

Negishi Coupling of Secondary Alkylzinc Halides with Aryl Bromides and Chlorides

Chong Han and Stephen L. Buchwald*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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The transition metal catalyzed cross-coupling reactions involving sp^2 -hybridized carbon nucleophiles and aryl or vinyl halides have been extensively examined during the past three decades.¹ Yet, few comprehensive studies have been published concerning the analogous cross-coupling of secondary $C(sp^3)$ -hybridized organometallics with aryl halides.²

A simplified scheme of the course of the reaction for the coupling of an isopropyl metal with an aryl halide is shown (Scheme 1).¹ Oxidative addition followed by transmetalation would produce intermediate **B**, which can reductively eliminate to form the desired product *i*-PrAr with concomitant reformation of $L_nPd(0)$. Competitive with this is the reversible β -hydride elimination to form **C**, from which reductive elimination can take place producing reduced arene. **C** can undergo a migratory insertion reaction to produce **D** which can reductively eliminate to form the undesired product *n*-PrAr. Of obvious importance to developing a successful catalytic method is to have ligands that will facilitate the rate of reductive elimination from **B** relative to the rate of β -hydride elimination.

Pioneering work by Kumada and Hayashi demonstrated, with a limited set of substrates, that dichloro[1,3-bis(diphenylphosphino)propane] nickel(II) ($NiCl_2(dppp)$)^{2h} and dichloro[1,1'-bis(diphenylphosphino)ferrocene] palladium(II) ($PdCl_2(dppf)$)²ⁱ could be used for the coupling of secondary alkyl Grignard reagents with aryl and vinyl halides. Recently, Dreher and Molander reported an elegant and more comprehensive study of the Pd-catalyzed Suzuki–Miyaura coupling of secondary alkyltrifluoroborates with aryl chlorides.^{2g} These publications describe the formation of good ratios of secondary to primary alkyl coupling products in a number of cases. Yet, the product ratios obtained when electron-deficient and/or ortho-substituted aryl halide substrates were used were poor to moderate, and the substrate scope was somewhat limited in terms of the functional groups that were demonstrated to be tolerated.

Here, we report a general catalyst for the Pd-catalyzed Negishi coupling of secondary alkylzinc halides with aryl bromides and chlorides in high yield with excellent ratios of secondary to primary coupling products based on a new biarylphosphine ligand, CPhos.

We initiated our studies by evaluating a series of biaryldialkylphosphine ligands³ with both an electron-deficient and -rich ortho-substituted aryl bromide, 2-bromobenzonitrile, and 2-bromoanisole,

Scheme 1. A Simplified Reaction Course for the Coupling of *i*-PrM with an Aryl Halide

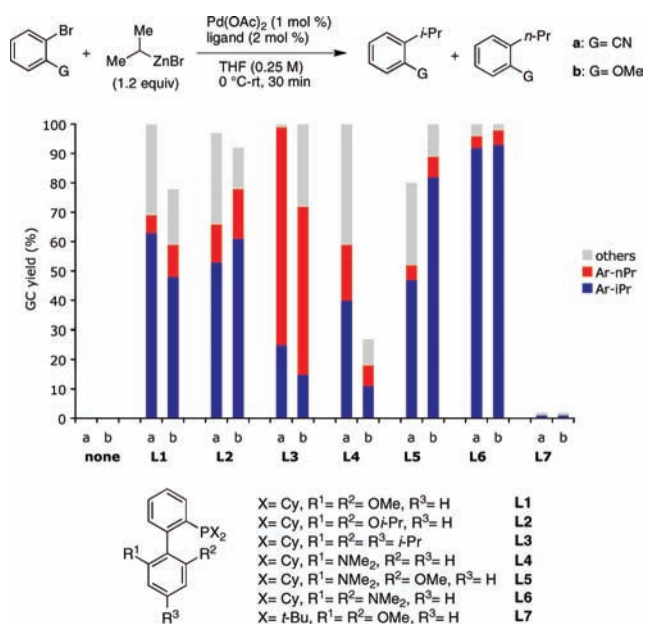
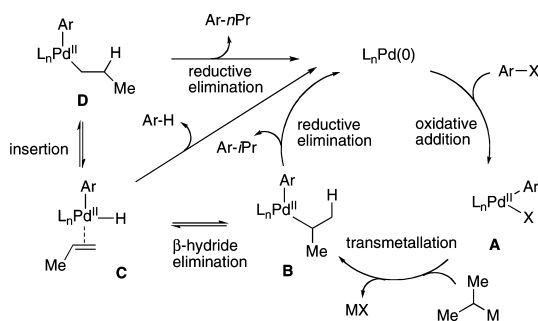
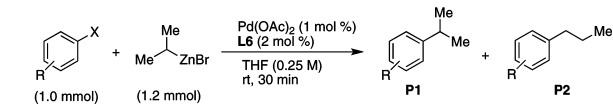


Figure 1. Ligand effects in the coupling of ortho-substituted aryl bromides with isopropyl zinc bromide.

in combination with isopropyl zinc bromide using 1 mol % $Pd(OAc)_2$ at ambient temperature in THF (Figure 1). SPhos (**L1**), RuPhos (**L2**), and XPhos (**L3**), previously reported to be excellent ligands for Suzuki–Miyaura⁴ and Negishi coupling⁵ reactions, including those with primary alkyl boron and zinc reagents reported by Molander^{4b–d} and Knochel,^{5b,c} gave moderate results. In contrast, a new ligand (**L6**), CPhos, bearing ortho,ortho'-dimethylamino substituents on the lower (nonphosphine-containing) ring was found to give results superior to those of other biarylphosphine ligands in terms of the ratio of branched (*i*-Pr) to linear (*n*-Pr) products and the yield. The use of $PdCl_2(dppf)$ ²ⁱ provided low (<10%) conversion of products under the same conditions.

We next examined the coupling of a range of aryl halides with isopropylzinc bromide, which was readily prepared as a THF solution by LiCl-assisted zinc insertion into isopropyl bromide according to Knochel's method⁶ (Table 1). Our coupling conditions at ambient temperature were successfully applied to a series of ortho- and para-substituted aryl bromides; the selectivity for the branched product remains high (>20:1, *i*-Pr/*n*-Pr) in all cases.⁷ In general, the selectivities realized for ortho-substituted aryl bromides were lower than those obtained with corresponding para-substituted ones, presumably due to steric effects (entries 1–4 vs 7–10); this is consistent with what has been previously reported.^{2f} Employing toluene as a cosolvent afforded higher yields and selectivities in the cases of electron-deficient aryl bromides and chlorides (entries 3–5 and 9–10). Esters (entry 3 and 9), nitriles (entry 4 and 10), aldehydes (entry 5), and unprotected indoles (entry 12) were well tolerated.^{5b,c} Yet, the coupling of 4-bromonitrobenzene provided a modest yield of the desired product due to formation of unidentified side products (entry 6). In addition, activated aryl chlorides⁸ (entries 3–5 and 9–10) were also suitable

Table 1. Negishi Cross-Coupling of Isopropylzinc Bromide with Aryl Bromides and Chlorides


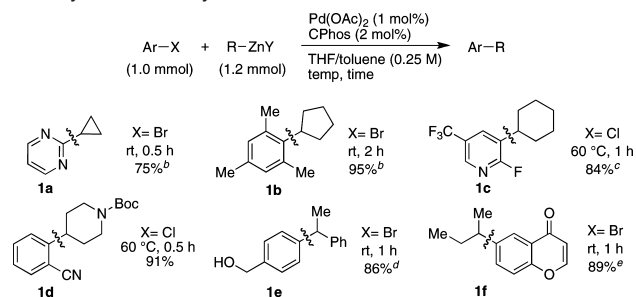
entry	ArX	yield ^a	P1:P2
1	R = 4-OMe, X = Br	92%	37:1
2	R = 4-Ph, X = Br	95%	39:1
3	R = 4-CO ₂ Me	X = Br 94% ^{b,c} X = Cl 98% ^{b,c}	46:1 45:1
4	R = 4-CN	X = Br 87% ^b X = Cl 94% ^b	59:1 43:1
5	R = 4-CHO	X = Br 89% ^b X = Cl 93% ^{b,d}	43:1 47:1
6	R = 4-NO ₂ , X = Br	50% ^{b,d}	28:1
7	R = 2-OMe, X = Br	97%	27:1
8	R = 2-Ph, X = Br	97% ^c	22:1
9	R = 2-CO ₂ Me	X = Br 91% ^b X = Cl 97% ^{b,e}	37:1 30:1
10	R = 2-CN	X = Br 89% ^b X = Cl 94% ^{b,c}	20:1 22:1
11	R = 2-SMe, X = Br	95% ^f	30:1
12	5-bromoindole	96%	58:1

^a Isolated yields of mixtures of *i*-Pr and *n*-Pr products; average of at least two runs. ^b Toluene employed as a cosolvent. ^c Rt, 3 h. ^d 0 °C, 30 min. ^e Rt, 6 h. ^f Rt, 1 h.

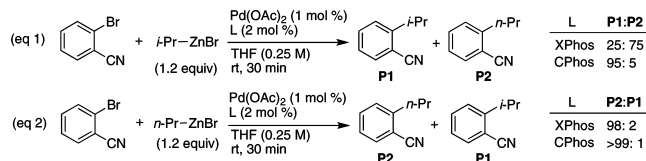
substrates at ambient temperature providing products in high yield and with good selectivity, although longer reaction times were often needed compared to those for the reactions of the corresponding aryl bromides.

To probe the generality of the coupling reaction with respect to secondary alkylzinc halides, a variety of cyclic and acyclic zinc reagents were prepared using Knochel's protocol.^{6,9} Coupling reactions of these alkylzinc reagents with aryl bromides and activated aryl chlorides could be performed efficiently employing 1–2 mol % catalyst (Scheme 2). The ratio of branched to linear product remained high for reactions involving acyclic zinc reagents (**1e–f**). Additionally, no isomeric products were observed for the reaction with the *N*-Boc piperazine substrate (**1d**).

There are two most probable scenarios to explain the differences seen with CPhos and XPhos (cf. Scheme 1): (1) The ratio of branched to linear products is determined by the relative rates of corresponding reductive elimination steps if a fast equilibrium exists between species **B** and **D**. In this case, similar product ratios should be obtained for couplings of both *i*-Pr and *n*-Pr zinc reagents. (2) The product ratio is largely dependent on the relative rates of reductive elimination versus β -hydride elimination–reinsertion. To distinguish between these, we examined the coupling of 2-bromobenzonitrile with *n*-propyl zinc bromide (Scheme 3, eq 2) to compare the results to those obtained with isopropyl zinc bromide (Scheme 3, eq 1). Consistent with the

Scheme 2. Negishi Cross-Coupling of Secondary Alkylzinc Halides with Aryl or Heteroaryl Bromides and Chlorides^a

^a Isolated yields; average of two runs. ^b Reaction conducted in THF. ^c 2 mol % Pd(OAc)₂ and 4 mol % CPhos. ^d The alkylzinc reagent (1.5 equiv) was slowly added over 30 min. ^e 23:1 branched/linear.

Scheme 3. Comparison of Product Distribution for the Coupling of Isopropyl and *n*-Propyl Zinc Bromide with 2-Bromobenzonitrile

latter explanation are the different product distributions seen for the coupling of *i*-Pr versus *n*-Pr zinc reagents (CPhos, P1/P2 = 95:5 in eq 1 versus P1/P2 < 1:99 in eq 2; XPhos, P1/P2 = 25:75 in eq 1 versus P1/P2 = 2:98 in eq 2). This explanation is further supported by an observed kinetic isotope effect on the product distribution ($k_{\text{H}}/k_{\text{D}} = 3.1$) for the coupling of fully deuterated isopropyl zinc bromide using XPhos.⁹

In summary, we have established an efficient new catalyst system for Negishi coupling of secondary alkylzinc halides with a wide range of aryl bromides and activated chlorides in which the undesired β -hydride elimination pathway is effectively suppressed employing the new ligand CPhos, **L6**. The broad substrate scope and excellent selectivity of the coupling process provide a general and useful means for the forging of C(sp³)–C(sp²) bonds. Further, we have provided evidence that the excellent selectivity observed for branched versus linear products with secondary alkyl zincs using CPhos is due to the slow relative rates of β -hydride elimination–reinsertion versus reductive elimination.

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Supporting Information Available: Experimental procedures, structural proofs, and spectral data for all new compounds are provided. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) For recent reviews, see: (a) *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds., Wiley-VCH: New York, 2004. (b) Tamao, K.; Miyauchi, N. *Top. Curr. Chem.* **2002**, *219*, 1. (c) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.
- (2) For representative references, see: Negishi coupling: (a) Boudier, A.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 687. (b) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719. (c) Corley, E. G.; Conrad, K.; Murry, J. A.; Savarin, C.; Holko, J.; Boice, G. J. *Org. Chem.* **2004**, *69*, 5120. (d) Kondolff, I.; Doucet, H.; Santelli, M. *Organometallics* **2006**, *25*, 5219. (e) Luo, X.; Zhang, H.; Duan, H.; Liu, Q.; Zhu, L.; Zhang, T.; Lei, A. *Org. Lett.* **2007**, *9*, 4571. (f) Melzig, L.; Gavryushin, A.; Knochel, P. *Org. Lett.* **2007**, *9*, 5529. Suzuki–Miyaura coupling: (g) Dreher, S. D.; Dormer, P. G.; Sandrock, D. L.; Molander, G. A. *J. Am. Chem. Soc.* **2008**, *130*, 9257 and references cited therein. Kumada coupling: (h) Tamao, K.; Kiso, Y.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 9268. (i) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158.
- (3) (a) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461. (b) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338.
- (4) (a) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871. (b) Molander, G. A.; Sandrock, D. L. *Org. Lett.* **2007**, *9*, 1597. (c) Molander, G. A.; Petrillo, D. E. *Org. Lett.* **2008**, *10*, 1795. (d) Molander, G. A.; Canturk, B. *Org. Lett.* **2008**, *10*, 2135.
- (5) For aryl–aryl Negishi coupling using RuPhos, see: (a) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028. For Negishi coupling of aryl halides with primary alkyl zinc halides using SPhos, see: (b) Manolikakes, G.; Schade, M. A.; Hernandez, C. M.; Mayr, H.; Knochel, P. *Org. Lett.* **2008**, *10*, 2765. (c) Manolikakes, G.; Hernandez, C. M.; Schade, M. A.; Metzger, A.; Knochel, P. *J. Org. Chem.* **2008**, *73*, 8422.
- (6) Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 6040.
- (7) Less than 2% reduction products (Ar–H) were observed in all cases.
- (8) Attempted coupling of 4-chloroanisole using standard conditions at 60 °C provided low conversion (<2%).
- (9) See Supporting Information for experimental details.

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