

# Synthesis of Functionalized Isoquinolines via Sequential Cyclization/ Cross-Coupling Reactions

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CuX<sub>2</sub>-mediated cyclization of 2-alkynylbenzaldehyde *O*-methyl oximes in *N,N*-dimethylacetamide (DMA) gave rise to 4-chloroisoquinolines in good yield, which underwent the palladium-catalyzed cross-coupling reactions of arylboronic acids subsequently to afford the functionalized isoquinolines.

## Introduction

Methodology development for the construction of privileged scaffolds in pharmaceutical sciences is highly demanded due to the increasing significance of combinatorial chemistry. In particular, the development of novel methods using diversity-oriented synthesis strategies for the efficient generation of small molecules is an important goal in the field of chemical genetics.<sup>1</sup> It is well recognized that isoquinolines are common structural motifs in many natural products and pharmaceuticals that exhibit remarkable biological activities.<sup>2,3</sup> In addition, isoquinoline derivatives are also utilized as chiral ligands for transition metal catalysts,<sup>4</sup> and their iridium complexes are used in organic light-emitting diodes.<sup>5</sup> Thus, continuous efforts have been given for the development of new methods for their constructions.<sup>6,7</sup> For instance, Larock and co-workers reported the efficient synthesis of isoquinoline derivatives via transition metal catalyzed cyclization of *ortho*-alkynylaryl aldimines.<sup>6</sup> However, the stability issue of *ortho*-alkynylaryl aldimine limited the applications of the developed methods. As part of a continuing effort in our laboratory for accessing natural productlike compounds,<sup>8,9</sup> we became interested in exploring the efficient strategies to facilitate the isoquinolines generation, with a hope for finding better hits for our specific biological assays.

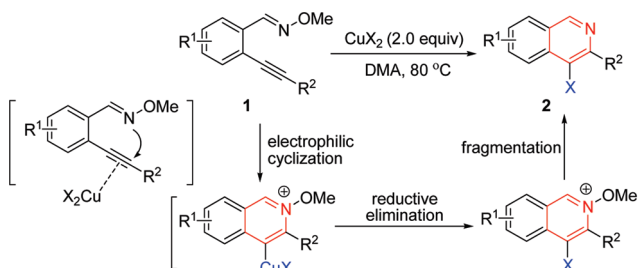
Recently, much attention has been focused on 2-alkynylbenzaldehydes for accessing privileged organic architectures.<sup>10</sup> We also utilized 2-alkynylbenzaldehydes as starting materials for the synthesis of 1,2-dihydroisoquinoline derivatives.<sup>9</sup> Prompted by these results, we conceived 2-alkynylbenzaldehyde *O*-methyl oximes might be used for further transformations due to the structural similarity. We reasoned that in the presence of copper(II) halide, 2-alkynylbenzaldehyde *O*-methyl oxime would undergo electrophilic cyclization, reductive elimination, and fragmentation leading to the corresponding 4-haloisoquinolines (Scheme 1). Sub-

sequently, these compounds could be further elaborated via palladium-catalyzed cross-coupling reactions to generate the functionalized isoquinolines. To verify this hypothesis, we started to investigate the possibility to build up the 4-haloisoquinoline scaffold via the tandem reactions as shown in Scheme 1.

## Result and Discussion

The initial attempt was carried out with 2-alkynylbenzaldehyde *O*-methyl oxime **1a** as the substrate for reaction development. The reaction was performed in benzene at 50 °C in the presence of 2.0 equiv of copper(II) chloride (Table 1, entry 1). Gratifyingly, we observed the formation of the desired product **2a** (16% yield). The yield increased to 31% when the reaction occurred at 100 °C (Table 1, entry 2). Further investigation revealed that the result dramatically improved when *N,N*-dimethylacetamide (DMA) was used as the solvent in the reaction (Table 1, entry 3, 70% yield). Only 2 h were needed for completion of reaction under the conditions. Inferior yields were displayed when other solvents were employed as replacements (Table 1, entries 4–8). The usage of copper(II) chloride was examined as well. A similar result was obtained when 4.0 equiv of CuCl<sub>2</sub> was utilized in the reaction (Table 1, entry 9). However, lower yield was afforded when the amount of CuCl<sub>2</sub> was reduced to 1.2 equiv (Table 1, entry 10, 58% yield). The subsequent temperature survey revealed that the reaction worked efficiently at 80 °C and the desired product could be generated in 74% yield (Table 1, entry 11). The reaction was retarded at 50 °C (Table

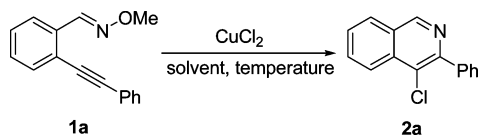
## Scheme 1



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**Table 1.** Initial Studies for the CuCl<sub>2</sub>-Mediated Cyclization of 2-Alkynylbenzaldehyde *O*-Methyl Oxime **1a**

entry	equiv of CuCl <sub>2</sub>	solvent	temperature (°C)	time (h)	yield (%) <sup>a</sup>
1	2.0	benzene	50	12	16
2	2.0	benzene	100	12	31
3	2.0	DMA	100	2	70
4	2.0	DMF	100	12	22
5	2.0	DMSO	100	12	48
6	2.0	1,4-dioxane	100	12	32
7	2.0	NMP	100	12	23
8	2.0	<sup>t</sup> BuOH	100	12	34
9	4.0	DMA	100	2	69
10	1.2	DMA	100	12	58
11	2.0	DMA	80	2	74
12	2.0	DMA	50	24	50

<sup>a</sup> Isolated yield based on 2-alkynylbenzaldehyde *O*-methyl oxime **1a**.

1, entry 12). In this reaction process, no palladium catalyst was presented and only copper(II) salt was involved. Moreover, the 2-alkynylbenzaldehyde *O*-methyl oxime was very stable and could be easily accessible via condensation of 2-alkynylbenzaldehyde with the corresponding amine.

Having identified the optimal conditions [CuX<sub>2</sub> (2.0 equiv), DMA, 80 °C], the scope of this reaction was then investigated and the results are summarized in Table 2. For all cases, the reaction proceeded smoothly to afford the corresponding 4-haloisoquinoline **2** in moderate to good yields. As expected, both electron-rich and electron-poor 2-alkynylbenzaldehyde *O*-methyl oximes are suitable substrates in this process. With respect to the substituents attached to the triple bond, the reactions also worked well to generate the desired product. For instance, 2-alkynylbenzaldehyde *O*-methyl oxime **1b** reacted with copper(II) chloride leading to the corresponding 3-cyclopropyl-4-chloroisoquinoline **2b** in 63% yield (Table 2, entry 2). Reactions of fluoro-substituted 2-alkynylbenzaldehyde *O*-methyl oximes **1c–1f** gave rise to the desired products in moderate to good yields (Table 2, entries 3–6). Similar results were observed when [1,3]dioxolyl-substituted 2-alkynylbenzaldehyde *O*-methyl oximes **1g–1i** were employed in the reactions of CuCl<sub>2</sub>. Besides copper(II) chloride, copper(II) bromide was a good partner as well in the reactions of 2-alkynylbenzaldehyde *O*-methyl oximes. For example, 60% yield was obtained when 2-alkynylbenzaldehyde *O*-methyl oxime **1e** was utilized as substrate in the reaction (Table 2, entry 11).

With the resulting halo-containing isoquinolines **2** in hands as well as in order to introduce more diversity in the scaffold, we started to explore the subsequent cross-coupling reactions by using the known organopalladium chemistry. Due to their easy handling and long shelf life, arylboronic acid derivatives would be the starting materials of choice. Thus, the Suzuki–Miyaura coupling reaction<sup>11</sup> was investigated by using the halo-substituted isoquinoline **2** as an electrophile for the synthesis of functionalized isoquinoline derivatives. After optimization of the reaction conditions, we found that the reactions proceeded efficiently in the presence of Pd(OAc)<sub>2</sub> (5 mol %), SPhos (5 mol %), and K<sub>3</sub>PO<sub>4</sub> in toluene

(Table 3). All the reactions worked well to generate the desired product **3** in good to excellent yields.

## Conclusion

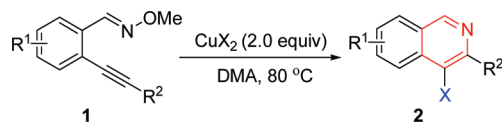
In conclusion, the copper(II)-mediated cyclization of 2-alkynylbenzaldehyde *O*-methyl oximes in DMA was described, which gave rise to the corresponding 4-haloisoquinolines in moderate to good yield. These compounds could undergo the palladium-catalyzed cross-coupling reactions of arylboronic acids subsequently to afford the functionalized isoquinoline derivatives. The method disclosed herein represented a simple, general, efficient, and practical synthesis of 3,4-disubstituted isoquinolines.

## Experimental Section

All reactions were performed in test tubes under a nitrogen atmosphere. Flash column chromatography was performed using silica gel (60 Å pore size, 32–63 μm, standard grade). Analytical thin-layer chromatography was performed using glass plates precoated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography (TLC) plates were visualized by exposure to ultraviolet light. Organic solutions were concentrated on rotary evaporators at ~20 Torr (house vacuum) at 25–35 °C. Commercial reagents and solvents were used as received.

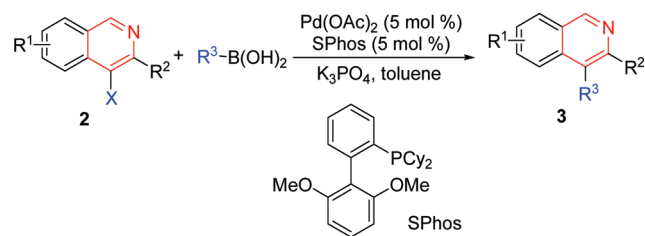
**General Procedure for CuX<sub>2</sub>-Mediated Cyclization of 2-Alkynylbenzaldehyde *O*-Methyl Oxime **1**.** DMA (1.0 mL) was added to a mixture of 2-alkynylbenzaldehyde *O*-methyl oxime **1** (0.30 mmol) and CuX<sub>2</sub> (0.60 mmol) at 80 °C. After completion of reaction as indicated by TLC, the mixture was cooled to room temperature, diluted with ethyl acetate (5 mL), and quenched with water (5 mL). The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluting with polyethylene/ethyl acetate (PE/EA) = 50/1 to 8/1) to provide the desired 4-haloisoquinoline **2**. Data of selected example, 4-chloro-3-cyclopropylisoquinoline (**2b**): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 1.06–1.11 (m, 2H), 1.18–1.22 (m, 2H), 2.70–2.75 (m, 1H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.74 (t, *J* = 7.2 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 8.99 (s, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 9.4, 13.8, 123.0, 125.5, 126.4, 127.5, 127.7, 131.1, 133.9, 150.2, 152.2; HRMS calcd for C<sub>12</sub>H<sub>10</sub>ClN (M<sup>+</sup> + H) 204.0580, found 204.0573.

**General Procedure for Palladium-Catalyzed Cross-Coupling Reactions of 4-Chloroisoquinoline **2** with Arylboronic Acids.** Toluene (1.0 mL) was added to a mixture of Pd(OAc)<sub>2</sub> (0.9 mg, 2 mol %), SPhos (3.3 mg, 4 mol %), 4-haloisoquinoline **2** (0.2 mmol, 1.0 equiv), arylboronic acid (0.3 mmol, 1.5 equiv), and powdered, anhydrous K<sub>3</sub>PO<sub>4</sub> (84.8 mg, 0.4 mmol, 2.0 equiv). The reaction was stirred at 80 °C with vigorous stirring until 4-haloisoquinoline **2** had been completely consumed. Then the mixture was allowed to cool to room temperature, diluted with ethyl acetate (5 mL), filtered through a thin pad of silica gel (eluting with ethyl acetate), and concentrated under reduced pressure. The crude residue obtained was

**Table 2.** CuX<sub>2</sub>-Mediated Cyclization of 2-Alkynylbenzaldehyde *O*-Methyl Oxime **1**

Entry	Compound <b>1</b>	CuX <sub>2</sub>	Product <b>2</b>	Yield (%) <sup>a</sup>
1		CuCl <sub>2</sub>		74
2		CuCl <sub>2</sub>		63
3		CuCl <sub>2</sub>		55
4		CuCl <sub>2</sub>		50
5		CuCl <sub>2</sub>		72
6		CuCl <sub>2</sub>		66
7		CuCl <sub>2</sub>		67
8		CuCl <sub>2</sub>		45
9		CuCl <sub>2</sub>		60
10		CuBr <sub>2</sub>		50
11		CuBr <sub>2</sub>		60
12		CuBr <sub>2</sub>		45
13		CuBr <sub>2</sub>		50

<sup>a</sup> Isolated yield based on 2-alkynylbenzaldehyde *O*-methyl oxime **1**.

**Table 3.** Palladium-Catalyzed Cross-Coupling Reactions of 4-Chloroisoquinoline **2** with Arylboronic Acids

Entry	Compound <b>2</b> / R <sup>3</sup>	Product <b>3</b>	Yield <sup>a</sup> (%)
1	<b>2a</b> / C <sub>6</sub> H <sub>5</sub>		89
2	<b>2a</b> / 4-MeOC <sub>6</sub> H <sub>4</sub>		94
3	<b>2a</b> / 4-MeC <sub>6</sub> H <sub>4</sub>		99
4	<b>2a</b> / 3-AcC <sub>6</sub> H <sub>4</sub>		98
5	<b>2a</b> / 4-NCC <sub>6</sub> H <sub>4</sub>		75
6	<b>2c</b> / 4-MeC <sub>6</sub> H <sub>4</sub>		94
7	<b>2e</b> / 4-MeC <sub>6</sub> H <sub>4</sub>		98
8	<b>2f</b> / 4-MeC <sub>6</sub> H <sub>4</sub>		87
9	<b>2i</b> / 4-MeC <sub>6</sub> H <sub>4</sub>		98

<sup>a</sup> Isolated yield based on 4-chloroisoquinoline **2**.

purified by flash chromatography on silica gel (eluting with PE/EA = 50/1 to 4/1) to provide the desired product **3**. Data of selected example, 3,4-diphenylisoquinoline (**3a**): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 7.13–7.24 (m, 5H), 7.28–7.38 (m, 5H), 7.52–7.59 (m, 2H), 7.64–7.66 (m, 1H), 7.98–8.01 (m, 1H), 9.35 (s, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 125.4, 126.7, 126.9, 127.1, 127.2, 127.3, 127.4, 128.1, 130.1, 130.3, 130.4, 131.0, 135.8, 137.0, 140.6, 150.5, 151.5; HRMS calcd for C<sub>21</sub>H<sub>15</sub>N (M<sup>+</sup> + H) 282.1283, found 282.1273. (For details, please see the Supporting Information).

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**Supporting Information Available.** Experimental procedures, characterization data, <sup>1</sup>H and <sup>13</sup>C NMR spectra of compounds **2** and **3**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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