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Nickel-catalyzed tandem reaction of functionalized arylacetonitriles with arylboronic acids in 2-MeTHF: eco-friendly synthesis of aminoisoquinolines and isoquinolones

Qianqian Zhen,[a] Lepeng Chen,[a] Linjun Qi,[a] Kun Hu,[a] Yinlin Shao,[a] Renhao Li[b] and Jiuxi Chen*[a]

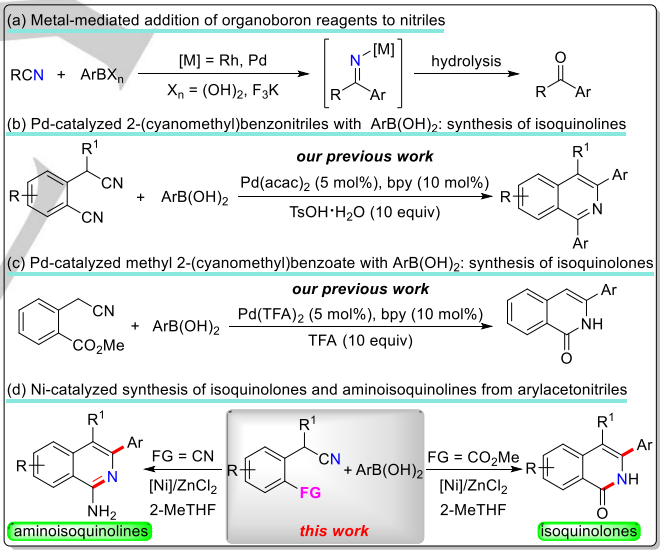
Dedication ((optional))

Abstract: The first example of the nickel-catalyzed tandem addition/cyclization of 2-(cyanomethyl)benzonitriles with arylboronic acids in 2-MeTHF has been developed, which provides the facile synthesis of aminoisoquinolines with good functional group tolerance under mild conditions. This chemistry has also been successfully applied to the synthesis of isoquinolones by the tandem reaction of methyl 2-(cyanomethyl)benzoates with arylboronic acids. The use of the bio-based and green solvent 2-MeTHF as the reaction medium makes the synthesis process environmentally benign. The synthetic utility of this chemistry is also indicated by the synthesis of biologically active molecule.

Introduction

The development of new transformations in which the inherently inert nature of the cyano group reacts as a dormant functional group holds great promise for expediting organic synthesis. In the past decade, transition-metal-catalyzed addition of organoborons or other surrogates to nitriles is one of the most powerful strategies for the synthesis of ketones and derivatives (Scheme 1a), especially for palladium[1] and rhodium.[2] In recent years, we developed palladium-catalyzed tandem reactions involving the addition of organoborons to nitriles as the initial step for the synthesis of benzofurans and indoles.[3] To improve the atom economy and reduce the amount of waste generated in these types of transformations, recent research focused on the development of efficient synthetic methods for the construction of various *N*-heterocycles skeletons in a selective manner to avoid the formation of ketone products from hydrolysis of ketimine intermediates without further tandem transformation. Very recently, our group[4] and others[5] have achieved several tandem transformation of functionalized nitriles with arylboronic acids for access to *N*-heterocycles. For example, palladium-catalyzed tandem addition/cyclization of 2-(cyanomethyl)benzonitriles (Scheme 1b) and methyl 2-(cyanomethyl)benzoates (Scheme 1c) with arylboronic acids for the synthesis of isoquinolines[4a] and isoquinolones[4b] via catalytic carbopalladation of nitriles, respectively. Nickel, as a first-row transition-metal in the same group as that of palladium, has attracted significant attention due to its low cost and abundance, meeting the requirements for sustainable chemical synthesis.[6] Despite the remarkable success of nickel-catalyzed transformations using alkyne with C≡C bond as the substrate,[7] nickel-catalyzed nitrile insertion reactions have not been extensively documented.[8] The development of nickel-catalyzed addition of organoboron reagents to nitriles has remained a great challenge due to the lack of reactivity of the inert C≡N bonds and the competing side reaction.[9]

Scheme 1. Transformation of organonitriles.



Additionally, 2-methyltetrahydrofuran (2-MeTHF) as the bio-based and green reaction medium has recently received increased attention in organic synthesis due to its environmental acceptability, abundance and low cost, and would thus be highly advantageous alternatives to other organic solvents from both economical and ecological perspectives.[10] Herein, we report a challenging nickel-catalyzed tandem reaction of 2-(cyanomethyl)benzonitrile with arylboronic acids for the preparation of unexpected aminoisoquinolines under mild reaction conditions (Scheme 1d, left). When methyl 2-(cyanomethyl)benzoates were used as substrates, tandem reaction in 2-MeTHF delivered isoquinolones which could be amenable to further synthetic elaborations (Scheme 1d, right).

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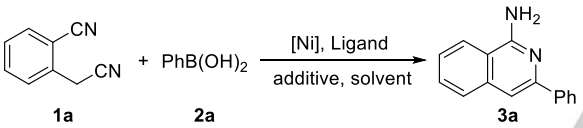
Results and Discussion

Our study began with the reaction of 2-(cyanomethyl)benzonitrile (**1a**) and phenylboronic acid (**2a**). As shown in Table 1, no desired product 3-phenylisoquinolin-1-amine (**3a**) was observed using the combination of $NiCl_2$, bpy and $ZnCl_2$ in THF (entry 1). However, replacement of bpy with phosphine ligands (e.g., dppf, dppe and dppp), **3a** could be obtained 28-41% yields (entries 2-4). Other nickel catalysts, including $Ni(dppf)Cl_2$, $Ni(dppe)Cl_2$, $Ni(dppp)Cl_2$, $Ni(PPh_3)Cl_2$ and $Ni(acac)_2$ were evaluated (entries 5-9). Delightedly, the yield of **3a** was improved to 72% in the presence of $Ni(dppp)Cl_2$ and $ZnCl_2$ (entry 7). A brief screen of additives showed that $ZnCl_2$ remained the optimal choice (entries 7, 10-13). Alternative zinc salts proved to be ineffective for this transformation (entries 14-16). Finally, among various solvents that we screened (entries 17-22), 2-MeTHF afforded **3a** in the highest yield (89%, entry 22). In the presence of $Ni(dppe)Cl_2$ and $ZnCl_2$ in 2-MeTHF, **3a** was obtained in 82% yield (entry 23). The reaction in the absence of nickel catalyst or additive proved to be inefficient (entries 24-25).

Table 1. Optimization of the reaction conditions[a]

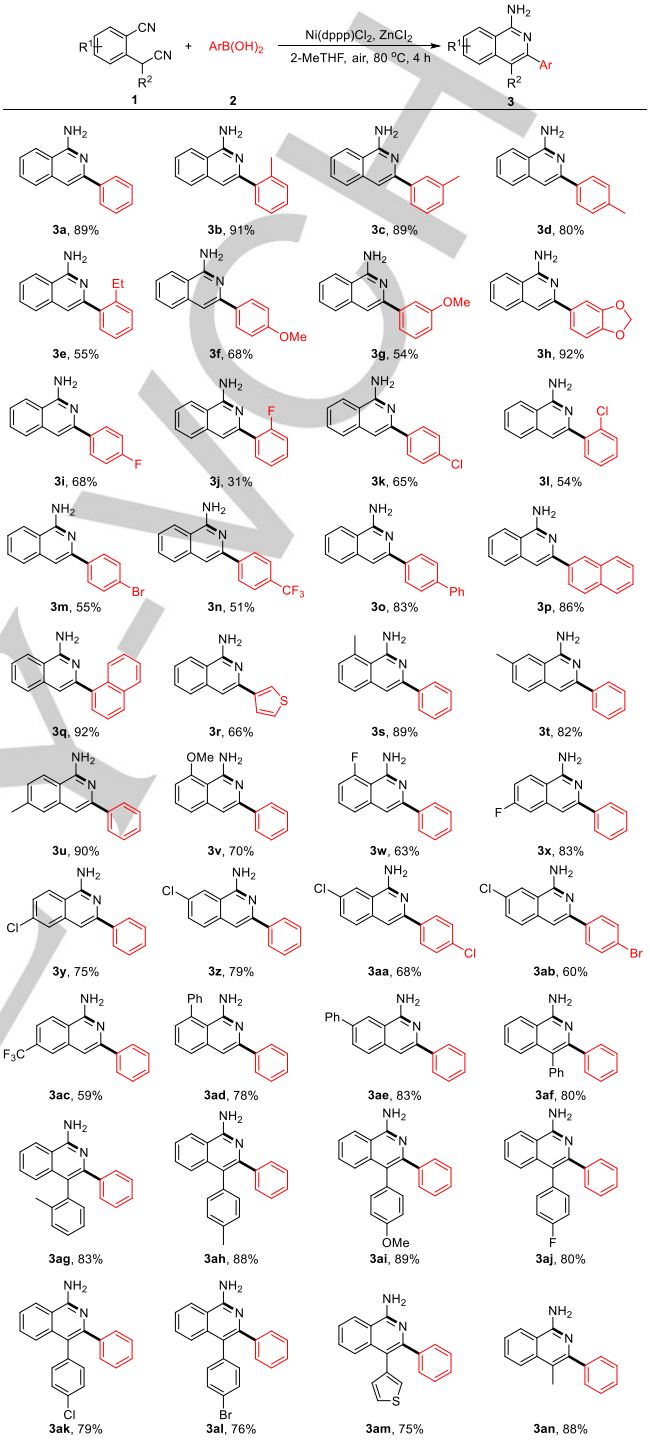


1a **2a** **3a**

Entry	Ni catalyst	Ligand	Additive	Solvent	Yield (%)[b]
1	$NiCl_2$	bpy	$ZnCl_2$	THF	0
2	$NiCl_2$	dppf	$ZnCl_2$	THF	28
3	$NiCl_2$	dppe	$ZnCl_2$	THF	37
4	$NiCl_2$	dppp	$ZnCl_2$	THF	41
5	$Ni(dppf)Cl_2$		$ZnCl_2$	THF	42
6	$Ni(dppe)Cl_2$		$ZnCl_2$	THF	67
7	$Ni(dppp)Cl_2$		$ZnCl_2$	THF	72
8	$Ni(PPh_3)Cl_2$		$ZnCl_2$	THF	0
9	$Ni(acac)_2$		$ZnCl_2$	THF	0
10	$Ni(dppp)Cl_2$		$ZnBr_2$	THF	47
11	$Ni(dppp)Cl_2$		ZnI_2	THF	55
12	$Ni(dppp)Cl_2$		$Zn(OAc)_2$	THF	37
13	$Ni(dppp)Cl_2$		$Zn(OTf)_2$	THF	11
14	$Ni(dppp)Cl_2$		$CuCl_2$	THF	0
15	$Ni(dppp)Cl_2$		$FeCl_3$	THF	0
16	$Ni(dppp)Cl_2$		CF_3CO_2H	THF	0
17	$Ni(dppp)Cl_2$		$ZnCl_2$	DMF	8
18	$Ni(dppp)Cl_2$		$ZnCl_2$	H_2O	27
19	$Ni(dppp)Cl_2$		$ZnCl_2$	toluene	38
20	$Ni(dppp)Cl_2$		$ZnCl_2$	1,4-dioxane	42
21	$Ni(dppp)Cl_2$		$ZnCl_2$	acetone	48
22	**$Ni(dppp)Cl_2$**		**$ZnCl_2$**	**2-MeTHF**	**89**
23	$Ni(dppe)Cl_2$		$ZnCl_2$	2-MeTHF	82
24			$ZnCl_2$	2-MeTHF	0
25	$Ni(dppp)Cl_2$			2-MeTHF	0

[a] Conditions: **1a** (0.4 mmol), **2a** (0.8 mmol), Ni catalyst (5 mol %), additive (0.6 mmol), solvent (2.5 mL), 80 °C, 4 h, air. [b] Isolated yield. bpy = 2,2'-bipyridine, dppf = 1,1'-bis(diphenylphosphino)ferrocene, dppe = 1,2-bis(diphenylphosphino)ethane, dppp = 1,3-bis(diphenyphosphino)propane.

Table 2. Ni-catalyzed synthesis of aminoisoquinolines[a]

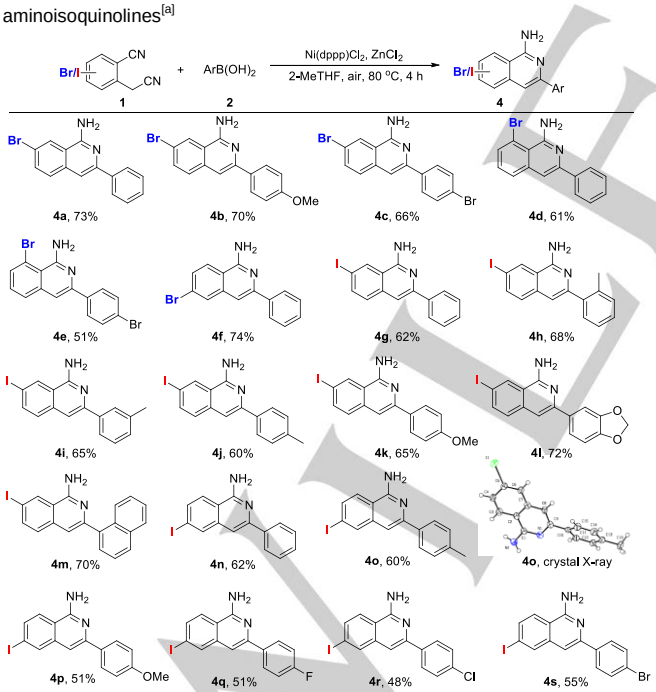


[a] Conditions: **1** (0.4 mmol), **2** (0.8 mmol), $Ni(dppp)Cl_2$ (5 mol%), $ZnCl_2$ (0.6 mmol), 2-MeTHF (2.5 mL), air, 80 °C, 4 h. Isolated yield.

The reaction scope was then investigated under the optimized reaction conditions (Table 2). This transformation proceeded efficiently with electron-rich methyl- (**3b**-**3d**), ethyl- (**3e**), methoxy- (**3f**-**3g**), and [1,3]-dioxolo- (**3h**) substituted arylboronic acids, providing the corresponding aminoisoquinolines in

moderate to good yields. It is worth noting that substrate bearing a more-hindered ethyl group (**3e**) was also shown to be possible, albeit in lower yield. The reaction tolerates electron-deficient halogen, such as fluoro (**3i**-**3j**), chloro (**3k**-**3l**), bromo (**3m**) and trifluoromethyl (**3n**) substituents, although lower yields were obtained. Phenyl-, and naphthyl-substituted arylboronic acids undergo tandem reaction well, leading to the corresponding products **3o** (83%), **3p** (86%), and **3q** (92%), respectively. Of note, thiophen-3-ylboronic acid was compatible for this Ni-catalyzed tandem reaction, albeit giving the desired **3r** in 66% yield. Next, the scope of 2-(cyanomethyl)benzonitriles was examined. Substrates bearing electron-rich methyl (**3s**-**3u**), methoxy (**3v**), or electron-deficient fluoro (**3w**-**3x**), chloro (**3y**-**3ab**), trifluoromethyl (**3ac**), phenyl (**3ad**-**3ae**) substituents (R^1) on the aromatic ring were compatible for this reaction to afford the desired products in 59-90% yields. As expected, we also found this Ni-catalyzed tandem protocol to be compatible with a wide variety of substrates bearing either electron-donating groups, such as methyl (**3ag**-**3ah**), methoxy (**3ai**), or electron-withdrawing groups, such as fluoro (**3aj**), chloro (**3ak**), bromo (**3al**) on the aromatic ring (R^2 = Ar). A representative thienyl-containing substrate, was also compatible substrate for this tandem reaction, affording the desired product **3am** in 75% yield. The reaction of 2-(1-cyanoethyl)benzonitrile with phenylboronic acid proceeded smoothly to produce the desired **3an** in 88% yield.

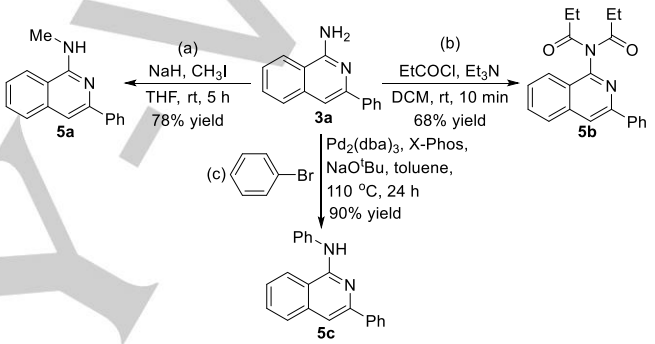
Table 3. Ni-catalyzed synthesis of bromo- or iodo-substituted aminoisoquinolines[a]



[a] Conditions: **1** (0.4 mmol), **2** (0.8 mmol), Ni(dppp)Cl_2 (5mol%), $ZnCl_2$ (0.6 mmol), 2-MeTHF (2.5 mL), air, 80 °C, 4 h. Isolated yield.

The selective synthesis of bromo- or iodo-substituted *N*-heterocycles has received increasing attention because they could be amenable to diverse functionalization. We next examined the reaction of bromo- or iodo-substituted 2-(cyanomethyl)benzonitriles with arylboronic acid to give various bromo- or iodo-substituted aminoisoquinolines (Table 3). Various functional groups (halogen, Me, OMe, OCH_2O and naphthyl) were well tolerated. In addition, the steric effects of substituents had no obvious effects on the yields. For example, the reaction with *o*-, *m*-, and *p*-tolylboronic acid proceeded smoothly to afford **4h**, **4i**, and **4j** in 68%, 65%, and 60% yields, respectively. In general, this Ni-catalyzed tandem reaction proceeded selectively to the desired bromo- or iodo-substituted products, which could be amenable to further transformations. The structure of **4o** was further confirmed by single crystal X-ray structure analysis.

Scheme 2. Synthetic applications.



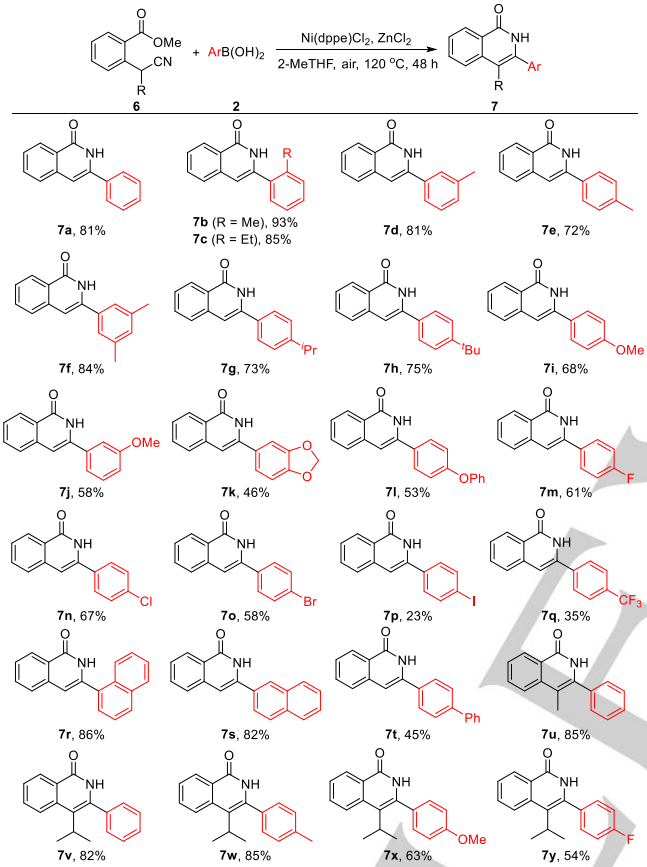
The synthetic utility of the as-synthesized aminoisoquinolines was examined by the amenability of the amino group to further synthetic applications (Scheme 2). We performed the methylation, acylation, and Buchwald-Hartwig coupling of **3a** with methyl iodide (Scheme 2a), propionyl chloride (Scheme 2b) and bromobenzene (Scheme 2c), affording the corresponding **5a**, **5b** and **5c** in 68%, 78% and 90% yields, respectively.

We further discovered that methyl 2-(cyanomethyl)benzoates could be used as substrates by this tandem reaction to afford a new synthetic method for the synthesis of isoquinolones (Table 4). The desired product 3-phenylisoquinolin-1(2*H*)-one (**7a**) was obtained in 81% yield in the presence of Ni(dppe)Cl_2, $ZnCl_2$ in 2-MeTHF at 120 °C for 48 h under air (for optimization of the reaction conditions, see Table S1 in ESI). A wide range of arylboronic acids were compatible for this Ni-catalyzed tandem reaction. Electron-donating groups (methyl-, ethyl-, *iso*-propyl-, *tert*-butyl-, methoxy-, [1,3]-dioxolo-, and phenoxy) and electron-withdrawing groups (fluoro, chloro, bromo, iodo, trifluoromethyl, naphthyl and phenyl) undergo tandem reaction well, which affords the desired products in moderate to good yields. In addition, 2-(cyanomethyl)benzoates bearing methyl or *iso*-propyl substituents, were compatible with this tandem reaction to give the expected products **7u**-**7y** in 54-85% yields.

In addition, the synthetic utility of this chemistry is also indicated by the synthesis of biologically active compound 1-(4-methyl-1,4-diazepan-1-yl)-3-phenylisoquinoline (**9a**) that showed good topoisomerase I inhibitory activity (Scheme 3).[11]

To gain further insight into the mechanism of the transformation, an intermolecular competition experiment was investigated under standard conditions (Table 5). Individual reactions for benzonitrile (**10a**) and 2-phenylacetonitrile (**10b**) under the same conditions afforded benzophenone (**11a**) and 1,2-diphenylethan-1-one (**11b**) in 23% and 99% yields, respectively (entries 1-2). Competition reaction in the presence of an equimolar amount of **10a** and **10b** with **2a** revealed that the transformation occurred more favourably with the substrate **10b** (entry 3). This observation suggests that the reactivity of the C(sp^3)–CN is more favourable than the C(sp^2)–CN in this Ni-catalyzed addition reaction.

Table 4. Ni-catalyzed synthesis of isoquinolones[a]



[a] Conditions: **1** (0.4 mmol), **2** (0.8 mmol), Ni(dppe)Cl_2 (10 mol%), $ZnCl_2$ (2 mmol), 2-MeTHF (2 mL), air, 120 °C, 48 h. Isolated yield.

Scheme 3. Synthesis of biologically active compound.

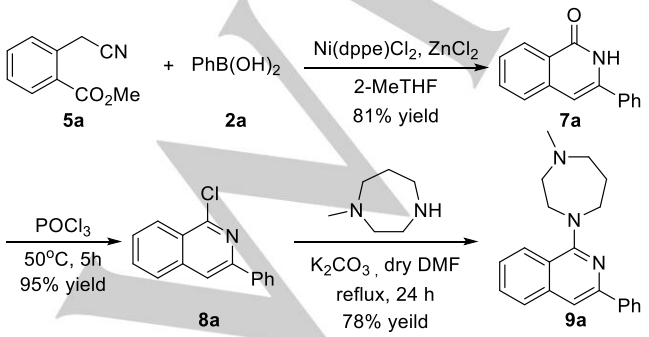
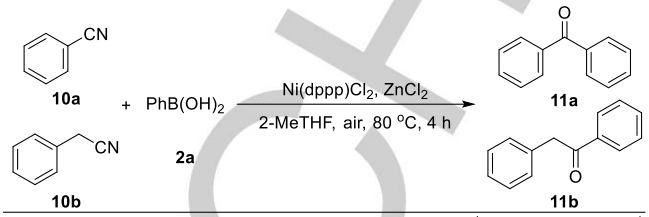


Table 5. Competition reaction[a]

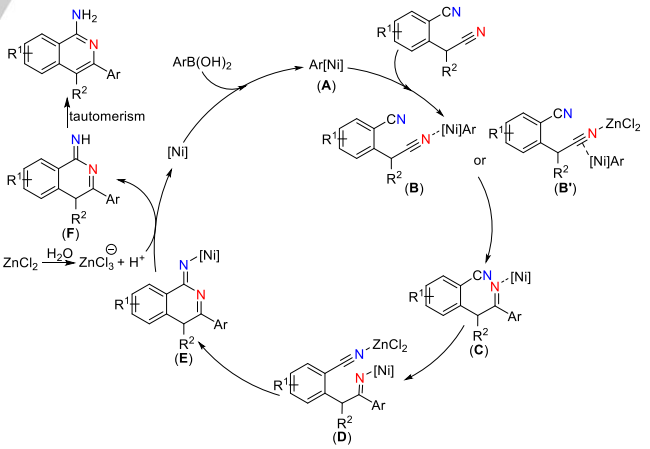


Entry	**10a** (mmol)	**10b** (mmol)	Yield of **11a** (%)[b]	Yield of **11b** (%)[b]
1	0.4	0	32	-
2	0	0.4	-	99
3	0.2	0.2	24	91

[a] Conditions: **2a** (0.8 mmol), Ni(dppp)Cl_2 (5 mol%), $ZnCl_2$ (0.6 mmol), 2-MeTHF (2 mL), 80 °C, 4 h, air. [b] Isolated yield.

The mechanism of this nickel-catalyzed tandem reaction of 2-(cyanomethyl)benzonitriles with arylboronic acids for the formation of aminoisoquinolines was proposed in Scheme 4. It involves the following key steps: (i) transmetallation of the nickel active species with $ArB(OH)_2$ to produce aryl-nickel species **A**; (ii) the coordination of cyano group to the Ni for the formation of the nickel intermediate **B** or **B'**; (iii) 1,2-addition of the coordinated aryl group to the cyano group to form the nickel intermediate **C**; (iv) cyclization of **D** to give nickel complex **E**; (v) protonation of **E** in the presence of $ZnCl_2$ and water, which affords imine intermediate **F** and regenerates the Ni catalyst. Finally, tautomerism of intermediate **F** delivers the desired aminoisoquinolines.

Scheme 4. Plausible mechanism.



Conclusions

In conclusion, we have developed a Ni-catalyzed tandem reaction of functionalized arylacetonitriles with arylboronic acids in 2-MeTHF, which affords a new synthetic strategy for the

synthesis of diverse aminoisoquinolines with excellent chemoselectivity and functional group tolerance. In addition, this chemistry has also been applied to the synthesis of isoquinolones.

Experimental Section

General Methods: Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were measured on a 500 MHz spectrometer using DMSO-d_6 or $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. Chemical shifts are given in δ relative to TMS, and the coupling constants J are given in hertz. High-resolution mass spectrometry (HRMS) was recorded on an ESI-Q-TOF mass spectrometer. 2-(Cyanomethyl)benzonitriles and methyl 2-(cyanomethyl)benzoates were synthesized according to the literature procedures.[12] Other commercially obtained reagents were used without further purification. Column chromatography was performed using EM silica gel 60 (300−400 mesh).

General procedure for the synthesis of aminoisoquinolines： 2-(Cyanomethyl)benzonitriles **1** (0.4mmol), arylboronic acid **2** (0.8 mmol), Ni(dppp)Cl_2 (5 mol%), $ZnCl_2$ (0.6 mmol), and 2-MeTHF (2.5 mL) were successively added into a Schlenk reaction tube under air. The mixture was stirred for 5 minutes at room temperature for proper mixing of the reactants, and then heated at 80 ^{o}C with vigorous stirring for 4 hours. The mixture was poured into ethyl acetate, which was washed with saturated $NaHCO_3$ (3×10 mL) and then brine (10 mL). After the aqueous layer was extracted with ethyl acetate, the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under a vacuum. The residue was purified by flash column chromatography (hexane/ethyl acetate) to afford 3-arylisoquinolin-1-amines.

General procedure for the synthesis of isoquinolones： Methyl 2-(cyanomethyl)benzoates **6** (0.4 mmol), arylboronic acid **2** (0.8 mmol), Ni(dppe)Cl_2 (10 mol%), $ZnCl_2$ (2 mmol), and 2-MeTHF (2 mL) were successively added into a Schlenk reaction tube under air. The reaction mixture was stirred for 5 minutes at room temperature for proper mixing of the reactants, and then heated at 120 ^{o}C with vigorous stirring for 48 hours. The mixture was poured into ethyl acetate, which was washed with saturated $NaHCO_3$ (3×10 mL) and then brine (10 mL). After the aqueous layer was extracted with ethyl acetate, the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under a vacuum. The residue was purified by flash column chromatography (hexane/ethyl acetate) to afford 3-arylisoquinolin-1(2*H*)-ones.

Acknowledgements

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Keywords: Nickel • Aminoisoquinolines • Isoquinolones • Arylacetonitriles • 2-MeTHF

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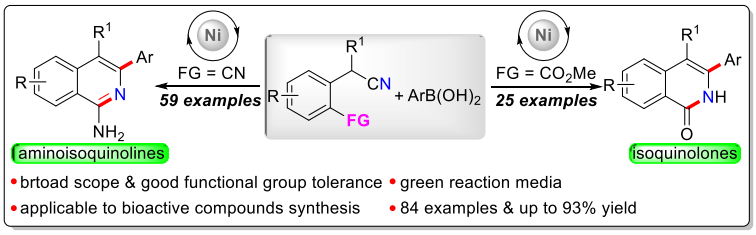

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