

An Extremely Active Catalyst for the Negishi Cross-Coupling Reaction

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Abstract: A new catalyst system for the Pd-catalyzed cross-coupling of organozinc reagents with aryl halides (Negishi coupling) has been developed. This system permits efficient preparation of hindered biaryls (tri- and tetra-ortho-substituted), functions effectively at low levels of catalyst, and tolerates a wide range of functional groups and heterocyclic substrates. A systematic study of ligand structure was performed and was correlated with catalyst activity.

Introduction

The biaryl motif is found in numerous classes of natural products and pharmaceutically active compounds. Over the past 30 years, Pd-catalyzed cross-coupling reactions have revolutionized the way organic synthesis is practiced. The most widely studied of these cross-coupling reactions involve the formation of C(sp²)–C(sp²) bonds by the union of aryl or vinyl halides and organometallic reagents (ArM; M = B, Sn, Si, Zn, Mg).¹ Among the possible nucleophilic partners, organotin (Stille) and organoboron (Suzuki–Miyaura) reagents have been studied most widely; organozinc (Negishi) and organomagnesium (Kumada) reagents have been employed to a lesser extent.

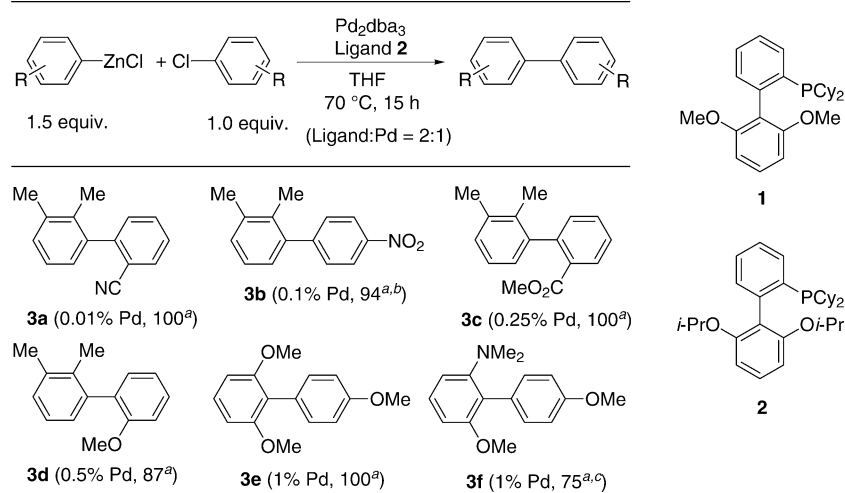
Studies have shown that the choice of supporting ligand on Pd is crucial in many transformations.^{1b,2} Pioneering work by Dai and Fu afforded the first general protocol for performing Negishi cross-coupling reactions of unactivated and deactivated aryl chlorides, in which the electron-rich complex Pd[P(*t*-Bu)₃]₂ was used as the precatalyst.³ Using a standard set of conditions (2% Pd[P(*t*-Bu)₃]₂, THF/NMP, 100 °C), the synthesis of quite hindered biaryls was accomplished in excellent yield.

Recently, we reported that the use of commercially available **1** (SPhos) provided a catalyst with unparalleled reactivity in Suzuki–Miyaura cross-coupling processes. It allowed for the efficient construction of hindered biaryls, couplings with exceptionally high turnover numbers, couplings at room temperature and could be employed with a broad substrate scope.⁴ Despite the widespread use of boronic acids for Suzuki–Miyaura cross-couplings, and the advantages associated with

these reagents, difficulties remain.⁵ Problems include the frequent need for recrystallization of the arylboronic acid prior to use, their tendency to form varying amounts of boroxines, and their propensity to undergo competitive protodeboronation under the reaction conditions used for cross-coupling, as well as problems involving the preparation and application of sterically hindered boronic acids. In addition, the presence of either electron-donating or -withdrawing groups may reduce the stability of the arylboronic acid. For example, our efforts to synthesize the electron-rich [2-(*N,N*-dimethylamino)-6-methoxyphenyl]boronic acid by halogen–lithium exchange of the corresponding aryl bromide, followed by treatment with B(O*i*-Pr)₃, resulted in deboronation upon attempted conversion of the initially formed intermediate to the boronic acid. A potential solution in such cases is to employ an alternative nucleophilic partner, such as an arylzinc reagent.⁶ However, previous attempts in our group to effect Pd-catalyzed Negishi cross-coupling reactions using our biaryldialkylphosphine ligands gave little or no yield of the desired products.⁷ Since these early efforts, a new generation of biphenyl-based monophosphines has been developed which are ortho,ortho'-disubstituted on the lower (non-phosphine-containing) ring. Due to our recent advances in both C–N⁸ and C–C⁹ bond forming transformations employing these new ligands, we decided to reinvestigate the Negishi reaction. As a result of this study into the construction of biaryls, we report herein a new, highly active and general catalyst system derived from ligand **2** for the Negishi cross-coupling reaction.

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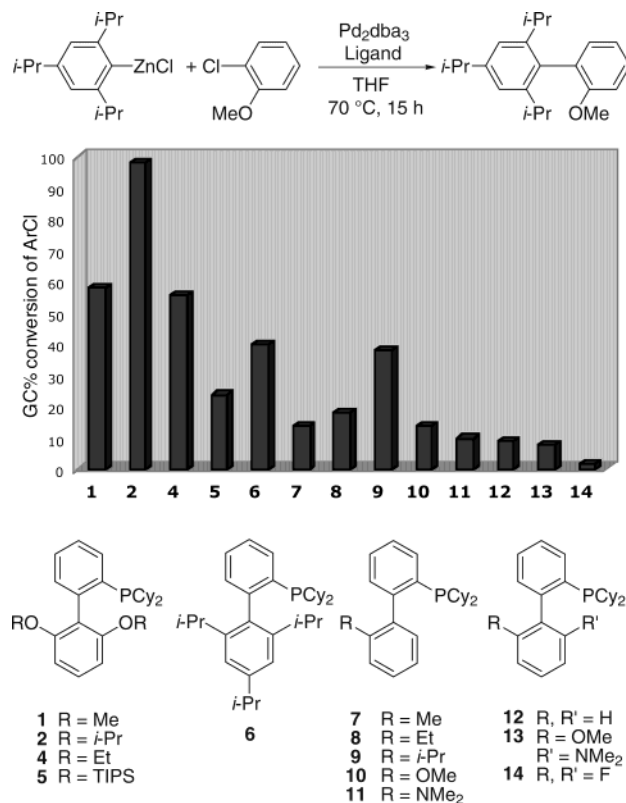
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Table 1. Negishi Cross-Coupling of Aryl Chlorides to Generate Biaryls

^a Isolated yield; average of at least two runs. ^b Reaction run at room temperature. ^c Reaction run at 100 °C, in THF/NMP (1:1).

Results and Discussion

Initial studies indicated that phosphine **2** was an excellent supporting ligand for the Pd-catalyzed coupling of aryl chlorides with organozinc reagents. The arylzinc chlorides were typically prepared in situ from the corresponding aryl bromides. Halogen–lithium exchange followed by transmetalation with zinc(II) chloride furnished the desired organozinc species. Zinc(II) bromide could also be employed; however, the arylzinc chlorides were more effective in the subsequent cross-coupling step. As shown in Table 1, the use of a catalyst derived from **2** and Pd₂dba₃ in THF at 70 °C (standard conditions) demonstrated a tolerance to a variety of common functional groups including cyano, nitro, ester, alkoxy, and amino substituents (Table 1, **3a–3f**) and operated efficiently at low levels of catalyst. Previously reported systems required higher temperatures and quantities of catalyst for similar cross-couplings. For example, 2'-cyano-2,3-dimethylbiphenyl (**3a**) (Table 1) was prepared using only 0.01% Pd, which, to our knowledge, is the lowest quantity of Pd ever employed for the Negishi cross-coupling of an aryl chloride. The reaction of 1-chloro-4-nitrobenzene with (2,3-dimethylphenyl)zinc chloride in THF at 70 °C resulted in low yields of the desired biaryl **3b**. However, carrying out the process at room temperature provided **3b** in 94% yield using as little as 0.1% Pd. In some cases, a directed ortho lithiation approach¹⁰ could be used to access the required arylzinc reagents, obviating the need to start with an aryl bromide. For example, ortho lithiation of 1,3-dimethoxybenzene, followed by Li → Zn exchange and cross-coupling of the resulting arylzinc reagent with 4-chloroanisole, afforded the biaryl in quantitative yield. Initial attempts to couple [2-(*N,N*-dimethylamino)-6-methoxyphenyl]zinc chloride with 4-chloroanisole in THF at 70 °C led to poor conversions of aryl chloride. However, employing a 1:1 mixture of THF/NMP,¹¹ as described by Fu,³ as the solvent system and increasing the reaction temperature to 100 °C furnished the desired biaryl **3f** in 75% yield. The use

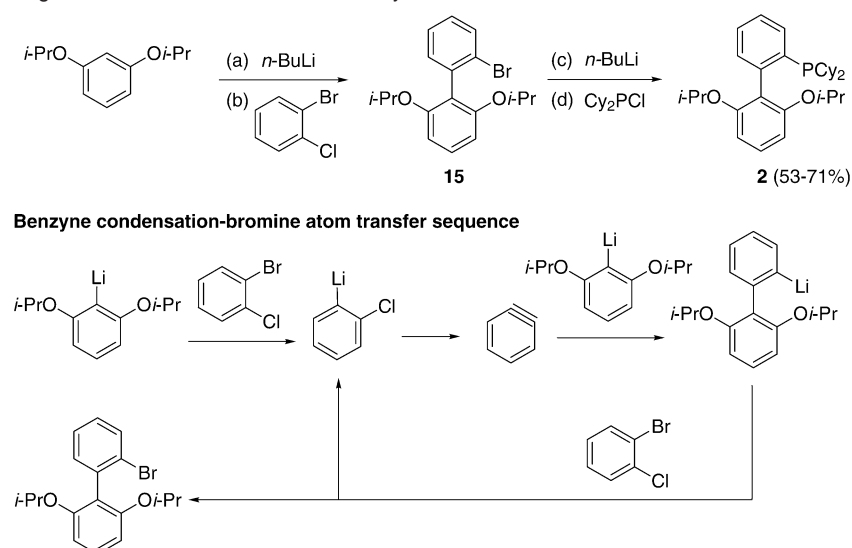
**Figure 1.** Ligand effects in the coupling of hindered substrates.

of electron-rich arylzinc reagents, as described above, demonstrates how this protocol complements the Suzuki–Miyaura reaction.

As part of our study, the effect of the structure of the phosphine ligand on the challenging coupling reaction between (2,4,6-triisopropylphenyl)zinc chloride and 2-chloroanisole was examined (Figure 1). During this investigation we confirmed previous work in our laboratory which had shown that use of ligand **11** gave poor conversions to the desired product.⁷ However, increasing the size of the substituent on the lower aromatic ring (ligands **6–9**) enhanced the effectiveness of the ligand. Moreover, increasing the electron density by introducing methoxy groups on the lower ring (ligands **10** and especially

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Scheme 1. Preparation of Ligand **2** via an Efficient Lithium–Benzyne Procedure

1) markedly improved catalyst performance. A number of new ligands with variations in the steric and electronic properties of the lower (non-phosphine-containing) ring were prepared to aid the investigation. A fine-tuning of the size of the *o*-alkoxy substituents on the lower ring (ligands **1**, **2**, and **4**) confirmed **2** as the superior ligand. Unfortunately, we have been unable to prepare the ligand with two *o*-*tert*-butoxy groups on the lower ring. However, a further increase in the size of the two ortho *O*-substituents by installing OTIPS groups at this position (with concomitant loss of electron-donating capability) provided a ligand whose use gave a catalyst of diminished activity. These results suggest that ligand **2** is suitably bulky to allow sufficient quantities of LPd intermediates to be present in the reaction mixture.¹² Additionally, the level of bulk is small enough to do this without slowing the transmetalation step. To ascertain the effect of an electron-deficient lower ring, the difluoro ligand **14** was prepared. Comparing the catalysts derived from ligands **12** and **14** revealed that decreasing the electron density on the lower ring may diminish catalyst activity. Interestingly, the use of ligands **11** and **13**, which possess *N,N*-dimethylamino groups, gave poor conversion of the starting aryl chloride to biaryl product. For these ligands it is possible that the organozinc species coordinates to the amino group, slowing the desired reaction.

Given its utility, it was necessary to develop a concise and inexpensive route to ligand **2**. We have previously demonstrated that biaryldialkylphosphine ligands can be prepared by the addition of an aryl Grignard reagent to benzyne (generated *in situ*), followed by trapping of the newly formed organomagnesium species, in the presence of a copper catalyst, with ClPR₂.¹³ However, the presence of both the excess magnesium metal from the Grignard formation in the first step and the copper salts added to facilitate C–P bond formation can complicate the workup of the reaction. Optimization of the synthesis of **2** revealed that a modified one-pot protocol employing a lithium–benzyne step afforded the ligand cleanly in 53–71% yield

(Scheme 1). The route begins with the directed ortho lithiation of 1,3-diisopropoxybenzene (1.1 equiv) achieved by heating at 80 °C in hexanes for 2 h in the presence of *n*-butyllithium (1.2 equiv). Maintaining the reaction at reflux, dropwise addition of neat 2-bromochlorobenzene (1.0 equiv) over 50 min generated the bromobiphenyl **15** via a tandem benzyne condensation–bromine atom transfer sequence.¹⁴ Cooling of the reaction mixture to –78 °C and halogen–lithium exchange with *n*-butyllithium (1.1 equiv), followed by treatment with chlorodicyclohexylphosphine (1.0 equiv), furnished ligand **2**. This method offered a number of advantages over previous methods for the preparation of the ligands on a small scale: it was faster and cleaner, eliminated the need for Cu(I) salts, and avoided an additional step to prepare an aryl halide as the precursor. Ligands **4**, **5**, and **14** were prepared using the same method.

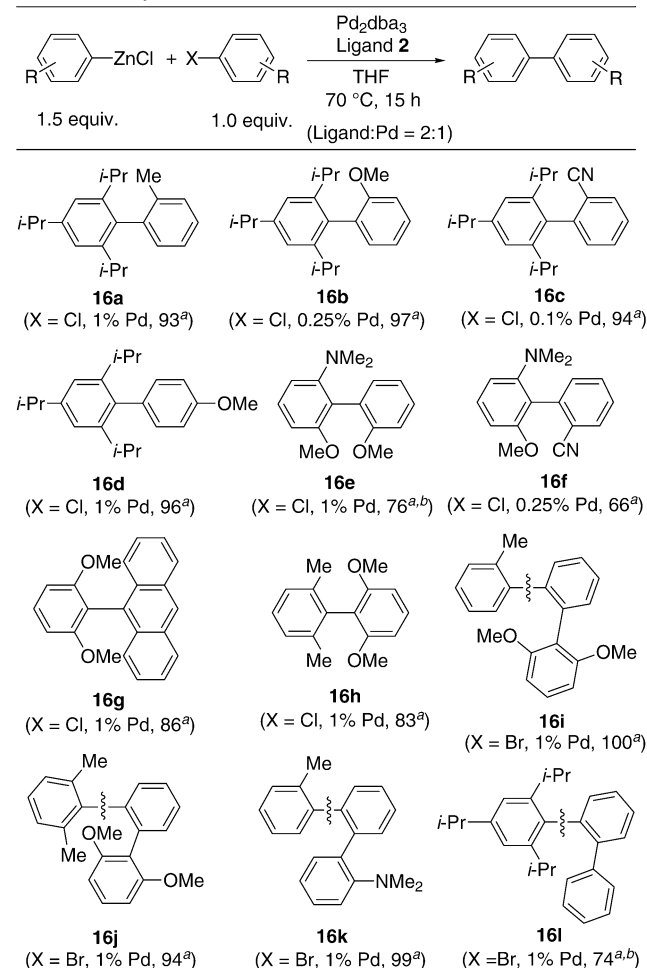
A challenging problem in Negishi coupling processes is the ability to combine sterically hindered substrates. This is particularly difficult when both coupling partners have large ortho substituents. Using the standard conditions, a range of exceptionally hindered di- and tri-ortho-substituted biaryls were prepared from aryl chlorides using only 0.1–1% Pd. Arylzinc chlorides containing ortho substituents such as methyl, alkoxy, isopropyl, and *N,N*-dimethylamino groups also underwent smooth cross-coupling with complete conversion of the starting aryl chlorides. We also found that it was possible to efficiently couple (2,4,6-triisopropylphenyl)zinc chloride with a variety of ortho-substituted aryl chlorides (**16a–c**). To our knowledge, this is the most highly hindered arylzinc species ever employed in a cross-coupling process. The reaction of [2-(*N,N*-dimethylamino)-6-methoxyphenyl]zinc chloride with 2-chlorobenzonitrile proceeded smoothly in 66% yield; however, when 2-chloroanisole was employed, no reaction was observed under the standard conditions. Employing the procedure using THF/NMP as the solvent mixture at 100 °C resulted in complete conversion of the substrates and produced **16e** in 76% yield.

Due to the high level of catalyst activity displayed by 2/Pd(0), we decided to investigate its use for the preparation of tetra-ortho-substituted biaryls. To our delight, biaryls **16g** and **16h** could be prepared in high yield from 9-chloroanthracene and

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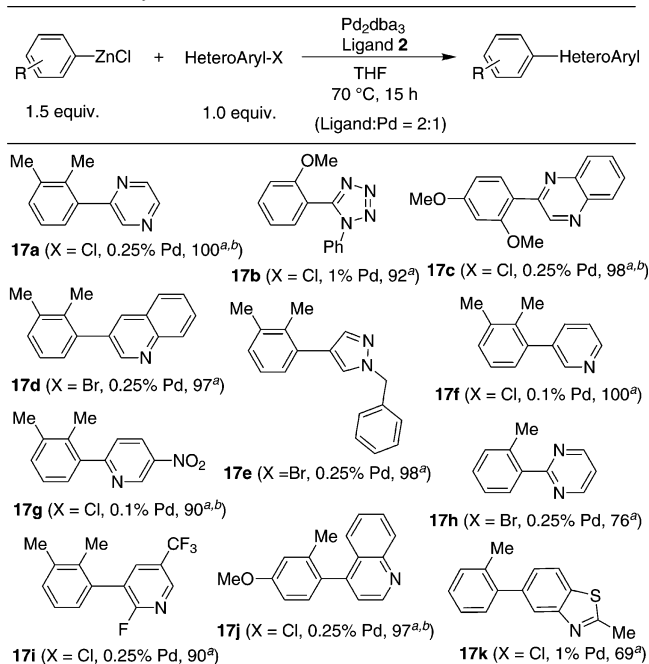
Table 2. Negishi Cross-Coupling of Aryl Halides to Generate Hindered Biaryls

^a Isolated yield; average of at least two runs. ^b Reaction run at 100 °C, in THF/NMP (1:1).

1-chloro-2,6-dimethoxybenzene, respectively. To our knowledge, the reaction of electron-rich 1-chloro-2,6-dimethoxybenzene with (2,6-dimethylphenyl)zinc chloride is the first example of a Negishi reaction that forms a biaryl with four ortho substituents employing a deactivated aryl chloride. Unfortunately, the preparation of biaryls with four *o*-methyl groups was plagued by homocoupling as a side reaction, along with the desired cross-coupling, resulting in inseparable mixtures of products.

The new catalyst system was also found to be quite useful for coupling unactivated aryl bromides as shown in Table 2 (**16i–l**). First, we investigated the challenging formation of triaryls **16i–k** in THF at 70 °C; these reactions all proceeded in >90% yield. However, the coupling of (2,4,6-trisopropylphenyl)zinc chloride with 2-bromobiphenyl only proceeded to 41% conversion under the standard conditions using 1% Pd. Increasing the catalyst loading to 2% Pd resulted in only a moderate increase in efficiency (56% conversion). As before, by using THF/NMP as the solvent system and increasing the temperature to 100 °C, **16l** could be isolated in 74% yield.

There are an increasing number of heteroaryl compounds being discovered as lead structures for new pharmaceuticals. Despite their importance, the cross-coupling reaction of heteroaryl halides remains challenging. With this in mind, we next

Table 3. Negishi Cross-Coupling of Heteroaryl Halides to Generate Biaryls

^a Isolated yield; average of at least two runs. ^b Reaction run at room temperature.

examined the catalyst derived from **2**/Pd(0) for Negishi coupling reactions involving heterocyclic substrates. As shown in Table 3, the cross-coupling of a variety of heterocyclic chlorides and bromides was accomplished in good to excellent yields, including a quinoxaline, benzothiazole, pyrimidine, pyrazine, quinoline, tetrazole, and pyrazole as well as substituted pyridines. Unfortunately, to date, our limited attempts to couple heteroarylzinc reagents have been unsuccessful. Current efforts are focused in this area.

In summary, structural refinements to the ligand framework of previously reported biarylphosphines gave a ligand whose use provides a catalyst of unparalleled reactivity for Negishi cross-coupling reactions. This system is the most effective of any known for Negishi cross-couplings with respect to turnover numbers for aryl chlorides, for the efficient formation of hindered biaryls, and for substrate scope.

Experimental Section

The following are representative procedures for the Pd(0)-catalyzed Negishi cross-coupling reaction. A full account of the reaction conditions and characterization of products can be found in the Supporting Information.

General Procedure: Pd-Catalyzed Negishi Couplings of Aryl Halides and Arylzinc Chlorides. An oven-dried resealable Schlenk tube containing a magnetic stir bar was capped with a rubber septum and then evacuated and backfilled with argon (this sequence was repeated three times). The Schlenk tube was charged with the aryl bromide (0.75 mmol, 1.5 equiv) and dry THF (1.0 mL). The resulting solution was cooled to −78 °C, then *n*-butyllithium (0.825 mmol, 1.65 equiv) was added dropwise via syringe through the septum, and the resulting solution was stirred at −78 °C for 1 h. ZnCl₂ (0.9 mmol, 1.8 equiv) was added in one solid portion by removal of the septum. After 30 min at −78 °C, the Schlenk tube was removed from the cooling bath and the resulting solution stirred at room temperature for 1 h. Pd₂(dba)₃ (2.3 mg, 0.5 mol %), **2** (4.7 mg, 2.0 mol %), and the aryl chloride (0.5 mmol, 1.0 equiv) were added with the aid of THF (0.5

mL), which was used to rinse the walls of the tube. The septum was replaced with a Teflon screwcap, and the Schlenk tube was sealed. The reaction mixture was placed in a preheated oil bath at 70 °C and magnetically stirred until the aryl halide had been completely consumed as judged by GC analysis. The reaction mixture was then cooled to room temperature, diluted with water (1 mL), and extracted with diethyl ether (4×10 mL). The combined organic phases were dried over Na₂SO₄ and concentrated under reduced pressure. The crude material obtained was purified by flash chromatography on silica gel.

Modified Procedure for Pd-Catalyzed Negishi Couplings at Low Catalyst Loading ($\leq 0.5\%$ Pd). The general procedure was used with the following changes: A separate vial was charged with Pd₂(dba)₃ (2.3 mg, 0.5 mol %) and **2** (4.7 mg, 2.0 mol %). The vial was sealed with a Teflon-coated screwcap, a needle was inserted through the cap, and the vial was purged with argon. Dry THF (2 mL) was added, and the mixture was sonicated for ~ 1 min to afford a homogeneous solution. The required quantity of catalyst solution (e.g., 20 μ L for reactions carried out at 0.01% Pd) was added to the reaction mixture.

Modified Procedure for Pd-Catalyzed Negishi Couplings to Generate Hindered Biaryls. The general procedure was used with the following changes: After the addition of the catalyst and the aryl halide, NMP (1.0 mL) was used to rinse the walls of the tube. The septum was replaced with a Teflon screwcap, and the Schlenk tube was sealed. The reaction mixture was placed in a preheated oil bath at

100 °C and magnetically stirred until the aryl halide had been completely consumed as judged by GC analysis.

Modified Procedure for Pd-Catalyzed Negishi Couplings to Generate Biaryls Combining a Directed Ortho Metalation Approach. The general procedure was used with the following changes to the preparation of the arylzinc species: To a cold (0 °C), stirred solution of 1,3-dimethoxybenzene (98 μ L, 0.75 mmol) in dry THF (1 mL) was added *n*-butyllithium (0.33 mL, 2.5 M in hexanes, 0.825 mmol) dropwise via syringe over 10 min. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The aryllithium was cooled to -78 °C, and ZnCl₂ (0.9 mmol, 1.8 equiv) was added in one solid portion by removal of the septum. After 30 min at -78 °C, the reaction was removed from the cooling bath and the resulting solution stirred at room temperature for 1 h.

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Supporting Information Available: Preparation and characterization of ligands and products (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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