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# Efficient Cross-Coupling of Aryl Chlorides with Arylzinc Reagents Catalyzed by Amido Pincer Complexes of Nickel

**Li Wang and Zhong-Xia Wang***

*Department of Chemistry, University of Science and Technology of China,*
*Hefei, Anhui 230026, PRC*

*zxwang@ustc.edu.cn*

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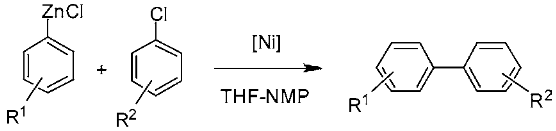
## ABSTRACT



[Ni] = amido pincer complexes of nickel
$R^2$ = OMe, $NMe_2$, C(O)Ph, COOEt, $C(O)NEt_2$ etc.

**The nickel-catalyzed Negishi cross-coupling reaction of aryl chlorides with arylzinc compounds was investigated. The nickel complexes with the amido pincer type of ligands exhibited high catalytic activity and good functional group tolerance.**

Transition-metal-catalyzed cross-coupling reactions between aryl organometallic reagents and aryl halides are reliable and versatile tools for generating biaryl compounds, which are important in pharmaceuticals, agrochemicals, liquid crystals, and advanced materials.[1,2] The Negishi cross-coupling reaction is one of the most useful methods for constructing the biaryl motif because of the ready availability and the functional group compatibility of the organozinc reagents.[1,3] Aryl bromides or iodides are usually employed as electrophilic substrates in the reaction.[4] The use of aryl chlorides as electrophiles has proven more difficult due to the low reactivity of the C−Cl bond but would economically benefit a number of industrial processes.[5] Herrmann and co-workers reported the first example of a palladium-catalyzed Negishi coupling of an unactivated aryl chloride in 1999.[6] Dai and Fu reported the first general method for palladium-catalyzed Negishi cross-coupling of aryl chlorides in 2001.[5a] More recently, Milne and Buchwald found an extremely active palladium catalyst for the coupling reaction of aryl chlorides.[7] However, inexpensive nickel-based catalysts are less successful for the coupling reaction of unactivated aryl chlorides

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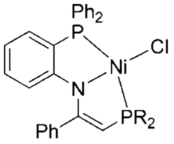
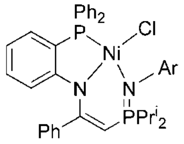
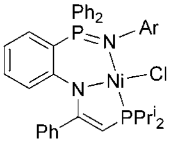
with organozinc reagents.[8,9] Reported examples include the reaction between $p$-$MeC_6H_4Cl$ and PhZnCl catalyzed by $(Ph_3P)_2NiCl_2$ and the reactions of aryl chlorides with arylzinc or functionalized organozinc reagents catalyzed by nickel on charcoal (Ni/C) in the presence of $Ph_3P$.[8] Recently, we synthesized a series of amido pincer complexes of nickel (**1a**−**4**) and demonstrated the complexes to be active catalysts for the Kumada cross-coupling of aryl halides.[10] Herein, we wish to report the catalysis of the nickel complexes in the cross-coupling of aryl chlorides with arylzinc reagents.



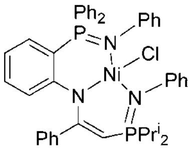
**1a** R = Ph
**1b** R = Pr$^i$



**2a** Ar = $o$-$MeC_6H_4$
**2b** Ar = 2,6-$Pr^i_2C_6H_3$



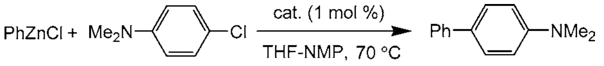
**3a** Ar = Ph
**3b** Ar = $o$-$MeC_6H_4$
**3c** Ar = 2,6-$Pr^i_2C_6H_3$



**4**

We first chose the reaction between $p$-$Me_2NC_6H_4Cl$ and PhZnCl to evaluate the catalysis of complexes **1a**−**4** (1.5 equiv of PhZnCl prepared from PhLi and $ZnCl_2$, 1 mol % of catalyst, THF−NMP 1:1, 70 °C, 30 h). The conversion of $p$-$Me_2NC_6H_4Cl$ was calculated on the basis of the integration of the $^1H$ NMR spectral signals of $NMe_2$ groups of the unreacted $p$-$Me_2NC_6H_4Cl$ and the coupling product in the reaction mixture. The screening results are listed in Table 1. From the table, it can be found that complexes **1a** and **3c** exhibit relatively low catalytic activity, whereas complexes **3b** and **4** show the highest activity. The low activity of **3c** compared with **3a** and **3b** may be due to steric hindrance of the ligand. However, the activity of **2b** seems not to be affected by the steric hindrance of the ligand compared with **2a**. Complexes **1b**, **2a**, **2b**, and **3a** display nearly equal catalytic activity. Further experiments using smaller amounts of catalyst and having a shorter reaction time led to the same conclusion. For example, the same reaction catalyzed by 0.5 mol % of **1b**, **2a**, **2b**, and **3a**, respectively, run at 70 °C (bath temperature) in a 1:1 mixture of THF and NMP for 24 h led to 16−22% conversions of $p$-$Me_2NC_6H_4Cl$.

**Table 1.** Reaction of 4-Chloro-*N*,*N*-dimethylaniline with Phenylzinc Chloride Catalyzed by **1a**−**4**[a]



| entry | catalyst | convn (%)[b] | entry | catalyst | convn (%)[b] |
|---|---|---|---|---|---|
| 1 | **1a** | 38 | 5 | **3a** | 91 |
| 2 | **1b** | 83 | 6 | **3b** | 98 |
| 3 | **2a** | 82 | 7 | **3c** | 53 |
| 4 | **2b** | 85 | 8 | **4** | 97 |

[a] The reactions were carried out according to the conditions indicated by the above equation. 1.5 equiv of PhZnCl was used. [b] Conversion was calculated based on the amount of 4-chloro-*N*,*N*-dimethylaniline added.

The most active complexes **3b** and **4** were then tested using different aryl chlorides and arylzinc reagents (Table 2). All reactions were performed in a 1:1 mixture of THF and NMP which was proved to give the best results. In each reaction, the arylzinc reagent was prepared in situ by reaction of aryllithium with $ZnCl_2$. If the arylzinc reagents were prepared from the corresponding Grignard reagents and $ZnCl_2$ or extra $MgBr_2$ was added to the reaction system, the coupling reaction became much slower and led to lower product yields. From Table 2, it can be seen that most reactions catalyzed by **3b** and **4** were performed at relatively low temperature (70 °C) and required low quantities of catalyst. Functional groups like $CO_2Et$, $Et_2NC(O)$, PhC(O), CN, OMe, and $NMe_2$ were tolerated. However, the catalysis with **3b** and **4** is incompatible with $NO_2$ and CHO groups. It is also noticed that $p$-$NCC_6H_4Cl$ is less active (entries 3, 14, and 30, Table 2). Its reaction with arylzincs required much higher catalyst loading compared with those of $p$-$EtO_2CC_6H_4Cl$ and, in some examples, gave low product yields. Knochel and co-workers reported similar phenomena and indicated that this was probably due to the coordination of the nitrile group with the catalyst species.[9d] Heterocyclic substrate 2-chloropyridine also reacted smoothly with arylzinc chlorides in the presence of catalyst, affording desired coupling products in high yields (entries 16 and 33, Table 2). The electronic properties of the reactants affect the reactions to some extent. Electron-poor aryl chlorides such as $p$-$Et_2NC(O)C_6H_4Cl$, $p$-$EtO_2CC_6H_4Cl$, and $p$-$PhC(O)C_6H_4Cl$ are more reactive than the electron-rich ones such as $p$-$MeOC_6H_4Cl$ and $p$-$Me_2NC_6H_4Cl$. Electron-rich arylzinc reagents such as $p$-$Me_2NC_6H_4ZnCl$ display higher reactivity than the other ones. These are the expected consequences. 2-Furylzinc chloride was also demonstrated to couple with activated aryl chlorides in the presence of relatively high quantities of catalyst (entries 29−33, Table 2). However, its coupling with unactivated aryl chlorides gave poor results, although much higher quantities of catalyst (2.5 mol %) and a higher reaction temperature (100 °C) were employed (entries 8, 34, and 35, Table 2). Sterically hindered substrates were also tested. Reactions of $o$-methylphenylzinc chloride with chlorobenzene or *para*-substituted chlorobenzenes catalyzed by **4** gave cross-coupling products in excellent yields (entries 21−24, Table 2). However, the catalyst loading was higher than that in

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**Table 2.** Reaction of Aryl Chlorides with Arylzinc Chlorides Catalyzed by Complexes **3b** and **4**[a]

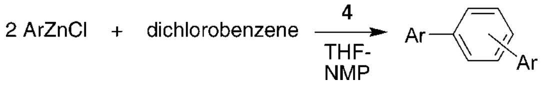
$$Ar^1ZnCl + Ar^2Cl \xrightarrow[\text{THF-NMP}]{\text{cat.}} Ar^1{-}Ar^2$$

| entry | $Ar^1$ | $Ar^2$ | catalyst (mol %) | time (h) | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | $p$-$MeC_6H_4$ | $p$-$Et_2NC(O)C_6H_4$ | **3b** (0.01) | 10 | 99 |
| 2 | $p$-$MeC_6H_4$ | $p$-$PhC(O)C_6H_4$ | **3b** (0.01) | 12 | 91.2 |
| 3 | $p$-$MeC_6H_4$ | $p$-$NCC_6H_4$ | **3b** (3) | 16 | 59 |
| 4 | $p$-$MeC_6H_4$ | Ph | **3b** (0.02) | 12 | 97 |
| 5 | $p$-$MeC_6H_4$ | $p$-$MeOC_6H_4$ | **3b** (0.02) | 12 | 97.3 |
| 6[c] | $p$-$MeC_6H_4$ | $o$-$PhC(O)C_6H_4$ | **3b** (1.5) | 24 | 98 |
| 7 | 2-furyl | $p$-$PhC(O)C_6H_4$ | **3b** (0.2) | 10 | 99 |
| 8[c] | 2-furyl | $p$-$MeOC_6H_4$ | **3b** (2.5) | 11 | 30 |
| 9 | Ph | $p$-$Et_2NC(O)C_6H_4$ | **4** (0.01) | 10 | 99 |
| 10 | Ph | $p$-$PhC(O)C_6H_4$ | **4** (0.02) | 6 | 99 |
| 11 | Ph | $p$-$MeOC_6H_4$ | **4** (0.02) | 12 | 99.2 |
| 12 | $p$-$MeC_6H_4$ | $p$-$EtOC(O)C_6H_4$ | **4** (0.03) | 6 | 98 |
| 13 | $p$-$MeC_6H_4$ | $p$-$PhC(O)C_6H_4$ | **4** (0.01) | 12 | 96 |
| 14 | $p$-$MeC_6H_4$ | $p$-$NCC_6H_4$ | **4** (1) | 12 | 70.3 |
| 15 | $p$-$MeC_6H_4$ | $p$-$CF_3C_6H_4$ | **4** (0.01) | 12 | 95.7 |
| 16 | $p$-$MeC_6H_4$ | 2-$C_5H_4N$ | **4** (0.01) | 12 | 99.5 |
| 17 | $p$-$MeC_6H_4$ | $p$-$MeOC_6H_4$ | **4** (0.02) | 12 | 99 |
| 18[c] | $p$-$MeC_6H_4$ | $o$-$PhC(O)C_6H_4$ | **4** (1.5) | 24 | 95 |
| 19 | $p$-$MeC_6H_4$ | $o$-$PhC(O)C_6H_4$ | **4** (2.5) | 8 | 98 |
| 20[c] | $p$-$MeC_6H_4$ | $o$-$MeOC_6H_4$ | **4** (2.5) | 12 | 97 |
| 21 | $o$-$MeC_6H_4$ | $p$-$PhC(O)C_6H_4$ | **4** (0.03) | 5 | 95 |
| 22 | $o$-$MeC_6H_4$ | $p$-$EtOC(O)C_6H_4$ | **4** (0.05) | 3.5 | 96.5 |
| 23 | $o$-$MeC_6H_4$ | $p$-$Et_2NC(O)C_6H_4$ | **4** (0.03) | 5 | 99 |
| 24 | $o$-$MeC_6H_4$ | $p$-$MeOC_6H_4$ | **4** (0.1) | 12 | 96 |
| 25[c] | $o$-$MeC_6H_4$ | $o$-$PhC(O)C_6H_4$ | **4** (2.5) | 40 | 88 |
| 26 | $p$-$Me_2NC_6H_4$ | $p$-$PhC(O)C_6H_4$ | **4** (0.01) | 8 | 99 |
| 27 | $p$-$Me_2NC_6H_4$ | Ph | **4** (0.01) | 12 | 99 |
| 28 | $p$-$Me_2NC_6H_4$ | $p$-$MeOC_6H_4$ | **4** (0.01) | 12 | 98.5 |
| 29 | 2-furyl | $p$-$EtOC(O)C_6H_4$ | **4** (0.5) | 12 | 99 |
| 30 | 2-furyl | $p$-$NCC_6H_4$ | **4** (1) | 10 | 98 |
| 31 | 2-furyl | $p$-$PhC(O)C_6H_4$ | **4** (0.2) | 12 | 99 |
| 32 | 2-furyl | $p$-$CF_3C_6H_4$ | **4** (0.4) | 10 | 96 |
| 33 | 2-furyl | 2-$C_5H_4N$ | **4** (0.2) | 12 | 98 |
| 34[c] | 2-furyl | Ph | **4** (2.5) | 11 | 58 |
| 35[c] | 2-furyl | $p$-$MeOC_6H_4$ | **4** (2.5) | 11 | 49 |
| 36 | 2,6-$(MeO)_2$-$C_6H_3$ | $p$-$PhC(O)C_6H_4$ | **4** (5) | 54 | 76 |

[a] Reactions were carried out in a 1:1 mixture of THF and NMP at 70 °C unless otherwise stated. 1.5 equiv of arylzinc chlorides was employed. [b] Isolated product yield. [c] Reactions were carried out at 100 °C.

the reaction of $p$-$MeC_6H_4ZnCl$. For example, 0.02 mol % of **4** could catalyze the reaction of $p$-$MeC_6H_4ZnCl$ with $p$-$MeOC_6H_4Cl$ to go to completion within 12 h (entry 17, Table 2), while under the same conditions, 0.1 mol % of **4** was necessary to drive the reaction of $o$-$MeC_6H_4ZnCl$ with $p$-$MeOC_6H_4Cl$ to reach completion (entry 24, Table 2). Reaction of 2,6-$(MeO)_2C_6H_4ZnCl$ with $p$-$PhC(O)C_6H_4Cl$ was much more difficult. It required higher quantities of catalyst (5 mol %) and longer reaction time (54 h) and gave a relatively low product yield (76%). The reaction is sensitive to the *ortho*-substituents of chlorobenzenes, requiring much higher quantities of catalyst and higher reaction temperature compared with those of *para*-substituted chlorobenzenes (entries 6, 18−20, and 25, Table 2). It was also noticed that higher catalyst loading can significantly reduce the reaction time. For example, 0.03 mol % of **4** catalyzed the reaction of $o$-$MeC_6H_4ZnCl$ with $p$-$PhC(O)C_6H_4Cl$ to go to completion in 5 h, while in the presence of 0.2 mol % of **4**, the reaction was completed within 15 min.

**Table 3.** Reaction of Dichlorobenzene with Arylzinc Chlorides Catalyzed by Complexes **4**[a]



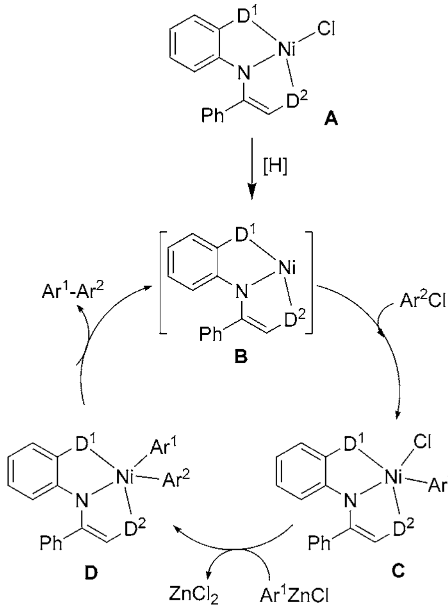
| entry | Ar | dichlorobenzene | amount of cat. (mol %) | time (h) | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | 2-furyl | 1,4-$Cl_2C_6H_4$ | 1 | 10 | 65 |
| 2 | $o$-$MeC_6H_4$ | 1,4-$Cl_2C_6H_4$ | 1 | 1 | 85.2 |
| 3 | $o$-$MeC_6H_4$ | 1,4-$Cl_2C_6H_4$ | 0.2 | 5 | 87.5 |
| 4 | $p$-$MeC_6H_4$ | 1,2-$Cl_2C_6H_4$ | 0.1 | 12 | 93 |

[a] Reactions were carried out in a 1:1 mixture of THF and NMP at 70 °C. 3 equiv of arylzinc chloride was employed. [b] Isolated product yield.

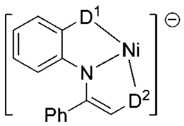
The catalytic reaction between 1,4- or 1,2-dichlorobenzene and arylzinc chlorides was also studied. Treatment of 1,4-dichlorobenzene with 3 equiv of arylzinc chlorides in the presence of complex **4** gave diarylbenzene in good yields (entries 1−3, Table 3). Reaction of 1,2-dichlorobenzene is not affected by the hindrance of the *ortho*-substituent, giving the cross-coupling product in excellent yield (entry 4, Table 3).

The postulated mechanism of the catalytic reaction is shown in Scheme 1. The Ni(II) complex **A** is first reduced by $Ar^2ZnCl$ to a Ni(I) complex (**B**). This reduction requires the presence of $Ar^1Cl$. Otherwise, the reduction reaction

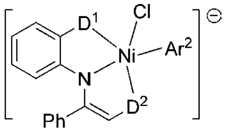
**Scheme 1.** Proposed Mechanism



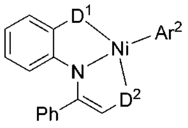
cannot occur. $Ar^1Cl$ may act as a mediator of single-electron transfer (SET) from $Ar^2ZnCl$ to the nickel complex, as those observed in the reaction of aryl halides with Grignard reagents catalyzed by complexes **1**−**4**.[10] Such behavior of aryl halides as a mediator in SET processes has been proved.[11] The reactive unsaturated **B** undergoes oxidative addition of $Ar^2Cl$ to give a five-coordinate Ni(III) complex (**C**), which reacts with $Ar^1ZnCl$ to form another five-coordinate Ni(III) complex (**D**). **D** then undergoes reductive elimination to afford the cross-coupling products $Ar^1{-}Ar^2$ and the catalytically active species **B**. A Ni(I)-catalyzed alkyl−alkyl Negishi reaction has been reported, and the catalytically active species (terpyridyl)NiR was characterized.[12] Attempts to isolate and characterize **B** were unsuccessful. If complex **A** is reduced to a Ni(0) complex (**E**), the oxidative addition of **E** with $Ar^2Cl$ should form anionic complex **F**. **F** could release the $Cl^-$ to generate neutral complex **G**,[13] and the final cross-coupling product should be formed through the reaction of **G** with arylzinc reagent $Ar^1ZnCl$. However, we found that complex **H** could not react with $Ar^1ZnCl$ to form any coupling products. Hence the possibility is ruled out. However, if complex **F** reacts with $Ar^1ZnCl$ followed by reductive elimination, the catalytic cycle can be completed.[14] We cannot exclude other mechanisms based on the present study.



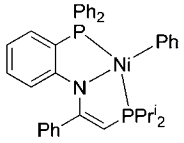
**E**



**F**



**G**



**H**

In summary, we have demonstrated amido pincer complexes of nickel to be highly active catalysts for the Negishi cross-coupling reaction. The catalysts are effective for the reactions of unactivated aryl chlorides and heteroaryl chloride with aryl and heteroaryl zinc reagents. An extremely small amount of catalyst is required in most cases, and the reaction displays good functional group tolerance.

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

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