

# Highly Efficient Synthesis of Isoquinolines via Nickel-Catalyzed Annulation of 2-Iodobenzaldimines with Alkynes: Evidence for Dual Pathways of Alkyne Insertion

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## ABSTRACT



A wide range of substituted isoquinolines were synthesized via a highly efficient nickel-catalyzed annulation of the *tert*-butyl imines of 2-iodobenzaldehydes and various alkynes; examination of the regiochemistry of isoquinolines synthesized indicates that there are two different alkyne insertion pathways for the catalytic reactions.

Functionalized isoquinolines are known to show important pharmacological properties such as antitumor, analgesic, antihistaminic, and antifertility activity.<sup>1</sup> Furthermore, these compounds are useful ligands in phosphorescent emitters for organic light-emitting diodes.<sup>2</sup> Classical methods for the synthesis of isoquinolines including the Bischler–Napieralski, the Pomeranz–Fritsch, and the Pictet–Spengler reactions<sup>1a,3</sup> generally require either harsh conditions or tedious reaction procedures. Transition-metal-catalyzed synthesis of isoquinolines from *tert*-butylimine of 2-iodobenzaldehydes and alkynes (or allenes) was a promising method. Initially, Heck<sup>4</sup> first observed a stoichiometric version of this

reaction with palladium complexes and Larock<sup>5</sup> developed the catalytic version of the reaction. Later, some other related catalytic reactions appeared.<sup>6</sup> All of these reactions were based on palladium catalysis in the presence of base and suffered from limitation of alkynes due to various competitive reactions.<sup>5</sup> The use of dialkylalkynes is restricted due to the possible  $\beta$ -hydride elimination after alkyne insertion into the arylpalladium bond or multiple insertion of the alkynes.<sup>4a,5a</sup> Terminal alkynes and trimethylsilyl alkynes underwent Sonogashira-type coupling easily under the reaction conditions instead of the direct annulation reaction, although these coupling products can be converted further to the final isoquinoline products using CuI as the catalyst.<sup>5d</sup> Other drawbacks for these palladium-catalyzed reactions were the higher reaction temperatures, lengthy reaction intervals, and

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requirement of excess alkynes that led to the formation of naphthalene derivatives.<sup>4a</sup> Herein, we report an exceedingly efficient and convenient nickel-catalyzed annulation of *tert*-butylimine of 2-iodobenzaldehydes with various alkynes under milder reaction conditions that eliminates the above-mentioned problems. In addition, the regioselectivities of products indicate two different possible alkyne insertion pathways for this nickel-catalyzed reaction.

Our interest in nickel- and cobalt-catalyzed cyclization reactions<sup>7</sup> prompted us to investigate the possibility of synthesizing isoquinolines from alkynes and 2-iodobenzaldimine. We started the investigation by evaluating the influence of catalyst and the ligands on the annulation of 2-iodobenzaldimine (**1a**) with diphenylacetylene (**2a**). The reaction carried out in the presence of NiBr<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> and zinc powder in CH<sub>3</sub>CN at 80 °C afforded 3,4-diphenylisoquinoline (**3a**) in 91% yield. Control experiments revealed that in the absence of nickel complex or zinc powder, no reaction occurred. Under similar reaction conditions, other nickel(II) complexes tested including NiBr<sub>2</sub>(dppe), NiCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, and NiBr<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> were also active, giving 3,4-diphenylisoquinoline in 98, 80, and 91% yields,<sup>8</sup> respectively. Nickel complexes with bidentate phosphine ligands appear slightly more effective than those with monodentate ligands, but the difference is relatively narrow compared to other nickel-catalyzed reactions<sup>7</sup> reported previously. All of the reactions were very fast and completed in just 20 min. In addition, Ni(COD)<sub>2</sub> and 2 equiv of P(*o*-tol)<sub>3</sub> without zinc powder also effectively catalyzed the annulation of **1a** with **2a** to give **3a** in essentially quantitative yield. The solvents employed for the present catalytic reaction are crucial to the product yield. The reactions of **1a** with **2a** in the presence of NiBr<sub>2</sub>(dppe) and zinc powder in various solvents were examined. The yields of **3a** in CH<sub>3</sub>CN, DMF, and THF (at ~70 °C) were 98, 94, and 63%, respectively. Only a trace of the product was observed in *o*-xylene. These results show that acetonitrile is the solvent of choice and that polar solvents are more effective than nonpolar solvent.<sup>8</sup> Based on the above studies, we chose NiBr<sub>2</sub>(dppe) in the presence of zinc in acetonitrile at 80 °C as the standard reaction condition for the following annulation reactions.

Next, the scope of this nickel-catalyzed annulation was examined, and the results are summarized in Table 1. In addition to 2-iodobenzaldimine **2a**, the corresponding bromo species also underwent annulation with **1a** effectively to yield **3a** in 76% (entry 2). It is interesting to note that product **3a** has shown significant biological activities such as stimulation of cell growth and inhibition of estradiol binding.<sup>1b</sup> Under similar reaction conditions, diethylacetylene **2b** reacts smoothly with **1a** to give 3,4-diethylisoquinoline in 87% yield.

Several unsymmetrical alkyne substrates were investigated to understand the regioselectivity of the present catalytic reaction. 1-Phenyl-1-butyne underwent cyclization successfully with **1a** to give regioisomers **3c** and **3c'** (Table 1, entry

**Table 1.** Results of Ni-Catalyzed Annulation Reactions<sup>a</sup>

<b>1a:</b> R <sup>1</sup> = R <sup>2</sup> = H, X = I <b>1b:</b> R <sup>1</sup> = R <sup>2</sup> = H, X = Br <b>1c:</b> R <sup>1</sup> , R <sup>2</sup> = OCH <sub>2</sub> O, X = I				
entry	imine	alkyne	product	yield % <sup>b</sup>
1	<b>1a</b>	Ph—C≡C—Ph <b>2a</b>		92 (98)
2	<b>1b</b>	<b>2a</b>	<b>3a</b>	76
3	<b>1a</b>	Et—C≡C—Et <b>2b</b>		87
4	<b>1a</b>	Et—C≡C—Ph <b>2c</b>	 	78:9
5	<b>1a</b>	EtO <sub>2</sub> C—C≡C—Ph <b>2d</b>	 	86:6
6	<b>1a</b>	MeOC—C≡C—Ph <b>2e</b>		83
7	<b>1a</b>	HOCH <sub>2</sub> —C≡C—Ph <b>2f</b>		70
8 <sup>c</sup>	<b>1a</b>	TMS—C≡C—Ph <b>2g</b>	 	76:5
9	<b>1a</b>	MeOC—C≡C—Et <b>2h</b>		83
10	<b>1a</b>	MeO <sub>2</sub> C—C≡C— <i>n</i> -Bu <b>2i</b>	 	82:4
11	<b>1a</b>	<i>n</i> -Bu—C≡C— <i>n</i> -Bu <b>2j</b>		76
12	<b>1a</b>	Et—C≡C—(CH <sub>2</sub> ) <sub>4</sub> —Et <b>2k</b>	 	44 40
13	<b>1a</b>	≡C—Ph <b>2l</b>		94
14	<b>1a</b>	≡C— <i>n</i> -Bu <b>2m</b>		76
15	<b>1a</b>	≡C—(CH <sub>2</sub> ) <sub>3</sub> —N≡N <b>2n</b>		84
16 <sup>c</sup>	<b>1c</b>	Ph—C≡C—Ph <b>2a</b>		94
17	<b>1a</b>	 <b>2o</b>		86
18	<b>1d</b>	Ph—C≡C—Ph <b>2a</b>		86

<sup>a</sup> Unless otherwise stated, all reactions were carried out under nitrogen atmosphere using **1a–d** 0.10 mmol, alkynes (**2a–o**, 0.10 mmol), NiBr<sub>2</sub>(dppe) (0.0050 mmol), and Zn (0.30 mmol) in CH<sub>3</sub>CN (3.0 mL) at 80 °C for 20 min. <sup>b</sup> Isolated yields. <sup>c</sup> Reaction time for entries 8 and 16 was 3 h.

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(8) The yields were calculated from crude NMR spectra using mesitylene as internal standard.

4) in 78 and 9% yields, respectively. Phenylpropiolate **2d** also reacts with **1a** regioselectively to give the annulation products **3d** and **3d'** in 86 and 6% yields, respectively (entry 5). As shown in entries 4 and 5, both major products **3c** and **3d** of these two reactions have the phenyl substituent at the C-3 position. The observations are surprising in view of the very different polarity of the alkyne carbons where the phenyl group is attached in **2c** and **2d**. The regiochemistry of compound **3c** was established by NOE experiments and of **3d** was determined by comparing its spectral data with those reported.<sup>6b</sup>

The observed regiochemistry of products **3c** and **3d** prompted us to investigate the annulation of other unsymmetrical phenyl-substituted alkynes **2e–g**. Under the standard reaction conditions, alkynes **2e** and **2o**, both with a keto substituent, reacted smoothly with **1a** in a highly regioselective fashion to provide products **3e** and **3p** exclusively with the regiochemistry similar to that of **3d**. For phenyl-substituted alkynes **2f,g**, in which the phenyl group is slightly more electron withdrawing than the hydroxymethyl substituent in **2f** and the TMS group in **2g**, the annulation of alkynes **2f,g** gave highly regioselective products **3f,g** (entries 6 and 7), respectively. Due to the presence of the bulkier TMS substituent in **2g**, the annulation of this alkyne with **1a** required a longer reaction time of 3 h. In addition, a minor regioisomer **3g'** in 5% was also observed. These results indicate that irrespective of the electron-withdrawing and electron-donating group bonded to the phenylalkynyl moiety, the phenyl group in the major isoquinoline products is generally attached to the carbon near to the nitrogen atom.

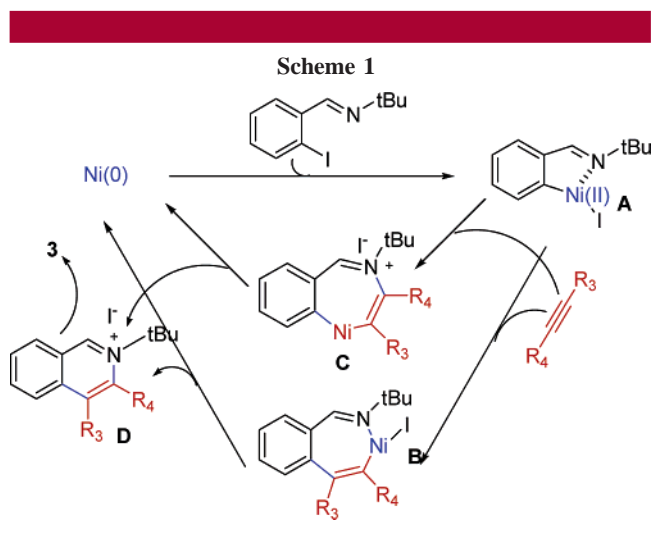
The scope and utility of this method was further extended by the reaction with alkylalkynyl derivatives<sup>9</sup> **2h** and **2i** consisting of a keto and ester group, respectively. For alkyne **2h**, completely regioselective product **3h** was isolated, but for **2i**, a mixture of products **3i** and **3i'** in an 82:4 ratio was found. Driven by curiosity, we treated 1,3-diyne **2j** and 3,9-diyne **2k** with **1a** under the standard reaction conditions. For **2j**, only product **3j** with the 1-hexynyl group attached to the C-3 of the isoquinoline product was isolated. In the case of **2k**, the reaction gave two regioisomers in ca. 1:1 ratio due to the lack of major functionality difference of the two substituents over the acetylene moiety. There was no further annulation of the second alkyne group, even for **2k**, where the second alkyne group is at a distance of four carbons apart.

Encouraged by the above results, terminal alkynes were tested for the present annulation reaction. Under the standard catalytic conditions, phenylacetylene (**2l**) reacted successfully with **1a** to give the corresponding annulation product **3l** in excellent yields. In a similar manner, 1-hexyne (**2m**) and 5-cyanopentyne (**2n**) afforded isoquinoline derivatives **3m** and **3n** in 76 and 84% yields, respectively. In all these cases, the competitive Sonogashira reaction was efficiently suppressed.<sup>5</sup> Also, no cyclotrimerization of the alkyne or minor regioisomer are observed. Again, the substituents of the terminal alkynes are all attached to the C-3 of isoquinolines. Finally, we evaluated the reaction of electron rich *o*-

iodopiperonaldimine with **2a**. The annulation gave the expected product **3o** in excellent yield, but a longer reaction time of 3 h was required. To see whether the present methodology can be applied to the preparation of pyridine derivative. Aldimine **1d**<sup>10</sup> was treated with **2a** under similar reaction conditions affording the expected product **3q** in 86% yield (entry 18).

There are several intriguing features of the present nickel-catalytic reaction. (i) Terminal alkynes and alkynes with a TMS or alkyl group were all successfully used as substrates for the annulation of **1a** to give the corresponding isoquinoline derivatives. This is in contrast with the previously reported palladium-catalyzed reactions. In the latter, these substrates first underwent Sonogashira-type alkynylation with **1a**. The presence of CuI is necessary for further annulation to give product **3**. (ii) For alkynes without a strong electron-withdrawing substituent including **2c,f,g,j,l–n**, the regioselectivity of alkyne insertion is similar to that reported for the nickel-catalyzed carbocyclization of *o*-iodophenyl ketone with these alkynes,<sup>11</sup> but for alkynes with a strong electron-withdrawing substituent such as a keto or ester group, the regiochemistry is entirely different from that of the carbocyclization (see eq 1). (iii) For all of the present annulation reactions, very high regioselectivity and fast reaction rates were observed. For each of the present nickel-catalyzed annulation, the regioselectivity is similar, but the reaction rate is much faster (at least 20 times) compared to the corresponding palladium-catalyzed reaction.

To account for the results of the present catalytic reaction, we propose the mechanism shown in Scheme 1. The reaction



likely starts with reduction of Ni(II) to Ni(0) by zinc powder. The oxidative addition of 2-iodobenzaldimine to Ni(0) leads to the formation of a five-membered-ring nickelacycle **A**. Coordinative insertion of alkyne into the nickelacycle,

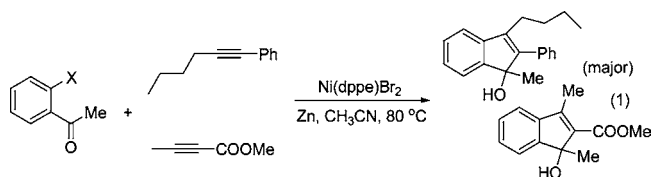
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followed by reductive elimination<sup>12</sup> gave an iminium cation<sup>6c</sup> **D** and the regeneration of the Ni(0) catalyst. The tertiary butyl group on the iminium ion was then removed by the attack of iodide ion produced during the reaction to give the final product **3**.

There are two possible pathways for the insertion of a coordinated alkyne into nickelacycle **A**. One is the insertion into the nickel–carbon bond of **A** to give intermediate **B**; the other is the insertion<sup>13,14</sup> into the nickel–nitrogen bond to give **C**. For alkynes without a strong electron-withdrawing substituent, we propose the alkyne insertion is via the nickel–carbon bond. The observed insertion regiochemistry is consistent with that reported previously for the nickel-,<sup>11b,c</sup> palladium-<sup>5</sup> and cobalt-catalyzed<sup>11a</sup> carbocyclization that involved insertion of alkyne into carbon–metal bonds with the carbon atom generally attacked the more positive carbon of the alkyne substrate. On the other hand, the observed regiochemistry for the annulation of **1a** with alkynes possessing a strong electron-withdrawing group such as a keto or ester group is very different from that reported for the metal-catalyzed carbocyclization. Examples of the regiochemistry of metal-catalyzed carbocyclization are shown in eq 1.<sup>11c</sup> Only one regioisomer, similar to a Michael addition product, was observed. As a result, it is unlikely that the insertion of electron-deficient alkyne into the nickelacycle

is via the nickel–carbon bond to give intermediate **B**. We thus believe that the main pathway for the insertion of these alkynes including **2d–e** and **2h–i** is into the nickel–nitrogen bond of the nickelacycle. Facile Michael-type addition of an imine or pyridine group to an electron-deficient carbon–carbon triple bond is known.<sup>13</sup> For the annulation of propiolates **2d** and **2i** with **1a** (entries 5 and 10), the minor isomers **3d'** and **3i'** likely via intermediate **B** were detected, indicative of competition between the two pathways for substrate **2**.



In conclusion, we have demonstrated a very convenient and highly regioselective synthetic approach for the preparation of substituted isoquinolines. This nickel-catalyzed annulation is much more efficient than the known palladium-catalyzed reaction in terms of the catalytic reaction rate and the scope of the alkyne substrates. The method tolerates a wide variety of functional groups and utilizes nonexpensive catalysts. In addition, the unusual regioselectivity indicated two pathways of the alkyne insertion into the nickelacycle intermediate. Further studies along this line are in progress.

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**Supporting Information Available:** Experimental procedures, spectral data of new compounds, and NOE data of selected compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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