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Room-Temperature Kumada Cross-Coupling of Unactivated Aryl Chlorides Catalyzed by *N*-Heterocylic Carbene-Based Nickel(II) Complexes

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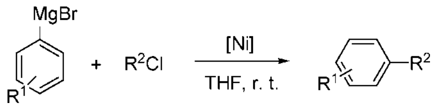

The Kumada cross-coupling reaction of a variety of unactivated aryl chlorides, vinyl chlorides, and heteroaryl chlorides catalyzed by nickel(II) complexes containing pyridine-functionalized NHC ligands is described. The catalysts are so active that the reactions proceed at room temperature in excellent yields.

The reaction between aryl Grignard reagent and aryl halide is one of the most powerful and versatile approaches for construction of a variety of biaryls, terphenyls, and oligoaryls, which are important building blocks of functional materials, natural products, and medicines.[1] A number of nickel and palladium complexes have been reported to catalyze the coupling of Grignard reagents with aryl bromides and iodides.[2] However, the exploration of the catalytic systems for less expensive and more available aryl chlorides is still challenging.[3] Several successful couplings of unactivated aryl chlorides have been reported, and some of these reactions require air-sensitive nickel(0)[4] or expensive palladium[5] as catalysts or environmentally unfriendly phosphine, phosphine oxide, phosphonate, and their derivatives as ligands.[6] The development of efficient catalyst systems of nonphosphine ligands[7] is of practical interest, which has been receiving attention.

Recently, *N*-heterocyclic carbenes (NHCs) have proven to be suitable alternatives and powerful complements for phosphine ligands. Metal complexes of NHCs show enhanced catalytic activities in various organic processes including C−C and C−N coupling reactions.[8] Metal−NHC complexes have also found applications in Kumada reactions of aryl halides.[7b–d,9] Nolan et al. described Pd-NHC catalyzed Kumada coupling of aryl chlorides at elevated reaction temperature (80 °C), but its utility is limited because of low functional group tolerance.[5a] Subsequent report by Hermann et al. disclosed the first Kumada cross-coupling using nickel−NHC catalyst at a catalyst loading of 3 mol %.[7b] Matsubara et al. found that the nickel complexes supported by NHC/PPh_3 mixed ligands were only efficient for cross-coupling of aryl iodides and bromides.[9a] We have recently reported that the nickel(II) complexes containing pyridine-functionalized bis(NHC) ligands are highly efficient catalysts for Suzuki coupling reactions of aryl chlorides and bromides under mild conditions.[10a] As a continuation, herein we report the coupling reaction of aryl chlorides, vinyl chlorides, and heteroaryl chlorides with aromatic Grignard reagents at ambient temperature using nickel(II) complexes of NHCs as catalysts.

Nickel complexes **1**−**3** were prepared according to the previously reported procedures and the structures of **1**−**3** have been described elsewhere.[10] Complex **4** can also be synthesized via carbene transfer reaction of the corresponding silver complex with $Ni(PPh_3)_2Cl_2$. ^1H and ^{13}C NMR spectra of **4** are well consistent with its proposed structure, which was further

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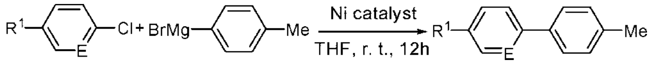
10.1021/jo800197u CCC: $40.75

TABLE 1. Cross-Coupling of Aryl Chlorides with Grignard Reagent Catalyzed by 1−4[a]



entry	catalyst (mol %)	R^1	E	yield (%)[b]
1	**1** (0.5)	H	C	43
2	**1** (1)	H	C	88
3	**1** (2)	H	C	98
4	**1** (3)	H	C	98
5	**1** (2) + PPh$_3$ (4)	H	C	72
6	**1** (2)	H	N	>99
7	**1** (2)	OMe	C	99
8	**2** (0.5)	H	C	35
9	**2** (1)	H	C	79
10	**2** (2)	H	C	91
11	**2** (3)	H	C	93
12	**2** (2)	H	N	>99
13	**2** (2)	OMe	C	59
14	**3** (0.5)	H	C	38
15	**3** (1)	H	C	87
16	**3** (2)	H	C	97
17	**3** (3)	H	C	98
18	**3** (2)	H	N	>99
19	**3** (2)	OMe	C	99
20	**4** (0.5)	H	C	34
21	**4** (1)	H	C	83
22	**4** (2)	H	C	94
23	**4** (3)	H	C	93
24	**4** (2)	H	N	>99
25	**4** (2)	OMe	C	97

[a] Reaction conditions: aryl chloride, 1.0 mmol; *p*-tolylMgBr, 1.2 mmol; THF, 3 mL, room temperature. [b] Isolated yields.

confirmed by X-ray crystallography.[11] The nickel ion of **4** is located in a square-planar geometry. Both two NHC and two pyridine groups are *cis*-positioned as required by the geometry of the tetradentate bis(NHC) ligand. The Ni−C and Ni−N bond distances are similar to those of the known nickel complexes.[10] These compounds are all air-stable even at elevated temperature.

To evaluate the catalytic activity of complexes **1**−**4** for Kumada coupling reaction, we first investigated the catalytic reaction of aryl chlorides with *p*-tolylMgBr. The results are listed in Table 1 and show that when 0.5 mol % catalyst was used, the reactions gave moderate yields (Table 1, entries 1, 8, 14, and 20). However, all four complexes exhibit excellent catalytic activities, and the desired biaryls are isolated in good yields by using 1 mol % catalyst in THF even at room temperature. In the case of **1**, the coupled product was isolated in 88% yield (Table 1, entry 2). At the same catalyst loading, complexes **2**, **3**, and **4** catalyzed the couplings to afford the biphenyls in 79%, 87%, and 83%, respectively (entries 9, 15, and 21). Complex **1** is more active than **2**−**4**, although complexes **2**−**4** contain more labile ligands since pyridyl groups are linked to imidazolylidene via a methylene moiety. When the amount of catalyst loading was increased to 2 mol %, higher yields above 90% were obtained (entries 3, 10, 16, and 22). However, further increase of the amount of the nickel catalyst afforded the product in yields similar to those under catalyst loading of 2 mol % (entries 4, 11, 17, and 23). These results illustrated that the employment of 2 mol % catalyst loading is sufficient for the reaction, and 2 mol % catalyst was used for the Kumada coupling reactions described below.

Two kinds of aryl chlorides, electron-deficient 2-chloropyridine and electron-rich 4-chloroanisole, were chosen as substrates to study the catalyst activities of four nickel catalysts **1**−**4**. It was observed that all four nickel catalysts showed high activities for the coupling of 2-chloropyridine that yielded 2-*p*-tolylpyridine in nearly quantitative yields (Table 1, entries 6, 12, 18, and 24). For electron-rich 4-chloroanisole, nickel catalysts **1**, **3**, and **4** also allow the coupling reactions to nearly completion within 12 h. However, complex **2** is much less efficient as illustrated by the low isolated yield of 2-*p*-tolylanisole (entry 13).

We have shown that in Suzuki coupling reactions of various aryl bromides catalyzed by the same nickel catalysts addition of 2 equiv of triphenylphosphine can significantly enhance their activities.[10a] It has also been demonstrated that mixed phosphine/NHC nickel complex exhibits higher catalytic activity than [NiCl$_2$(PPh$_3$)$_2$] and [Ni(NHC)$_2$Cl$_2$] complexes in the Grignard coupling reactions.[9a] However, in the present Kumada coupling reaction, the presence of PPh$_3$ has a negative effect on the coupling reaction of phenyl chloride and *p*-tolylmagnesium chloride (entry 5).

Under the optimized conditions, we next tried to extend the Kumada coupling reactions to other aryl or heteroaryl chlorides. As can be seen from Table 2, at room temperature a number of biphenyls or terphenyls could be obtained by using aryl chlorides, vinyl chlorides, or heteroaryl chlorides with different Grignard reagents in moderate to excellent yields (62−99%) by using 2 mol % of **1** as catalyst (Table 2, entries 1−32). It is worth noting that our nickel−NHC catalyst also works well for a few heteroaryl chlorides.[6c,7c] Obviously, the heteroaryl chloride bearing two nitrogen atoms in the neighboring positions such as 2-chloropyrimidine is more easily coupled, and the desired product was isolated in nearly quantitative yield (entry 1). Also at room temperature, 7-chloro-2,4-dimethyl-1,8-naphthyridine could afford the corresponding product in 94% yield (entry 2). Aryl chloride bearing electron-withdrawing group such as trifluoromethyl could give a high product yield (entry 3). We also investigated that 2-chlorobenzonitrile reacted with *p*-tolylMgBr to afford the desired the *o*-(*p*-tolyl)benzonitrile (OTBN) in 78% yield (entry 4). It is worth noting that OTBN

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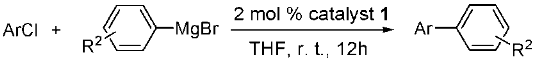
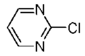
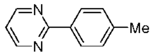
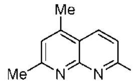
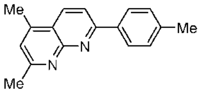
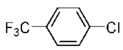
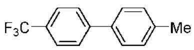
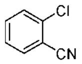
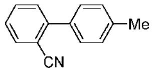
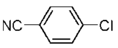
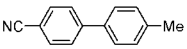
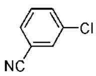
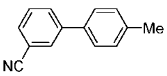
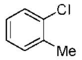
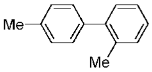
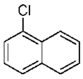
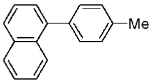
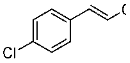
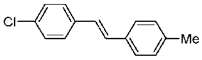
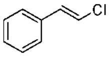
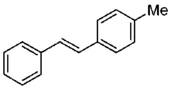
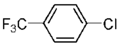
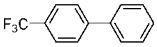
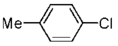
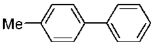
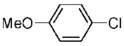
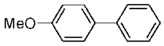
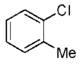
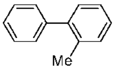
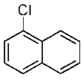
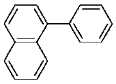
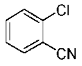
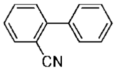
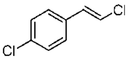
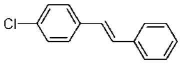
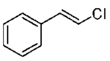
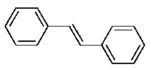
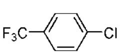
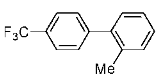
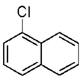
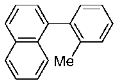
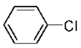
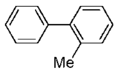
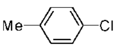
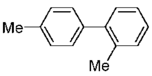
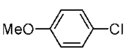
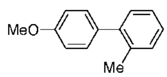
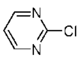
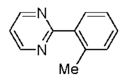
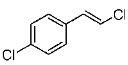
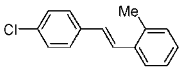
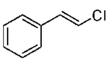
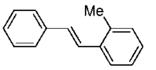
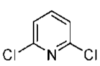
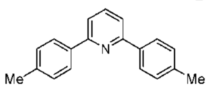
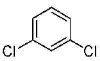
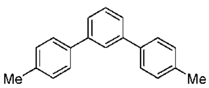
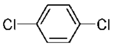
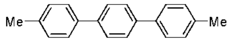
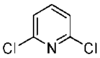
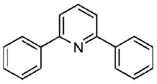
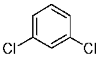
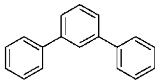
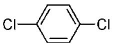
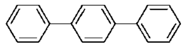
(11) See Supporting Information.

TABLE 2. Cross-Coupling of Aryl Chlorides, Heteroaryl Chlorides, and Vinyl Chlorides with Grignard Reagents Catalyzed by 1[a]



entry	ArCl	R_2	products	yield (%)[b]
1		*p*-Me	 **2a**	99
2		*p*-Me	 **2b**	94
3		*p*-Me	 **2c**	98
4		*p*-Me	 **2d**	78
5		*p*-Me	 **2e**	84
6		*p*-Me	 **2f**	86
7		*p*-Me	 **2g**	69
8		*p*-Me	 **2h**	83
9		*p*-Me	 **2i**	>99
10		*p*-Me	 **2j**	>99
11		H	 **2k**	93
12		H		83
13		H	 **2l**	86
14		H	 **2m**	64
15		H	 **2n**	79
16		H	 **2o**	73
17		H	 **2p**	98
18		H	 **2q**	97
19		*o*-Me	 **2r**	84
20		*o*-Me	 **2s**	62
21		*o*-Me	 **2m**	76
22		*o*-Me	 **2g**	75
23		*o*-Me	 **2t**	78
24		*o*-Me	 **2u**	89
25		*o*-Me	 **2v**	92
26		*o*-Me	 **2w**	90
27		*p*-Me	 **2x**	95[c]
28		*p*-Me	 **2y**	88[c]
29		*p*-Me	 **2z**	89[c]
30		H	 **2a'**	94[c]
31		H	 **2b'**	81[c]
32		H	 **2c'**	85[c]

[a] Reaction conditions: aryl chloride, 1.0 mmol; Grignard reagent, 1.2 mmol; Ni catalyst, 2 mol %; THF, 3 mL; room temperature, under N_2. [b] Isolated yields. [c] Reaction conditions: aryl chloride, 1.0 mmol; Grignard reagent, 2.4 mmol; Ni catalyst, 4 mol %; THF, 3 mL; room temperature.

is a key intermediate for the synthesis of antihypertensive drugs.[12] The reactions of 3- and 4-chlorobenzonitrile also gave good yields (above 80%) of the required products (entries 5 and 6). Obviously, under these mild conditions the nitrile group, which is generally not compatible with Grignard reagents, is tolerated. As expected, the coupling reactions of aryl chlorides bearing *ortho* substituents gave lower conversions as a result of hindrance influence. For instances, the coupling reaction of 2-chlorotoluene and 1-chloronaphthalene with *p*-tolylMgBr gave the corresponding product in 69% and 83% yields, respectively (entries 7 and 8) under the mild conditions.

The nickel catalyst is also applied to Kumada coupling of unactivated vinyl chlorides. For example, the reaction of

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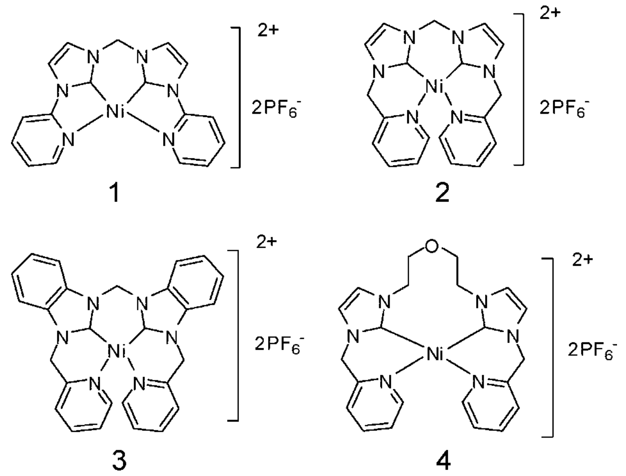
(12) (a) Kageyama, H.; Miyazaki, T.; Kimura, Y. *Synlett* **1994**, 371. (b) Miller, J. A.; Farrell, R. P. *Tetrahedron Lett.* **1998**, *39*, 6441. (c) Walla, P.; Kappe, C. O. *Chem. Commun.* **2004**, 564.



1 2 3 4

FIGURE 1. Schematic illustration of **1**−**4**.

1-chloro-4-(2-chlorovinyl)benzene proceeded with complete conversion and transformed to 1-chloro-4-(4-methylstyryl)benzene in quantitative yield (entry 9). It showed excellent chemoselectivity owing to that the activity of 2-chlorovinyl group is higher than aryl chloride. Similarly, 1-(2-chlorovinyl)-benzene behaved analogously and afforded the corresponding product in excellent yield (entry 10). So far the coupling reactions of vinyl chlorides with Grignard reagents have only been rarely reported.[5b]

To examine the influence of the Grignard reagents on the catalytic activity of **1**, a survey of the cross-coupling of C_6H_5MgBr and *o*-tolyMgBr with aryl chlorides under the same conditions used above has been performed. As expected, C_6H_5MgBr behaves similarly as *p*-tolyMgBr in the coupling reactions with various aryl chlorides. Aryl chlorides bearing either electron withdrawing or donating groups at *para* positions such as 1-chloro-4-(trifluoromethyl)benzene, 4-chlorotoluene, and 4-chloroanisole could be coupled with C_6H_5MgBr to afford the corresponding products in good yields of 83−93% (entries 11−13). However, the aryl chloride having a substituent group at its *ortho* position often leads to lower conversion. In the cases of 2-chlorotoluene, 1-chloronaphthalene, and 2-chlorobenzonitrile, the coupled products were isolated in yields of 64%, 79%, and 73% (entries 14−16), respectively. Furthermore, the coupling of vinyl chlorides such as 1-chloro-4-(2-chlorovinyl)-benzene and 1-(2-chlorovinyl)benzene could be accomplished in excellent yield (97−98%) (entries 17 and 18). In general, the yields of the coupling reactions of C_6H_5MgBr with aryl chlorides are lower than those of *p*-tolylMgBr as a result of low reactivity of C_6H_5MgBr. When *o*-tolylMgBr was employed, the coupling of aryl chlorides could proceed in moderate yields (entries 19−26). Representative aryl chlorides such as 1-chlorobenzene, 4-chlorotoluene, and 4-chloroanisole could react with *o*-tolylMgBr with isolated yields of ca. 75%, whereas the coupling reactions of heteroaryl chlorides and vinyl chlorides could still achieve up to 90% yields (entries 24−26). It should be noted that the reactivities of these aryl chlorides with *o*-tolylMgBr follow the same order as with *p*-tolylMgBr. In addition, when *p*-tolylMgCl was employed instead of *p*-tolylMgBr, the reactions of PhCl and 2-chloropyrimidine gave lower yields of 91% and 92%, respectively.

Complex **1** also shows excellent catalytic activity for the double couplings of aryl dichlorides. As shown in Table 2 (entries 27−32), *m*- and *p*-dichlorobenzene and 2,6-dichloropyridine could be converted to the corresponding terphenyls by using a 2.4 equimolar amount of Grignard reagents in excellent yields at room temperature. Terphenyls could be obtained in 81−89% isolated yields, and especially, 2,6-dichloropyridine could also be coupled with *p*-C_6H_5MgBr and C_6H_5MgBr in more than 95% yields (entries 27 and 30).

Homocoupling products of Grignard reagent were observed in most of the reactions as minor products. It appears that the electronic influence of the aryl chloride plays an important role in the amount of the byproduct. For example, there was no homocoupling product found in the coupling of 2-chloropyridine and 2-chloropyimidine; however, the byproducts increased in the coupling of the electron-rich chlorides.

In summary, we have demonstrated that the nickel(II) complexes supported by multidentate NHCs are highly active catalysts for Kumada couplings reactions of various aryl chlorides at room temperature. This method also allows formation of biphenyls in high yields even when electron-rich aryl chlorides are used. The catalysts are economical, air-stable, and easily available. The high catalytic activities of these nickel complexes are probably because of the stabilization effect of the pyridine-functionalized bis(NHC) ligands on the catalytically active species by forming stable Ni−C bonds and the hemilability of the pyridine group on the metal. Room temperature reaction makes the coupling of the substrate bearing substituents not compatible with Grignard reagents possible.

Experimental Section

General Procedure for Cross-Coupling Reaction. A Schlenk tube was charged with nickel complexes (0.02 mmol), anhydrous THF (3 mL), and aryl chloride (1.0 mmol). To the solution was added a solution of Grignard reagent (1.2 mL, 1.0 M in THF) at room temperature with stirring. After 12 h of stirring, the reaction was ended by addition of water. The mixture was extracted with ethyl acetate (3 × 5 mL), and the combined organic layer was dried by $MgSO_4$. The filtrate was concentrated by rotary evaporation, and the crude product was purified by column chromatography on sillca gel to afford the desired product.

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Supporting Information Available: Experimental details, characterization data, and crystallographic data in CIF format for **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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