Non-ligated Nickel Chloride-Catalyzed Cross-Coupling of Aromatic Grignard Reagents with Aryl Halides

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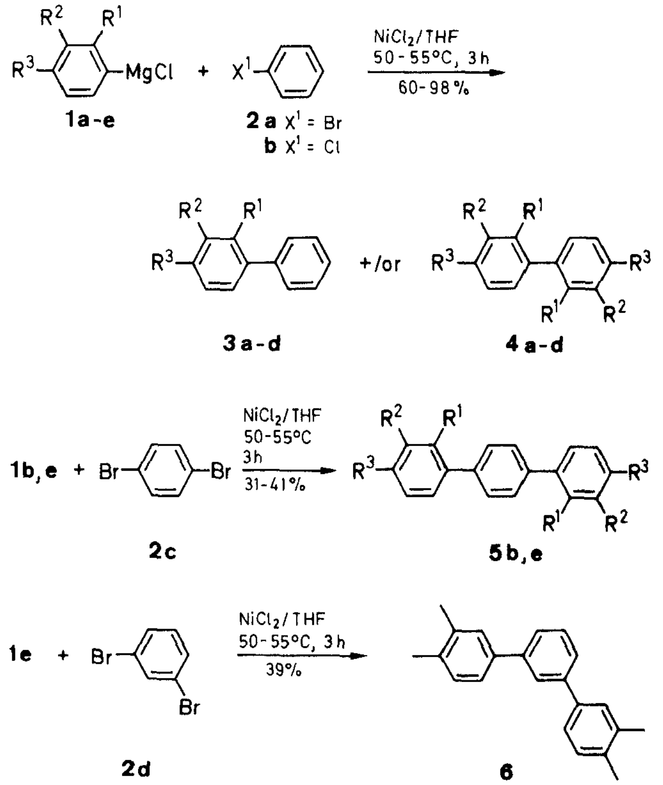
The reaction between aryl Grignard reagents and aryl halides in the presence of non-ligated nickel(II) chloride affords the cross-coupling products in high yields (60–98%).

Many reports on the homo- and cross-coupling reactions between aryl Grignard reagents and aryl halides using nickel complexes as catalysts have appeared.[1-3] Cases of aryl-aryl homo-coupling using nickel(II) chloride ($NiCl_2$) as a catalyst have been reported.[4-6] In the case of cross-coupling, however, most of the reported reactions were carried out using NiL_2X_2 type catalysts and no example using NiX_2 type catalysts has hitherto been reported; there are a few examples using palladium(II) chloride ($PdCl_2$).[7]

We found that $NiCl_2$ can act as an active catalyst for aryl cross-coupling reactions. When aryl Grignard reagents were reacted with aryl halides in tetrahydrofuran, using $NiCl_2$ as a catalyst, the cross-coupling products were obtained (Table 1).

When bromobenzene (**2a**) was used as an aryl halide, the yield of the cross-coupling product was higher than that obtained in the case of chlorobenzene (**2b**).

The substituent effects in the aryl Grignard reagent on the cross-coupling reaction were also examined. When a methyl group was introduced at an *o*-position of the aryl Grignard reagent (**1b**), cross-coupling reaction occurred preferentially, and no homo-coupling product was obtained. On the other hand, a methyl group at *meta*- or *para*-position results in both cross- and homo-coupling; the ratio is 3:1 (**3c**/**4c** = 60:25, **3d**/**4d** = 60:20). In each case, biphenyl was formed in 15% yield. These results clearly show that this cross-coupling reaction is sensitive to steric congestion at the reaction site.



1, 3-5	R^1	R^2	R^3
a	CH_3	Cl	H
b	CH_3	H	H
c	H	CH_3	H
d	H	H	CH_3
e	H	CH_3	CH_3

Table 1. Non-ligated $NiCl_2$ Catalyzed Cross-Coupling

Grignard Reagent	Halide	Product	Yield[a] (%)	bp (°C)/ Torr[b]	mp[b] (°C)	Lit. bp (°C)/ Torr mp (°C)
1a	**2b**	**3a**	24	106–108/2	–	
		4a	23	152/2	74.3–75.0	
1a	**2a**	**3a**	88 (97)			
1b	**2a**	**3b**	(98)	254–256	–	67–68[8]/ 0.27
1c	**2a**	**3c**	(60)	270–272	–	264–266[9]
		4c	(25)	138–139/5	8–9	8–9[10]
1d	**2a**	**3d**	(60)	266–268	44–47	48–49[11]
		4d	(20)	–	121–122	121[12]
1b	**2c**	**5b**	41 (60)	–	145–146	145.5–146[11]
1e	**2c**	**5e**	31 (37)	–	168–169	168–169[13]
1e	**2d**	**6**	39 (60)	–	72–73	72–73[13]

[a] Isolated yield, GLC analytical yield based on **1** in parentheses.
[b] Uncorrected.

Table 2. Variation of Catalyst on Cross-Coupling of **1a** and **2a**

Catalyst	Yield (%)[a]	
	3a	**4a**
$NiCl_2$	97[b]	2
$Ni(acac)_2$	95	5
$NiCl_2(diphos)$	94	2
$PdCl_2$	80	12
Li_2CuCl_4	25	75
$FeCl_3$	20	1

[a] GLC analytical yield, based on **1a**.
[b] Isolated yield 88%.

This reaction can also be applied to the preparation of terphenyls. When dibromobenzene **2c** and Grignard reagent **1b,e** were used, terphenyls **5b** and **5e** were obtained in 41% and 31% yield, respectively. Cross-coupling of dibromobenzene **2d** with Grignard reagent **1e** gave the terphenyl **6** in 39% yield. The yields of terphenyls are about 20% lower than those obtained when 1,2-bis(diphenylphosphino)ethanenickel(II) chloride [$NiCl_2$(diphos)] is used as a catalyst.

The catalytic activity of $NiCl_2$ was compared with those of other metal compounds, such as nickel(II) acetylacetonate [$Ni(acac)_2$], $NiCl_2$(diphos), $PdCl_2$, dilithium tetrachlorocuprate(II) (Li_2CuCl_4), and iron(III) chloride ($FeCl_3$) using the cross-coupling of **1a**–**2a** as a standard. The results are listed in Table 2. The highest activity for formation of **3a** was observed for $NiCl_2$. The order of the catalytic activity is as follows: $NiCl_2 \approx Ni(acac)_2 \approx NiCl_2(diphos) > PdCl_2 > FeCl_3$. The cross-coupling product **3a** is produced preferentially when $NiCl_2$, $Ni(acac)_2$, $NiCl_2$(diphos), $PdCl_2$, or $FeCl_3$ were used as catalyst. On the other hand, the homo-coupling product **4a** was predominant when Li_2CuCl_4 was used (**3a**/**4a** = 25:75).

These results show that non-ligated nickel(II) chloride is a useful catalyst in cross-coupling reactions, especially when there is steric hindrance at an *ortho*-position of the aryl Grignard reagents.

$NiCl_2$(diphos)[14] and Li_2CuCl_4[15] were prepared by reported procedures. All the other catalysts used are commercially available.

3-Chloro-2-methylphenylmagnesium Chloride (1a); Typical Procedure:

A 500 mL-flask is charged with magnesium (24.3 g, 1.00 mol) and THF (20 mL). To this is added dropwise a solution of 2,6-dichlorotoluene (161 g, 1.00 mol) in THF (200 mL) and the mixture refluxed for 3 h. The flask is then cooled to r.t. and the Grignard reagent **1a** used directly in the following experiment. Yield of mono-Grignard reagent is 70%.

3-Chloro-2-methylbiphenyl (3a); Typical Procedure:

A 1000 mL-flask is charged with $NiCl_2$ (1.0 g, 0.0011 mol), THF (30 mL), and bromobenzene (**2a**, 133 g, 0.85 mol). To this is added dropwise the Grignard reagent solution (**1a** contains 0.70 mol mono-Grignard reagent) while maintaining the temperature at 50–55 °C under an atmosphere of N_2, and the mixture is heated to 55 °C for 2 h. The flask is then cooled to r.t., and 1.4 N HCl (140 mL) is added. The organic layer is separated and dried ($MgSO_4$). The solvent is removed *in vacuo* and the residue is distilled under reduced pressure to give **3a**; yield: 124 g (88%), (Table 1).

$C_{13}H_{11}Cl$ calc. C 77.04 H 5.47
(202.7) found 76.97 5.40

MS (70 eV): m/z (%) = 202 (M^+, 100), 167 (95), 152 (20).

^1H-NMR ($CDCl_3$/TMS): δ = 2.3 (s, 3 H), 7.1–7.5 (m, 8 H).

3,3′-Dichloro-2,2′-dimethylbiphenyl (4a):

Prepared from a solution of 3-chloro-2-methylphenylmagnesium chloride (**1a**, 0.30 mol) in THF (95 mL), chlorobenzene (**2b**, 40.5 g, 0.36 mol) and $NiCl_2$ (0.43 g, 0.33 mmol) as described above. The compound **4a** can be isolated from a mixture of **3a** and **4a** by distillation followed by recrystallization from MeOH; yield: 17 g (23%); (Table 1).

$C_{14}H_{12}Cl_2$ calc. C 66.95 H 4.82
(251.2) found 66.97 4.79

MS (70 eV): m/z (%) = 250 (M^+, 100), 215 (88), 180 (78), 165 (67).

^1H-NMR ($CDCl_3$/TMS): δ = 2.1 (s, 6 H), 7.0–7.4 (m, 6 H).

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