Synthesis of isoquinolines by palladium-catalyzed cyclization, followed by a Heck reaction

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Abstract—A variety of 4-(1-alkenyl)-3-arylisoquinolines have been prepared by the Pd(II)-catalyzed cyclization of 2-(1-alkynyl)benzaldimines, followed by alkenylation (Heck reaction) in good to excellent yields. The introduction of an *ortho*-methoxy group on the benzaldimine promotes the Pd-catalyzed cyclization and stabilizes the resulting Pd(II) intermediate improving the yields of the desired isoquinoline products. © 2002 Elsevier Science Ltd. All rights reserved.

The isoquinoline backbone appears in numerous natural products. Thus, the synthesis of isoquinolines has received much recent attention.[1] Although classical methods[2] have frequently been employed in the total synthesis of isoquinoline alkaloids, these approaches often have drawbacks, encouraging the development of new methodology.

The synthesis of 3,4-disubstituted isoquinolines has been achieved by the annulation of internal alkynes by cyclopalladated *N,N*-dimethylbenzylamine complexes,[3] cyclopalladated *N-tert*-butylbenzaldimine tetrafluoro borates,[4] cyclopalladated *N-tert*-butylarylaldimines,[5] and *N-tert*-butyl-*o*-iodobenzaldimines plus a palladium catalyst.[6] 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,[7] and reactions promoted by vinylic, aryl, and alkynylpalladium complexes,[8] have also been shown to be extremely effective for the synthesis of a wide variety of carbo- and heterocycles. We have recently shown that *N-tert*-butyl-*o*-(1-alkynyl)-benzaldimines,[1a] readily react with aryl, allylic and 1-alkynyl halides, but not vinylic halides, to produce 3,4-disubstituted isoquinolines (Eq. (1)).[9] We now wish to report that the corresponding vinylic products can be readily prepared by palladium-catalyzed cyclization of *N-tert*-butyl-*o*-(1-alkynyl)benzaldimines, followed by a Heck reaction with a variety of olefins (Eq. (2)).

$$\text{(1)}$$

R^2 = aryl, allylic, 1-alkynyl
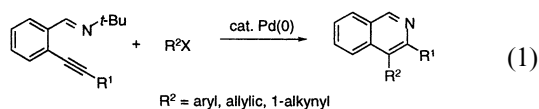
* Corresponding author.

$$\text{(2)}$$
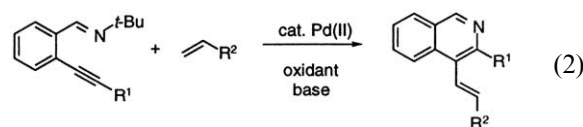
Our initial studies of this process focused on the development of an optimum set of reaction conditions for the isoquinoline alkenylation process. All optimization reactions have been carried out using *N-tert*-butyl-*o*-(phenylethynyl)benzaldimine (**1**) and *n*-butyl acrylate. Upon examination of a variety of Pd(II) catalysts, oxidants, bases, solvents and temperatures, we finally developed two procedures to synthesize *n*-butyl (*E*)-3-(3-phenylisoquinolin-4-yl)acrylate (**2**). Procedure A: 0.25 mmol of imine **1**, 5 equiv. of *n*-butyl acrylate, 10 mol% of PdBr₂, 2 equiv. of Cu(OAc)₂, and 3 equiv. of NaOAc are stirred in 3 mL of DMSO under 70°C—the desired isoquinoline **2** was obtained in 61% yield after 10 h (Table 1, entry 1). Procedure B: 0.25 mmol of imine **1**, 5 equiv. of *n*-butyl acrylate, 10 mol% of PdBr₂, 10 mol% of CuCl₂, and 3 equiv. of NaHCO₃ are stirred in 3 mL of DMSO at 70°C under O₂—this afforded the isoquinoline **2** in 56% yield after 8 h (entry 2).

By employing these protocols, a variety of 4-(1-alkenyl)-3-arylisoquinolines have been prepared. The results are summarized in Table 1. As mentioned above, isoquinoline **2** has been prepared in 61 and 56% yields by using imine **1** (entries 1 and 2, Table 1). Several olefins, including electron-deficient and electron-rich alkenes, have been allowed to react with imine **1** using procedure B. The use of *t*-butyl acrylate afforded a 50% yield of isoquinoline **3** (entry 3). However, none of the

Table 1. Isoquinoline olefination by palladium-catalyzed cyclization of N-tert-butyl-o-(1-alkynyl)arylaldimines, followed by a Heck reaction[a]

entry	imine	(alkene) R	time (h), procedure	product		% isolated yield[b]
1	(1)	R = CO$_2$-n-Bu	10, A		R = CO$_2$-n-Bu (2)	61 (5)
2		R = CO$_2$-n-Bu	8, B		R = CO$_2$-n-Bu (2)	56 (11)
3		R = CO$_2$-t-Bu	24, B		R = CO$_2$-t-Bu (3)	50 (6)
4		R = SO$_2$Ph	18, B		R = SO$_2$Ph (4)	0 (31)
5		R = Ph	17, B		R = Ph (5)	53 (29)
6		R = C(CH$_3$)$_2$OH	24, B		R = C(CH$_3$)$_2$OH (6)	34 (30)
7		R = O-n-Bu	24, B		(7)	31 (6)
8	(8)	R = CO$_2$-n-Bu	24, B		(9)	35 (18)
9	(10)	R = CO$_2$-n-Bu	18, A		R = CO$_2$-n-Bu (11)	65 (12)
10		R = CO$_2$-n-Bu	36, B		R = CO$_2$-n-Bu (11)	64 (13)
11		R = CO$_2$-t-Bu	24, B		R = CO$_2$-t-Bu (12)	68 (15)
12		R = Ph	72, B		R = Ph (13)	64 (20)
13		R = SO$_2$Ph	72, B		R = SO$_2$Ph (14)	20 (15)
14	(15)	R = CO$_2$-t-Bu	48, B		R = CO$_2$-t-Bu (16)	51 (0)
15		R = CONMe$_2$	18, B		R = CONMe$_2$ (17)	51 (0)
16	(18)	R = CO$_2$-t-Bu	10, B		R = CO$_2$-t-Bu (19)	92 (0)[c]
17		R = CONMe$_2$	14, B		R = CONMe$_2$ (20)	97 (0)[c]
18	(21)	R = CO$_2$-n-Bu	48, A		R = CO$_2$-n-Bu (22)	51 (19)[c]
19		R = CO$_2$-t-Bu	36, B		R = CO$_2$-t-Bu (23)	62 (0)[c]
20		R = Ph	16, B		R = Ph (24)	78 (0)[c]

[a] See the text for the detailed reaction conditions for procedures A and B.

[b] The numbers in parentheses are the isolated yields of the corresponding monosubstituted isoquinolines.

[c] The reaction was run at 90 °C.

desired product was observed when phenyl vinyl sulfone, an electron-deficient alkene, was allowed to react with imine **1** (entry 4).

In entries 5 and 6, relatively electron-rich olefins, styrene and 2-methyl-3-buten-2-ol have been allowed to react with imine **1**, and the corresponding isoquinolines **5** and **6** have been obtained in 53% yield (entry 5) and 34% yield (entry 6), respectively. Instead of forming an internal alkene, the reaction of n-butyl vinyl ether afforded isoquinoline **7** bearing a terminal double bond (entry 7), albeit in low overall yield.[10]

Sakamoto et al. have reported that N-protected alkyl-substituted o-(1-alkynyl)anilines can react with electron-deficient alkenes in the presence of PdCl$_2$ and CuCl$_2$ producing 2-substituted 3-(1-alkenyl)indoles.[11] However, in our chemistry, N-tert-butyl alkyl-substituted o-(1-alkynyl)benzaldimines, such as **25** and **26**, do not react with either electron-deficient or electron-rich terminal alkenes.

25   **26**
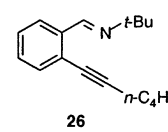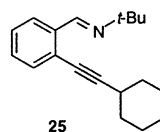
When imine **8** bearing an electron-donating methoxy group was employed, the yield dropped from 56% (entry 2) to 35% (entry 8) for reasons that are not obvious. However, the introduction of an *ortho*-methoxy group on the phenyl moiety promoted the isoquinoline olefination process. When imine **10** reacted with *n*-butyl acrylate under procedures A and B, the yields increased to 65% (entry 9) and 64% (entry 10) from 61% (entry 1) and 56% (entry 2), respectively. By employing procedure B, the reactions of imine **10** with *t*-butyl acrylate and styrene afforded a 68% yield of isoquinoline **12** (entry 11) and a 64% yield of isoquinoline **13** (entry 12), respectively, which are much better than the results from the corresponding reactions of imine **1** (entries 3 and 5). As mentioned above, the reaction of imine **1** and phenyl vinyl sulfone gave none of the desired product (entry 4). However, a 20% yield of isoquinoline **14** was observed when imine **10** was allowed to react with phenyl vinyl sulfone (entry 13). This *ortho*-methoxy promotion can be explained by Scheme 1. Basically, the introduction of an *ortho*-methoxy group helps direct the PdBr₂ to the vicinity of the internal triple bond where attack by the imine nitrogen on the activated triple bond takes place generating a Pd(II) intermediate, which is stabilized by the *ortho*-methoxy group. Subsequent Heck olefination and fragmentation of the *t*-butyl group affords the desired isoquinoline olefin.

When imine **15** with two electron-donating groups on the benzylidene moiety was allowed to react with *t*-butyl acrylate, isoquinoline **16** was obtained in a 51% yield (entry 14), which is comparable to the 50% yield from the reaction of imine **1** and *t*-butyl acrylate (entry 3). The reaction of *N,N*-dimethylacrylamide and imine **15** also gave the corresponding isoquinoline **17** in a 51% yield (entry 15).

The reactions of imine **18** and *t*-butyl acrylate or *N,N*-dimethylacrylamide are very slow at 70°C. These reactions need to be run at 90°C and the corresponding isoquinolines **19** and **20** have been obtained in 92 and 97% yields, respectively (entries 16 and 17). Comparing the results from entries 11, 14 and 16, one can see that both electronic effects and *ortho*-methoxy substitution play a role in forming isoquinoline **19** in such a high yield (entry 16).
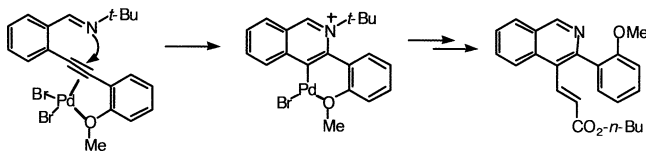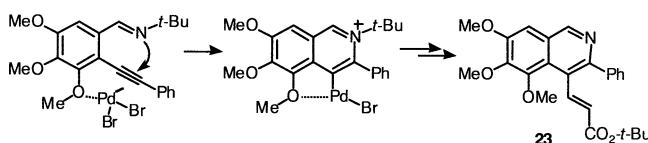
The reactions of imine **21** with *n*-butyl acrylate, *t*-butyl acrylate, and styrene gave the corresponding isoquinolines **22**, **23** and **24** in 51, 62 and 78% yields, respectively (entries 18–20). Similar to the reactions of imine **18**, the reactions of imine **21** with olefins also involve both an electronic effect and *ortho*-methoxy promotion (Scheme 2). Comparing the results from imine **21** with those of imine **18**, one can see that the introduction of an *ortho*-methoxy group onto the phenyl moiety promotes this isoquinoline olefination better than the introduction of a methoxy group onto the benzylidene nitrogen moiety.

The palladium-catalyzed cyclization, followed by alkenylation with a variety of olefins, provides a simple and straightforward route to 4-(1-alkenyl)-3-aryl-isoquinolines under fairly mild reaction conditions in good to excellent yields. Research on the scope and limitations of this methodology is currently underway in our laboratory.

Acknowledgements

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Scheme 1.

Scheme 2.

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