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Synthesis of 4-(1-Alkenyl)isoquinolines by Palladium(II)-Catalyzed Cyclization/Olefination

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Received July 2, 2002

A variety of 4-(1-alkenyl)-3-arylisoquinolines have been prepared in moderate to excellent yields by the Pd(II)-catalyzed cyclization of 2-(1-alkynyl)arylaldimines in the presence of various alkenes. The introduction of an *o*-methoxy group on the arylaldimine promotes the Pd-catalyzed cyclization and stabilizes the resulting Pd(II) intermediate, improving the yields of the isoquinoline products. Ketone-containing isoquinolines **36** and **49**−**51** have also been prepared by this process when unsaturated alcohols are employed as the alkenes.

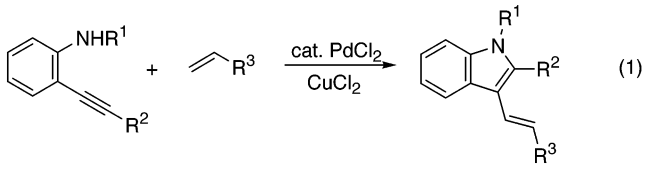
Introduction

The synthesis of isoquinolines has received considerable attention due to the fact that the isoquinoline ring system is present in numerous naturally occurring alkaloids.[1] Although classical methods have frequently been employed in the total synthesis of isoquinoline alkaloids, these approaches often have drawbacks. For example, the Bischler−Napieralski,[2] Pictet−Spengler,[3] and Pomeranz−Fritsch[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.

Substituted isoquinoline heterocycles have also been synthesized by employing palladium methodology. For instance, 3,4-disubstituted isoquinolines have been achieved by the annulation of internal alkynes by cyclopalladated *N*,*N*-dimethylbenzylamine complexes,[5] cyclopalladated *N*-*tert*-butylbenzaldimine tetrafluoroborates,[6] cyclopalladated *N*-*tert*-butylarylaldimines,[7] and *N*-*tert*-butyl-*o*-iodobenzaldimines plus a palladium catalyst.[8]

The transition metal-catalyzed cyclization of alkynes,[9] which possess nucleophilic centers in close proximity to the carbon−carbon triple bond, by in situ coupling/cyclization reactions,[10] and reactions promoted by vinylic, aryl, alkynyl, and acylpalladium complexes,[11] have also been shown to be extremely effective for the synthesis of a wide variety of carbo- and heterocycles.

The palladium(II)-catalyzed cyclization/olefination reaction of 2-(1-alkynyl)aniline derivatives to indoles has been reported by Sakamoto et al.[12] They report that the reaction of *N*-protected 2-(1-alkynyl)anilines with electron-deficient alkenes in the presence of $PdCl_2$ and $CuCl_2$ gives 2-substituted 3-(1-alkenyl)indoles (eq 1). Our interest in



(1)

4-(1-alkenyl)isoquinolines has prompted us to develop a convenient new synthesis of these isoquinolines by the

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10.1021/jo0261303 CCC: $25.00
Published on Web 12/19/2002

TABLE 1. Optimization of the Reaction of Benzaldimine 1 and Methyl Acrylate by Examination of Different Oxidizing Reagents, Bases, and Solvents (eq 2)[a]

entry	oxidant	base	solvent	time (h)	% yield of **2**[b]	% yield of **3**[b]	% yield of **4**[b]
1	O_2		DMF	24	33 (37[c])	20	0
2	$CuCl_2$		DMF	20	0	0	0
3	$CuCl_2$	Et_3N	DMF	36	10	15	trace
4	$CuCl_2$	K_2CO_3	DMF	36	17	trace	15
5	$CuCl_2$	NaOAc	DMF	36	20	trace	20
6	$Cu(OAc)_2$	NaOAc	DMF	24	35	0	0
7	$Cu(OAc)_2$	NaOAc	CH_3CN	12	18	25	0
8	$Cu(OAc)_2$	NaOAc	DMSO	12	61	5	0
9	$Cu(CO_3)_2$	NaOAc	DMSO	24	23	34	0
10	$Cu(NO_3)_2$	NaOAc	DMSO	24	37	19	0
11	benzoquinone	NaOAc	DMSO	24	40	30	0

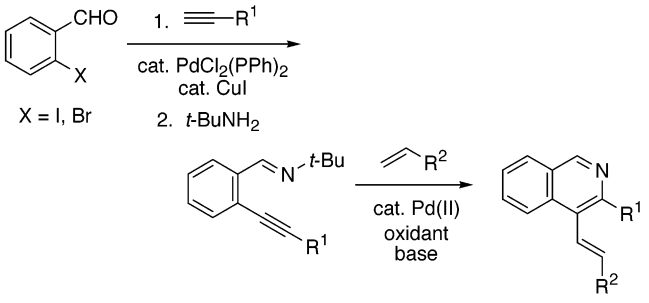
[a] All reactions were run under the following reaction conditions: 0.25 mmol of benzaldimine **1**, 5 equiv of methyl acrylate, 10 mol % $PdBr_2$, 2 equiv of the oxidant, and 3 equiv of the base were stirred in 3 mL of the indicated solvent at 70 °C for the specified period of time. [b] Isolated yields. [c] Yield based on ^1H NMR spectroscopic analysis.

TABLE 2. Optimization of the Reaction of Benzaldimine 1 and *n*-Butyl Acrylate Using Catalytic Amounts of the Copper Reagent (eq 3)[a]

entry	catalyst	oxidant	base	additive	time (h)	% yield of **5**[b]	% yield of **3**[b]
1	$PdCl_2(PPh_3)_2$	$CuCl_2$	NaOAc		24	38	21
2			pyridine		24	48	9
3			Et_3N		28	46	12
4			Cs_2CO_3		24	trace[c]	20
5			K_2CO_3		28	29	18
6			$KHCO_3$		20	39	16
7			Na_2CO_3		20	47	12
8			$NaHCO_3$		14	51	11
9			$NaHCO_3$	TBAC	20	45	25
10	$PdCl_2$	$CuCl_2$	$NaHCO_3$		16	49	12
11	PdI_2				24	46	20
12	$Pd(O_2CCF_3)_2$				24	48	15
13	$Pd(OAc)_2$				20	45	11
14	$PdBr_2$				8	56	17
15	$PdBr_2$				36	53[d]	11
16	$PdBr_2$				6	45[e]	26
17	$PdBr_2$			PPh_3	20	48	17
18	$PdBr_2$	CuF_2			18	54	14
19		$Cu(OAc)_2$			19	45	27
20		$Cu(NO_3)_2$			24	45	21
21		$CuCO_3$			24	39	14
22		CuI			16	23	46

[a] All reactions were run under the following reaction conditions, unless otherwise specified: 0.25 mmol of benzaldimine **1**, 5 equiv of *n*-butyl acrylate, 10 mol % of the indicated Pd(II) salt, 10 mol % of the indicated oxidant, and 3 equiv of the indicated base in 3 mL of DMSO were stirred at 70 °C for the specified period of time under a balloon of O_2. [b] Isolated yield. [c] Benzaldimine **1** was recovered in 40% yield. [d] The reaction was run under 55 °C. [e] The reaction was run under 90 °C.

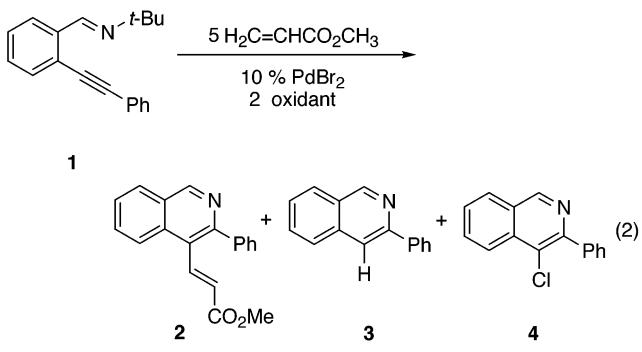
SCHEME 1



Pd(II)-promoted cross coupling of a variety of alkenes and 2-(1-alkynyl)arylaldimines, which can be easily prepared from the corresponding 2-halobenzaldehydes in two steps (Scheme 1).

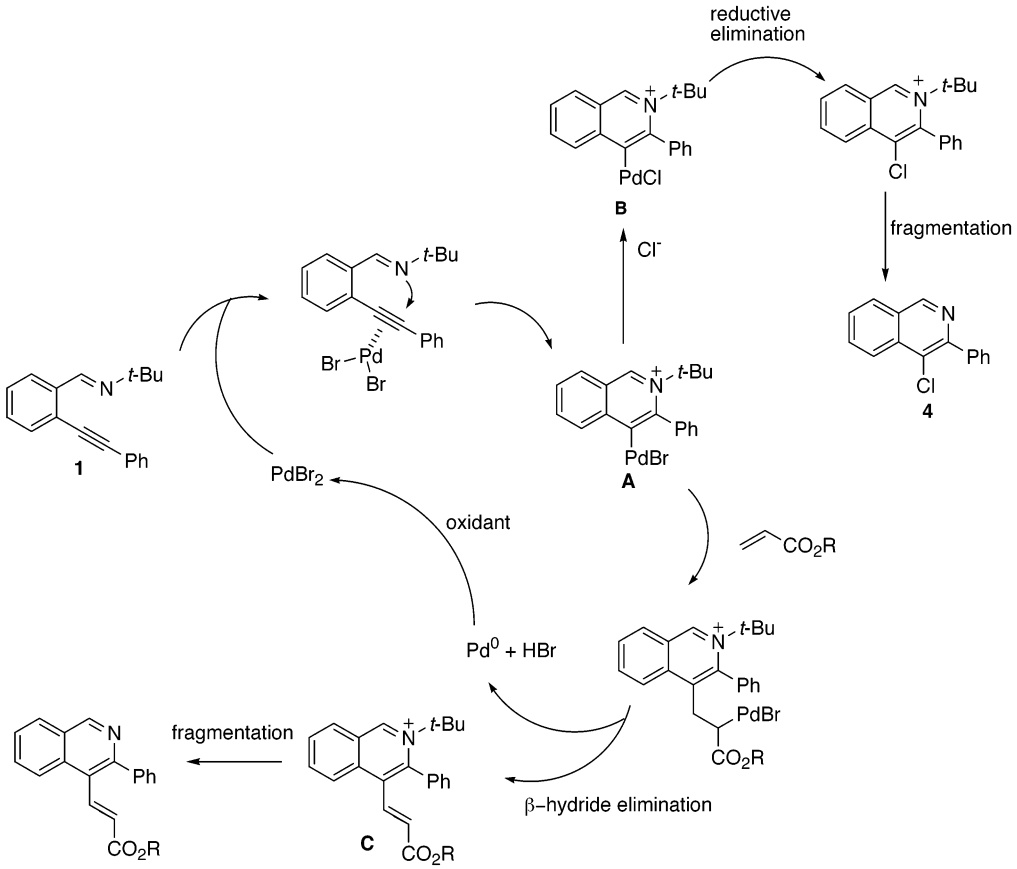
Results and Discussion

Our initial studies on the synthesis of 4-(1-alkenyl)-isoquinolines focused on the development of an optimum set of reaction conditions for their formation. A variety of Pd(II) catalysts, oxidants, bases, solvents, and temperatures have been examined on the reaction of arylaldimine **1** and methyl acrylate (eq 2) and only some representative optimization reactions are summarized in Tables 1 and 2.



The optimization reactions shown in Table 1 employed 2 equiv of the oxidant (eq 2). In entry 1 (Table 1),

SCHEME 2



benzaldimine **1** has been allowed to react with 5 equiv of methyl acrylate in the presence of 10 mol % of $PdBr_2$ under an O_2 balloon, and a 33% yield of isoquinoline **2** was isolated in the absence of a base. However, the use of 2 equiv of $CuCl_2$ as the oxidant afforded none of the desired product, although all starting materials disappeared within 20 h (entry 2). The use of $CuCl_2$ and the bases Et_3N, K_2CO_3, and NaOAc resulted in 10−20% yields of the desired product **2** (entries 3−5). In entries 4 and 5, 4-chloro-3-phenylisoquinoline (**4)** was obtained in 15% and 20% yields, respectively.

Possible mechanisms for the formation of isoquinolines **2** and **4** are shown in Scheme 2. The cyclization of benzaldimine **1** by $PdBr_2$ presumably forms intermediate **A**, which is an electron-deficient arylpalladium bromide. The cis addition of intermediate **A** to the carbon−carbon double bond of the olefin affords an alkylpalladium(II) intermediate, which undergoes subsequent *β*-hydride elimination to afford intermediate **C** and Pd(0). Further fragmentation of the *tert*-butyl group from intermediate **C** generates the desired 4-(1-alkenyl)isoquinolines. The Pd(0) generated can be reoxidized back to $PdBr_2$ by the oxidant present in the reaction mixture.

With the presence of excess chloride in the reaction mixture, the intermediate **A** is converted into intermediate **B** by halide exchange, because the Pd−Cl bond is much stronger than the Pd−Br bond.[13] Isoquinoline **4** is then generated by the reductive elimination of intermediate **B**, followed by fragmentation of the *tert*-butyl group. This reductive elimination is apparently promoted by the presence of the copper salt, since arylpalladium halides do not normally undergo this process spontaneously. The use of $Cu(OAc)_2$ as the oxidant increased the yield of the desired isoquinoline **2** from 20% (entry 5) to 35% (entry 6). Obviously, the use of $Cu(OAc)_2$ eliminates the formation of intermediate **B** and eventual formation of the chloroisoquinoline **4**.

When CH_3CN was chosen as the solvent, an 18% yield of isoquinoline **2** was isolated, alongside a 25% yield of isoquinoline **3** (entry 7). However, the use of DMSO resulted in a 61% yield of isoquinoline **2** and only a 5% yield of **3** in 12 h (entry 8). Obviously, DMSO is a better solvent than DMF or CH_3CN for this isoquinoline olefination process, presumably due to improved oxidation of Pd(0) to Pd(II). Thus, DMSO has been chosen as the solvent for all subsequent optimization reactions. From entries 9−11, other oxidants $Cu(CO_3)_2$, $Cu(NO_3)_2$, and 1,4-benzoquinone have been employed and only 23−40% yields of product **2** have been isolated. On the basis of the above results, the following reaction conditions have been chosen as the standard reaction conditions for procedure A: 0.25 mmol of benzaldimine, 5 equiv of the olefin, 10 mol % of $PdBr_2$, 2 equiv of $Cu(OAc)_2$, and 3 equiv of NaOAc are stirred in 3 mL of DMSO at 70 °C.

The drawback of procedure **A** is the use of 2 equiv of $Cu(OAc)_2$. We have therefore tried to develop an alternative procedure using only catalytic amounts of the copper reagent (eq 3). In this optimization study, it has been found that only catalytic amounts of $PdCl_2(PPh_3)_2$ in the presence of 10 mol % of $CuCl_2$, 3 equiv of NaOAc, and an

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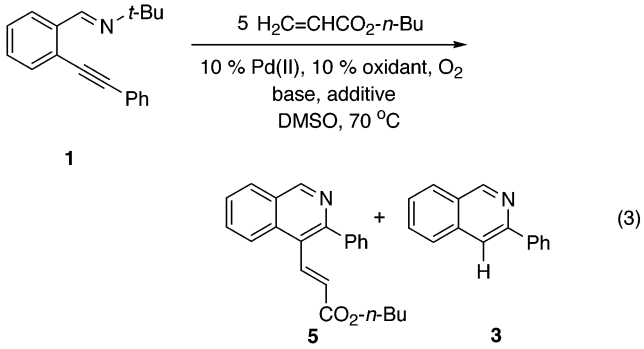
O_2 atmosphere can cyclize benzaldimine **1**, affording a 38% yield of isoquinoline **5** (entry 1, Table 2). On the basis of this reaction, various bases have been examined and the results are summarized in entries 1−8.



(3)

The use of 3 equiv of the organic bases pyridine or Et_3N afforded a 48% (entry 2) or a 46% (entry 3) yield of isoquinoline **5**, respectively. In entries 4−8, the carbonate salts Cs_2CO_3, K_2CO_3, $KHCO_3$, Na_2CO_3, and $NaHCO_3$ have been examined. The results show that the more soluble carbonate bases, such as Cs_2CO_3 (entry 4), disfavor the reaction and the less soluble carbonates, such as $NaHCO_3$ (entry 8), favor the formation of isoquinoline **5**. The addition of *n*-Bu_4NCl resulted in a slight decrease in the yield of isoquinoline **5** (entrie 9). Thus, the reaction conditions employed in entry 8, which are the best reaction conditions shown in entries 1−9, have been chosen for further optimization reactions employing a variety of Pd(II) catalysts and difference reaction temperatures. The results for this latter study are summarized in entries 10−16 in Table 2.

When catalytic amounts of $PdCl_2$, PdI_2, $Pd(O_2CCF_3)_2$, $Pd(OAc)_2$, or $PdBr_2$ have been employed, the desired product, isoquinoline **5**, was isolated in 45−56% yields with $PdBr_2$ giving the best yield (entries 10−14). When the reaction was carried out under 55 °C, isoquinoline **5** was observed in 53% yield after 36 h (entry 15), while the reaction gave 45% yield in 6 h under 90 °C (entry 16). It is clear that 70 °C is a good reaction temperature for this palladium-catalyzed cyclization process. In entry 17, the addition of PPh_3 resulted in a slight decrease in the yield of isoquinoline **5**. Again, the reaction conditions in entry 14, which have afforded the best result so far, have been chosen for further optimization.

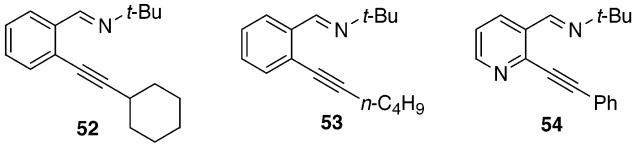
On the basis of the reaction conditions in entry 14, a variety of oxidants have been examined and the results are summarized in entries 18−22. As mentioned above, a 56% isolated yield of isoquinoline **5** was obtained in the presence of 10 mol % of $CuCl_2$ (entry 14). The use of 10 mol % of CuF_2 gave a 54% yield of isoquinoline **5** (entry 18). Other copper(II) reagents, such as $Cu(OAc)_2$, $Cu(NO_3)_2$, and $CuCO_3$, have also been examined and isoquinoline **5** was isolated in 39−45% yields (entries 19−21). The use of CuI, a copper(I) reagent as the oxidant, resulted in a decrease in the yield of isoquinoline **5** from 56% (entry 14) to 23%, while the side product **3** was isolated in a 46% yield (entry 22).[14]

After the above optimization work, we have adopted the following standard reaction conditions using only a catalytic amount of Cu(II) reagent as procedure B: 0.25 mmol of arylaldimine, 5 equiv of the olefin, 10 mol % of $PdBr_2$, 10 mol % of $CuCl_2$, 3 equiv of $NaHCO_3$ in 3 mL of DMSO at 70 °C under an O_2 atmosphere.

By employing procedures A and B, a variety of 4-(1-alkenyl)- and 4-alkyl-3-arylisoquinolines have been prepared (Table 3). As mentioned above, using procedure A, isoquinoline **2** was isolated in a 61% yield from the reaction of benzaldimine **1** and methyl acrylate (entry 1, Table 3). An identical yield of isoquinoline **5** was isolated from the reaction of benzaldimine **1** and *n*-butyl acrylate with use of procedure A (entry 2).

Several olefins, including electron-deficient and electron-rich alkenes, have been allowed to react with benzaldimine **1** following procedure B (entries 3−7). The use of *n*-butyl acrylate and *tert*-butyl acrylate afforded a 56% yield of isoquinoline **5** (entry 3) and a 50% yield of isoquinoline **6** (entry 4), respectively. However, none of the desired isoquinoline product was observed when phenyl vinyl sulfone, an electron-deficient alkene, was allowed to react with benzaldimine **1**. The relatively electron-rich olefins styrene and 2-methyl-3-buten-2-ol have been allowed to react with benzaldimine **1**. A 53% yield of isoquinoline **7** (entry 5) and a 34% yield of **8** (entry 6) were obtained, respectively. Instead of forming an internal alkene, the reaction of *n*-butyl vinyl ether afforded isoquinoline **9** bearing a terminal double bond, albeit in low overall yield (entry 7).[15]

Sakamoto et al. have reported that *N*-protected *alkyl*-substituted *o*-(1-alkynyl)anilines react with electron-deficient alkenes in the presence of $PdCl_2$ and $CuCl_2$ producing 2-substituted 3-(1-alkenyl)indoles.[12] However, in our chemistry, the *N*-*tert*-butyl *alkyl*-substituted *o*-(1-alkynyl)benzaldimines **52** and **53** did not react with either electron-deficient or electron-rich terminal alkenes under either procedure A or B to afford isoquinoline products. Although *N*-*tert*-butyl *alkyl*-substituted *o*-(1-alkynyl)benzaldimines do not react with olefins, benzaldimine **10**, which is a *N*-*tert*-butyl *alkenyl*-substituted *o*-(1-alkynyl)benzaldimine, did react with *n*-butyl acrylate affording a 41% isolated yield of isoquinoline **11** (entry 8).



The reaction of arylaldimine **54**, bearing a pyridine moiety, and olefins gave none of the desired product. However, when arylaldimine **12** with an alkynyl group attached to C-3 of the pyridine nucleus was allowed to react with *n*-butyl acrylate, naphthyridine **13** was isolated in a 51% yield (entry 9).

It is known that electron-deficient aryl halides or vinylic halides disfavor the Heck reaction.[13] Thus, electron-donating groups have been introduced into the arylaldimine to increase the electron density in intermediate **A**

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TABLE 3. Synthesis of Isoquinolines by Palladium(II)-Catalyzed Cyclization/Olefination[a]

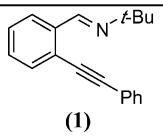
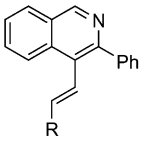
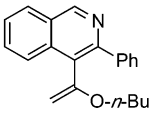
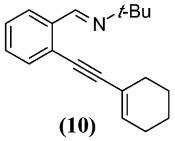
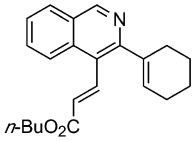
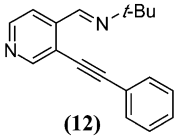
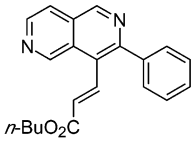
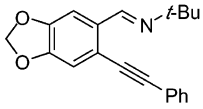
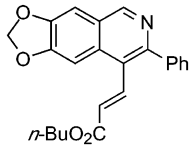
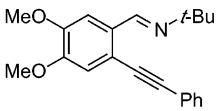
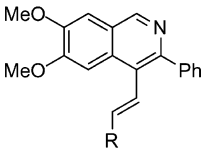
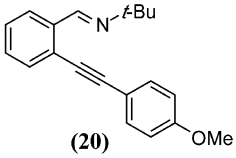
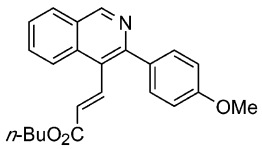
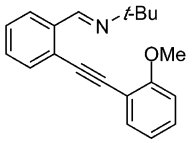
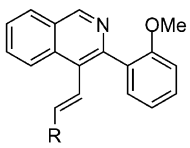
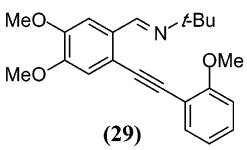
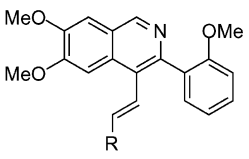
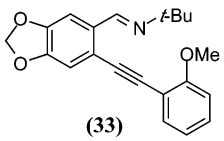
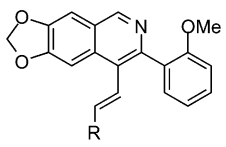
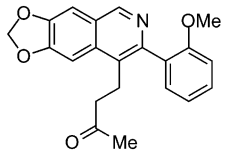
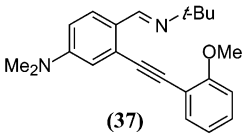
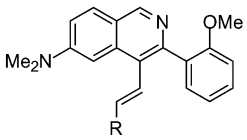
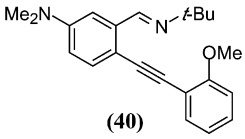
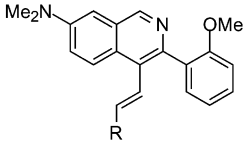
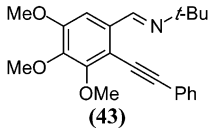
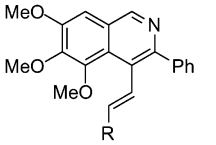
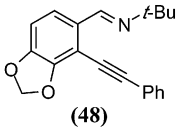
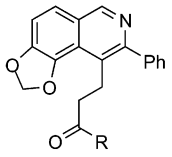
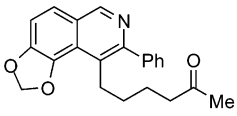
entry	arylaldimine	H_2C=CHR	procedure, time (h)	product	% isolated yield
1	 **(1)**	R = CO_2Me	A, 12	 R = CO_2Me **(2)**	61
2		R = CO_2-*n*-Bu	A, 10	R = CO_2-*n*-Bu **(5)**	61
3		R = CO_2-*n*-Bu	B, 8	R = CO_2-*n*-Bu **(5)**	56
4		R = CO_2-*t*-Bu	B, 24	R = CO_2-*t*-Bu **(6)**	50
5		R = Ph	B, 18	R = Ph **(7)**	53
6		R = CMe_2OH	B, 17	R = CMe_2OH **(8)**	34
7		R = O-*n*-Bu	B, 24	 **(9)**	31
8	 **(10)**	R = CO_2-*n*-Bu	B, 24	 **(11)**	41
9	 **(12)**	R = CO_2-*n*-Bu	B, 18	 **(13)**	51
10	 **(14)**	R = CO_2-*n*-Bu	A, 18	 **(15)**	43
11		R = CO_2-*n*-Bu	B, 24		48
12	 **(16)**	R = CO_2-*t*-Bu	B, 48	 R = CO_2-*t*-Bu **(17)**	51
13		R = $CONMe_2$	B, 18	R = $CONMe_2$ **(18)**	51
14		R = SO_2CH_3	B, 17	R = SO_2CH_3 **(19)**	27
15	 **(20)**	R = CO_2-*n*-Bu	B, 24	 **(21)**	35
16	 **(22)**	R = CO_2-*n*-Bu	A, 18	 R = CO_2-*n*-Bu **(23)**	65
17		R = CO_2-*n*-Bu	B, 36	R = CO_2-*n*-Bu **(23)**	64
18		R = CO_2-*t*-Bu	B, 24	R = CO_2-*t*-Bu **(24)**	68
19		R = Ph	B, 72	R = Ph **(25)**	64
20		R = SO_2Ph	B, 72	R = SO_2Ph **(26)**	20
21		R = $CONMe_2$	B, 18	R = $CONMe_2$ **(27)**	65
22		R = CMe_2OH	B, 48	R = CMe_2OH **(28)**	25
23	 **(29)**	R = CO_2-*t*-Bu	B, 14	 R = CO_2-*t*-Bu **(30)**	92[b]
24		R = $CONMe_2$	B, 10	R = $CONMe_2$ **(31)**	97[b]
25		R = SO_2CH_3	B, 12	R = SO_2CH_3 **(32)**	52[b]

Table 3 (Continued)

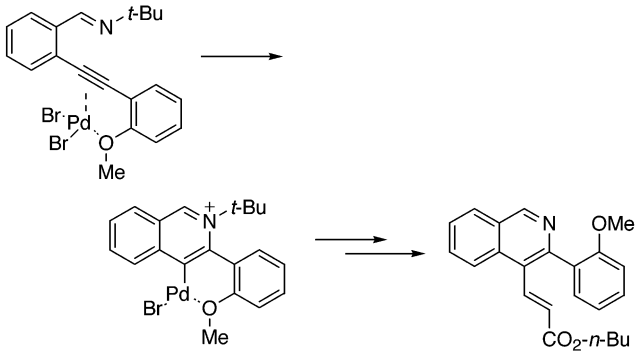
entry	arylaldimine	H_2C=CHR	procedure, time (h)	product	% isolated yield
26	 **(33)**	R = CO_2-*t*-Bu	A, 12	 R = CO_2-*t*-Bu **(34)**	61
27		R = CO_2-*t*-Bu	B, 10	R = CO_2-*t*-Bu **(34)**	82[b]
28		R = $CONMe_2$	B, 5	R = $CONMe_2$ **(35)**	89[b,c]
29		R = $CH(OH)CH_3$	B, 24	 **(36)**	48
30	 **(37)**	R = CO_2-*t*-Bu	B, 16	 R = CO_2-*t*-Bu **(38)**	69
31		R = CO_2-*t*-Bu	B, 2	R = CO_2-*t*-Bu **(38)**	67[b]
32		R = $CONMe_2$	B, 1.5	R = $CONMe_2$ **(39)**	70[b,d]
33	 **(40)**	R = CO_2-*t*-Bu	B, 12	 R = CO_2-*t*-Bu **(41)**	71[b]
34		R = $CONMe_2$	B,16	R = $CONMe_2$ **(42)**	70[b]
35	 **(43)**	R = CO_2-*n*-Bu	A, 48	 R = CO_2-*n*-Bu **(44)**	51[b]
36		R = CO_2-*t*-Bu	B, 36	R = CO_2-*t*-Bu **(45)**	62[b]
37		R = $CONMe_2$	B, 48	R = $CONMe_2$ **(46)**	50[b]
38		R = Ph	B,16	R = Ph **(47)**	78[b]
39	 **(48)**	R = $CH(OH)CH_3$	B, 72	 R = CH_3 **(49)**	50
40		R = CH(OH)Ph	B, 4	R = Ph **(50)**	36[b]
41		R = $(CH_2)_2CH(OH)CH_3$	B, 8	 **(51)**	27[b]

[a] See the text for the detailed reaction conditions for procedures A and B. [b] The reaction was run at 90 °C. [c] The product was isolated as a 73:27 mixture of *E*/*Z* isomers. [d] The product was isolated as a 91:9 mixture of *E*/*Z* isomers.

(Scheme 1) and hopefully favor formation of the desired isoquinoline products. However, the experimental results indicate that the introduction of electron-donating groups into the arylaldimine does not really favor the isoquinoline olefination process, and instead results in a decrease in the yields of the desired isoquinoline products in most cases. For example, when benzaldimine **14** bearing a methylenedioxo group on the benzylidene moiety was allowed to react with *n*-butyl acrylate following procedures A and B, the yield dropped from 61% (entry 2) to 43% (entry 10) or from 56% (entry 3) to 48% (entry 11), respectively. The reaction of **16**, another electron-rich arylaldimine, and *tert*-butyl acrylate afforded isoquinoline **17** in a 51% yield (entry 12), comparable to the 50% yield from the reaction of benzaldimine **1** and *tert*-butyl acrylate (entry 4). When *N*,*N*-dimethylacrylamide or methyl vinyl sulfone was allowed to react with arylaldimine **16**, a 51% yield of isoquinoline **18** (entry 13) and a 27% yield of isoquinoline **19** (entry 14) were obtained, respectively. The sulfone result is a bit surprising in view of our earlier failure to obtain any isoquinoline product from benzaldimine **1** and phenyl vinyl sulfone. The introduction of a *p*-methoxy group on the phenyl moiety resulted in the yield of the desired isoquinoline **21** dropping from 56% (entry 3) to only 35% (entry 15).

The presence of electron-donating groups increases the electron density of the carbon−carbon triple bond, which apparently disfavors cyclization by attack of the imine nitrogen on the activated triple bond and consequently results in low conversion of the arylaldimine to intermediate **A** and eventual formation of the isoquinoline (Scheme 2). Although the reactivity of intermediate **A**

SCHEME 3



toward olefins is presumably improved by introducing electron-donating groups, the low conversion of arylaldimine to intermediate **A** results in a decrease in the overall yield of isoquinoline products.

The position of the electron-donating methoxy group in the arylaldimine is critical to the success of this process. Thus, the introduction of an *o*-methoxy group on the phenyl moiety facilitates isoquinoline formation. When benzaldimine **22** was allowed to react with *n*-butyl acrylate following procedures A and B, the yields increased to 65% (entry 16) and 64% (entry 17) from 61% (entry 2) and 56% (entry 3), respectively. Employing procedure B, a variety of olefins have been allowed to react with arylaldimine **22** (entries 18−22). The reactions of **22** with *tert*-butyl acrylate and styrene afforded a 68% yield of isoquinoline **24** (entry 18) and a 64% yield of isoquinoline **25** (entry 19), respectively. These yields are much better than the yields of 50% and 53% from the corresponding reactions of benzaldimine **1** (entries 4 and 5). As mentioned above, the reaction of benzaldimine **1** and phenyl vinyl sulfone gave none of the desired product. However, a 20% yield of isoquinoline **26** was observed when benzaldimine **22** was allowed to react with phenyl vinyl sulfone (entry 20). When *N*,*N*-dimethylacrylamide was allowed to react with arylaldimine **22**, isoquinoline **27** was isolated in a 65% yield (entry 21), much better than the yield of 51% from the reaction of benzaldimine **16** and *N*,*N*-dimethylacrylamide (entry 13). The reaction of arylaldimine **22** and 2-methyl-3-buten-2-ol afforded isoquinoline **28** in a 25% yield (entry 22). For some reason, this yield is lower than the 35% yield obtained with benzaldimine **1** (entry 6).

The beneficial effects of an *o*-methoxy group can be explained by Scheme 3. Basically, the introduction of an *o*-methoxy group helps direct the $PdBr_2$ to the vicinity of the triple bond where attack by the imine nitrogen on the activated triple bond takes place generating an arylpalladium intermediate, which is stabilized by chelation with the *o*-methoxy group. Subsequent Heck olefination and fragmentation of the *tert*-butyl group affords the desired isoquinoline olefin.

The reactions of benzaldimine **29** and *tert*-butyl acrylate or *N*,*N*-dimethylacrylamide are very slow at 70 °C. These reactions were thus run at 90 °C and the corresponding isoquinolines **30** and **31** have been obtained in 92% and 97% yields, respectively (entries 23 and 24). Comparing the results from entries 12, 13, 18, 21, 23, and 24, one can see that both electronic effects and facilitation by the *o*-methoxy group play a role in forming isoquinolines **30** and **31** in such high yields. The *o*-methoxy group improves the conversion of the arylaldimine to intermediate **A** and the introduction of electron-donating groups on the arylaldimine moiety presumably increases the reactivity of intermediate **A** toward olefins,[14] affording mostly improved yields. When methyl vinyl sulfone was allowed to react with arylaldimine **29**, the yield of isoquinoline **32** increased to 52% (entry 25) from the 27% obtained without the *o*-methoxy group (entry 14).

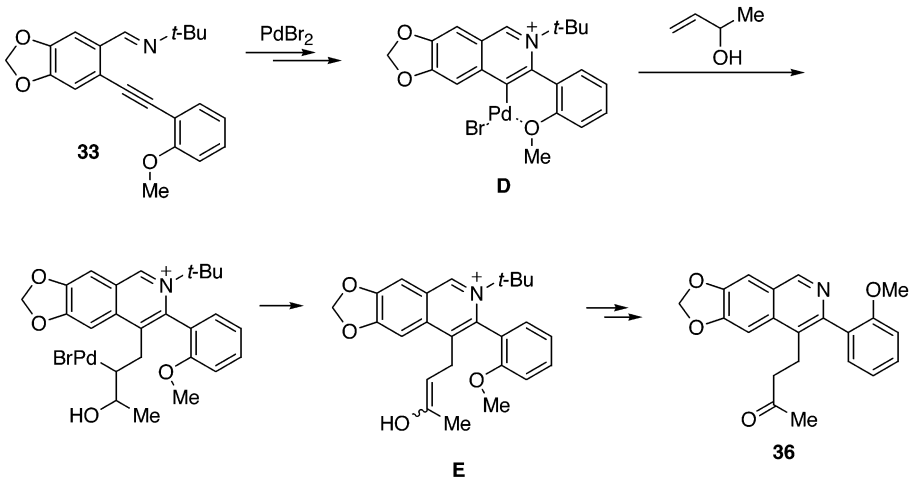
Arylaldimine **33**, bearing a methylenedioxo group on the benzylidene moiety and an *o*-methoxy group on the phenyl moiety, has been allowed to react with several olefins (entries 26−29). The reactions of arylaldimine **33** with *tert*-butyl acrylate afforded a 61% (entry 26) or an 82% (entry 27) yield of isoquinoline **34** following procedures A and B, respectively. For this specific arylaldimine, procedure A is not as efficient as procedure B. When *N*,*N*-dimethylacrylamide was allowed to react with arylaldimine **33**, an 89% yield of isoquinoline **35** was isolated as a 73:27 *E*/*Z* mixture (entry 28). Comparing entries 23, 24, 27, and 28, one can see that the introduction of two methoxy groups onto the benzylidene moiety is much more efficient in promoting the Heck reaction than the introduction of a methylenedioxo group onto the benzaldimine moiety.

Unsaturated alcohols undergo reaction to afford ketone-containing products. Thus, 3-buten-2-ol has been allowed to react with arylaldimine **33** (entry 29). The corresponding ketone **36** was isolated in a 48% yield. The formation of ketone **36** can be explained by the mechanism shown in Scheme 4. The cyclization of arylaldimine **33** by $PdBr_2$ affords an arylpalladium(II) intermediate **D**, which is stabilized by the *o*-methoxy group. The cis addition of intermediate **D** to 3-buten-2-ol results in an alkylpalladium bromide intermediate, which undergoes β-hydride elimination to form enol **E**.[16] Subsequent tautomerization and fragmentation of intermediate **E** affords the desired ketone **36**.

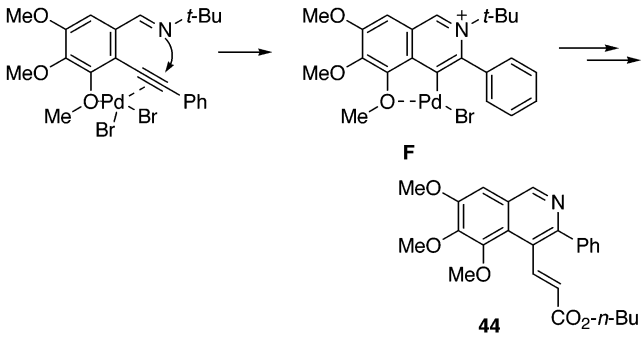
To further test the electronic effects of substituents on the isoquinoline olefination process, arylaldimines **37** and **40** have been prepared and allowed to react with *tert*-butyl acrylate and *N*,*N*-dimethylacrylamide. The reaction of arylaldimine **37**, bearing a dimethylamino group *meta* to the alkynyl group, and *tert*-butyl acrylate at 70 °C was complete in 16 h and afforded isoquinoline **38** in a 69% yield (entry 30). When the reaction was run at 90 °C, it was complete in 2 h and gave isoquinoline **38** in a 67% yield (entry 31). By employing *N*,*N*-dimethylacrylamide at 90 °C, the reaction was complete in 1.5 h and a 70% yield of isoquinoline **39** was isolated as a 91:9 *E*/*Z* mixture (entry 32). While the introduction of a *m*-dimethylamino group shortens the reaction time, the introduction of a dimethylamino group *para* to the alkynyl moiety slows the reaction down. Thus, arylaldimine **40** has been allowed to react with *tert*-butyl acrylate and *N*,*N*-dimethylacrylamide at 90 °C affording a 71% yield of isoquinoline **41** in 12 h (entry 33) and a 70% yield of isoquinoline **42** in 16 h (entry 34). The reason for the slow reactions is apparently because the dimethylamino group *para* to the alkynyl group in arylaldimine **40** significantly

(16) (a) Chalk, A. J.; Magennis, S. A. *J. Org. Chem.* **1976**, *41*, 273. (b) Tamaru, Y.; Yamada, Y.; Yoshida, Z. *Tetrahedron Lett.* **1978**, 919.

SCHEME 4



SCHEME 5



increases the electron density on the carbon−carbon triple bond and has little influence on the electron density of the imine nitrogen, disfavoring attack of the imine nitrogen on the triple bond. However, the dimethylamino group in arylaldimine **37** significantly increases the electron density on the imine nitrogen, favoring attack of the imine nitrogen on the carbon−carbon triple bond. Thus, the reactions of arylaldimine **37** reach completion in shorter reaction times.

The reactions of arylaldimine **43** with *n*-butyl acrylate, *tert*-butyl acrylate, *N*,*N*-dimethylacrylamide, and styrene gave the corresponding isoquinolines **44**−**47** in 51−78% yields (entries 35−38). Similar to the reactions of arylaldimine **29**, the reactions of arylaldimine **43** with olefins also involve electronic effects and facilitation by the *o*-methoxy group (Scheme 5). However, the reactions of arylaldimine **43**, having an *o*-methoxy group on the benzylidene moiety are very slow. For example, when benzaldimine **43** was allowed to react with *n*-butyl acrylate or *N*,*N*-dimethylacrylamide, the reactions are not complete even in 48 h at 90 °C (entries 35 and 37). The reason is probably because the intermediate **F** (Scheme 4) is quite hindered, preventing approach of the olefins. Comparing the results from arylaldimine **29** (entries 23 and 24) with those of arylaldimine **43** (entries 36 and 37), we conclude that the introduction of an *o*-methoxy group onto the phenyl moiety promotes this isoquinoline olefination better than the introduction of an *o*-methoxy group onto the benzylidene moiety.

To further test the effect of oxygen substituents in this isoquinoline olefination process, arylaldimine **48** has been prepared and allowed to react with olefins. The reaction of arylaldimine **48** and styrene afforded none of the desired product for reasons which are not obvious. When 3-buten-2-ol and 1-phenyl-2-propen-1-ol have been allowed to react with arylaldimine **48**, a 50% yield of ketone **49** (entry 39) and a 36% yield of ketone **50** were obtained, respectively. Using procedure B, the reaction of arylaldimine **48** and 5-hexen-2-ol afforded compound **51** by palladium migration, albeit in a low yield (entry 41).[17]

Conclusions

An efficient and straightforward route to synthesize 4-(1-alkenyl)isoquinolines and 4-alkyl-3-arylisoquinolines containing a ketone group has been developed with use of a palladium(II)-catalyzed cyclization, followed by olefination (Heck reaction). A wide variety of olefins undergo this process in moderate to excellent yields with high regioselectivity being observed. The introduction of an *o*-methoxy group on the benzaldimine moiety promotes the Pd-catalyzed cyclization and stabilizes the resulting Pd(II) intermediate, improving the yields of the desired isoquinoline products. Moreover, the introduction of an *o*-methoxy group onto the phenyl moiety has been shown to promote this isoquinoline olefination more efficiently than the introduction of an *o*-methoxy group onto the benzylidene moiety. To form isoquinolines in high yields, both electronic effects and facilitation by an *o*-methoxy group are necessary.

Experimental Section

General. ^{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 with use of commercially prepared 60-mesh silica gel plates (Whatman K6F), 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].

Reagents. All reagents were used directly as obtained commercially unless otherwise noted. All palladium salts were donated by Johnson Matthey Inc. and Kawaken Fine Chemicals Co. Ltd. Compounds **1**,[1a] **10**,[1a] **12**,[1a] **14**,[1a] **20**,[1a] **52**,[1a] **53**,[12] **54**,[1a] 4-(dimethylamino)-2-iodobenzaldehyde,[8b] 5-(dimethylami-

(17) Larock, R. C.; Leung, W.; Stolz-Dunn, S. *Tetrahedron Lett.* **1989**, *30*, 6629.

no)-2-iodobenzaldehyde,[8b] 2-iodo-3,4,5-trimethoxybenzaldehyde,[8b] and *N*-(benzo[1,3]dioxol-5-ylmethylene)-*tert*-butylamine[14] were prepared according to previous literature procedures. The preparation and characterization of the other starting materials can be found in the Supporting Information.

Preparation of Arylaldimines: *N*-[4,5-Dimethoxy-2-(phenylethynyl)benzylidene]-*tert*-butylamine (16). To a solution of 2-bromo-4,5-dimethoxybenzaldehyde (1.23 g, 5.0 mmol) and phenylacetylene (0.62 g, 6.0 mmol) in Et_3N (20 mL) were added $PdCl_2(PPh_3)_2$ (70 mg, 2 mol %) and CuI (10 mg, 1 mol %). The resulting mixture was then heated under an Ar atmosphere at 55 °C. The reaction was monitored by TLC to establish completion. When the reaction was complete, the reaction mixture was allowed to cool to 25 °C, 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 to afford the corresponding arylalkyne. To the purified arylalkyne in a 4-dram vial was added *t*-$BuNH_2$ (12 equiv). The mixture was then stirred under an Ar atmosphere at 25 °C 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 1.32 g of the indicated arylaldimine in an 82% overall yield as a yellow solid: mp 137−140 °C; ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 9H), 3.95 (s, 3H), 4.00 (s, 3H), 7.01 (s, 1H), 7.36−7.38 (m, 3H), 7.52−7.55 (m, 2H), 7.63 (s, 1H), 8.86 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 30.1, 56.2, 56.3, 57.8, 86.9, 93.8, 107.9, 113.9, 117.1, 123.5, 128.5, 128.7, 131.5, 132.1, 149.9, 150.5, 153.9; IR ($CHCl_3$, cm^{-1}) 3019, 2969, 1681, 1593, 1507; HRMS calcd for $C_{21}H_{23}O_2N$ 321.1729, found 321.1735.

The preparation and characterization of other arylaldimines employed in this study can be found in the Supporting Information.

General Procedure A for the Palladium-Catalyzed Formation of Isoquinolines. Dried DMSO (3 mL), $PdBr_2$ (6.7 mg, 0.025 mmol), $Cu(OAc)_2$ (0.091 g, 0.50 mmol), NaOAc (0.062 g, 0.75 mmol), and the arylaldimine (0.25 mmol) were placed in a 4-dram vial. The contents were then stirred for 1 min, and the appropriate olefin (1.25 mmol) was added. The vial was sealed carefully and heated in an oil bath at 70 °C for the indicated period of time. The reaction was monitored by TLC to establish completion. The reaction mixture was cooled to 25 °C, diluted with 20 mL of EtOAc, washed with 20 mL of brine, dried (Na_2SO_4), and filtered. The solvent was evaporated under reduced pressure, and the product was isolated by chromatography on a silica gel column.

General Procedure B for the Palladium-Catalyzed Formation of Isoquinolines. Dried DMSO (3 mL), $PdBr_2$ (6.7 mg, 0.025 mmol), $CuCl_2$ (3.4 mg, 0.025 mmol), $NaHCO_3$ (0.063 g, 0.75 mmol), and the arylaldimine (0.25 mmol) were placed in a 4-dram vial. The contents were then stirred for 1 min and the appropriate olefin (1.25 mmol) was added. The vial was flushed with O_2 and heated in an oil bath at 70 or 90 °C under an O_2 balloon for the indicated period of time. The reaction was monitored by TLC to establish completion. The reaction mixture was cooled to 25 °C, diluted with 20 mL of EtOAc, washed with 20 mL of brine, dried (Na_2SO_4), and filtered. The solvent was evaporated under reduced pressure, and the product was isolated by chromatography on a silica gel column.

***n*-Butyl (*E*)-3-(3-Phenylisoquinolin-4-yl)acrylate (5).** The reaction mixtures were chromatographed with use of 3:1 hexane/EtOAc to afford 51 mg (Table 3, entry 2) or 46 mg (entry 3) of the indicated compound as a yellow oil in a 61% or a 56% yield following procedure A or B, respectively: ^{1}H NMR ($CDCl_3$) δ 0.96 (t, J = 7.2 Hz, 3H), 1.37−1.46 (m, 2H), 1.64−1.72 (m, 2H), 4.23 (t, J = 6.8 Hz, 2H), 6.32 (d, J = 16.4 Hz, 1H), 7.42−7.49 (m, 3H), 7.63 (d, J = 7.2 Hz, 2H), 7.67 (d, J = 7.2 Hz, 1H), 7.78 (t, J = 7.6 Hz, 1H), 7.99 (d, J = 16.4 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 8.26 (d, J = 8.8 Hz, 1H), 9.31 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9, 19.4, 30.9, 64.8, 123.9, 124.4, 126.6, 127.4, 127.6, 128.4, 128.5, 128.5, 130.6, 131.5, 134.4, 140.2, 141.3, 152.0, 152.8, 166.4; IR (neat, cm^{-1}) 3412, 3058, 2958, 2872, 1716, 1636, 1570; HRMS calcd for $C_{22}H_{21}O_2N$ 331.1572, found 331.1577.

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

Acknowledgment. We gratefully acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research and Johnson Matthey Inc. and Kawaken Fine Chemicals Co. Ltd. for generous donations of palladium catalysts.

Supporting Information Available: Preparation and characterization of the starting materials **16**, **22**, **29**, **33**, **37**, **40**, **43**, and **48**; characterization data for compounds **2**, **5**−**9**, **11**, **13**, **15**, **17**−**19**, **21**, **23**−**28**, **30**−**32**, **34**−**36**, **38**, **39**, **41**, **42**, **44**−**47** and **49**−**51**; copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **2**, **5**−**9**, **11**, **13**, **16**−**19**, and **21**−**51**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0261303