 (0)
34	**15**		48		(**36**)	55 (0)
35	R^1 = 1-cyclohexenyl (**17**)		48		(**37**)	30 (<3)
36	R^1 = *p*-$MeOC_6H_4$ (**20**)		24		(**38**)	88 (0)

Table 2 (Continued)

	alkynyl imine	R^2X	time (h)	isoquinoline		yield (%)[b]
37	 (**23**)		72		(**39**)	59 (0)
38	 (**25**)		24		(**40**)	42 (0)
39	**1**	$PhCH_2Cl$	24		(**41**)	45 (0)
40	**1**	p-$CH_3OC_6H_4CH_2Cl$	24		(**42**)	52 (0)
41	$R^1 = C_6H_5$ (**1**)	$EtO_2C{\equiv}I$	4		(**43**)	38 (0)[d]
42	**1**	n-$C_8H_{17}{\equiv}I$	6		(**44**)	56 (0)
43	**1**	$CH_3OCH_2{\equiv}I$	10		(**45**)	53 (0)
44	$R^1 = p$-$MeOC_6H_4$ (**20**)	n-$C_8H_{17}{\equiv}I$	11		(**46**)	56 (0)
45	$R^1 = n$-Bu (**15**)	n-$C_8H_{17}{\equiv}I$	10		(**47**)	0 (<2)
46	R^1 = 1-cyclohexenyl (**17**)	n-$C_8H_{17}{\equiv}I$	10		(**48**)	0 (0)
47	**1**	EtO_2C-CH=CH-I	24		(**49**)	55 (0)

[a] Reaction conditions are specified in the text. [b] Yields are given for isolated products and refer to single runs. Numbers in parentheses are the yields of the corresponding 3-substituted isoquinolines. [c] Only 2.5 equiv of K_2CO_3 was used as the base. [d] 4-Iodo-3-phenylisoquinoline was isolated in an 8% yield.

employed. This reaction took 30 h to reach completion and gave only a 13% yield of **27** and 34% of side product **2b**. On the basis of this observation, the extra base is considered to play an important role in improving the selectivity between the two competing processes.

The reactions of imine **1** with methallyl chloride and cinnamyl chloride both proceeded smoothly to generate the corresponding 4-allylic-3-phenylisoquinolines **28** and **29** in good yields and side product **2b** in only 0−1% yields (entries 26 and 27). Thus, the reactions of allylic chlorides exhibit excellent product selectivity. However, with 3,3-dimethylallyl bromide and 3-bromocyclohexene, two other allylic halides with hydrogens next to the π-allylic moiety, the reactions of imine **1** afforded none of the desired products **30** and **31** and produced only 3-phenylisoquinoline (**2b**) in the former case (entries 28 and 29).

The reactions of imine **1** and two electron-deficient allylic bromides displayed completely different reactivities. Ethyl 4-bromo-2-butenoate did not produce any of the desired product **32**, but instead a significant amount of cyclization product **2b** was generated (entry 30). Ethyl 2-(bromomethyl)propenoate, however, did afford the desired product **33** in a 59% yield, and **2b** was produced in only an 18% yield (entry 31). The reaction between imine **1** and 2,3-dichloropropene did not generate any of the expected 4-allylic-3-phenylisoquinoine (**34**) for reasons that are not obvious (entry 32).

Unlike the reactions of imines with aryl halides, the reactions of imine **15** with R^1 = *n*-butyl provided good yields when methallyl chloride and allyl chloride were employed (entries 33 and 34). However, the reaction of imine **17** with R^1 = 1-cyclohexenyl afforded only a 30% yield of the desired product after 48 h (entry 35).

Since the highest yield from allylic halides was obtained in the reaction of imine **1** with methallyl chloride, other imines were all examined with this allylic chloride. The influence of electronic factors present in the imines on the reactions is obvious. Generally, electron-rich imine substrates **20** and **23** result in better yields than their electron-deficient pyridine counterpart **25** (entries 36−38). The problem here might also be that the pyridine moiety in imine **25** could also be reacting directly with the allylic chloride (entry 38).

Besides the allylic halides and esters, benzyl chloride and 4-methoxybenzyl chloride have also been successfully employed in the isoquinoline cyclization and afford reasonably good yields of the corresponding cross-coupling products **41** and **42**, respectively (entries 39 and 40). However, the reaction with 4-nitrobenzyl chloride failed.

Cross-Coupling of *N*-*tert*-Butyl-2-(1-alkynyl)arylaldimines with Alkynyl Halides. Inspired by the success of the reactions of imines with electron-poor aryl halides, we examined the cross-coupling of ethyl 3-iodopropiolate. This alkynyl halide gave a 38% yield of the desired product **43** after only 4 h (entry 41). Although we did not observe 3-phenylisoquinoline (**2b**) as a side product this time, we isolated another side product, 4-iodo-3-phenylisoquinoline (**2c**), in an 8% yield. At the same time, a significant amount of I_2 appeared to be generated during the reaction.[15] The decomposition of ethyl 3-iodopropiolate to I_2 could account for the formation of the side product **2c**[12] and the low yield of the 4-(1-alkynyl) 3-substituted isoquinoline **43**.

Encouraged by this preliminary result, we next examined the reactions of two different alkynyl iodides that do not possess any electron-withdrawing groups. Both of them produced the desired products in yields of 53 and 56% (entries 42 and 43).

Different imine substrates have been investigated in the reactions with 1-iodo-1-decyne. While the electron-donating group in imine substrate **20** did not affect the yield of product **46** (entry 44), the presence of the R^2 groups *n*-butyl in **15** and 1-cyclohexenyl in **17** both had a very strong negative influence on the outcome. No 3,4-disubstituted isoquinoline products were observed in these latter two reactions (entries 45 and 46). The possible 3-monosubstituted isoquinoline side products were not observed either.

Cross-Coupling of *N*-*tert*-Butyl-2-(1-alkynyl)arylaldimines with Vinylic Halides. Several vinylic halides have been utilized in this chemistry. Only ethyl *cis*-3-iodoacrylate produced the expected 4-vinylic-substituted isoquinoline in a good yield (entry 47). Ethyl *trans*-3-iodoacrylate, *cis*-β-iodostyrene, (iodomethylene)cyclohexane, 3-iodo-2-cyclohexen-1-one, and 2-iodo-2-cyclohexen-1-one all failed to generate the expected isoquinolines.

Mechanism. The present synthesis of 3,4-disubstituted isoquinolines is believed to proceed as outlined in Scheme 2, which is similar to previously reported Pd-catalyzed syntheses of benzofurans,[1h,13a,b] indoles,[3c] and other heterocyclic compounds.[4i,j] The process consists of the following key steps: (1) oxidative addition of the organic halide to the Pd(0) catalyst,[17] (2) coordination of the resulting palladium intermediate **A** to the triple bond of the imine forming complex **B**, which activates the triple bond toward nucleophilic attack,[1h] (3) intramolecular nucleophilic attack of the nitrogen atom of the imine on the activated carbon−carbon triple bond to afford intermediate **C**,[1h] (4) reductive elimination to form the carbon−carbon bond between R^2 and the carbon of the isoquinoline ring with simultaneous regeneration of the Pd(0) catalytic species,[18] and (5) cleavage of the *tert*-butyl group from the N atom to generate the 3,4-disubstituted isoquinoline and also release the strain between the *tert*-butyl group and the group R^1.[10−13]

If the 2-(1-alkynyl)benzaldimine does not coordinate well to the palladium(II) intermediate **A**, cyclization by either thermal or Pd(II) catalysis to the monosubstituted isoquinoline can occur. This latter chemistry can also be accomplished by employing a catalytic amount of CuI.[10] Therefore, the selectivity between the mono- and disubstituted isoquinolines is determined by whether the triple bond of the 2-alkynyl imine coordinates the $R^2Pd^{II}X$ intermediate **A**.

In the reactions of imines and aryl halides R^2X, we observed a significant effect of the electronic nature of the substituents present in R^2X on the yields of 3,4-disubstituted isoquinolines and the ratios of the di- and monosubstituted isoquinolines. The strong dependence

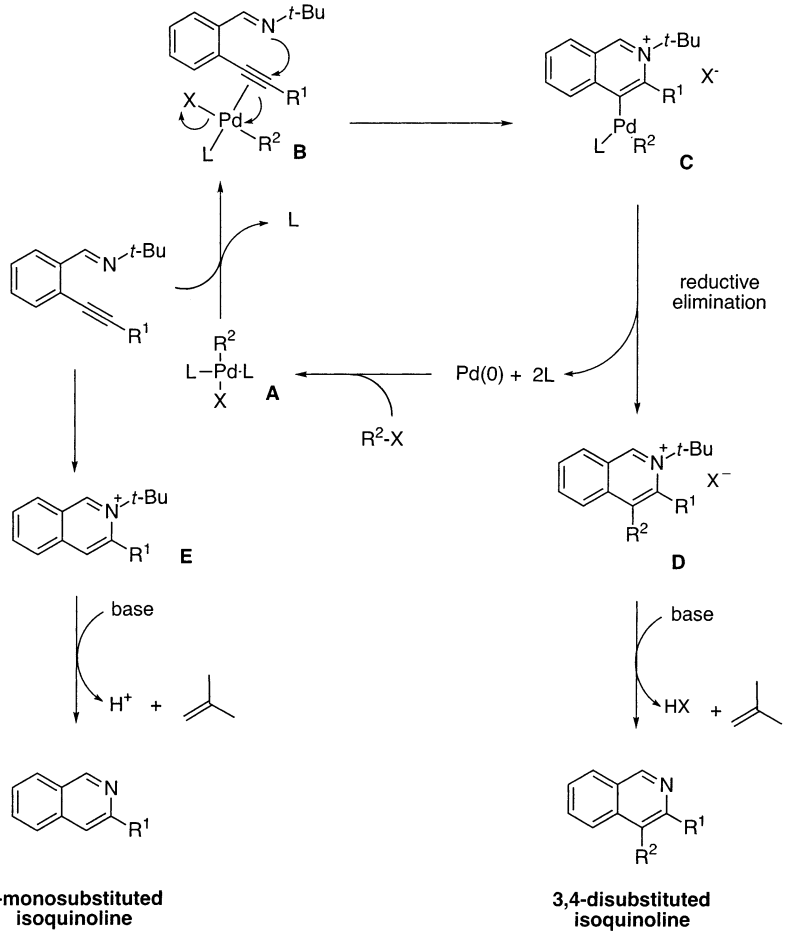
(15) During the workup procedure described in the Experimental Section, the reaction mixture in diethyl ether solution could be decolored by the addition of $Na_2S_2O_3$.

(16) Wu, G.; Rheingold, A. L.; Geib, S. J.; Heck, R. F. *Organometallics* **1987**, *6*, 1941.

(17) Stille, J. K.; Lau, K. S. Y. *Acc. Chem. Res.* **1977**, *10*, 434.

(18) Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett.* **1965**, 4387.

SCHEME 2



of the reaction yields on the electronic nature of the aryl halides used provides useful mechanistic data. For the aryl iodides containing a para or meta electron-withdrawing substituent, the more electron-deficient intermediate **A** would be expected to coordinate more strongly to the triple bond in the imine substrate producing complex **B**. The coordination step therefore may be crucial in formation of the 3,4-disubstituted isoquinoline, because without it the imine substrate may cyclize by either a thermal or Pd(II)-catalyzed process to form the side product with no incorporation of the R^2 group onto the isoquinoline ring.[10]

This assumption is supported by the results from electron-rich imine **20** and electron-deficient imine **25**. Imine **20** possesses a higher electron density on the carbon−carbon triple bond than imine **1**, and imine **25** has decreased electron density on the triple bond. The experiments show that the higher electron density in imine **20** affords a slightly improved 80% yield of the corresponding 3,4-disubstituted isoquinoline product **21** when using 4-iodonitrobenzene, compared to the 75% yield obtained from imine **1** and the same aryl iodide (Table 1, entries 2 and 18). On the other hand, the corresponding reaction of imine **25** with a lower electron density on the triple bond results in a significant decrease in the yield of 3,4-disubstituted isoquinoline product **26** (23%), and an 11% yield of the monosubstituted side product was also isolated (Table 1, entry 21).

Conclusions

We have developed a new, efficient, palladium-catalyzed synthesis of 3,4-disubstituted isoquinolines from readily available *N-tert*-butyl-2-(1-alkynyl)arylaldimines and various organic halides. This synthetic strategy exhibits considerable structural flexibility in both the types of iminoalkynes and organic halides that can be employed. The overall yields are reasonably good. Despite some limitations, such as electron-rich and *o*-substituted aryl halides giving lower yields, the process holds promise as a useful tool for the construction of complex heterocycles containing the isoquinoline unit.

Experimental Section

General Procedures. All ^{1}H and ^{13}C NMR spectra were recorded at 300 and 400 and 75.5 and 100.7 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 a 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. Compounds **1**, **15**, **17**, **20**, **23**, and **25** have been previously reported.[13] For characterization of compounds **3**, **4**, **6**, **7**, **14**, **16**, **18**, **21**, **26**−**28**, **35**, **37**, **41**, and **44**, see ref 13. For characterization of the rest of the 3,4-disubstituted isoquinolines, see Supporting Information.

Typical Procedure for Synthesis of the *N-tert*-Butyl-2-(1-alkynyl)arylaldimines: *N-tert*-Butyl-2-(phenylethynyl)benzaldimine (1). To a solution of 2-bromo-benzaldehyde

(1.85 g, 10 mmol) and phenylacetylene (1.23 g, 12.0 mmol) in Et_3N (40 mL) was added $PdCl_2(PPh_3)_2$ (140 mg, 2 mol %). The mixture was stirred for 5 min, and CuI (20 mg, 1 mol %) was added. The resulting mixture was then heated under a nitrogen atmosphere at 50 °C for 4 h. The reaction was monitored by TLC to establish completion. The reaction 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 column chromatography on silica gel using 20:1 hexanes/EtOAc to afford 1.88 g (91%) of 2-(phenylethynyl)benzaldehyde as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.37−7.40 (m, 3H), 7.45 (t, J = 7.2 Hz, 1H), 7.54−7.65 (m, 4H), 7.95 (dd, J = 0.8, 7.6 Hz, 1H), 10.65 (d, J = 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 85.1, 96.5, 122.4, 126.9, 127.3, 128.6, 128.7, 129.2, 131.8, 133.3, 133.9, 135.9, 191.7. To a mixture of the prepared 2-(phenylethynyl)-benzaldehyde (0.80 g, 3.88 mmol) and H_2O (0.25 mL/mmol) was added *tert*-butylamine (11.64 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 dried (Na_2SO_4) and filtered. Removal of the solvent afforded 1.00 g (97%) of the indicated compound **1** with spectral properties identical to those previously reported:[10,12,13] mp 52−53 °C (lit.[10,12] 52−53 °C).

Typical Procedure for the Palladium-Catalyzed Formation of 3,4-Disubstituted Isoquinolines: 3,4-Diphenylisoquinoline (2a). A mixture of DMF (5 mL), $Pd(PPh_3)_4$ (14.4 mg, 0.0125 mmol), K_2CO_3 (0.1725 g, 1.25 mmol), *N*-*tert*-butyl-*o*-(phenylethynyl)benzaldimine (**1**) (0.0653 g, 0.25 mmol), and phenyl iodide (0.2551 g, 1.25 mmol) was flushed with Ar at room temperature for 5 min and then heated to 100 °C with stirring for 12 h. The reaction mixture was then cooled to room temperature, diluted with diethyl ether (30 mL), and washed with brine (30 mL). The aqueous layer was re-extracted 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 using 10:1 hexanes/EtOAc to afford 34 mg (49%) of the indicated compound: mp 154−155 °C (lit.[11a,16] 154−155 °C). The spectral properties were identical to those previously reported.[11a,16] Complete characterization of the isoquinolines prepared by this process can be found 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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