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

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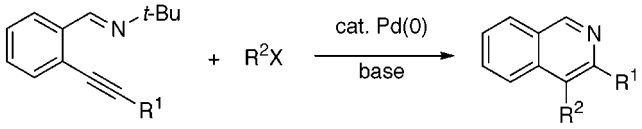
ABSTRACT



3,4-Disubstituted isoquinolines have been prepared in good yields by the palladium-catalyzed cross-coupling of *N-tert*-butyl-*o*-(1-alkynyl)-benzaldimines with aryl, allylic, and alkynyl halides.

The isoquinoline ring system is present in drug candidates possessing interesting biological activity[1] and numerous natural alkaloids that cover a wide range of structural types.[2] This has encouraged the development of a number of traditional approaches for the synthesis of the isoquinoline ring system, including the Bischler−Napieralski, the Pictet−Spengler, and the Pomeranz−Fritsch reactions.[3]

The synthesis of 3,4-disubstituted isoquinolines has been achieved by the annulation of internal alkynes by cyclopalladated *N,N*-dimethylbenzylamine complexes,[4] cyclopalladated *N-tert*-butylbenzaldimine tetrafluoroborates,[5] cyclopalladated *N-tert*-butylarylaldimines,[6] and *N-tert*-butyl-*o*-iodobenzaldimines plus a palladium catalyst.[7] The transition metal-catalyzed cyclization of alkynes, which possess nucleophilic centers in close proximity to the carbon−carbon triple bond, by *in situ* coupling/cyclization reactions,[8] and reactions promoted by vinylic, aryl, and alkynylpalladium complexes,[9] have also been shown to be extremely effective

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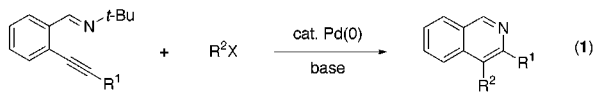
for the synthesis of a wide variety of carbo- and heterocycles. We hereby wish to report that the palladium-catalyzed cross-coupling of *N*-*tert*-butyl-*o*-(1-alkynyl)benzaldimines and a variety of organic halides offers an efficient, direct route to 3,4-disubstituted isoquinolines (eq 1).



(1)

Our initial studies of this process focused on developing an optimum set of reaction conditions for the palladium-catalyzed cross-coupling reaction. All optimization reactions were carried out using *N*-*tert*-butyl-*o*-(phenylethynyl)benzaldimine (**1**) and phenyl iodide in DMF as the solvent. When 5 mol % of $Pd_2(dba)_3$ was utilized as the catalyst at 100 °C with the addition of 10 mol % of PPh_3 and 3 equiv of Na_2CO_3, 3,4-diphenylisoquinoline (**2**) was isolated in only a modest yield. A side product, 3-phenylisoquinoline (**3**), was also generated, and the selectivity between the two isoquinoline products was not satisfactory.

On the other hand, 5 mol % of $Pd(PPh_3)_4$ gave the desired product **2** in a 49% yield and none of the 3-monosubstituted isoquinoline **3**, when the reaction was run using 5 equiv of K_2CO_3 as the base at 100 °C (Table 1, entry 1). Changing the base to KOAc, Na_2CO_3, Li_2CO_3, Cs_2CO_3, or organic amine bases failed to improve the yield of the product **2**. Raising the temperature to 120 °C only promoted the formation of more 3-phenylisoquinoline (**3**). The optimum reaction conditions thus far developed employ 1 equiv of the *o*-(1-alkynyl)benzaldimine (0.25 mmol), 5 equiv of the organic halide, 5 mol % of $Pd(PPh_3)_4$, and 5 equiv of K_2CO_3 in DMF (5 mL) at 100 °C. Phenyl triflate failed to afford 3,4-diphenylisoquinoline (**2**) under these standard reaction conditions.

By employing this protocol, aryl iodides bearing an electron-withdrawing group in the *para* or *meta* position afford the corresponding 4-aryl-3-phenylisoquinolines in good to high yields and very little of the side product **3** is observed (Table 1, entries 2−5). 4-Bromonitrobenzene affords 4-(4-nitrophenyl)-3-phenylisoquinoline (**4**) in a lower yield, 48%, compared to the 75% yield obtained from 4-iodonitrobenzene (Table 1, entry 2). The reaction of the bromide is also slower than the iodide reaction. The reactions of substrate **1** and aryl iodides with an electron-withdrawing group in the *ortho* position (Table 1, entries 6 and 7) fail to produce any of the desired 3,4-disubstituted isoquinolines. We assume that this is due to steric hindrance to coordination of the arylpalladium intermediate to the alkyne triple bond (see the later mechanistic discussion). When 4-iodoanisole is employed in the reaction with substrate **1** (Table 1, entry 8), the corresponding product **10** and the side product 3-phenylisoquinoline (**3**) are isolated in 13% and 14% yields, respectively. Thus, electron-rich aryl iodides give poor results in this cyclization chemistry.

The reactions of *N*-*tert*-butyl-*o*-(phenylethynyl)benzaldimine (**1**) and allylic halides or esters have also proven successful. Allyl chloride or bromide and diallyl carbonate have all generated the corresponding 4-allyl-3-phenylisoquinoline (**11**) in decent yields (entries 9−11). Substituted allylic chlorides, such as methallyl chloride, work equally well (entry 12). Benzylic halides and alkynyl iodides have also been successfully employed in this process. For example, the reaction of benzyl chloride produces a modest 45% yield of the cross-coupled isoquinoline product **13** (entry 13). The alkynyl iodide 1-iodo-1-decyne affords 4-(1-decynyl)-3-phenylisoquinoline (**14**) in a 56% yield (entry 14).

We have also investigated the reactions of imino alkynes containing different R^1 groups at the end of the triple bond with an aryl iodide and an allylic halide. With 4-iodonitrobenzene, imino alkyne **17** bearing a 1-cyclohexenyl group affords the corresponding 3,4-disubstituted isoquinoline (**18**) in a good yield, 59% (entry 16). Imine **20** containing an *n*-butyl group affords the desired product **21** in only a 35% yield (entry 18). The reactions of these two starting materials and methallyl chloride have given quite different results. Imine **17** affords a 30% yield (entry 17), while imine **20** with an *n*-butyl group gives over twice that yield (62%, entry 19).

The mechanism shown in Scheme 1 is proposed for this process. It consists of the following key steps: (1) oxidative addition of the organic halide to the Pd(0) catalyst, (2) coordination of the resulting palladium intermediate **A** to the alkyne triple bond to form complex **B**, which activates the triple bond toward nucleophilic attack, (3) intramolecular nucleophilic attack of the nitrogen atom on the activated carbon−carbon triple bond to afford intermediate **C**, (4) reductive elimination to form the carbon−carbon bond between R^2 and the isoquinoline ring in **D** with simultaneous regeneration of the Pd(0) catalyst, and (5) cleavage of the *tert*-butyl group from the nitrogen to release the strain between the *tert*-butyl group and the R^1 group to produce the 3,4-disubstituted isoquinoline.

The strong dependence of the reaction yields on the electronic nature of the aryl halides employed can be easily understood by this mechanism. For aryl iodides containing a *para* or *meta* electron-withdrawing substituent, the electron-deficient intermediate **A** more strongly coordinates to the triple bond in the imine substrate to produce complex **B**. The coordination step is most likely crucial to the forma-

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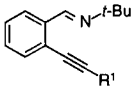
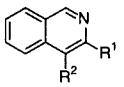
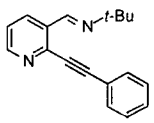
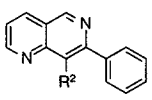
Table 1. Pd-Catalyzed Cross-Coupling of *N*-*tert*-Butyl-*o*-(1-alkynyl)arylaldimines and Organic Halides (eq 1)[a]

entry	substrate 	R^2X	time (h)	product 	% isolated yield[b]
1	R^1 = Ph (**1**)	PhI	12	$R^2 = C_6H_5$ (**2**)	49 (0)
2	**1**	*p*-$NO_2C_6H_4I$	12	R^2 = *p*-$NO_2C_6H_4$ (**4**)	75 (0)
3	**1**	*p*-$EtO_2CC_6H_4I$	7	R^2 = *p*-$EtO_2CC_6H_4$ (**5**)	67 (<2)
4	**1**	*m*-$NO_2C_6H_4I$	8	R^2 = *m*-$NO_2C_6H_4$ (**6**)	49 (0)
5	**1**	*m*-$EtO_2CC_6H_4I$	11	R^2 = *m*-$EtO_2CC_6H_4$ (**7**)	55 (<2)
6	**1**	*o*-$NO_2C_6H_4I$	48	R^2 = *o*-$NO_2C_6H_4$ (**8**)	0 (42)
7	**1**	*o*-$EtO_2CC_6H_4I$	11	R^2 = *o*-$EtO_2CC_6H_4$ (**9**)	0 (48)
8	**1**	*p*-$MeOC_6H_4I$	24	R^2 = *p*-$MeOC_6H_4$ (**10**)	13 (14)
9	**1**	allyl chloride	18	R^2 = allyl (**11**)	69 (0)
10	**1**	allyl bromide	24	R^2 = allyl (**11**)	65 (0)
11[c]	**1**	diallyl carbonate	24	R^2 = allyl (**11**)	68 (0)
12	**1**	methallyl chloride	24	R^2 = methallyl (**12**)	71 (0)
13	**1**	benzyl chloride	24	R^2 = benzyl (**13**)	45 (0)
14	**1**	1-iodo-1-decyne	6	R^2 = 1-decynyl (**14**)	56 (0)
15	R^1 = *p*-$MeOC_6H_4$ (**15**)	*p*-$NO_2C_6H_4I$	10	R^2 = *p*-$NO_2C_6H_4$ (**16**)	80 (0)
16	R^1 = 1-cyclohexenyl (**17**)	*p*-$NO_2C_6H_4I$	10	R^2 = *p*-$NO_2C_6H_4$ (**18**)	59 (0)
17	**17**	methallyl chloride	48	R^2 = methallyl (**19**)	30 (2)
18	R^1 = *n*-butyl (**20**)	*p*-$NO_2C_6H_4I$	6	R^2 = *p*-$NO_2C_6H_4$ (**21**)	35 (0)
19	**20**	methallyl chloride	48	R^2 = methallyl (**22**)	62 (0)
20	 (**23**)	*p*-$NO_2C_6H_4I$	10	 R^2 = *p*-$NO_2C_6H_4$ (**24**)	23 (11)[d]

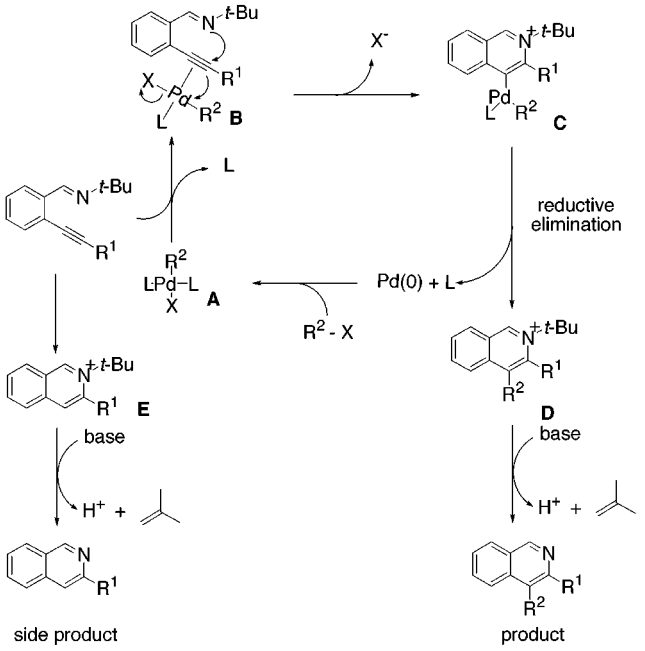
[a] All reactions were carried out under the optimal conditions reported in the text. [b] The numbers in parentheses are the isolated yields of the corresponding 3-monosubstituted isoquinoline. [c] Only 2.5 equiv of K_2CO_3 was used. [d] Yields determined by ^1H NMR spectroscopy.

tion of the 3,4-disubstituted isoquinoline, because without it the imine substrate can cyclize by either a thermal or a Pd(II)-catalyzed process to the monosubstituted side product with no incorporation of the R^2 group into the isoquinoline ring.[10]

To prove the importance of coordination of the triple bond in the process, imines **15** and **23** have been prepared. Imine **15** has a higher electron density on the triple bond than imine

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

Scheme 1



1, while imine **23** has a lower electron density on the triple bond. Subsequent experiments have shown that the imine **15** (entry 15) with a more electron-rich triple bond provides an improvement in the yield of the 3,4-disubstituted isoquinoline product **16** from 4-iodonitrobenzene to 80%, compared to the 75% yield obtained from imine **1** and the same aryl iodide (compare entries 2 and 15). On the other hand, the reaction of imine **23** with lower electron density on the triple bond results in a significant decrease in the yield of the 3,4-disubstituted isoquinoline product **24** (23%), and 11% of the corresponding monosubstituted side product is also isolated (entry 20).

This palladium-catalyzed reaction provides a simple and straightforward route to 3,4-disubstituted isoquinolines with a variety of substituents in the 4 position under fairly mild reaction conditions. Research on the scope and limitations of this methodology is currently underway in our laboratory.

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Supporting Information Available: Experimental procedures and characterization data for all compounds in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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