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Bidentate P, N−P Ligand for Nickel-Catalyzed Cross-Coupling of Aryl or Benzyl Chlorides with ArMgX

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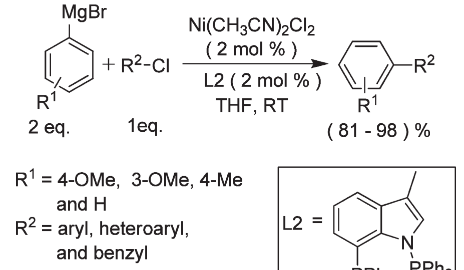

A cross-coupling reaction of a variety of aryl, heteroaryl, and benzyl chlorides with ArMgX is catalyzed by 2 mol % of a nickel−phosphine complex prepared in situ from an equimolar amount of Ni(CH$_3$CN)$_2$Cl$_2$ and ligand (L2) to yield products in excellent yield in THF at room temperature. This new bidentate ligand (L2) is stable in air and forms a stable complex upon reaction with Ni(CH$_3$CN)$_2$Cl$_2$. Structures of the ligand and the complex were confirmed by single-crystal X-ray diffraction.

Transition-metal catalyzed C−C cross-coupling reactions are powerful and versatile tools for the construction of variety of biaryls, which are useful building blocks for the synthesis of natural products, functional materials, medicine, and polymers.[1] Organoboronic acids and esters,[2] organostannanes,[3] organosilicon,[4] and organozinc[5] reagents used in such metal-catalyzed C−C coupling reactions are generally derived from the corresponding Grignard or lithium reagents. Therefore, direct use of Grignard reagents is an attractive alternative that eliminates an additional synthetic step. Kumada and Corriu independently reported in 1972 the first cross-coupling reaction of aryl halides and Grignard reagents.[6] The Kumada−Corriu reaction has received greater attention after Knochel et al. introduced well-designed synthetic routes to organomagnesium and organozinc compounds featuring functionalities like ester, nitro, aldehyde, nitrile, etc.[7]

Aryl bromides and iodides have been regularly used in this reaction.[8] Chlorides, on the other hand, are much less used despite their lower cost and greater availability.[9] The work of Buchwald, Hartwig, Fu, and others demonstrated that electron-rich alkyl- or arylalkylphosphines play a crucial role in C−Cl bond activation.[10] More recently, new catalytic systems have been developed to make the aryl chlorides participate in the reaction.[11,12] We have recently reported the use of air-stable aminophosphine ligand **L1** (Figure 1) for

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(1) For reviews, see: (a) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002. (b) *Cross-Coupling Reactions: A Practical Guide*; Miyaura, N., Ed.; Springer: Berlin, 2002. (c) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: New York, 2004.

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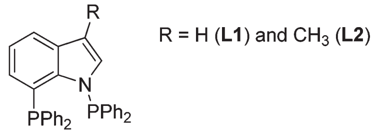
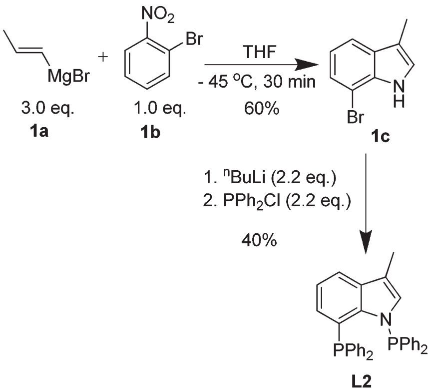


FIGURE 1. Ligand structure.

the palladium-catalyzed Suzuki–Miyaura cross-coupling reaction of chloroarenes.[13]

In continuation of this study, we report the use of an analogous air-stable, chelating aminophosphine ligand **L2** (Scheme 1) for Kumada–Corriu cross-coupling reaction of chloroarenes catalyzed by nickel.

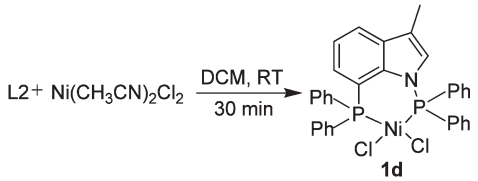
SCHEME 1. Synthesis of Ligand



The indole scaffold of the ligand (**L2**) was constructed by a two-step process. Condensation of commercially available 1-bromo-2-nitrobenzene (**1b**) and propenylmagnesium bromide solution (**1a**) at −45 °C gave 7-bromo-3-methyl-1*H*-indole (**1c**) as reported.[14] Treatment of this compound with 2.2 equiv of ^{n}BuLi at −78 °C resulted in the formation of a dianion which was quenched by 2.2 equiv of PPh_2Cl to afford the desired bidentate phosphine ligand (**L2**) in 40% yield. The pure product was obtained after column chromatography followed by crystallization from petroleum ether as colorless, transparent crystals adequate for crystallographic structure determination (see the Supporting Information). This newly synthesized ligand (**L2**) is stable in air both as a solid and in solution for more than a week.

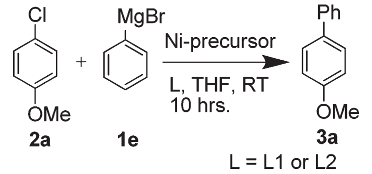
The Ni–**L2** complex (**1d**) was synthesized by treatment of $Ni(CH_3CN)_2Cl_2$ with the phosphine ligand (**L2**) in a 1:1 ratio in dichloromethane (Scheme 2).[13] A single crystal of the air-stable complex (**1d**) was grown from DCM/CH_3CN (4:1) for X-ray diffraction analysis. The nickel complex (**1d**) was found to have a distorted square-planar geometry.

SCHEME 2. Synthesis of Nickel–Phosphine Complex



Kumada–Corriu coupling reaction was carried out with chloroanisole (**2a**) and phenylmagnesium bromide (**1e**) in THF. The catalytic species is generated in situ when a nickel(II) salt was added to the ligand (**L2**). It was observed that the reaction proceeded well at ambient temperature for 10 h. The bis-acetonitrile complex of $NiCl_2$ was clearly the best catalyst precursor (see Table 1). As seen from entry 1, Table 1, **L2** gives a better yield of product (92%) compared to that obtained with **L1** (73%).

TABLE 1. Optimization of the Cross-Coupling Reaction of Aryl Chloride with Grignard reagent[a]



entry	Ni precursor (mol %)	L (mol %)	yield (%)
1	$Ni(CH_3CN)_2Cl_2$ (2)	2	92 (73)[b]
2	$Ni(CH_3CN)_2Cl_2$ (2)	2	75[c]
3	$Ni(CH_3CN)_2Cl_2$ (2)	1.5	77
4	$Ni(CH_3CN)_2Cl_2$ (2)	1.75	84
5	$Ni(CH_3CN)_2Cl_2$ (1)	1	71
6	$Ni(CH_3CN)_2Cl_2$ (1)	2	62
7	$NiCl_2$ (2)	2	76
8	$Ni(acac)_2$ (2)	2	72
9	$Ni(DME)_2Br_2$ (2)	2	66

[a] 4-Chloroanisole (1.0 mmol), Ni precursor, and **L2** in 1 mL of THF under argon atmosphere was treated with 1 M PhMgBr (2.0 mmol) and then stirred at rt. [b] **L1** was used. [c] Reaction at −20 °C.

The results show that optimal yield of product was obtained with 2 mol % of $Ni(CH_3CN)_2Cl_2$ (entry 1) with a ligand–metal ratio of 1:1 under the conditions employed. The yield of product decreased if the Ni/L ratio was altered (entries 3, 4, and 6 vis-à-vis entry 1).

As depicted in Table 2, a variety of aryl and heteroaryl chlorides were coupled with an aryl Grignard reagent in excellent yield. It was observed that use of 2 equiv of Grignard reagent gave the most consistent and highest yield.[15] The products were identified on the basis of their ^1H and ^{13}C NMR spectra. As anticipated, in case of aryl iodide the reaction was complete within 30 min (entry 12), while the corresponding aryl bromide required 2 h for completion (entry 13).

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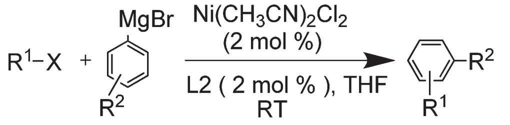
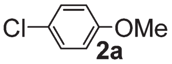
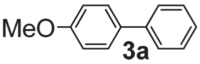
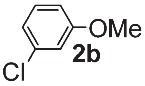
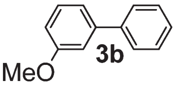
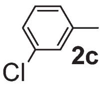
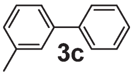
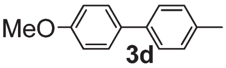
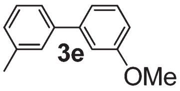
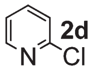
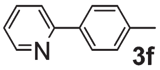
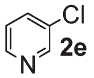
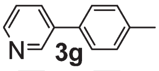
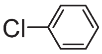
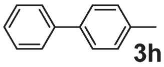
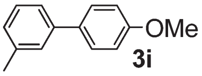
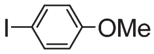
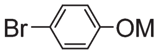
(15) Part of the reagent is used up in the reduction of Ni(II) to Ni(0), and operation of Schlenck equilibrium to further reduce active ArMgX also cannot be ruled out; for previous examples of using 2 equiv of reagent, see refs 8h and 16b.

TABLE 2. Kumada−Corriu Cross-Coupling Reaction of Aryl and Heteroaryl Chlorides[a]

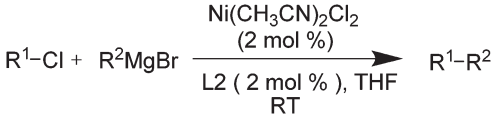


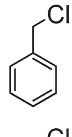
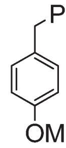
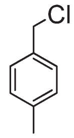
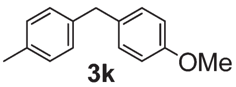
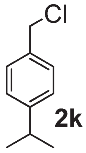
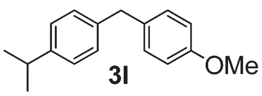
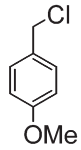
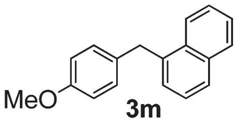
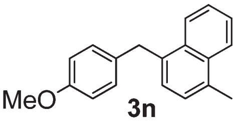
X = I,Cl,Br R^2 = H, 4-Me, 3-OMe, 4-OMe

entry	R^{1}X	time(h)	product	yield(%)
1	 **2a**	10	 **3a**	92
2	 **2b**	10	 **3b**	93
3	 **2c**	10	 **3c**	91
4	**2a**	10	 **3d**	92
5	**2c**	10	 **3e**	90
6	 **2d**	3	 **3f**	97
7	 **2e**	3	 **3g**	98
8	 **2f**	10	 **3h**	90
9	**2f**	10	**3a**	91
10	**2c**	10	 **3i**	92
11	**2f**	10	**3b**	92
12	 **2g**	0.5	**3a**	90
13	 **2h**	2	**3a**	91

[a]Aryl chloride (1 mmol), Ni(CH$_3$CN)$_2$Cl$_2$ (2 mol %), and phosphine ligand (2 mol %) in 1 mL of THF under argon atmosphere was treated with Grignard reagent (2 mmol) and then stirred at rt.

TABLE 3. Kumada−Corriu Cross-Coupling Reaction of Benzyl Chlorides[a]



entry	R^1−Cl	R^1−R^2	time(h)	yield(%)
1	 **2i**	 **3j**	8	81 (5)[b]
2	 **2j**	 **3k**	8	83 (7)[b]
3	 **2k**	 **3l**	8	87 (9)[b]
4	 **2l**	**3j**	8	95
5	**2l**	**3k**	8	97
6	**2l**	 **3m**	7	91
7	**2l**	 **3n**	7	93

[a]Chloroarene (1 mmol), Ni(CH$_3$CN)$_2$Cl$_2$ (2 mol %), and phosphine ligand (2 mol %) in 1 mL of THF under argon atmosphere was treated with Grignard reagent (2 mmol) and then stirred at rt. [b]Reaction without Ni catalyst.

Although Kumada−Corriu coupling reaction of benzyl chlorides has been rarely reported,[16] benzyl chlorides smoothly reacted under the present reaction condition (Table 3).[17]

In summary, we have described an air-stable, bidentate ligand featuring an indole scaffold and a N−P donor that can be used very effectively in nickel-catalyzed Kumada−Corriu cross-coupling reactions of aryl, heteroaryl, and benzyl chlorides.

Experimental Section

Preparation of Ligand L2 from 7-Bromo-3-methyl-1*H*-indole (1c). To a stirred solution of 7-bromo-3-methyl-1*H*-indole (**1c**) (2.10 g, 10 mmol) in THF (50 mL), under argon atmosphere, was added ^{n}BuLi (13.75 mL, 22 mmol, 1.60 M in hexane) dropwise at −78 °C. The mixture was slowly warmed to room temperature and then stirred for an additional 2 h at rt. After the mixture was cooled to −78 °C, chlorodiphenylphosphine (4.06 mL, 22 mmol) in THF (10 mL) was added dropwise. The mixture was then warmed to room temperature and stirred for an additional 2 h. It was then quenched with saturated NH$_4$Cl solution at 0 °C and extracted with diethyl ether (2 × 100 mL). The combined organic layer was washed subsequently with water and brine and dried over anhydrous Na$_2$SO$_4$. Evaporation of solvent under

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(16) (a) Tsai, F.; Lin, B.; Chen, M.; Mou, C.; Liu, S. *Tetrahedron* **2007**, *63*, 4304. (b) Chowdhury, R. R.; Crane, A. K.; Fowler, C.; Kwong, P.; Kozak, C. M. *Chem. Commun.* **2008**, 94.

(17) We observed that with allyl chloride the coupling product can be obtained in high yield without any catalyst. Hence, such examples were not included in this revision. We thank a reviewer for bringing this issue to our attention.

reduced pressure gave the crude product. Purification by flash column chromatography (silica gel, 2.2% ethyl acetate/pet ether) afforded ligand **L2** as a white solid (2.0 g, 40%): ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.56 (d, J = 7.7 Hz, 1H), 7.38−7.27 (m, 17H), 7.08 (t, J = 7.3 Hz, 4H), 6.73 (t, J = 6.5 Hz, 1H), 6.67 (s, 1H), 2.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 138.2, 138.1, 138.0, 138.0, 137.8, 137.7, 134.7, 134.7, 134.5, 134.4, 132.3, 132.0, 131.2, 129.5, 129.3, 128.6, 128.5, 128.5, 128.5. 128.2, 120.6, 119.9, 116.0, 10.0; ^{31}P NMR (202.44 MHz, $CDCl_3$, ppm) δ 35.08 (d, J = 159.9 Hz), −16.26 (d, J = 161.9 Hz). Anal. Calcd for $C_{33}H_{27}NP_2$: C, 79.35; H, 5.45; N, 2.80. Found: C, 79.33; H, 5.42; N, 2.79.

Typical Procedure for the Cross-Coupling Reaction. To a stirred solution of ligand (10.0 mg, 0.02 mmol), $Ni(CH_3CN)_2Cl_2$ (4.2 mg, 0.02 mmol), and chloroarene (1.0 mmol) in 1 mL of dry THF under argon atmosphere was added aryl Grignard reagent 1(M) in THF (2.0 mmol) at ambient temperature. The reaction mixture was then stirred for a further 3−10 h (depending on substrate) at rt. It was then quenched with saturated NH_4Cl solution at 0 °C and extracted with diethyl ether (2 × 10 mL). The combined organic layer was washed subsequently with water and brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (230−400 mesh) with either a mixture of petroleum ether and acetone (2−8%) or petroleum ether alone as eluent.

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Supporting Information Available: Detailed experimental procedures and characterization data for all compounds and X-ray data for **1d** and **L2** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.