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Arylation of non-activated C–Cl bond with Grignard reagents catalyzed by pincer [PCP]-nickel complexes

Yunqiang Sun, Xiaoyan Li, Hongjian Sun *

School of Chemistry and Chemical Engineering, Key Laboratory of Special Functional Aggregated Materials, Ministry of Education, Shandong University, Shanda Nanlu 27, 250199 Jinan, People's Republic of China

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ABSTRACT

A series of pincer Ni(II) complexes were prepared and utilized in the cross-coupling reaction of non-activated aryl chlorides with Grignard reagents (The Kumada reaction). Catalytic studies revealed that complex **5** ([Ph-PNCNP-Ph]-Ni-Cl) showed the highest catalytic activity for the cross-coupling reaction in the presence of 2 mol% catalyst under mild reaction condition.

1. Introduction

Biaryls are important building blocks for the synthesis of functional materials [1,2], natural products [3] and liquid crystals [4,5]. Transition-metal-catalyzed cross-coupling reactions are versatile and powerful tools to construct biaryls [6]. Among the cross-coupling reactions, Suzuki [7], Negishi [8,9] and Stille [10,11] reactions have been extensively studied due to their better functional group tolerance. However, organoboronic acids, organostannanes, and organozinc reagents are generally prepared from either Grignard or Lithium reagents [12]. Therefore, the direct application of Grignard reagents in cross-coupling reactions could efficiently reduce an unnecessary synthetic step and makes the synthetic route less expensive [13]. For a long time, electrophilic substrates are predominately iodides and bromides in the Kumada reactions. Recently, much more research work is focused on the usage of low-reactive organic chlorides due to their low prices and plenty of industrial sources [14,15].

In the last two decades, both palladium and nickel complexes have been reported and turned out to be excellent catalysts for the Kumada reactions [16–20]. Due to the formation of two chelate rings, pincer ligands can not only stabilize transition metal complexes, but also control and adjust their catalytic activity and even their selectivity in catalytic processes [21,22]. Some catalytically efficient pincer metal complexes have been employed in coupling, reduction, and dehydrogenation reactions [23,24]. Pincer [PCP]-ligands were studied because they can be directly prepared and their structures are easily modified [25,26]. Some of the PCP-type pincer-metal complexes have been utilized in different kinds of reactions, such as Heck [27], Suzuki [28] and C–S cross-coupling reactions [29]. However, for those coupling reactions the electrophilic substrates were mainly iodides and bromides. Aryl chlorides as electrophilic substrates have been rarely reported. This observation led us to broaden the application scope of pincer [PCP]-metal complexes as catalysts in the Kumada reactions of non-activated aryl chlorides with Grignard reagents.

In the family of [PCP]-ligands, one of their outstanding features is the fact that their ligand skeleton could be easily changed in the benzylic positions and phosphino-R groups [30]. In this work, we studied the catalytic activity of several [PCP]-nickel pincer complexes for the cross-coupling reactions of the non-activated aryl chlorides with Grignard reagents by changing the ligand skeletons and phosphino substituents so as to find the effective [PCP]-nickel pincer complex as catalyst in the Kumada reactions.

2. Experimental

2.1. Materials and methods

All reactions were carried out under N_2 atmosphere and all solvents were freshly distilled before use. Aryl chlorides were purchased from commercial sources and the Grignard reagents were prepared from corresponding bromide and magnesium turnings in anhydrous tetrahydrofuran (THF) according to known procedures [31]. The concentrations of the Grignard reagents were

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* Corresponding author. Tel.: +86 531 88361350; fax: +86 531 88564464.
E-mail address: hjsun@sdu.edu.cn (H. Sun).

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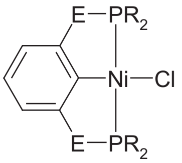
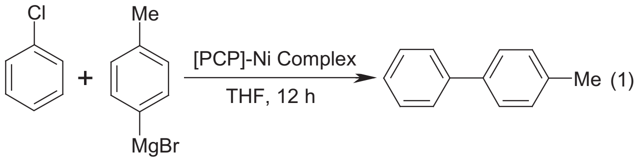


R \ E	CH_2	NH	O
Ph	**1**	**5**	**3**
*i*Pr		**4**	**2**

Fig. 1. [PCP]-nickel complexes with different ligand skeletons and phosphino R groups.

Table 1
Cross-coupling of 4-chlorobenzene with 4-methylbenzenemagnesium bromide catalyzed by nickel catalyst.[a]



Entry	Catalyst	mol%	Theta (°C)	Yield (%)[b]
1	1	2	40	40
2	2	2	40	96
3	3	2	40	68
4	4	2	40	56
5	5	2	40	97
6	$NiCl_2$	2	40	60
7	$Ni(acac)_2$	2	40	73
8	5	1	40	65
9	5	2	23	72
10	5	2	60	96

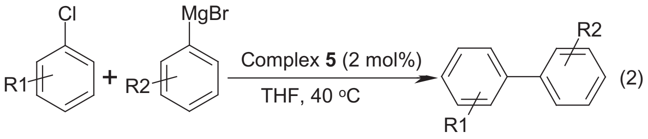
[a] Reaction condition: aryl chloride (1.0 mmol), Grignard reagent (1.5 mmol), THF (2 mL).
[b] GC yield with *n*-dodecane as an internal standard.

Table 2
Optimization the solvent and reaction time for Eq. (1).[a]

Entry	Solvent	Time (h)	Yield (%)[b]
1	Et_2O	12	77
2	Toluene	12	88
3	THF	12	98
4	NMP	12	70
5	DMF	12	47
6	DMSO	12	68
7	THF	3	41
8	THF	6	81

[a] Reaction condition: aryl chloride (1.0 mmol), Grignard reagent (1.5 mmol), Complex **5** (2.0 mol%), THF (2 mL).
[b] GC yield with *n*-dodecane as an internal standard.

Table 3
Kumada cross-coupling reaction of aryl chlorides with Grignard reagents catalyzed by complex **5** catalyst.[a]



Entry	R1	R2	Time (h)	Yield (%)[b]
1	H	*p*-Me	12	95.3[c]
2	H	*p*-MeO	12	89.7
3	*p*-Me	H	12	90.7
4	*p*-Me	*p*-Me	12	92.3
5	*p*-Me	*p*-MeO	12	94.0
6	*p*-MeO	*p*-MeO	12	96.0
7	*m*-Cl	H	18	95.7[d]
8	*m*-Cl	*p*-Me	18	89.1[d]
9	*m*-Cl	*p*-MeO	18	82.8[d]
10	*p*-Cl	H	18	91.3[d]
11	*p*-Cl	*p*-Me	18	87.2[d]

[a] Reaction condition: aryl chloride (1.0 mmol), Grignard reagent (1.5 mmol), pincer Ni catalyst (2.0 mol%), THF (2 mL).
[b] Isolated yield.
[c] GC yield with *n*-dodecane as an internal standard.
[d] Reaction condition: aryl chloride (1.0 mmol), Grignard reagent (3.0 mmol), pincer Ni catalyst (2.0 mol%), THF (2 mL).

determined by titration prior to use. NMR spectra were recorded on a Bruker 300 AV spectrometer. GC–MS was performed on Thermo Trace GC Ultra-DSQ. GC was performed on GC-9790.

2.2. Procedures for Synthesis of [PCP]-nickel Pincer Complexes

The synthesis of [PCP]-nickel pincer complexes (Fig. 1) was carried out according to the literature procedures [32,33,28].

2.3. Typical procedure for the Kumada coupling reaction

Aryl chloride (1.0 mmol), ArMgBr (1.5 mmol) in THF (2.0 mL), catalysts (2.0 mol%), were added to a Schlenk tube under an N_2 atmosphere. The reaction was stirred at 40 °C for 12 h.

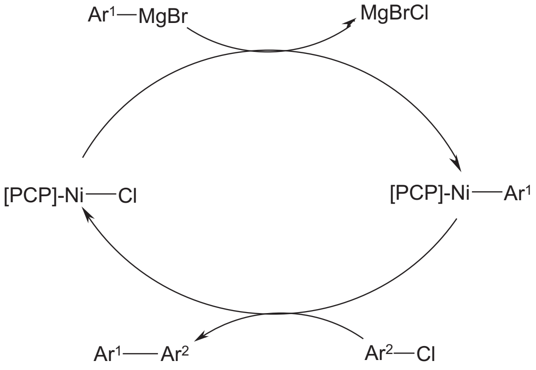
3. Results and discussion

The [PCP]-nickel complexes **1**–**5** (Fig. 1) were synthesized according to the literature methods [29–31]. The variation among the five complexes is either in the position-E or in the R group.

With the [PCP]-nickel complexes **1**–**5** as catalysts, the cross-coupling reaction of 4-chlorobenzene with 4-methylphenylmagnesium bromide was chosen as a probe reaction to evaluate the catalytic activities of complexes **1**–**5** (Eq. (1)). As shown in Table 1, compared to the pincer nickel complexes **2** and **5**, lower yields were obtained with the simple nickel complexes ($NiCl_2$ and $Ni(acac)_2$) as catalysts (Table 1, entries 6 and 7). By changing the pincer spacer from C, O to N, the catalytic activities changed remarkably (Table 1, entries 1–5) in the presence of 2 mol% of pincer complexes. The best yields were obtained for *i*Pr substituted O bridged pincer complex **2** while Ph substitution is preferred for NH bridged ligand (complex **5**). From the catalytic activity and economical perspective, complex **5** was chosen as the best catalyst. When the catalyst loading was reduced to 1 mol%, only moderate yield was obtained (Table 1, entry 8). Operating at a lower temperature led to significantly lower activity (Table 1, entry 9). The yield was excellent as the reaction temperature was increased to 60 °C (Table 1, entry 10), but a large amount of homo-coupling product of the Grignard reagent was formed according to GC–MS analysis.

The influence of solvents and reaction time on the yields with **5** as catalyst was investigated (Table 2). The solvent effect study showed that THF is the best reaction medium among the tested solvents for this reaction (Table 2, entries 1–6). The chemical reaction in a shorter reaction time is not complete (Table 2, entries 7 and 8). It was observed that 12 h are needed for the reaction to be completed (Table 2, entry 3).

Under the optimized condition, a variety of aryl chlorides were coupled with aryl Grignard reagents (Eq. (2)). The results are listed in Table 3. It is worth mentioning that for the double couplings of aryl dichlorides, complex **5** also showed excellent catalytic activity (Table 3, entries 7–11). *m*- and *p*-Dichlorobenzene could be converted to corresponding terphenyls in very high yields using 3.0 equiv. of Grignard reagents for 18 h.



Scheme 1. The proposed catalytic cycle.

According to literature reports [34–36], we supposed that the coupling reaction of aryl chloride with aryl Grignard reagent started with the transmetalation of the catalyst [PCP]–Ni–Cl with aryl Grignard reagent (Ar^1–MgBr) to form a [PCP]–Ni–Ar^1 intermediate (Scheme 1). Ligand replacement of Ar^1 by the chlorine atom from the aryl chloride Ar^2–Cl afforded the product Ar^1–Ar^2 via C,C-coupling with the regeneration of the catalyst [PCP]–Ni–Cl. More experiments on the catalytic mechanism with *in situ* IR and NMR data will be done with the help of computational study in the future.

4. Conclusion

It is confirmed that air-stable pincer nickel(II) complexes are very efficient catalysts for the cross-coupling of non-activated aryl chlorides with aryl Grignard reagents with the catalyst loading of 2 mol% under mild condition. The catalytic reaction might proceed via transmetalation at the beginning and the subsequent ligand substitution.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ica.2014.02.030.

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