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Synthesis of Highly Substituted 2-Arylindoles via Copper-Catalyzed Coupling of Isocyanides and Arylboronic Acids

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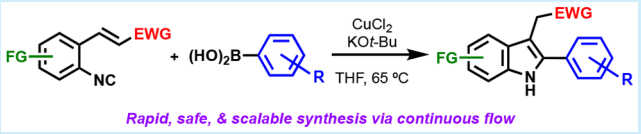
Supporting Information

ABSTRACT: Highly functionalized 2-arylindoles were synthesized from 2-alkenylarylisocyanides and arylboronic acids using a simple, inexpensive copper catalyst. The reaction exhibits excellent functional group tolerance for both the arylisocyanide and boronic acid coupling partners. To avoid the direct handling of the pungent arylisocyanide starting materials, continuous flow chemistry is further demonstrated to provide safe and effective access to 2-arylindoles through *in situ* dehydration and cyclization of easy-to-handle 2-alkenyl-*N*-formylanilines.



The 2-arylindole motif is found in a variety of natural products, therapeutics, and drug candidates.[1] Key examples include bazedoxifene,[1e] a treatment for postmenopausal osteoporosis, and the natural product cladoniamide G,[2] which demonstrates antibreast cancer activity. In addition, 2-arylindoles form the core of several medicines currently in development. Specifically, Kenpaullone has shown anticystic fibrosis activity,[3] 2-phenylindole-3-carboxaldehydes have shown high antiproliferative activity in breast cancer cell lines,[4] and 2-pyridylindole has potential application as an antidepressant (Figure 1).[5] Despite the vast array of methods to synthesize 2-arylindoles,[1c,6] new methods that efficiently access highly decorated indoles remain desirable.[7]

Recently, the amphoteric nature of arylisocyanides has been exploited in the preparation of nitrogen-containing heterocycles.[8,9] In the case of 2-arylindoles, the two current methods employing arylisocyanides provide modest yields, require stoichiometric amounts of palladium, or utilize difficult to handle 2-alkynylarylisocyanides (Scheme 1a).[10,11] Alternatively,

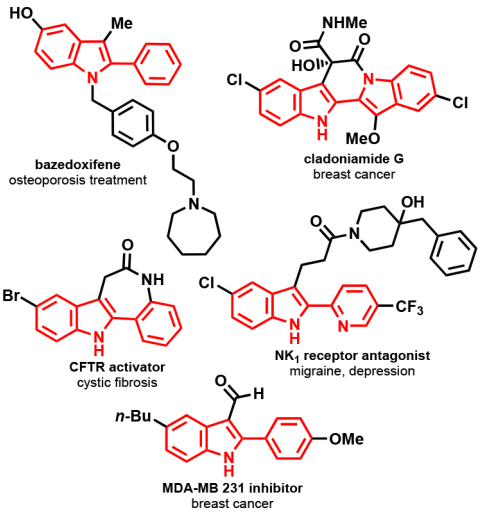
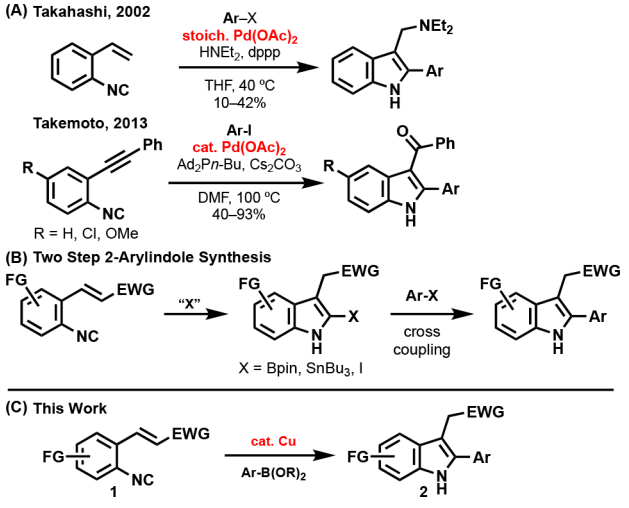


Figure 1. Representative examples of highly substituted 2-arylindole-containing molecules: current therapeutics, natural products, and drugs in development.

Scheme 1. (A) Current Methods To Synthesize 2-Arylindoles from Arylisocyanides; (B) Two-Step Synthesis of 2-Arylindoles from Arylisocyanides; (C) Synthesis of 2-Arylindoles via Copper-Catalyzed Cyclization of 2-Alkenylarylisocyanides



2-iodo, 2-stannyl, and 2-boryl-substituted indoles have been synthesized from isocyanides (Scheme 1b).[12−14] Subsequent cross-coupling has provided access to a variety of 2-arylindoles. A general, one-step catalytic approach to highly substituted 2-arylindoles directly from arylisocyanides has yet to be developed.

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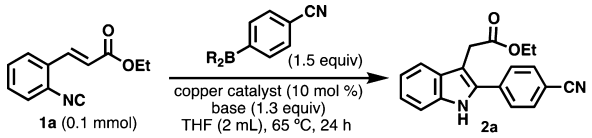
Table 1. Optimization of a Copper-Catalyzed Cyclization of Arylisocyanides with Arylboronic Acids[a]



entry	boron reagent	base	copper cat.	additive	conversion[b] (%)	yield[b] (%)
1	Ar–BMIDA	KO*t*-Bu	$CuCl_2$	–	87	<5[c]
2	Ar–Bpin	KO*t*-Bu	$CuCl_2$	–	72	6
3	**Ar–B(OH)$_2$**	**KO*t*-Bu**	**$CuCl_2$**	–	**93**	**56**
4	Ar–B(OH)$_2$	KO*t*-Bu	$CuOTf_2$	–	93	55
5	Ar–B(OH)$_2$	KO*t*-Bu	–	–	42	<1[d]
6	Ar–B(OH)$_2$	–	$CuCl_2$	–	68	<1[d]
7	Ar–B(OH)$_2$	LiO*t*-Bu	$CuCl_2$	–	49	14
8	Ar–B(OH)$_2$	KO*t*-Bu	$CuCl_2$	air	89	39

[a]Reaction conditions: aryl isocyanide **1a** (0.1 mmol), 4-cyanophenylboronic acid (1.5 equiv), potassium *tert*-butoxide (1.3 equiv), and $CuCl_2$ (0.1 equiv) were stirred in THF (2 mL) for 24 h at 65 °C under an inert atmosphere. [b]Conversion and yield were determined using HPLC with naphthalene as an internal standard. [c]Trace product detected. [d]No product detected.

Despite their unique and promising reactivity, arylisocyanides remain underutilized owing to their offensive odor.[15,16] Arylisocyanides are generally synthesized from the corresponding aniline via formylation followed by dehydration. These precursors to arylisocyanides, namely *N*-formylaniline and anilines, are bench-stable, easy to handle, and frequently commercially available. Thus, developing a telescoped procedure in which the arylisocyanides can be synthesized *in situ* from a benign precursor and immediately reacted would enable their use in organic synthesis.

Continuous flow is uniquely suited to enable the safe use of toxic, reactive, and dangerous reagents.[17] Unlike traditional batch chemistry, continuous flow reactors utilize narrow diameter tubing that enables improved heat transfer during exothermic reactions, improved mixing, and smaller quantities of dangerous reagents at any given time.[18] Additionally, reactions can be telescoped, allowing the safe generation and use of toxic or unstable intermediates.[19] Herein, we describe a facile copper-catalyzed cyclization of 2-alkenylarylisocyanides and readily available boronic acids to access highly substituted 2-arylindoles and demonstrate the safe use of 2-alkenylarylisocyanides via a continuous flow setup (Scheme 1c).

Inspired by the copper-catalyzed borylation of 2-alkenylarylisocyanides,[14] we began our studies by investigating the copper-catalyzed reaction between arylisocyanide **1a** and a variety of arylboron reagents to generate 2-arylindole **2a** (Table 1). Initial reactions using easy to handle BMIDA and Bpin reagents demonstrated the viability of the transformation, albeit with low yields of **2a**, <5% and 6%, respectively (Table 1, entries 1 and 2). Utilizing the more reactive 4-cyanophenylboronic acid gave indole **2a** in good yield (56%; Table 1, entry 3). Of note, these reactions were heterogeneous in nature, with the copper catalyst being incompletely solubilized. A more soluble copper(II) triflate was tested and showed no improvement in yield (Table 1, entry 4). As such, the inexpensive copper(II) chloride ($CuCl_2$) catalyst was used throughout. In the absence of a copper catalyst, product formation was not observed (Table 1, entry 5). Similarly, in the absence of a base, product formation was not observed (Table 1, entry 6). We hypothesize that, in solution, the alkoxide base activates the boronic acid, forming a nucleophilic aryl boronate salt, which more readily undergoes transmetalation with the copper catalyst. Consistent with this proposal, use of lithium *tert*-butoxide (LiO*t*-Bu), which is known to form a less activated boronate species, resulted in a significantly lower yield of **2a** (11%, Table 1, entry 7). Finally, we were pleased to find that the reaction is only marginally air-sensitive, with only a modest reduction in yield when the reaction is set up in the absence of air-sensitive techniques (Table 1, entry 8).

Encouraged by these promising results, we explored the scope of this copper-catalyzed cyclization of arylisocyanide **1a** with a variety of commercially available arylboronic acids to afford the corresponding 2-arylindoles (Scheme 2). We observed that both electron-donating and -withdrawing substituents on the arylboronic acids were tolerated (**2a–h**). Substrates containing a free amino group (**2i**) do not provide an indole product. However, nitro-substituted boronic acids (an amine surrogate) provided the corresponding indole in good yield (**2c**). Indoles containing functional handles capable of further elaboration, such as alkene, alkyne, bromide, and methyl ketone, were synthesized in modest to good yield (**2j–m**). Notably, our method allowed the synthesis of molecules containing multiple heterocycles in a single step (**2n** and **2o**).

A variety of 2-alkenylarylisocyanides were synthesized to explore the scope of this method (Scheme 3). Both electron-donating and -withdrawing groups on the 5, 6, and 7 positions of the aryl ring of isocyanide **1** were tolerated, affording the corresponding indole in good yield (**3a–g**). To expand the scope of this method further, orthogonal electrophilic vinyl components of aryl isocyanide **1** were explored. Both the vinylogous nitrile **1i** and, more interestingly, the poor Michael acceptor, enamide **1h**, proved competent in the reaction. Unsurprisingly, isocyanide **1j** containing the nonelectrophilic styrenyl functional group was not transformed to the desired indole **3j**, and a mixture of **1j** and decomposition were observed.

Our method featuring a copper-catalyzed cyclization of arylisocyanides with arylboronic acids demonstrates the potential of arylisocyanides in the synthesis of nitrogen-containing heterocycles. However, given their odor and variable toxicity, we have additionally developed a telescoped, continuous flow setup for their safe handling. The improved setup consists of synthesizing the arylisocyanide **1a** via dehydration of arylformamide **4** and then accessing the highly substituted aryl indole in a single step using the method described herein (Table 2). Initially, we explored conditions to

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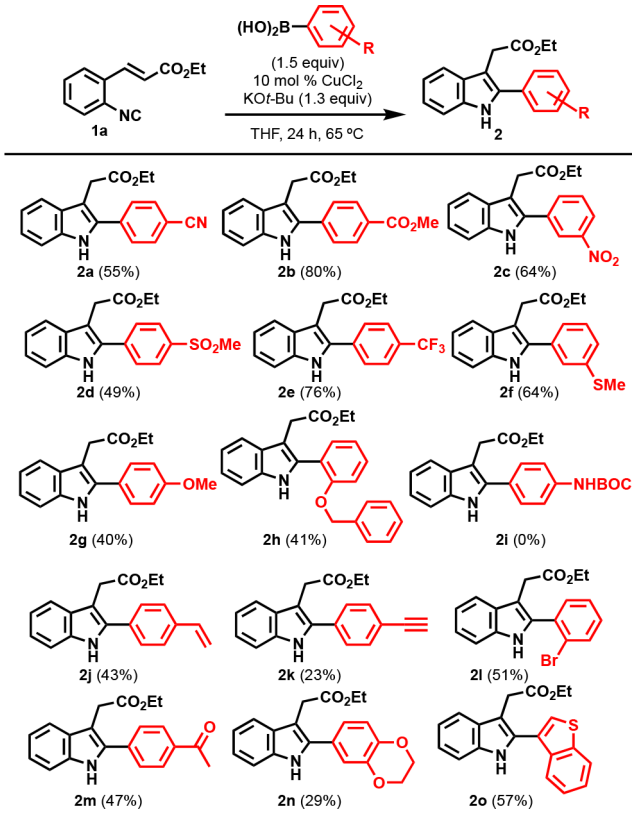
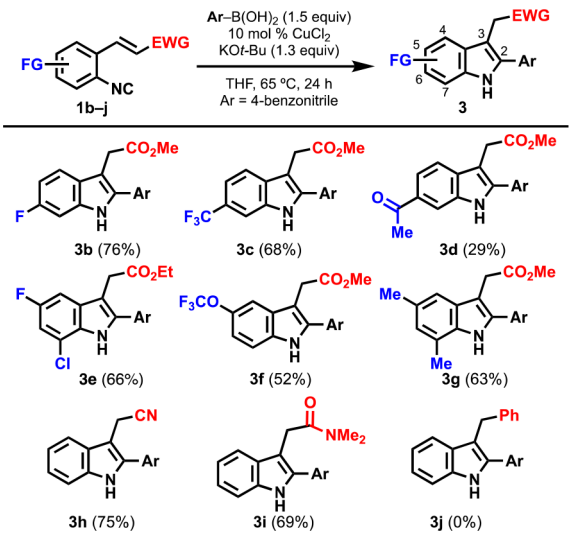
Scheme 2. Preparation of 2-Arylindoles from Various Commercially Available Arylboronic Acids[a,b]



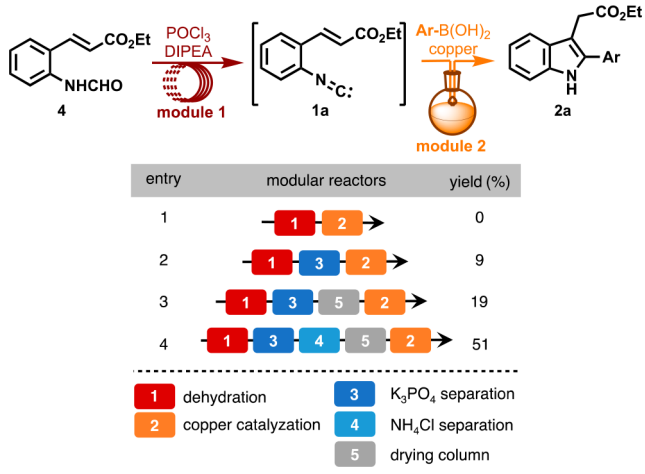
[a]Reaction conditions: aryl isocyanide **1a** (1 mmol), aryl boronic acid (1.5 equiv), potassium *tert*-butoxide (1.3 equiv), and $CuCl_2$ (0.1 equiv) were stirred in THF (15 mL) for 24 h at 65 °C under an inert atmosphere. [b]All yields in parentheses are the isolated product after silica gel chromatography.

Scheme 3. Preparation of 2-Arylindoles from Various 2-Alkenylarylisocyanides[a,b]



[a]Reaction conditions: aryl isocyanide **1** (1 mmol), 4-cyanophenylboronic acid (1.5 equiv), potassium *tert*-butoxide (1.3 equiv), and $CuCl_2$ (0.1 equiv) were stirred in THF (15 mL) for 24 h at 65 °C under an inert atmosphere. [b]All yields in parentheses are the isolated product after silica gel chromatography.

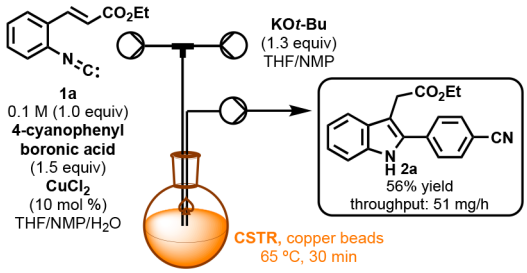
Table 2. Development of a Two-Step Continuous Flow Synthesis of Indole 2a from *N*-Formylaniline 4[a]



[a]Yields were determined using HPLC with naphthalene as an internal standard.

decrease the reaction time of the copper-catalyzed cyclization of arylisocyanide **1a** to increase throughput and decrease reactor size in the continuous flow setup. Copper flow reactors have been utilized to decrease reaction times compared to their batch reaction counterparts.[20] Our continuous flow system consists of mixing three streams containing arylisocyanide **1a**, arylboronic acid, and potassium *tert*-butoxide in a continuous stirred tank reactor (CSTR) containing copper beads heated to 65 °C for 30 min (Scheme 4). We were pleased to observe

Scheme 4. Copper-Catalyzed Cyclization of Arylisocyanide 1a to Indole 2a in a CSTR[a]



[a]Yields were determined using HPLC with naphthalene as an internal standard.

indole **2a** in 56% yield, providing similar yields to our isolated batch reactions (55% yield). NMP was added to increase solubility and reaction rate.[21,22]

We then developed the dehydration of *N*-formylaniline in continuous flow. Streams of **4**, phosphorus oxychloride ($POCl_3$), and diisopropylethylamine (DIPEA) were mixed for 2.5 min, providing isocyanide **1a** in 94% yield (Table 4, Module 1; see Supporting Information (SI) for details, Scheme S-3). Dichloromethane (DCM) was chosen as the ideal solvent for the dehydration of formamide **4** due to its compatibility with the subsequent copper-catalyzed cyclization step, solubility of starting materials, and its good separation from the aqueous streams.

Telescoping the dehydration of *N*-formylaniline **4** directly into the copper-catalyzed cyclization yielded no indole product (Table 2, entry 1; see SI for details). The acidic and amine

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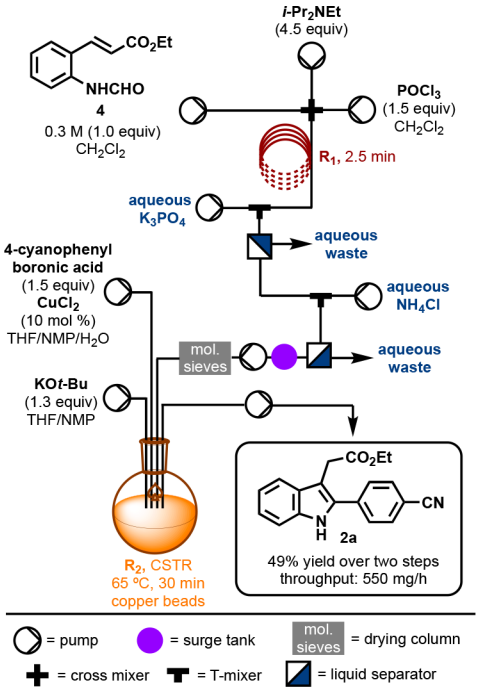
byproducts formed in the dehydration step are not compatible with the subsequent cyclization. The addition of liquid−liquid membrane separators helped to remove the byproducts of the dehydration through an aqueous extraction. After the addition of a single in-line basic separation with 0.5 M K_3PO_4, a 9% yield of indole **2a** was observed (Table 2, entry 2). After a single extraction, a stream of **1a** retained water, so a drying column consisting of a packed bed of 4 Å molecular sieves was added, resulting in an increased, yet modest yield of 19% (Table 2, entry 3). Finally, a slightly acidic separation with ammonium chloride was added after the basic separation to remove any remaining acid or amine byproducts. After two separations and a drying column, indole **2a** was observed in 51% yield over two steps, a comparable yield to both the batch isolated yield of 55% and the single step CSTR yield of 56% (Table 2, entry 4).

The integrated flow setup with increased throughput (550 mg/h) consists of one PEEK cross-mixer, one perfluoroalkoxyalkane (PFA) tubing reactor, two liquid−liquid membrane separators, a packed bed containing 4 Å molecular sieves, a surge tank, and a CSTR (35 mL) with copper beads (Scheme 5). This setup provided **2a** in 49% yield over two steps,

Scheme 5. Two-Step Continuous Flow Synthesis of Indole 2a from Simple *N*-Formylaniline 4[a]



[a]Yield of indole **2a** (1.8 mmol) is isolated product after silica gel chromatography.

demonstrating the scalability of the system. Additionally, we explored adding the formylation of a simple *ortho*-alkenylaniline to our two-step continuous flow setup. However, a low yield of 12% of indole **2a** was observed due to the increased complexity of the impurity profile (see the SI for details). Given that the batch preparation of **4** is straightforward, further inline purification modules were not explored after the formylation step.

In conclusion, we have developed a catalytic method for the synthesis of highly substituted 2-arylindoles from 2-alkenylisocyanides and arylboronic acids. Additionally, we have developed a safe and effective approach to the synthesis of 2-arylindoles from readily available 2-alkenyl-*N*-formylanilines in continuous flow. We have shown that multiple incompatible reaction steps can be telescoped through the use of liquid−liquid separators and a drying column, which has the potential to be adapted to a variety of sensitive isocyanide chemistry conducted in continuous flow.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01132.

Experimental procedures and spectral data for isocyanides **1a−j**, indoles **2a−o**, and indoles **3b−j** and experimental procedures for the continuous flow system (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

†Dedicated to Dr. Zhi He, deceased September 24, 2016.

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