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Direct Synthesis of Arylketones by Nickel-Catalyzed Addition of Arylboronic Acids to Nitriles

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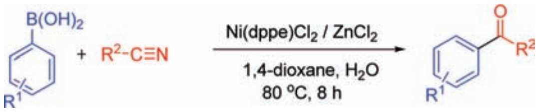
ABSTRACT



A convenient and efficient method for the synthesis of various arylketones by nickel-catalyzed addition of arylboronic acids to nitriles is described. A catalytic cycle involving Ni(II) species as the catalytic intermediates is proposed to account for the present catalytic reaction.

Arylketones are important building blocks in both natural products and functional materials.[1] The classical routes to the synthesis of arylketones rely on the oxidation of the corresponding secondary alcohols by chromium reagents,[2] Friedel−Crafts[3a−e] acylation of aromatic compounds in the presence of AlCl$_3$, in addition to a few other methods.[3f−i]

In recent years, the transition-metal-catalyzed addition reactions provide great opportunities for the synthesis of arylketones from nitriles.[4] Larock's group observed a palladium-catalyzed annulation reaction of 2-iodobenzonitriles with internal alkynes[5a−c] and the addition of an arene C−H bond to nitriles and arylboronic acids to nitriles.[5d,e] Later, Lu et al. developed a Pd(II)-catalyzed intramolecular addition of vinylpalladium species to nitriles[6a] and a cationic palladium-catalyzed addition of arylboronic acids to nitriles.[6b,c] In 2006, Miura and co-workers reported a rhodium-catalyzed addition of arylboronic acids to nitriles that led to the formation of arylketone derivatives.[7] Recenly Murakami et al. showed a rhodium-catalyzed synthesis of α-keto esters by the reaction of cyanoformate with arylboronic acids.[8] However, the methods described above for synthesizing arylketones generally require long reaction time, expensive catalyst, or harsh reaction conditions.

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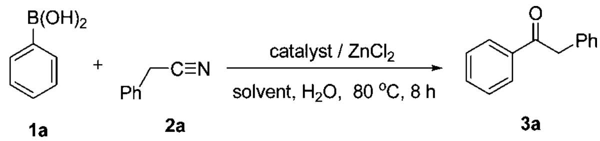
Up to now, there has been no example of using first-row transition metal complexes as catalyst for the addition of arylboronic acids to nitriles. Our continued interest in nickel-catalyzed addition reactions[9] and the activation of nitrile groups[10] prompted us to explore the possibility of using low-cost nickel complexes as catalysts for addition reactions. Herein, we wish to report a nickel-catalyzed addition of arylboronic acids to nitriles, providing a very convenient and efficient method for the synthesis of arylketones.

Our initial attempt to find an effective nickel catalyst system for the addition of phenylboronic acid (**1a**) to 2-phenylacetonitrile **2a** using nickel complexes[11a] with monodentate phosphine ligand PPh_3 in 1,4-dioxane in the presence of $ZnCl_2$ and H_2O at 80 °C for 8 h was not successful (Table 1, entries 2 and 3). Fortunately, when we switched to nickel complex $Ni(dppe)Br_2$, we started to observe product **3a** in 16% yield (entry 4). Product **3a** was thoroughly characterized by its ^1H and ^{13}C NMR and mass data.

Table 1. Effect of Catalyst and Solvent on the Addition Reaction of Phenylboronic Acid (**1a**) to Phenylacetonitrile **2a**[a]



entry	catalyst	solvent	yield (%)[b]
1[c]		1,4-dioxane	0
2	$Ni(PPh_3)_2Br_2$	1,4-dioxane	0
3	$Ni(PPh_3)_2Cl_2$	1,4-dioxane	0
4	$Ni(dppp)Br_2$	1,4-dioxane	16
5	$Ni(dppb)Br_2$	1,4-dioxane	22
6	$Ni(dppe)Br_2$	1,4-dioxane	75
7	**$Ni(dppe)Cl_2$**	**1,4-dioxane**	**95**
8	$Ni(dppe)Cl_2$	THF	68
9	$Ni(dppe)Cl_2$	toluene	trace
10	$Ni(dppe)Cl_2$	DCE	0
11	$Ni(dppe)Cl_2$	DMF	0
12	$Ni(dppe)Cl_2$	CH_3NO_2	0

[a] All reactions were carried out using boronic acid **1a** (1.0 mmol), nitrile **2a** (0.50 mmol), Ni complex (5 mol %), $ZnCl_2$ (0.75 mmol), H_2O (0.50 mmol), and solvent (1.0 mL) at 80 °C for 8 h under N_2. [b] Yields were measured by ^1H NMR, using mesitylene as an internal standard. [c] Reaction time was 12 h.

To understand the nature of this nickel-catalyzed addition reaction, the effect of nickel complex and solvent used on the yield of the reaction of **1a** with benzylnitrile (**2a**) was further investigated. Other bidentate phosphine nickel(II) complexes $Ni(dppb)Br_2$, $Ni(dppe)Br_2$, and $Ni(dppe)Cl_2$ are also effective for the addition reaction (Table 1, entries 4−7). Among these complexes examined, $Ni(dppe)Cl_2$ is most active, furnishing **3a** in 95% yield as determined by an NMR integration method (Table 1, entry 7) or 90% isolated yield (Table 2, entry 1). The solvent chosen for the present catalytic reaction also showed profound effect on the yield of product **3a**. The best solvent is 1,4-dioxane in which **3a** was obtained in 95% yield. THF is also effective, giving **3a** in 68% yield (Table 1, entry 8). Other solvents such as toluene, DCE, DMF, and nitromethane were ineffective for the catalytic reaction (Table 1, entries 9−12).

The presence of a Lewis acid was crucial to the reaction. Various Lewis acids were examined to understand the effect on the product yield. Among them, $ZnCl_2$ gave the best results and afforded **3a** in 95% yield. Other Lewis acids including ZnI_2, $ZnBr_2$, $ZnCl_2$, $Zn(OAc)_2$, CuI, CuBr, and CuCl are less effective for the catalytic reaction (see the Supporting Information for detailed studies). It is noteworthy that the present catalytic reaction required water for hydrolysis of the imine intermediate; without adding extra water, **3a** was obtained in only 62% yield. The use of 1.0 equiv of H_2O gave **3a** in nearly quantitative yield. On the basis of the above optimization studies, we choose the conditions in entry 7, boronic acid **1** (1.0 mmol), nitrile **2** (0.50 mmol), $Ni(dppe)Cl_2$ (5 mol %), $ZnCl_2$ (0.75 mmol), and H_2O (0.50 mmol) in 1,4-dioxane (1.0 mL) at 80 °C with a reaction time of 8 h as the standard reaction conditions for the following studies.

Under the standard reaction conditions, various arylboronic acids reacted smoothly with benzylnitrile (**2a**) to give the corresponding arylketones. Thus, 4-tolyl- and 4-anisylboronic acids (**1b** and **1c**) underwent addition with **2a** to give **3b** and **3c** in 81 and 80% yield, respectively (entries 2 and 3). Similarly, the reaction of 3-nitrophenylboronic acid **1d** with **2a** gave **3d** in 77% yield (entry 4). The above results indicate that electron-withdrawing and -donating arylboronic acids work equally well. In addition, this reaction is also compatible with fluoro, chloro, and bromo substituents on the aromatic ring of arylboronic acid **1**. Thus 3-fluoro-, 3-chloro-, and 4-bromophenylboronic acids **1e−g** reacted with **2a** to give addition products **3e**, **3f**, and **3g** in 93, 90, and 84% yield, respectively (entries 5−7). In addition, sterically bulkier 1-naphthyl- and 1-pyrenylboronic acids **1h**,**i** also reacted smoothly with **2a** to give the corresponding arylketones in excellent yields (entries 8 and 9).

The present nickel-catalyzed addition reaction is successfully extended to various substituted arylnitriles **2b−d**. Thus, benzonitrile (**2b**) reacted well with **1a** to afford benzophenone (**3j**) in 78% yield (entry 10). In a similar manner, the reaction of methyl 4-cyanobenzoate (**2c**) and 4-acetylbenzonitrile (**2d**) with **1a** gave arylketones **3k** and **3l** in 82 and 76% yield, respectively (entries 11 and 12). Alkyl nitriles also worked well for this reaction. Thus,

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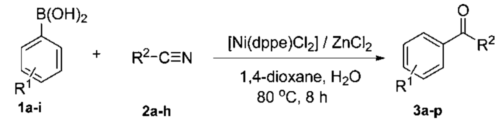
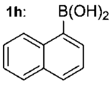
Table 2. Results of the Reaction of Arylboronic Acids with Nitriles[a]



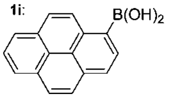
1a: R^1 = H
1b: R^1 = 4-Me
1c: R^1 = 4-OMe
1d: R^1 = 3-NO_2
1e: R^1 = 3-F
1f: R^1 = 3-Cl
1g: R^1 = 4-Br

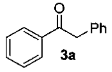
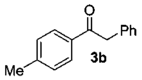
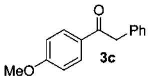
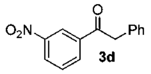
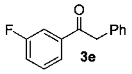
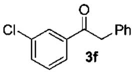
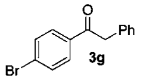
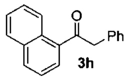
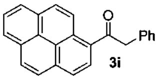
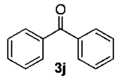
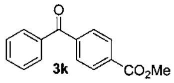
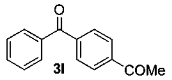
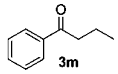
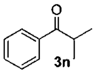
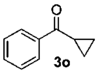
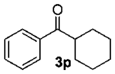
2a: R^2 = CH_2-Ph
2b: R^2 = Ph
2c: R^2 = 4-CO_2Me-C_6H_4
2d: R^2 = 4-COMe-C_6H_4
2e: R^2 = $(CH_2)_2$-CH_3
2f: R^2 = $CH(CH_3)_2$
2g: R^2 = cyclopropyl
2h: R^2 = cyclohexyl

1h:



1i:



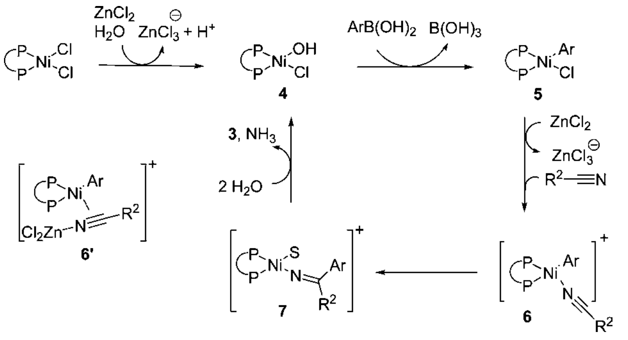
entry	1	2	product 3	yield (%)[b]
1	**1a**	**2a**	 **3a**	90
2	**1b**	**2a**	 **3b**	81
3	**1c**	**2a**	 **3c**	80
4	**1d**	**2a**	 **3d**	77
5	**1e**	**2a**	 **3e**	93
6	**1f**	**2a**	 **3f**	90
7	**1g**	**2a**	 **3g**	84
8	**1h**	**2a**	 **3h**	96
9	**1i**	**2a**	 **3i**	92
10	**1a**	**2b**	 **3j**	78
11	**1a**	**2c**	 **3k**	82
12	**1a**	**2d**	 **3l**	76
13	**1a**	**2e**	 **3m**	69
14	**1a**	**2f**	 **3n**	63
15	**1a**	**2g**	 **3o**	82
16	**1a**	**2h**	 **3p**	85

[a] Unless otherwise mentioned, all reactions were carried out with boronic acid **1a** (1.0 mmol), nitrile **2a** (0.50 mmol), Ni(dppe)Cl_2 (5 mol %), $ZnCl_2$ (0.75 mmol), H_2O (0.50 mmol), and 1,4-dioxane (1.0 mL) at 80 °C for 8 h under N_2. [b] Isolated yields.

butyronitrile (**2e**) and isobutyronitrile (**2f**) reacted smoothly with **1a** to give **3m** and **3n** in 69 and 63% yield, respectively (entries 13 and 14). Similarly, both cyclopropane and cyclohexanecarbonitriles **2g** and **2h** reacted with **1a** to provide the expected arylketone derivatives **3o** and **3p** in 82 and 85% yield, respectively (entries 15 and 16).

On the basis of known metal-catalyzed addition reactions of organometallic reagents with nitriles,[4−9] a possible reaction mechanism is proposed to account for the present nickel-catalyzed reaction (Scheme 1). The catalytic reaction is probably initiated by the formation of $Ni^{II}(OH)$ species **4** through substitution of a coordinated chloride in [Ni(PP)Cl_2] by water with the assistance of Lewis acid $ZnCl_2$. Intermediate **4** then undergoes transmetalation with arylboronic acid (**1a**) to give arylnickel(II) intermediate **5**. Coordination of phenylacetonitrile **2** to the nickel center gives intermediate **6** or **6′**.[11e] Then 1,2-addition of the coordinated aryl group to the nitrile group gives intermediate **7**. Hydrolysis of **7** afforded the final arylketone **3** and regenerates the active $Ni^{II}(OH)$ species **4** for the next catalytic cycle.

Scheme 1. Proposed Mechanism for the Addition Reaction of Arylboronic Acids with Nitriles



In the catalytic reaction, $ZnCl_2$ likely acts as a Lewis acid to remove chloride from the nickel(II) species (see Scheme 1), providing a coordination site for the water and nitrile substrate. Another possible role of $ZnCl_2$ is as an activator for a nitrile substrate, promoting the addition of aryl to the nitrile group in **6′**. It is interesting to note that no extra base is necessary for the transmetalation of arylboronic acid to the nickel center. The presence of a metal hydroxide[11,12] such as $Ni^{II}(OH)$ species **4** in the catalytic cycle accounts well for this observation.

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In conclusion, we have demonstrated that low-cost nickel complexes, instead of novel metal complexes, can also effectively catalyze the addition of arylboronic acids to nitriles to afford substituted arylketones in good to excellent yields. This method provides an opportunity for the synthesis of various unsymmetrical biarylketones and arylketones in one pot. Further extension of the reaction to an intramolecular version and a detailed mechanistic investigation are in progress.

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Supporting Information Available: General experimental procedure and characterization details. This material is available free of charge via the Internet at http://pubs.acs.org.

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