# Tandem Addition/Cyclization for Access to Isoquinolines and Isoquinolones via Catalytic Carbopalladation of Nitriles

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**S** *Supporting Information*

**ABSTRACT:** The first example of the palladium-catalyzed sequential nucleophilic addition followed by an intramolecular cyclization of functionalized nitriles with arylboronic acids has been achieved, providing an efficient synthetic pathway to access structurally diverse isoquinolines and isoquinolones. This methodology has also been successfully applied to the total synthesis of the topoisomerase I inhibitor CWJ-a-5 (free base).
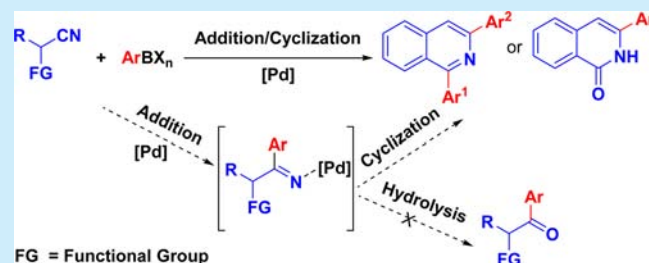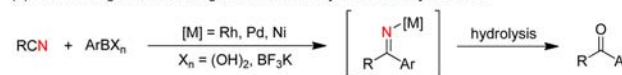
The cyano group is one of the most accessible polar unsaturated carbon−heteroatom multiple bonds, and it is widely used in synthetic and medicinal chemistry.[1] The nitrile may serve as a versatile precursor to structurally diverse compounds such as amines, carboxylic acids and derivatives, aldehydes, and heterocycles. By contrast, it is generally known that nitriles such as acetonitrile or benzonitrile have been used as solvents or ligands in organometallic reactions,[2] presumably due to the inherently inert nature of nitriles. Since Larock's pioneering contributions to the addition of arylpalladium species to the cyano group,[3] remarkable advances in transition-metal-catalyzed additions of organoboron reagents to nitriles have been documented, but they exclusively provide aryl ketone products (Scheme 1a).[4] We recently disclosed the palladium-catalyzed addition of organoboron reagents to nitriles for the synthesis of alkyl aryl ketones and diketones.[5] In addition, Lu's group and our group have also developed the palladium-catalyzed one-pot synthesis of benzofurans by the addition of organoboron reagents to functionalized nitriles (Scheme 1b).[5a,6] However, the nitrogen atoms of nitriles have not been used effectively due to the hydrolysis of ketimine intermediates. The development of a new synthetic strategy to enhance the selectivity and step economy for the synthesis of the target *N*-heterocycles products and to reduce the generation of undesired waste products is an important goal of chemists. Despite the prevalence of the transformation of the cyano group into various functional groups, the development of efficient synthetic approaches that incorporate the nitrogen atoms of nitriles into *N*-heterocycles products rather than have them follow pathways that result in hydrolysis of ketimine intermediates still remains a challenging research area.
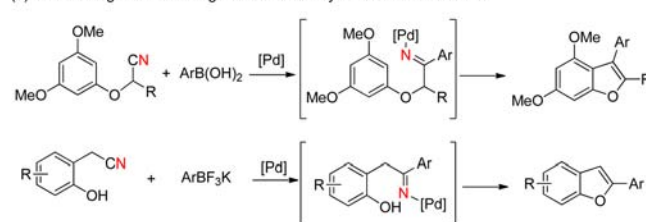
Isoquinoline and isoquinolone derivatives are important *N*-heterocycles found in biologically active natural products, including pharmaceuticals such as CWJ-a-5,[7] perafensine,[8] moxaverine,[9] and indeno[1,2-*c*]isoquinolone[10] (Figure 1).[11]
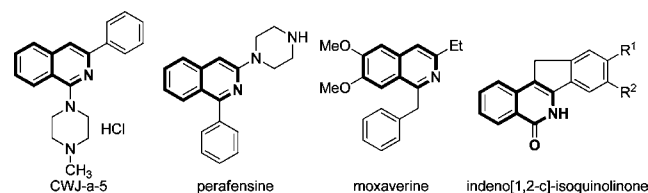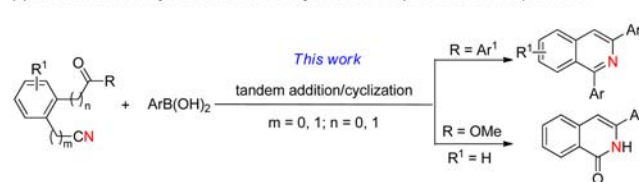
## Scheme 1. Reactions of Organoborons with Nitriles





**Figure 1.** Biologically active isoquinoline and isoquinolones.
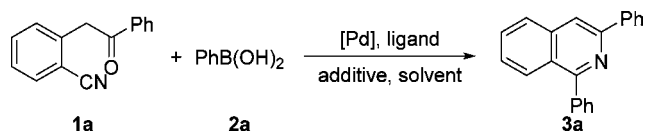
Due to the substantial applicability of isoquinolines and isoquinolones, the development of accessing isoquinolines[12] and isoquinolones[13] has received considerable attention. To the best of our knowledge, nitriles as substrate candidates involved in the transition-metal-catalyzed tandem addition and cyclization processes with organoboron reagents for the synthesis of isoquinolines and isoquinolones have not been demonstrated to date. This work is part of the continuing efforts in our laboratory toward the development of novel transition-metal-catalyzed addition or coupling reactions with organoboron reagents[14] and the synthesis of N-heterocycles.[15] Herein we describe a challenging Pd-catalyzed sequential nucleophilic addition followed by an intramolecular cyclization of functionalized nitriles (2-(2-oxo-2-arylethyl)benzonitriles, 2-(2-benzoyl-phenyl)acetonitrile, and 2-(cyanomethyl)benzoate) with arylboronic acids to afford structurally diverse isoquinolines and isoquinolones (Scheme 1c) and its application in the total synthesis of the topoisomerase I inhibitor CWJ-a-5.

Our study commenced by examining the reaction of 2-(2-oxo-2-phenylethyl)benzonitrile (**1a**) with phenylboronic acid (**2a**) using several palladium catalysts to identify the optimal reaction conditions (Table 1). Through the screening process,

**Table 1. Optimization of Reaction Conditions**[a]



| entry | Pd catalyst | ligand | additive | solvent | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | Pd(acac)$_2$ | L1 | PhCO$_2$H | THF | trace |
| 2 | Pd(acac)$_2$ | L1 | HCl | THF | 0 |
| 3 | Pd(acac)$_2$ | L1 | CF$_3$CO$_2$H | THF | 29 |
| 4 | Pd(acac)$_2$ | L1 | TsOH | THF | 45 |
| 5 | Pd(acac)$_2$ | L1 | TsOH | DMSO | 32 |
| 6 | Pd(acac)$_2$ | L1 | TsOH | EtOH | 58 |
| **7** | **Pd(acac)$_2$** | **L1** | **TsOH** | **H$_2$O** | **91** |
| 8 | Pd(acac)$_2$ | L2 | TsOH | H$_2$O | 0 |
| 9 | Pd(acac)$_2$ | L3 | TsOH | H$_2$O | 79 |
| 10 | Pd(OAc)$_2$ | L1 | TsOH | H$_2$O | 82 |
| 11 | Pd(CF$_3$CO$_2$)$_2$ | L1 | TsOH | H$_2$O | 84 |
| 12 | Pd(PPh$_3$)$_4$ | L1 | TsOH | H$_2$O | 0 |
| 13 | | L1 | TsOH | H$_2$O | 0 |
| 14 | Pd(acac)$_2$ | | TsOH | H$_2$O | 0 |

[a]Conditions: **1a** (0.4 mmol), **2a** (1.2 mmol), indicated Pd source (5 mol %), ligand (10 mol %), additive (10 equiv), solvent (2 mL), 80 °C, 24 h, air. [b]Isolated yield. TsOH = p-MeC$_6$H$_4$SO$_3$H, L1 = 2,2′-bipyridine, L2 = N,N,N′,N′-tetramethylethylenediamine, L3 = 1,10-phenanthroline.

no desired product was detected using a Lewis acid as the additive with a variety of parameters. To our delight, a trace amount of the desired product 1,3-diphenylisoquinoline (**3a**) was observed by GC/MS analysis using benzoic acid as an additive in THF in the presence of Pd(OAc)$_2$ (entry 1). The reaction failed to give the desired product using hydrochloric acid as an additive (entry 2). When either trifluoroacetic acid (TFA) or p-methylbenzenesulfonic acid (TsOH) was used as the additive, the yield of the desired product **3a** was improved to 29% and 45%, respectively (entries 3−4). Encouraged by this promising result, we further screened the reaction parameters including solvents, ligands, and catalysts. First, an investigation of the effect of solvent revealed that use of H$_2$O greatly

increased the yield of the reaction to 91% (entries 4−7). The role of the H$_2$O in the reaction is not clear. H$_2$O is known to be a unique ligand in many useful palladium transformations.[16] The choice of ligand was found to be important for the yield. For example, when either N,N,N′,N′-tetramethylethylene-diamine (**L2**) or 1,10-phenanthroline (**L3**) was used instead of 2,2′-bipyridine (**L1**), no desired product or a 79% yield was observed, respectively (entries 8−9). Replacement of Pd(acac)$_2$ with other catalysts, including Pd(OAc)$_2$ and Pd(CF$_3$CO$_2$)$_2$, resulted in relatively lower yields (entries 10−11). In contrast, this reaction did not work using Pd(0) such as Pd(PPh$_3$)$_4$ as a catalyst (entry 12). No desired product was observed if either Pd(acac)$_2$ or the ligand was absent (entries 13−14).

With the optimal reaction conditions in hand, we explored the substrate scope of this method (Scheme 2). First, the

**Scheme 2. Synthesis of Isoquinolines**[a]
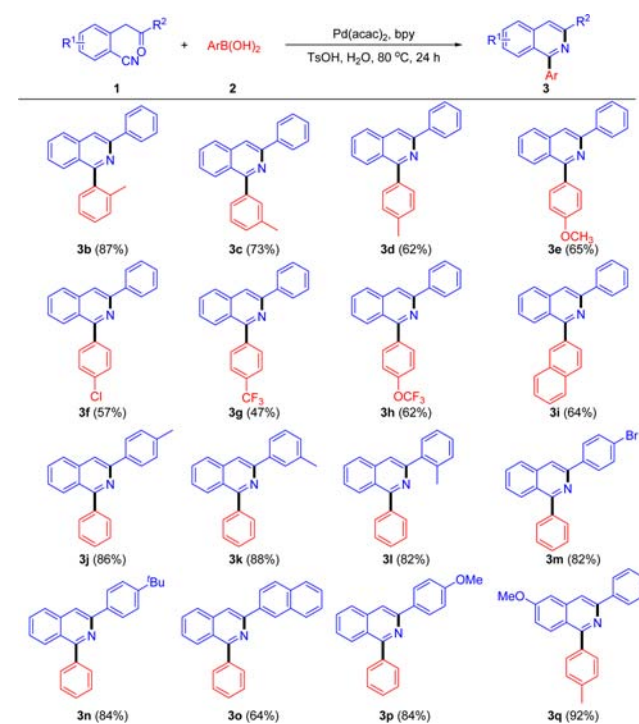


[a]Conditions: **1** (0.4 mmol), **2** (1.2 mmol), Pd(acac)$_2$ (5 mol %), bpy (10 mol %), TsOH (10 equiv), H$_2$O (2 mL), 80 °C, 24 h, air. Isolated yield.

reaction between 2-(2-oxo-2-phenylethyl)benzonitrile (**1a**) and arylboronic acids was investigated under standard conditions (**3a−3i**). The steric effects of substituents affected the yields of the reaction to some extent. For example, the tandem reaction of **1a** with para- and meta-tolylboronic acid gave yields of 62% and 73%, respectively (**3c**, **3d**), while the ortho-tolylboronic acid afforded a higher yield of 87% (**3b**). The electronic properties of the substituents on the phenyl ring of the arylboronic acids had little effect on the reaction. In general, the arylboronic acids bearing an electron-donating substituent produced a slightly higher yield of products than those analogues bearing an electron-withdrawing substituent. 1-(4-Methoxyphenyl)-3-phenylisoquinoline (**3e**) was isolated in 65% yield when p-methoxyphenylboronic acid was used as the substrate. Introduction of the moderately electron-with-drawing Cl group on the para-position of the arene was well

tolerated, and the desired product **3f** was obtained in 57% yield. However, using a substrate bearing the strong electron-withdrawing CF$_3$ group at the *para*-position decreased the yield of **3g** to 47%. Substrate *p*-trifluoromethoxyphenylboronic acid was amenable to the reaction conditions (**3h**). Notably, treatment of 2-naphthylboronic acid with **1a** also proceeded smoothly and gave the desired product **3i** in 64% yield. We next examined the scope of other 2-(2-oxo-2-phenylethyl)benzo-nitriles (**3j**–**3q**). Substrates bearing electron-donating *para*- and *meta*-methyl substitutents gave yields of 86% and 88%, respectively (**3j**, **3k**), while the *ortho*-methyl substituted substrate afforded a slightly lower yield of 82% due to the lesser steric hindrance of the substituted group (**3l**). The reaction worked well with the arylboronic acid containing the bromo group (commonly used for cross-coupling reactions) and to afford **3m** in 82% yield, leading to a useful handle for further cross-coupling reactions. Functional groups such as *tert*-butyl (**3n**), naphthyl (**3o**), and ethers (**3p**, **3q**) were well tolerated. However, substrate 2-(2-(4-cyanophenyl)-2-oxoethyl)benzonitrile (**1r**) bearing a cyano group reacted with **2a** to give phenyl(4-(1-phenylisoquinolin-3-yl)phenyl)-methanone (**3r**) in 67% yield, accompanied by a trace amount of 4-(1-phenylisoquinolin-3-yl)benzonitrile (Scheme 3). In addition, the structure of **3r** was unambiguously confirmed by X-ray crystallography.[17]

**Scheme 3. Synthesis of Isoquinolines**
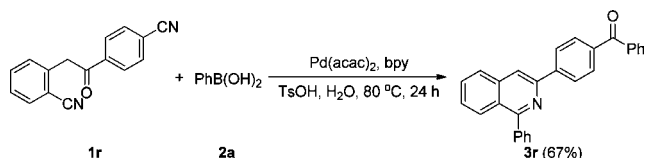
We next turned our attention to the rapid construction of isoquinolone. A trace amount of the desired product 3-phenylisoquinolin-1(2H)-one (**5a**) was observed by GC/MS analysis under standard conditions. We were delighted to find that the yield of **5a** was improved to 86% when the combination of Pd(CF$_3$CO$_2$)$_2$ 2,2′-bipyridine (**L1**) and trifluoroacetic acid (TFA) was employed in THF (for conditions screening, see Table S2 in the Supporting Information). As shown in Scheme 4, various isoquinolin-1(2H)-ones **5** were obtained by the palladium-catalyzed tandem reaction of methyl 2-(cyanomethyl)benzoate (**4**) with arylboronic acids **2**. Functional groups such as ethers (**5e**, **5f**), aryl fluorides, chlorides and bromides (**5g**, **5h**, **5i**), *tert*-butyl (**5j**), and naphthyl (**5k**, **5l**) were well tolerated.

Then, the utility of this methodology was further applied to the total synthesis of CWJ-a-5 (free base), which was the representative compound identified as a topoisomerase 1 inhibitor.[7] In the key step, the commercially available methyl 2-(cyanomethyl)benzoate (CAS: 5597-04-6) and phenylbor-onic acid (CAS: 98-80-6) were chosen as the starting material to undergo sequential nucleophilic addition followed by an intramolecular cyclization to deliver CWJ-a-5 (free base) in total yield of 73% (Scheme 5). Compared with other synthetic procedures, this process was easy to handle with commercially available starting materials.

A possible mechanism for the synthesis of isoquinolines from the tandem reaction between 2-(2-oxo-2-arylethyl)benzonitriles and arylboronic acids as a representative example is proposed in Scheme 6. First, transmetalation of the palladium species with
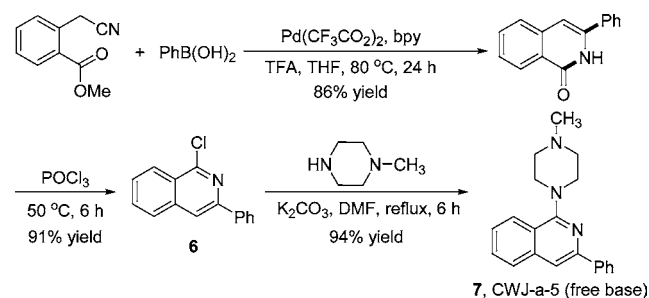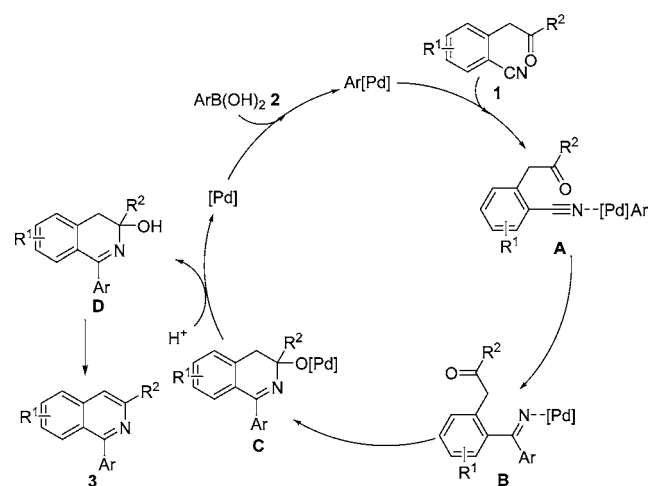
**Scheme 4. Synthesis of Isoquinolin-1(2H)-ones**[a]
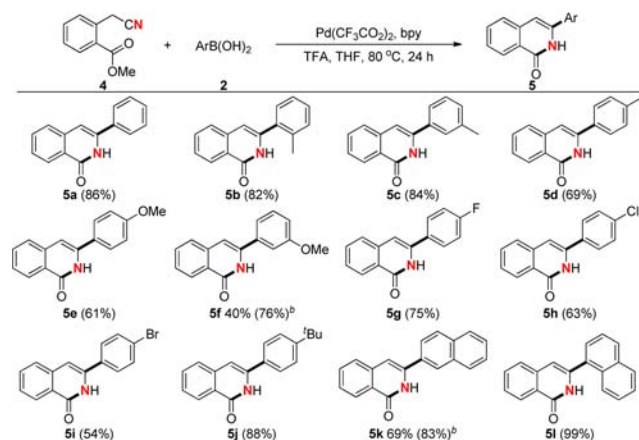
[a]Conditions: **4** (0.4 mmol), **2** (0.8 mmol), Pd(CF$_3$CO$_2$)$_2$ (5 mol %), bpy (10 mol %), TFA (0.3 mL), THF (2 mL), 80 °C, 24 h, air. [b]ArBF$_3$K (0.8 mmol), Pd(CF$_3$CO$_2$)$_2$ (10 mol %), bpy (20 mol %), TFA (0.3 mL), 4-dimethylaminopyridine (0.4 mmol), THF (2 mL), 80 °C, 24 h, air. Isolated yield.

**Scheme 5. Synthesis of CWJ-a-5**

**Scheme 6. Plausible Reaction Mechanism**

arylboronic acids would generate the aryl palladium species, which would be followed by the coordination of the cyano group giving intermediate **A**. Next, carbopalladation of the cyano group would result in formation of a palladium ketimine intermediate **B**. The intermediate **B** could undergo intra-molecular cyclization to palladium complex **C**. Protonation of the intermediate **C** by TsOH would afford the dihydro-isoquinolin-3-ol (**D**) and regenerate the palladium catalyst. Finally, dehydration of the dihydroisoquinolin-3-ol (**D**) would

deliver the corresponding isoquinolines **3** as the products. However, a detailed mechanism of the formation of the isoquinolines remains unclear currently.

In summary, we have developed an original approach for the synthesis of isoquinolines and isoquinolones by the Pd-catalyzed tandem addition/cyclization of functionalized nitriles with arylboronic acids. In addition, the protocol was successfully applied to the total synthesis of CWJ-a-5 (free base). This chemistry may find further applications for the construction of other useful *N*-heterocycles.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03499.

Experimental procedures, characterization data, NMR spectra and X-ray data for product **3r** (PDF)

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### Notes
The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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(17) Crystallographic data for compound **3r** have been deposited with the Cambridge Crystallographic Data Centre as entry CCDC 1518575.