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Nickel-Catalyzed Intermolecular Insertion of Aryl Iodides to Nitriles: A Novel Method to Synthesize Arylketones

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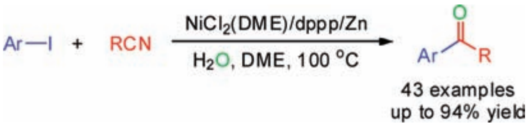
ABSTRACT



A novel procedure for the $NiCl_2$(DME)/dppp/Zn system catalyzed intermolecular insertion of aryl iodides to nitriles was developed, which afforded variously substituted arylketone derivatives in moderate to good yields with tolerance of a wide variety of functional groups.

Arylketone derivatives are very important compounds for organic synthesis because of their wide application in bioactive compounds[1] and frequent discovery in the core structure of natural products.[2] Most of them are prepared by the Friedel–Crafts acylation of an aromatic compound with acyl halides.[3] Other often-considered routes concern the oxidation of secondary alcohols[4] as well as the CN triple bond insertion.

The insertions of nitrile groups from Grignard reagents[5] and lithium reagents[6] are powerful methodologies to construct arylketones and heterocyclic compounds; however, the rigorous conditions have sometimes restricted its application and the variety of substrates. Transition-metal-catalyzed insertion of nitriles provided an alternative pathway to the main group metals.[5,6] Many reports showed that the insertion of nitrile groups was carried out by the early transition metal complexes, such as titanium,[7] tungsten,[8] zirconium,[9] molybdenum,[10] and scandium.[11] The late transition-metal-catalyzed insertion of nitriles was also reported. However, many of them were accomplished only by boronic acid compounds. In 2006, Larock[12] and Lu[13] respectively developed the palladium-catalyzed insertion of nitriles by arylboronic

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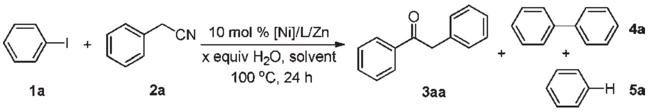
acids. Miura[14] at a similar time described that the addition of arylboron compounds to nitriles can be performed by the rhodium catalyst. Later, Murakami revealed the rhodium-catalyzed addition reaction of cyanoformate by arylboronic acids.[15] Very recently, Cheng reported the nickel-catalyzed insertion of arylboronic acids to nitriles, which is the first example to process the addition of nitriles by the first row late transition metal complex.[16]

The insertions of aryl halides to nitriles were performed via the palladium-catalyzed annulation reaction of 2-iodobenzonitriles, which were realized by Larock and his co-workers;[17,18] however, the exhibition was only in intramolecular manners. To the best of our knowledge, there is no report involving the transition-metal-catalyzed direct intermolecular insertion of aryl halides to nitriles. Herein, we wish to report the first example of an efficient and convenient nickel-catalyzed synthetic pathway with the direct intermolecular insertion of aryl iodides to nitriles, which is compatible with a wide variety of substrates under mild reaction conditions.

In a preliminary reaction, iodobenzene (**1a**) was treated with benzyl cyanide (**2a**) in the presence of 10 mol % $NiBr_2$(DME), 20 mol % PPh_3, 1.0 equiv of H_2O, and 2.0 equiv of zinc powder in 0.3 mL of 1,4-dioxane at 100 °C for 24 h; the corresponding 1,2-diphenylethanone (**3aa**) was obtained in 11% yield (Table 1, entry 1). Most of the starting materials were maintained, and some biphenyl (**4a**) was isolated. The protonation of iodobenzene to afford benzene (**5a**) was also observed by GC–MS.

To understand the nature of this nickel-catalyzed insertion, we investigated the effect of ligand, solvent, nickel complex, and the amount of H_2O. During the study of the effect of ligand, we discovered that the monodentate phosphine ligands were inefficient or functionless (entries 1–4); only bidentate phosphine ligands could effectively catalyze the reactions (entries 5–8). The best choice of the ligand was dppp (entry 7), which provided higher yield of **3aa** than others. Solvent also strongly affected the yields of **3aa** (entries 9–13). Thus, the highly polar solvent such as DMF and DMSO could not process the reaction (entries 10 and 11); THF successfully processed the reaction but gave **3aa** only in 34% yield (entry 12). Nonpolar solvent such as *m*-xylene provided **3aa** in a very low yield (12%) with the formation of a lot of compound **4a** (entry 13). When the DME was employed as solvent, the yield of **3aa** was slightly increased to 66% (entry 9). It is noteworthy that the present catalytic reaction required H_2O for hydrolysis of the intermediate; the desired product **3aa** was not obtained without loading of H_2O. In addition, the amount of H_2O significantly affected the yields of **3aa** (entries 14 and 15), and the condition with 1.2 equiv of H_2O provided the best yield of **3aa**. The presence of nickel sources were also crucial to the reaction (entries 16–20); among the various nickel complexes employed as catalysts, the $NiCl_2$(DME) was found to be the most effective, increasing the yield of **3aa** to 87% (entry 19).

Table 1. Optimization of Reaction Conditions[a]



entry	[Ni]	L	x	solvent	yield (%)[b]
1[c]	$NiBr_2$(DME)	PPh_3	1.0	1,4-dioxane	11
2[c]	$NiBr_2$(DME)	$PMePh_2$	1.0	1,4-dioxane	6
3[c]	$NiBr_2$(DME)	PCy_3	1.0	1,4-dioxane	0
4[c]	$NiBr_2$(DME)	P(2-furanyl)$_3$	1.0	1,4-dioxane	0
5	$NiBr_2$(DME)	dppm	1.0	1,4-dioxane	32
6	$NiBr_2$(DME)	dppe	1.0	1,4-dioxane	59
7	$NiBr_2$(DME)	dppp	1.0	1,4-dioxane	62
8	$NiBr_2$(DME)	dppf	1.0	1,4-dioxane	46
9	$NiBr_2$(DME)	dppp	1.0	DME	66
10	$NiBr_2$(DME)	dppp	1.0	DMF	0
11	$NiBr_2$(DME)	dppp	1.0	DMSO	0
12	$NiBr_2$(DME)	dppp	1.0	THF	34
13	$NiBr_2$(DME)	dppp	1.0	*m*-xylene	12
14	$NiBr_2$(DME)	dppp	1.2	DME	76
15	$NiBr_2$(DME)	dppp	1.4	DME	59
16	$NiBr_2$(dppp)	none	1.2	DME	79
17	$NiBr_2$(dppe)	none	1.2	DME	75
18	$NiBr_2\cdot O(EtOMe)_2$	dppp	1.2	DME	67
19	$NiCl_2$(DME)	dppp	1.2	DME	87
20	Ni(cod)$_2$	dppp	1.2	DME	51

[a] Reactions were carried out using 0.5 mmol (1.0 equiv) iodobenzene (**1a**), 1.0 mmol benzyl cyanide (**2a**) with 10 mol % nickel source, 10 mol % ligand, and 2.0 equiv of zinc powder and H_2O in 0.3 mL of solvent at 100 °C for 24 h. [b] ^1H NMR yield based on internal standard mesitylene. [c] 20 mol % ligand.

The Ni-catalyzed intermolecular insertion of nitrile was successfully extended to various aryl iodides (**1**) with substituted benzyl cyanides (**2**); the results are listed in Scheme 1. For the most cases, the reactions required 36 h to completely consume the aryl iodides (**1**). The electron density on the benzyl moiety would not affect the reaction yields; however, the size of the benzyl substrates strongly influenced the yields of **3** (**3ab**–**3ah**). Thus, the nitrile with a smaller substituent on the benzyl moiety provided higher yields of **3** than the benzyl cyanide with a larger substituent (**3ab**–**3ah**). The yields of **3** were also predominated by the electronic and steric properties of the aryl iodides (entries **3bf**–**3nb**). Both of the EDG and EWG gave lower yields but demonstrated different performance. The strong EDG on the para position of aryl iodides provided large amount of homo coupling adducts of aryl iodides (**3cf** and **3hf**);

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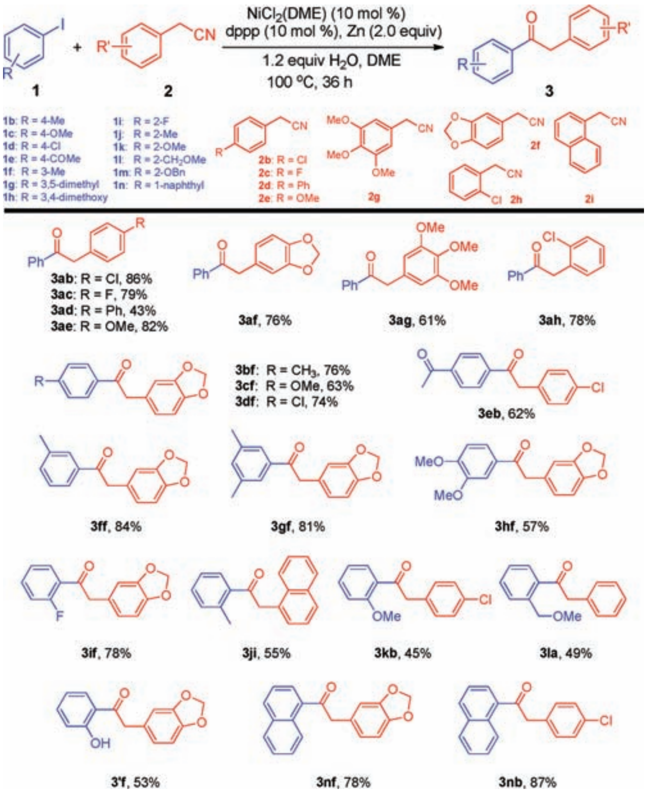
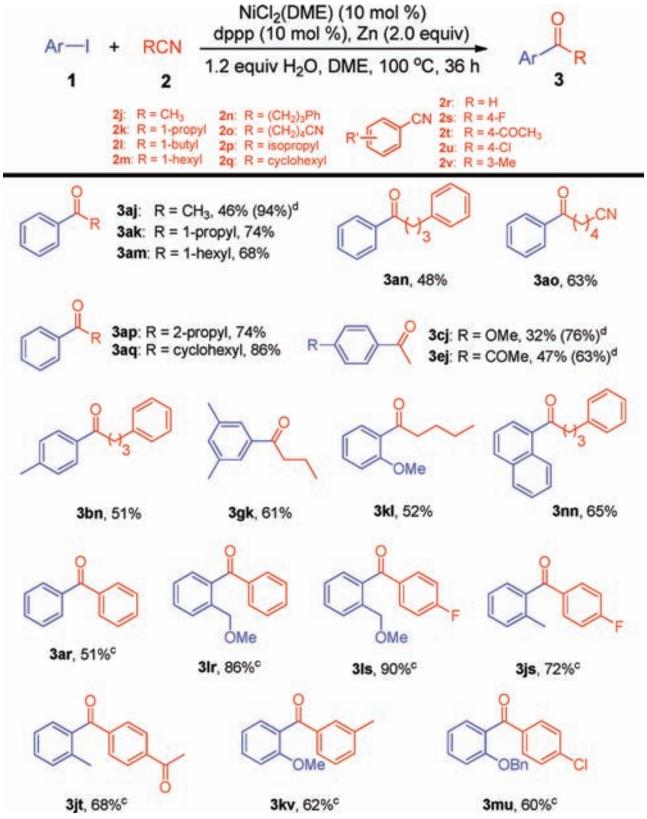
Scheme 1. Nickel-Catalyzed Intermolecular Insertion of Aryl Iodides with Substituted Benzyl Cyanides[a,b]



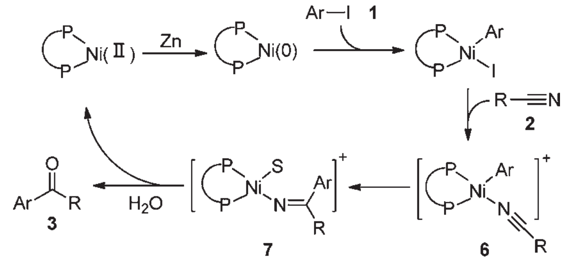
[a] Reactions were carried out using 0.5 mmol (1.0 equiv) aryl iodide (**1**), 1.0 mmol nitrile (**2**) with 10 mol % $NiCl_2$(DME), 10 mol % dppp, 2.0 equiv of zinc powder, and 1.2 equiv of H_2O in 0.3 mL of dimethoxyethane at 100 °C for 36 h. [b] Isolated yield after column chromatography and calculated on the basis of **1**.

Scheme 2. Nickel-Catalyzed Intermolecular Insertion of Iodoarenes with Nitriles[a,b]



[a] Reactions were carried out using 0.5 mmol (1.0 equiv) aryl iodide (**1**), 1.0 mmol nitrile (**2**) with 10 mol % $NiCl_2$(DME), 10 mol % dppp, 2.0 equiv of zinc powder, and 1.2 equiv of H_2O in 0.3 mL of dimethoxyethane at 100 °C for 36 h. [b] Isolated yields after column chromatography and calculated on the basis of **1**. [c] 10 mol % $NiBr_2$(dppe) as catalyst. [d] CH_3CN as solvent.

Scheme 3. Possible Mechanism



however, strong EWG on the para position of aryl iodides revealed the domination of the protonated compounds of aryl iodides (**3df** and **3eb**).

Substituents on the meta position of aryl iodides did not obviously affect the reaction yields (**3ff** and **3gf**). Ortho substituents on the aryl iodides generally resulted in lower yields because of their steric hindrance (**3if**–**3la**), and we also observed some protonated compounds of the ortho-substituted aryl iodides. Reaction involving **1m** with **2f** provided an unexpected deprotection product **3′f** instead of the desired product **3mf**, which is potentially applied to synthesize polysubstituted chromone derivatives.[19] 1-Naphthyl iodide (**1n**) also worked well with various substituted benzyl cyanides, and the yields depended only on the size of the substituent on the benzyl moiety.

By using the same protocol, we were also able to carry out the addition of aryl iodides (**1**) to various nitriles (**2**) (Scheme 2). All of the primary and secondary alkyl nitriles worked well with iodobenzene (**1a**) and provided the corresponding products **3** in moderate to good yields (**3aj**–**3aq**). The tertiary nitrile was inert and could not react with aryl iodide to afford the corresponding arylketone derivative. Substituents on the aryl iodide reduced the reactivity to the alkyl nitriles and afforded the resulting aryl ketone derivatives in comparatively lower yields (**3cj**–**3nn**). When the acetonitrile was directly employed as solvent, the reaction yields were significantly enhanced

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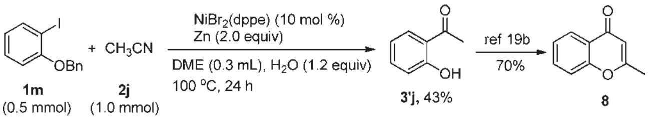
Scheme 4. Synthesis of Chromone Derivative



(**3aj**, **3cj**, and **3ej**). The aryl nitriles could be also well tolerated in the presence of NiBr$_2$(dppe) as catalyst (**3ar**–**3mu**). Although some cases with only moderate yields were caused by the protonation of aryl iodides, we did not observe homo coupling derivatives of aryl iodides in these cases.

Although a more detailed study is required to fully understand the mechanism of this nickel-catalyzed intermolecular insertion of aryl iodides to nitriles, a tentative pathway can be proposed according to the previous reports (Scheme 3).[16–18] The catalytic reaction is likely to be initiated by the reduction of the Ni(II) species to a Ni(0) species by zinc metal. Oxidative addition of aryl iodide by the Ni(0) complex and the subsequent coordination and insertion of the nitrile produce the intermediate **7**. Hydrolysis by a H$_2$O molecule provides the desired product **3** and regenerates Ni(II) species.

A further application to synthesize the chromone derivatives was performed by the resulting ortho hydroxy arylketone **3′j** by the reaction of **1m** with **2j** (Scheme 4). The chromone derivatives, which are very important core structures in natural products, can be easily constructed according to the reported pathway.[19b]

In conclusion, we have developed a novel methodology for the intermolecular insertion of aryl iodides to nitriles catalyzed by a nickel complex. This is the first report that nitriles can undergo intermolecular insertion with aryl iodides to furnish various arylketone derivatives in moderate to excellent yields with tolerance of a very wide variety of functional groups. Further studies to explore the possibility for the synthesis of various chromones as well as to extend the application of this catalytic system are currently underway.

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Supporting Information Available. Detailed experimental process, characterization, spectral data, and copies of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.