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High Ortho Preference in Ni-Catalyzed Cross-Coupling of Halophenols with Alkyl Grignard Reagents

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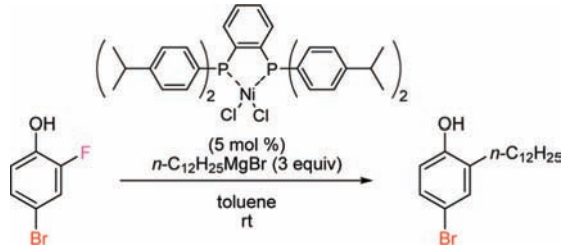
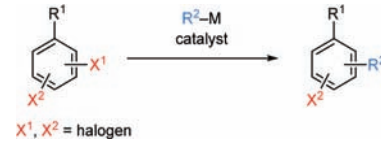
ABSTRACT



High preference of substitution at the position ortho to the hydroxy group was observed for Ni-catalyzed cross-coupling reactions of dihalophenols with alkyl Grignard reagents. Reactions of 2,4-dihalophenols, with various combinations of F, Cl, and Br, were shown to afford ortho-cross-coupled products selectively. In addition, high ortho preference was also observed in competitive cross-coupling reactions between 2-halophenols and other halophenols.

Transition-metal-catalyzed cross-coupling reactions in which haloarenes react with nucleophilic organometallic reagents constitute an important and practical synthetic methodology of multisubstituted arenes.[1] Unfortunately, the selective conversion of one halogen atom (mono-cross-coupling reactions) for dihalobenzenes that possess two identical halo groups has proven to not always be easy. In many cases, the reaction results in double-cross-coupling that involves both halo groups, even when the amount of the nucleophilic reagents was limited.[2] Furthermore, site-selective mono-cross-coupling reactions of dihalobenzene derivatives (Scheme 1) remain to be investigated in detail.[3] In general, the site-selective mono-cross-coupling reactions have been achieved using dissimilar halogen substituents (Scheme 1, $X^1 \neq X^2$) that exploit the differences in their reactivities (reactivity order: I > Br > Cl > F). It would be highly desirable, however, to employ substrates having two identical halo groups ($X^1 = X^2$) due to facile preparation and/or commercially availability.

Scheme 1. Site-Selective Cross-Coupling Reaction



Recently, we developed the ortho-selective cross-coupling of dihalobenzenes that possess electron-donating ortho-directing groups using Grignard reagents in the presence of palladium-based catalysts.[4] Our methodology sharply differs from most other ortho-selective cross-coupling reactions in which electron-withdrawing groups act as ortho-directing

(1) (a) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004. (b) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651.

(2) (a) Tamao, K.; Sumitani, K.; Kiso, Y.; Zembayashi, M.; Fujioka, A.; Kodama, S.-i.; Nakajima, I.; Minato, A.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1958. (b) Sinclair, D. J.; Sherburn, M. S. *J. Org. Chem.* **2005**, *70*, 3730. (c) Dong, C.-G.; Hu, Q.-S. *J. Am. Chem. Soc.* **2005**, *127*, 10006.

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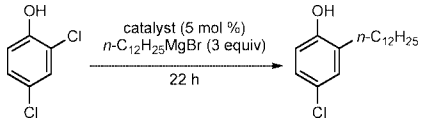
groups.[5] Although electron-donating groups typically retard the oxidative addition of a C−X bond to a transition metal in cross-coupling reactions, the presence of such groups is essential for the acceleration at the ortho position in our reactions. Aryl, alkenyl, and benzyl Grignard reagents were successfully utilized. For alkyl Grignard reagents that possess β-hydrogens, however, the reaction resulted in only the reduction of the starting halobenzenes, without the formation of the desired cross-coupled products. To overcome this problem, we tested various nickel catalysts that bear a bidentate phosphine ligand—as a note, such catalysts were employed in the original investigations of cross-coupling reactions using alkyl Grignard reagents, as reported by Tamao, Kumada, and co-workers.[2a,6] Although such nickel-based catalysts tend to undergo double cross-coupling,[2a] several catalysts have shown promising results toward promoting ortho-selective mono-cross-coupling of dihalophenols. Herein, we report such selective reactions, along with the high ortho preference in competitive cross-coupling reactions between two substrates.

We first tested nickel catalysts using the model reaction of 2,4-dichlorophenol with dodecylmagnesium bromide in ether. Representative examples are shown in Table 1.

Table 1. Optimization of Ortho-Selective Cross-Coupling Conditions



entry	catalyst	solvent	T (°C)	yield[a] (%)
1	$NiCl_2$(dppf)	Et_2O	reflux	0 (8)[b]
2	$NiCl_2$(dppp)	Et_2O	reflux	13 (15)[b]
3	$NiCl_2$(dppe)	Et_2O	reflux	24 (11)[b]
4	$NiCl_2$(dppbz)	Et_2O	rt	64 (9)[b]
5	$NiCl_2$(dppbz)	toluene	rt	76 (2)[b]

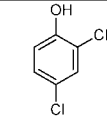
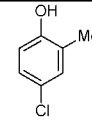
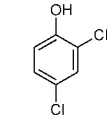
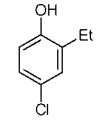
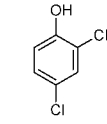
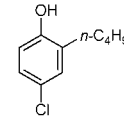
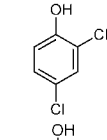
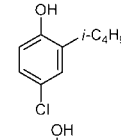
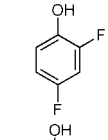
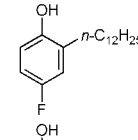
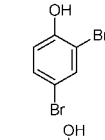
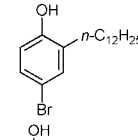
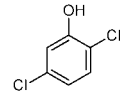
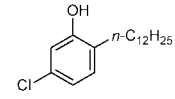
[a] The yield of the isolated product. [b] The yield of the double cross-coupled product (2,4-didodecylphenol).

Although the use of $NiCl_2$(dppf) resulted in the formation of the double-cross-coupled product in a low yield (entry 1), the use of $NiCl_2$(dppp) or $NiCl_2$(dppe) afforded the ortho-selective cross-coupling product, albeit in low yields (entries 2 and 3). For these reactions, the isomer, 2-chloro-4-dodecylphenol, was not obtained at all. Encouraged by these results, various multidentate phosphines were screened as ligands, and as a result, 1,2-bis(diphenylphosphino)benzene (DPPBZ)[7] was determined as the optimal ligand. The desired product was obtained in a high yield even at rt (entry 4). The yield was further improved when toluene was used as the solvent (entry 5).[8] Moreover, the formation of the double-cross-coupled product was effectively suppressed. Under these conditions, neither the cross-coupling nor the reduction was catalyzed by $PdCl_2$(dppbz), indicating the higher activity of the nickel species.

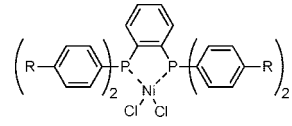
For these reactions, the hydroxy group of the substrate, which is deprotonated to form the corresponding magnesium phenoxide upon addition of the Grignard reagent, was shown to play an essential role for achieving high efficiencies. Using the methyl ether analogue (2,4-dichloroanisole) as a substrate, under the conditions shown in Table 1 (entry 5, 1.5 equiv of the Grignard reagent), the double-cross-coupled product was obtained in 44% yield, along with the ortho-cross-coupled product in 35% yield. Therefore, although a methoxy group can function as a directing group, it is significantly less effective than a magnesium oxido group.

As shown in Table 2, our catalytic system was applied to other substrates. In the cases of 2,4-dichloro-, 2,4-difluoro-,

Table 2. Ortho-Selective Cross-Coupling of Substrates Having Two Identical Halo Groups[a]

entry	substrate	Grignard reagent	product	yield (%)[b]
1[c]		MeMgBr		50
2		EtMgBr		65
3		*n*-BuMgCl		33
4		*i*-BuMgBr		37
5[d]		*n*-$C_{12}H_{25}$MgBr		75
6[d]		*n*-$C_{12}H_{25}$MgBr		36
7		*n*-$C_{12}H_{25}$MgBr		19

[a] Reaction conditions: substrate (0.5 mmol), Grignard reagent (1.5 mmol), $NiCl_2$(dppbz) (0.025 mmol) in toluene at rt for 22 h unless otherwise indicated. [b] The yield of the isolated product. [c] At 75 °C. [d] $NiCl_2$(dippbz) was used instead of $NiCl_2$(dppbz).



R = H: $NiCl_2$(dppbz)
R = *i*-Pr: $NiCl_2$(dippbz)

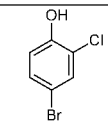
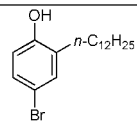
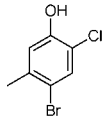
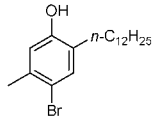
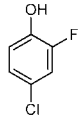
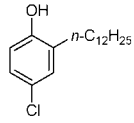
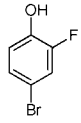
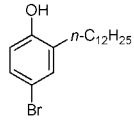
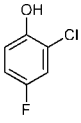
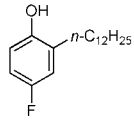
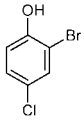
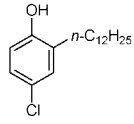
and 2,4-dibromophenol, reactions with alkyl Grignard reagents occurred ortho-selectively (entries 1−6). Although the yields of the desired products were modest in most cases,

the corresponding isomeric products were not obtained. With the exception of entry 1 (7%) and entry 6 (12%), only trace amounts of the double cross-coupled products were obtained. In the cases of difluoro- and dibromophenol (entries 5 and 6), the use of $NiCl_2$(dippbz) was slightly more effective than $NiCl_2$(dppbz) (DIPPBZ = 1,2-bis[di(4-isopropylphenyl)phosphino]benzene). Interestingly, the cross-coupling of a fluorobenzene derivative having an electron-donating group was shown to proceed at rt. For 2,5-dichlorophenol, the yield of the ortho-cross-coupled product was significantly lower (entry 7), while a significant amount of the double cross-coupled product was obtained (26%).[9]

As shown in Table 3, unusual behavior was observed using substrates that have two different halo groups. For the reaction of 4-bromo-2-chlorophenol or 4-bromo-2-chloro-5-methylphenol (entries 1 and 2), an *o*-chloro group was found to be more reactive than a *p*-bromo group. Accordingly, the reaction strongly favored the formation of the ortho-cross-coupled over the para-cross-coupled product, but a small amount of the double-cross-coupled product was formed (3%, entry 1; 8%, entry 2). More surprisingly, an *o*-fluoro group was more reactive than a *p*-chloro and even a *p*-bromo group (entries 3 and 4). In these cases, the para- and double-cross-coupled products were obtained in trace amounts. These results indicate that the directing effects of the hydroxy group take priority over the intrinsic reactivity order of the halo groups.[10] As expected, the reactions involving substrates shown in entries 5 and 6 selectively afforded the ortho-cross-coupled products.

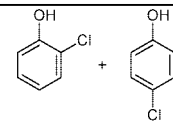
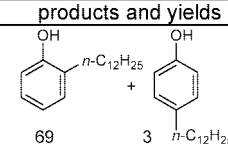
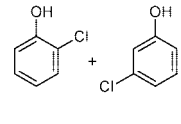
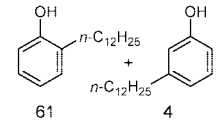
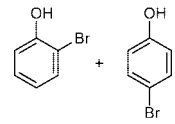
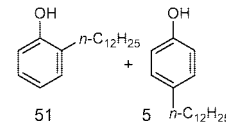
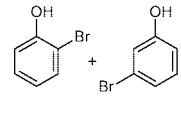
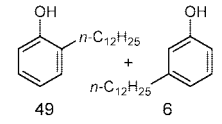
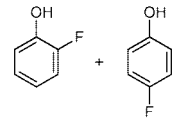
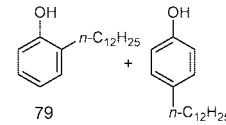
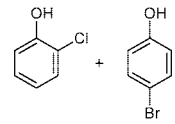
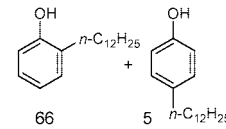
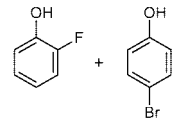
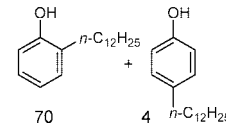
High ortho preference was also observed in the competitive cross-coupling between two substrates.[11] As shown in Table 4 (entry 1), the cross-coupling reaction involving a 1:1 mixture of 2-chlorophenol and 4-chlorophenol favored the former substrate. Similarly, preference for the ortho substrate was also observed for the competitive reactions between 2- and 3-chlorophenol (entry 2), between 2- and 4- (or 3-)bromophenol (entries 3 and 4), and between 2- and 4-fluorophenol (entry 5). Furthermore, 2-chlorophenol and

Table 3. Ortho-Selective Cross-Coupling of Substrates Having Two Different Halo Groups[a]

entry	substrate	product	yield (%)[b]
1			61
2			52
3			60
4[c]			65
5			57
6			43

[a] Reaction conditions: substrate (0.5 mmol), dodecylmagnesium bromide (1.5 mmol), $NiCl_2$(dppbz) (0.025 mmol) in toluene at rt for 22 h unless otherwise indicated. [b] The yield of the isolated product. [c] $NiCl_2$(dippbz) was used instead of $NiCl_2$(dppbz).

Table 4. Competitive Cross-Coupling of Two Substrates[a]

entry	substrates	products and yields (%)[b]
1		 69 3
2		 61 4
3		 51 5
4		 49 6
5[c]		 79 trace
6		 66 5
7[c]		 70 4

[a] Reaction conditions: two substrates (0.5 mmol each), dodecylmagnesium bromide (2.0 mmol), $NiCl_2$(dppbz) (0.025 mmol) in ether at rt for 22 h. [b] The yields after separation. [c] $NiCl_2$(dippbz) was used instead of $NiCl_2$(dppbz).

2-fluorophenol were found to be more reactive than 4-bromophenol (entries 6 and 7). These results clearly demonstrate that the ortho-directing effect of the hydroxy group is effective, not only for *intra*molecular differentiation between two halo groups but also for *inter*molecular differentiation between two halobenzene substrates.

Despite the following assumptions, the mechanism of the high ortho preference in these nickel-catalyzed cross-coupling reactions remains unclear. For the ortho-selective reactions of dihalophenols, the oxidative addition of the ortho-C−X bond to nickel(0) is presumably the selectivity-determining step. The oxidative addition step is assumed to be facilitated by the Lewis acidic magnesium of the magnesium phenoxide (substrate) (Figure 1).[10a,12,13] On the other hand, we cannot

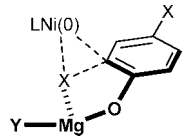


Figure 1. Proposed transition state of the oxidative addition step in which Lewis acidic Mg facilitates the C−X bond cleavage.

rule out the possibility that the nickel(0)/arene η^2-complex formation step,[14] prior to the oxidative addition, is the selectivity-determining step especially for the competitive cross-coupling of two substrates. Further studies are currently underway to gain insight into the origin of the high ortho preference.

In summary, the catalytic system involving $NiCl_2$(dppbz) and $NiCl_2$(dippbz) was shown to enhance the ortho-selective cross-coupling reactions of dihalophenols with alkyl Grignard reagents. Furthermore, high ortho preference was also observed in competitive cross-coupling between two substrates. Our studies show that the directing effects of the hydroxy group can override the intrinsic reactivities of halo groups. Although the mechanism of the high ortho preference has yet to be clarified, we believe that the unusual behavior described herein contributes to further development of cross-coupling methodology.

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Supporting Information Available: Experimental procedures, spectral data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Dichlorobenzene derivatives having other functional groups such as $-CH_2OH$, $-NH_2$, and −NHAc resulted in poor yields and ratios of the desired ortho-substituted and the disubstituted products. The yields of the desired ortho-substituted products (and the disubstituted products in parenthesis): 2,4-dichlorobenzyl alcohol, 6% (28%); 2,4-dichloroaniline, 19% (8%); 2,4-dichloroacetanilide, trace (13%).

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(13) One of the reviewers of this paper suggested possibilities of S_NAr and radical mechanisms instead of concerted oxidative addition of C−X bond to Ni(0). We cannot completely exclude these possibilities, although the S_NAr mechanism is unlikely because of the presence of the strongly electron-donating oxido group. We thank the reviewer for pointing out these possibilities.

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