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Cp$_2$Ni-KO*t*-Bu-BEt$_3$ (or PPh$_3$) Catalyst System for Direct C−H Arylation of Benzene, Naphthalene, and Pyridine

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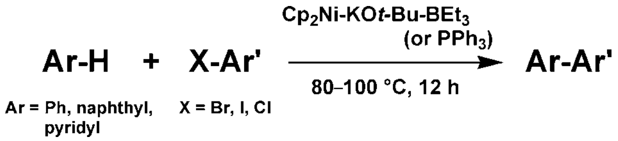
ABSTRACT



$$\text{Ar-H} + \text{X-Ar'} \xrightarrow[80\text{–}100\ ^\circ\text{C, 12 h}]{\text{Cp}_2\text{Ni-KO}t\text{-Bu-BEt}_3\ (\text{or PPh}_3)} \text{Ar-Ar'}$$

Ar = Ph, naphthyl, pyridyl X = Br, I, Cl

Ni-catalyzed direct C−H arylation of benzene and naphthalene using aryl halides was investigated. For the first time, the arylation was successfully catalyzed by Cp$_2$Ni (5 mol %) in the presence of KO*t*-Bu and BEt$_3$. This Ni catalyst system was also applied to direct C−H arylation of pyridine, an electron-deficient heteroarene; PPh$_3$ was used instead of BEt$_3$ in this case.

Metal-catalyzed intermolecular coupling of arenes is one of the useful methods in organic synthesis of biaryls.[1] Recently, catalytic direct C−H arylation of arenes using aryl halides, tosylates, or triflates for biaryl synthesis has attracted considerable attention as this process is environmentally benign. So far, many examples of direct C−H arylation of arenes having various functional groups have been reported. The arylation occurs selectively at the ortho-position of an N- or O-containing functional group by Ru,[2] Pd,[3] or Rh[4] catalysts. The highly acidic C−H bonds of highly fluorinated benzenes are arylated by aryl halides with Cu[5] or Pd[6] catalyst. Rh-catalyzed arylation of anisole using *p*-nitroiodobenzene provides a mixture of 2′-methoxy-4-nitrobiphenyl and 4′-methoxy-4-nitorobiphenyl; the ratio of this ortho- and para-isomer is consistent with the orientation of electrophilic metalation.[7]

In contrast, metal-catalyzed direct C−H arylation of unfunctionalized simple aromatic hydrocarbons using aryl halides has been reported in only a few studies: Pd-catalyzed arylation of benzene,[8,9] naphthalene,[8] and azulene[10] and Ir-

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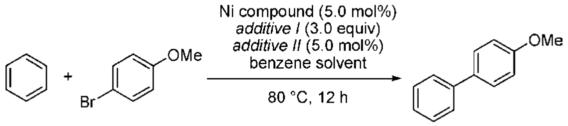
catalyzed arylation of benzene.[11] It should be noted that Pd and Ir are the only metals used as catalysts.

The first C−H activation of an arene by Ni was reported in 1963: the ortho metalation of diazobenzene by Cp_2Ni.[12] Thereafter, Ni-catalyzed reactions including C−H activation of some aryl compounds other than the synthesis of biaryls have been reported.[13] Very recently, Ni-catalyzed direct arylation of the C−H bond in heteroarenes using aryl halides or triflates was explored for the first time;[14] these reactions are noteworthy from an economical viewpoint as well.

In this study, we investigated direct C−H arylation of unfunctionalized simple aromatic hydrocarbons such as benzene and naphthalene using aryl halides with Ni compounds as a catalyst and found that a combination of Cp_2Ni, KO*t*-Bu, and BEt_3 is an effective catalyst system for the arylation. Moreover, when PPh_3 was used instead of BEt_3, this Ni catalyst system was also effective in direct C−H arylation of pyridine using aryl halides.[15]

First we examined arylation of benzene using 4-bromoanisole (Table 1). When Cp_2Ni (0.025 mmol) and 4-bromoanisole (0.5 mmol) were dissolved in benzene (5.0 mL, 56 mmol) and the resulting solution was heated at 80 °C for 12 h, 4-methoxybiphenyl was not obtained (entry 1). The addition of 1.5 mmol of KO*t*-Bu (*additive I*) and 0.025 mmol of BEt_3 (*additive II*) was found to provide the desired product in moderate yield (entry 2). Since the use of the two additives in the absence of Cp_2Ni did not yield any desired product (entry 3), it can be concluded that Cp_2Ni is indispensable for the arylation. We believe this is the first example of a Ni-catalyzed direct C−H arylation of an unfunctionalized simple aromatic hydrocarbon. When either KO*t*-Bu or BEt_3 was absent, the arylation did not take place (entries 4 and 5): this strongly suggests that Cp_2Ni, KO*t*-Bu, and BEt_3 are all essential for the arylation. The use of other potassium salts (entries 6−10) or *tert*-butoxides (entries 11 and 12) as *additive I* and radical initiators or reductants other than BEt_3 as *additive II* (entries 13−20) either afforded a small amount of the desired product or did not yield the desired product at all. Although other Ni compounds including a Ni(0) complex, $Ni(cod)_2$, gave 4-methoxybiphenyl in the presence of KO*t*-Bu or BEt_3, the yield of the desired product obtained by

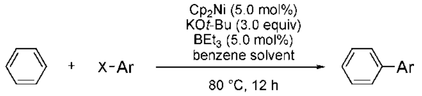
Table 1. Coupling of Benzene and 4-Bromoanisole with Ni Compounds[a]

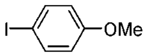
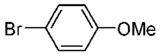
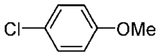
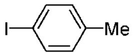
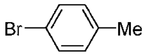
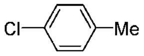
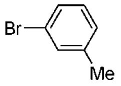
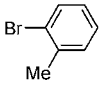
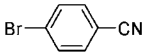
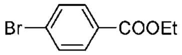
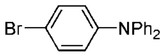
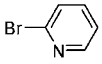
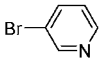


entry	Ni compound	*additive I*	*additive II*	yield (%)[b]
1	Cp_2Ni	–	–	0
2	Cp_2Ni	KO*t*-Bu	BEt_3	76
3	–	KO*t*-Bu	BEt_3	0
4	Cp_2Ni	KO*t*-Bu	–	0
5	Cp_2Ni	–	BEt_3	0
6	Cp_2Ni	KOMe	BEt_3	trace
7	Cp_2Ni	KOEt	BEt_3	7
8	Cp_2Ni	K_2CO_3	BEt_3	0
9	Cp_2Ni	K_3PO_4	BEt_3	0
10	Cp_2Ni	KOAc	BEt_3	trace
11	Cp_2Ni	LiO*t*-Bu	BEt_3	0
12	Cp_2Ni	NaO*t*-Bu	BEt_3	0
13	Cp_2Ni	KO*t*-Bu	BBu_3	46
14	Cp_2Ni	KO*t*-Bu	$BH_3{\cdot}THF$	14
15	Cp_2Ni	KO*t*-Bu	9-BBN	54
16	Cp_2Ni	KO*t*-Bu	AIBN	0
17	Cp_2Ni	KO*t*-Bu	$AlMe_3$	3
18	Cp_2Ni	KO*t*-Bu	$AlEt_3$	15
19	Cp_2Ni	KO*t*-Bu	$ZnEt_2$	12
20	Cp_2Ni	KO*t*-Bu	PPh_3	2−3[c]
21	$Ni(acac)_2$	KO*t*-Bu	BEt_3	37
22	NiF_2	KO*t*-Bu	BEt_3	47
23	$NiBr_2$	KO*t*-Bu	BEt_3	25
24	$Ni(cod)_2$	KO*t*-Bu	BEt_3	45
25[d]	Cp_2Ni	KO*t*-Bu	BEt_3	50
26[e]	Cp_2Ni	KO*t*-Bu	BEt_3	32

[a] Benzene 5.0 mL (56 mmol), 4-bromoanisole 0.5 mmol. [b] GC yield. [c] 100−150 °C. [d] Benzene 3.0 mL (34 mmol). [e] Benzene 1.0 mL (11 mmol).

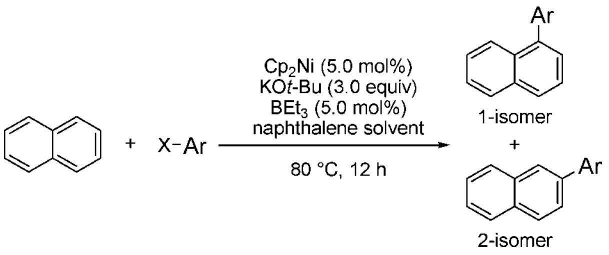
Table 2. Coupling of Benzene and Various Aryl or Pyridyl Halides[a]

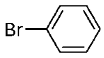
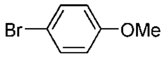
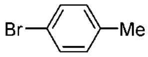
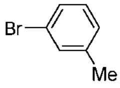
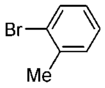
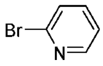


entry	X-Ar	yield (%)[b]
1		69
2		72
3		31
4		76
5		74
6		21
7		70
8		33
9		58
10		31
11		57
12		51
13		74

[a] Benzene 5.0 mL (56 mmol), X−Ar 0.5 mmol. [b] Isolated yield.

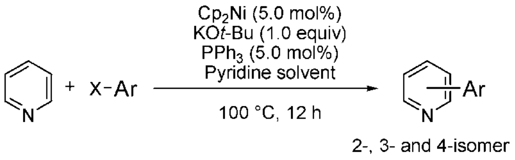
Table 3. Coupling of Naphthalene and Various Aryl Halides[a]

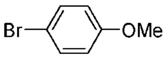
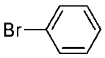
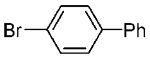
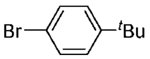


entry	X-Ar	total yield (%)^c	1-:2-isomer ratio^d
1		70	2.3:1
2		73	2.5:1
3		60	2.2:1
4		64	2.8:1
5		44	2.3:1
6		68	3.8:1

[a] Naphthalene 1.60 g (12.5 mmol), X−Ar 1.0 mmol. [b] Heating at 80 °C results in a homogeneous solution (see Supporting Information). [c] The sum of the isolated yields of 1- and 2-isomers. [d] Calculated from the isolated yields of 1- and 2-isomers.

Table 4. Coupling of Pyridine and Various Aryl Halides[a]



entry	X-Ar	total yield (%)^b	2-:3-:4-isomer ratio^c
1		53	48:36:16
2		70	46:43:11
3		73	48:41:11
4		60	46:36:18

[a] Pyridine 2.5 mL (31 mmol), X−Ar 0.5 mmol. [b] The sum of the isolated yields of 2-, 3-, and 4-isomers. [c] Calculated from the isolated yields of 2-, 3-, and 4-isomers.

the use of Cp$_2$Ni was the highest among those of all catalysts (entries 21−24). The use of a smaller amount of benzene than 5 mL afforded lower yields (entries 25 and 26).

Table 2 lists the yields of products by arylation of benzene using various aryl halides with a Cp$_2$Ni-KO*t*-Bu-BEt$_3$ catalyst system. 4-Methoxybiphenyl and 4-methylbiphenyl were obtained moderately from the corresponding 4-iodoanisole or 4-bromoanisole and 4-iodotoluene or 4-bromotoluene (entries 1, 2, 4, and 5), while the reaction using 4-chlorotoluene or 4-chloroanisole afforded the desired products in rather low yield (entries 3 and 6). This trend in the yield of the desired products is consistent with reactivity of aryl halides in coupling via oxidative addition of aryl halides, Ar−I, Ar−Br > Ar−Cl. The yield obtained with 2-bromotoluene was lower than those with 3- and 4-bromotoluene, presumably due to steric hindrance. This Ni catalyst system could also be used for arylation using bromopyridines, giving moderate yields (entries 12 and 13).

Naphthalene was also arylated by a Cp$_2$Ni-KO*t*-Bu-BEt$_3$ catalyst system, and the product was obtained in moderate yield (Table 3). The product was a mixture of 1-arylnaphthalene and 2-arylnaphthalen, and the ratio of the 1- and 2-isomer ranged from 2.3 to 3.8. In the previously reported C−H arylation of naphthalene using aryl halides, similar 1- and 2-isomer ratios were obtained. Núñez and co-workers reported that the reaction with naphthalene and the pyridyl radical formed from 2-bromopyridine by AIBN and tris(trimethylsilyl)silane produced a mixture of the 1-isomer and 2-isomer with the ratio of 3.0.[16] The 1- and 2-isomer ratios of 3.0−4.8 were observed in electrophilic Pd-catalyzed direct C−H arylation of naphthalene using various aryl iodides.[8]

Finally, we applied this Ni catalyst system to direct C−H arylation of pyridine with various aryl bromides. On comparing this reaction to the arylation of benzene and naphthalene, the reaction condition for moderate yield in this reaction is slightly different: (1) the higher reaction temperature (100 °C) was required, (2) 1.0 equiv of KO*t*-Bu was sufficient, and (3) as *additive II*, PPh$_3$ was superior to BEt$_3$.[17] Table 4 shows the results of the arylation of pyridine. The product was a mixture of 2-, 3-, and 4-arylpyridines, and the ratio of these isomers ranged from approximately 2:2:1 to 4:4:1. The formation of 3- and 4-arylpyridine indicates that the arylation of pyridine does not proceed through ortho metalation,[18] which should provide only 2-arylpyridine selectively. Moreover, the ratios of 2-, 3-, and 4-arylpyridine in Table 4 differ

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from those previously observed in the arylation of pyridine with an aryl radical formed from an aryl halide by Au catalyst[15] or by microwave irradiation.[19] We now consider that the mechanism seems so complex and cannot be presumed from the isomer ratios in Table 3 and Table 4 in this way. A detailed investigation of the mechanism is currently in progress.

In summary, we demonstrated the Ni-catalyzed direct C−H arylation of unfunctionalized aromatic hydrocarbons using aryl halides. To the best of our knowledge, this is the first time this reaction has been successfully carried out. The catalyst system consists of Cp_2Ni, KO*t*-Bu, and BEt_3, and all the components have been found to be indispensable for the arylation. We were able to apply this Ni catalyst system to the direct C−H arylation of pyridine; PPh_3 was more favorable than BEt_3. Because the catalyst is inexpensive, the process presented in this paper is more economical than the processes in the previous report.

Supporting Information Available: Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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