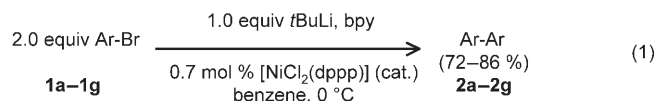


Nickel-Catalyzed Coupling of Aryl Bromides in the Presence of Alkylolithium Reagents

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Transition-metal-catalyzed coupling reactions of halogenated molecules leading to formation of new carbon–carbon bonds are a very important category of reactions used in the synthesis of complex compounds and conjugated polymers.^[1–3] Within the past decade, this methodology has evolved into a powerful synthetic tool for the preparation of a wide range of specialty polymers, composite materials, and pharmaceutically active compounds both in the laboratory and on the industrial scale. It is also widely appreciated in the context of parallel synthesis and combinational chemistry.^[4,5] We desired to develop an improved catalytic method for transition-metal-catalyzed aryl coupling reactions and report herein the one-pot, one-step, nickel-catalyzed coupling of aryl bromides in the presence of alkylolithium reagents [Eq. (1)].



Metallic reagents including palladium and nickel complexes have demonstrated to be quite effective in C–C coupling reactions. Typically, coupling reactions of aryl halides involving the use of catalytic amounts of nickel(II) complexes require the addition of either magnesium or zinc to facilitate efficient coupling and regeneration of active nickel(0) catalytic species. For example, Kumada coupling reactions use magnesium for the formation of active alkyl/aryl magnesium bromide species (Grignard formation),

which is generally a substrate- and solvent-specific reaction (working optimally in tetrahydrofuran or diethyl ether as solvents).^[6–10] Nickel reactions facilitated by the addition of zinc powder have been utilized in a similar fashion in organic synthesis,^[11–13] as well as in efficient condensation polymerizations.^[14–16] These reactions are not always well controlled, require prolonged heating at high temperatures, and the products have high levels of metal impurities that can be difficult and costly to remove. This trace-metal contamination is especially problematic if the end use is in pharmaceutical or microelectronic applications in which safety, performance, and reliability require stringent control of purity. Another known aryl–halide coupling reaction involves the use of highly reactive zinc (Rieke zinc), which is prepared by reduction of ZnCl₂ with lithium naphthalenide and has been shown to readily undergo oxidative addition with alkyl, aryl, and vinyl halides under mild conditions to generate the corresponding organozinc compounds. These reactive organozinc compounds are then cross-coupled with other aryl or vinyl halides using palladium(0) catalysts.^[17] Recently, homocoupling of bromide compounds has been facilitated through the combination of metallic magnesium and a catalytic amount of iron salts.^[18] Coupling reactions involving activated dihalogenated thiophene molecules catalyzed by nickel(II) complexes have also been demonstrated in the presence of reactive zinc (Rieke zinc)^[19] or an alkyl-magnesium reagent (GRIM/McCullough method)^[20] to form regioregular polythiophenes.

Coupling reactions of halogenated molecules involving nickel(0) complexes (Yamamoto coupling) require the employment of equimolar quantities of expensive nickel(0) complexes because the reaction pathway does not include a catalytic cycle for the regeneration of nickel(0) from nickel(II).^[21–24] These reaction also require the use of toxic ligands and elevated reaction temperatures. Coupling reactions of aryl bromides catalyzed by palladium generally require cross-coupling of a brominated aryl compound with functional aryl derivatives, such as boronic acids or esters (Suzuki coupling),^[25] terminal alkynes (Sonogashira coupling),^[26] alkenes (Heck coupling),^[27] or alkyl tin compounds

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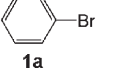
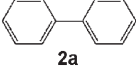
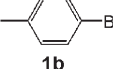
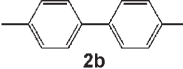
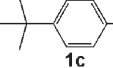
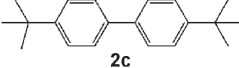
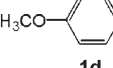
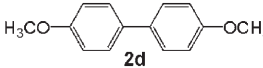
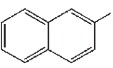
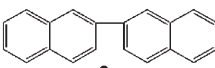
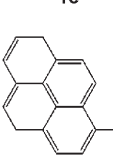
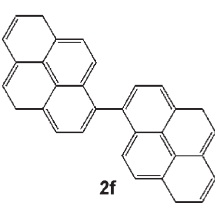
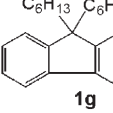
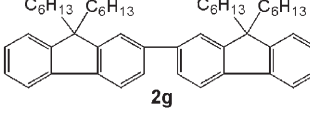
(Stille coupling).^[28] Due to the synthetic requirements of the generation of the desired aryl derivatives, the synthesis of new materials by these coupling methods is often challenging or technically arduous.

There have been few reported instances in the literature in which combinations of nickel and lithium reagents have been studied in coupling reactions. The reactions of nickelocene (NiCp_2) with alkyllithium^[29,30] and phenyllithium^[31] reagents have been studied and the products analyzed. Lithium hydride has been used to generate the active nickel(0) species from nickel acetate.^[32] Rieke and Kavaliunas have shown the formation of metallic nickel by the reduction of nickel halides with lithium and naphthalene as an electron carrier, and this active nickel was effective in the coupling of benzylic halides and polyhalides.^[33] They have demonstrated that this reactive nickel can react at near room temperature with one equivalent of iodopentafluorobenzene^[34] and the resulting solution contained a mixture of the solvated species $\text{Ni}(\text{C}_6\text{F}_5)_2$ and NiI_2 . It is important to note that in all of the above cases the reactions require a large excess of reducing agent and often an equimolar amount of nickel complex compared to the halogenated aromatic substrate.

Herein, we report the use of alkyllithium reagents in the presence of catalytic amounts of [1,3-bis(diphenylphosphino)propane]dichloronickel(II), $[\text{NiCl}_2(\text{dppp})]$, for coupling aryl bromide compounds in good yields. The scope of this method has been demonstrated with a variety of aryl bromides, including phenyl, pyrenyl, naphthyl, and fluorenyl bromide compounds. We believe this easy and convenient reaction, which only requires moderate cooling, can be employed for the synthesis of a broad range of aryl-based organic molecules and polymers. Equation 1 shows the one-step, one-pot synthetic scheme for the synthesis of various aryl molecules prepared by nickel-catalyzed homocoupling of halogenated molecules using alkyllithium reagents. Aryl bromides (**1a–1g**) in benzene were treated with an alkyllithium reagent, a catalytic amount of $[\text{NiCl}_2(\text{dppp})]$, and 2,2'-dipyridyl (bpy) at 0°C to give the expected biaryl products (**2a–2g**) in good to moderate yields (72–86%; Table 1).

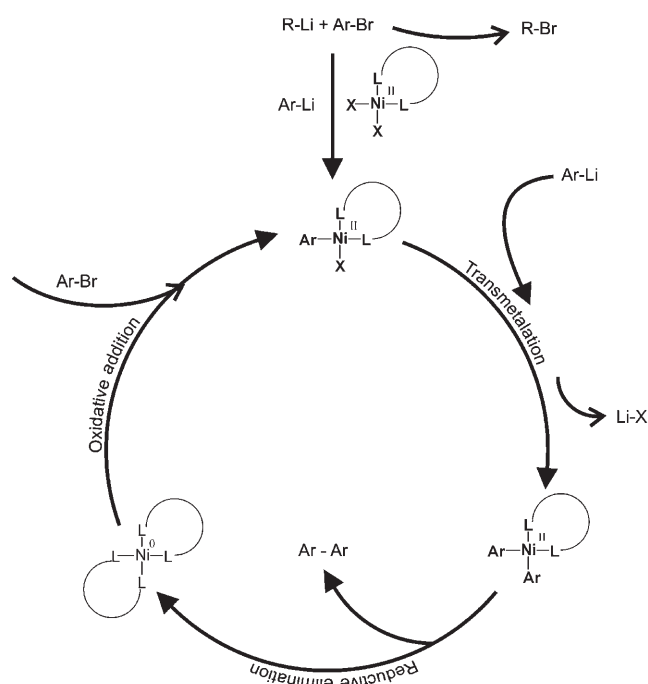
First, a comparison of different alkyllithium reagents was made by examining the coupling of bromobenzene (**1a**). The molar ratio of bromobenzene to catalyst was 138:1 using $[\text{NiCl}_2(\text{dppp})]$ (25 mg, 46.12 μmol) and bromobenzene (1.00 g, 6.37 mmol). Bpy (18 mg, 115.24 μmol) was added to the reaction solution as a ligand and was found to be necessary for the coupling reaction to proceed in higher yields.^[11] Commercially available *n*BuLi, *sec*BuLi, and *t*BuLi solutions were used for the reactions. Alkyllithium was added at half molar equivalents to that of phenyl bromide groups with the intention of generating an equimolar ratio of lithiated benzene anions to unreacted phenyl bromide groups. The alkyllithium reagents were added dropwise at 0°C to reduce interactions of alkyllithium with the solvent and the reactions were allowed to proceed at room temperature for 24 h. The reactions were monitored by TLC (with hexane as the eluting solvent) and showed the formation of biphenyl (**2a**) as the major product formed with no traces of bromobenzene

Table 1. A summary of the results of the $[\text{NiCl}_2(\text{dppp})]$ catalyzed homocoupling using *t*BuLi.

Substrate	Product	Yield [%]
		82
		86
		80
		82
		75
		72
		85

observed. It was observed that the reactions with *t*BuLi were more effective (82% yield) than those using *n*BuLi (72%) or *sec*BuLi (74%). GC analysis performed on the *n*BuLi reaction mixture revealed the formation of significant amounts of *n*butyl benzene as a side product, which indicates the preference for alkyl cross-coupling versus lithiation in this reaction. While the tendency for reactions to undergo alkyl cross-coupling in place of lithiation has been shown to be sensitive to the nature of the solvent used, secondary and tertiary alkyllithiums do not give cross-coupled products in appreciable yields.^[35] GC analysis performed on the *t*BuLi reaction did not show the formation of *t*-butyl benzene. When the coupling of bromobenzene using *t*BuLi was performed in THF, the yield of biphenyl product formed was observed to be slightly lower (76%) than with benzene (82%). This small difference could be due to the competing reaction of *t*BuLi with THF. Decreasing the amount of $[\text{NiCl}_2(\text{dppp})]$ from 25 to 12 mg, while maintaining the ratio of $[\text{NiCl}_2(\text{dppp})]$ to bpy, did not have a substantial effect on the yield of biphenyl formed (yield reduced from 82 to 78% in benzene as a solvent).

The exact nature of the catalytic cycle (Scheme 1) is proposed to involve the transmetalation of the aryllithium intermediate with a nickel(II) species. This is followed by a second transmetalation of the $\text{Ar-Ni}^{\text{II}}-\text{X}$ species to form an $\text{Ar-Ni}^{\text{II}}-\text{Ar}$, which undergoes reductive elimination to form the Ar-Ar coupled product and active nickel(0). The active



Scheme 1. The proposed mechanism of the nickel-catalyzed homocoupling reaction showing the catalytic cycle of nickel. L denotes the pyridine group of 2,2'-dipyridyl ligated to nickel.

nickel(0) species can subsequently undergo oxidative addition to another Ar-Br molecule. The reaction cycle allows the use of catalytic amounts of nickel and the reaction yields were not sensitive to the amount of $[\text{NiCl}_2(\text{dppp})]$, although the use of 0.5 equiv of *t*BuLi to Ar-Br was important. An excess or insufficient amount of *t*BuLi led to lower yields because the in situ nickel(0) species generated required sufficient amounts of aryl bromide for complete reactions. While we cannot exclude the possibility of some reduction of nickel(II) to nickel(0) by *t*BuLi, this is not a major factor in the coupling reaction. When *t*BuLi is first added to a solution containing nickel(II) followed by addition of Ar-Br, no product formation is observed. The order of addition is very important. This exact nature of the coupling mechanism is currently under study.

In summary, we have successfully demonstrated an easy and novel approach towards the synthesis of compounds using coupling reactions of bromide compounds. Alkyl lithium reagents reacted with a wide range of aryl bromides, including phenyl, pyrenyl, naphthyl, and fluorenyl bromide compounds in presence of catalytic amounts of $[\text{NiCl}_2(\text{dppp})]$ and 2, 2'-dipyridyl, which resulted in the formation of coupled aryl products in moderate to good yields after purification (72–86%). The efficient catalytic cycle affords the use of $[\text{NiCl}_2(\text{dppp})]$ in catalytic amounts for the coupling reactions and precludes the use of large quantities of Ni, Mg, or Zn. This one-pot synthetic technique demonstrates the first example of the use of alkyl lithium reagents with a catalytic amount of nickel to synthesize coupled aryl compounds. Using this easy, convenient, and inexpensive

technique, we can obtain coupled products in good yields. We believe this reaction has tremendous potential for use in the synthesis of target organic molecules, cross-coupling reactions, as well as the synthesis of aryl-based conjugated polymers, which will be the subject of a forthcoming publication.

Experimental Section

Detailed experimental procedures have been provided in the Supporting Information and a representative procedure for the synthesis of biphenyl (**2a**) is given here. In a reactor flask bromobenzene (1.00 g, 6.37 mmol), $[\text{NiCl}_2(\text{dppp})]$ (25 mg, 46.12 μmol), and 2,2'-dipyridyl (18 mg, 115.24 μmol) were added followed by the addition of benzene (3 mL). The flask was sealed under nitrogen and the reaction was cooled to 0°C with stirring. *t*BuLi (1.88 mL, 3.2 mmol, 1.7 M solution in pentane) was added to the cooled reaction mixture dropwise by using a syringe. The mixture was allowed to warm gradually to room temperature and was stirred for 24 h. The reaction mixture was concentrated by rotary evaporation and loaded onto a silica gel column. The product was purified using silica gel flash chromatography with hexane as the eluting solvent, and after solvent evaporation gave biphenyl as a white powder (0.40 g, 82%).

Acknowledgements

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