Mild and General Conditions for Negishi Cross-Coupling Enabled by the Use of Palladacycle Precatalysts

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Biaryls, particularly those containing one or more heterocyclic components, are ubiquitous among pharmaceutically active compounds, natural products, and agrochemicals. Palladium-catalyzed cross-coupling reactions have been extensively studied and practiced in both academic[1] and industrial[2] settings for their preparation. Although various palladium-catalyzed cross-coupling methods to form sp^2-sp^2 carbon-carbon bonds have been developed, the Negishi coupling is one of the most frequently utilized. The utility of Negishi couplings is partially due to the fact that organozinc reagents, despite considerable basicity, are compatible with a large number of sensitive functional groups.[3] Equally important is that a wide array of highly functionalized organozinc reagents can be readily accessed.[4] Additionally, the recent development of solid salt-stabilized organozinc reagents, which are much less sensitive towards air and moisture,[5,6] has also rendered the Negishi coupling a more practical and user-friendly technique for synthetic organic chemists.

Numerous studies have been devoted to the development of more general and efficient catalyst systems for Negishi cross-coupling reactions. In 2001, Fu described the first general protocol to effect the Negishi cross-coupling of aryl chlorides using Pd[P(tBu$_3$)]$_2$ (2 mol %) as the precatalyst in THF/NMP at 100 °C.[7] In 2004, our group reported a highly active catalyst based on dialkylbiarylphosphine **L1** (RuPhos), which permitted the efficient generation of a wide range of sterically hindered tri- and tetra-*ortho* substituted biaryls in THF at 70 °C with low catalyst loadings.[8] In a series of publications, Knochel demonstrated the utility of biarylphosphine **L2** (SPhos) as the supporting ligand for palladium-catalyzed Negishi coupling.[3,9] More recently, the Organ group has also developed a well-tailored Pd-PEPPSI-IPent precatalyst capable of combining a variety of extremely sterically hindered substrates to afford tetra-*ortho* substituted biaryls under exceptionally mild conditions with excellent yields.[10,11]

Despite these advances, significant challenges still remain. Notably, while simple aryl halides and arylzinc reagents are easily transformed, couplings involving heteroarylzinc reagents and heteroaryl halides are often less successful. This difficulty is due partly to the altered electronic properties of heterocyclic compounds, as well as to the presence of heteroatoms capable of binding to the transition-metal center and leading to catalyst deactivation and decomposition.[12] In particular, the transformation of five-membered heterocycles bearing more than one heteroatoms, such as pyrazoles and imidazoles, has

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proven to be challenging.[13,14] Thus, the development of a catalyst system capable of facilitating the coupling of a diverse range of heteroaryl and functionalized substrates under mild conditions is still highly desirable. Herein, we report a general catalyst system based on a palladacycle precatalyst ligated by dialkylbiarylphosphine ligand **L3** (XPhos) for the palladium-catalyzed Negishi cross-couplings at ambient temperature or with low catalyst loadings. With this system myriad heteroaryl coupling partners, many of which were previously unsuccessful substrates,[8] can now be effectively coupled. In addition, we report the success of this system for the Negishi coupling of polyfluoroarylzinc reagents.

We recently reported the development of a new class of easily prepared, air- and moisture-stable aminobiphenyl-based palladacycle mesylate precatalysts capable of rapidly and quantitatively generating the catalytically active $L_1Pd(0)$ species under basic conditions at room temperature.[15-18] Given their intrinsic basicity, we reasoned that organozinc reagents could readily activate these precatalysts *in situ*, and furthermore that the efficient and rapid formation of $L_1Pd(0)$ facilitated by these precatalysts would allow for Negishi cross-couplings under mild conditions and, potentially, with low catalyst loadings. Thus, palladacycle precatalyst **3c** was compared with other commonly used palladium sources in combination with **L3** for the Negishi cross-coupling of *p*-tolylzinc chloride (**4**) and 2-bromoanisole (**5**) (Figure 1). Interestingly, the protocol employing palladacycle precatalyst **3c** facilitated the coupling in 92% yield after just 20 minutes, whereas the use of other palladium sources such as $Pd(OAc)_2$ and Pd_2dba_3 resulted in product yields lower than 40% in the same amount of time. These results clearly indicate that palladacycle precatalyst **3** generates the catalytically active $L_1Pd(0)$ species most efficiently.

We next re-evaluated the ligand effects using palladacycle precatalysts of type **3**.[8] Given the success of bulky monophosphinobiaryl ligands **L3**[17,19] and **L5**[20] in facilitating Suzuki-Miyaura cross-coupling with high reactivity, we were interested in carefully evaluating their activity for Negishi cross-couplings. Differences in reaction rates for catalyst systems derived from ligand **L1, L3, L4** and **L5** were determined by monitoring the reaction progress using calorimetric analysis.[21a] As depicted by Figure 2, reaction rates for all of the catalyst systems derived from **L1, L4** and **L5** are significantly lower than that observed when **L3** was used as the supporting ligand. While catalyst systems employing **L3** and **L4** both facilitated full conversion of 2-bromoanisole after approximately 30 min, the initial rate of the catalyst generated from **L4** was about 50% lower than the rate of the catalyst derived from **L3**. This result illustrates the influence of the size of the substituents on the non-phosphorus-containing ring of the dialkylbiarylphosphine ligand on catalyst activity, in accordance with our previous findings.[21b,c] Further, the benefit of using a ligand with cyclohexyl rather than *tert*-butyl substituents on the phosphorous atom of the monophosphinobiaryl ligand is highlighted by the 10-fold difference in reaction rate between catalysts based on **L4** and **L5**. Interestingly, a catalyst derived from **L1** furnished only 55% conversion at 0.1 mol% Pd loading, indicating that the catalyst based on **L1** is less effective than that generated from **L3** at low palladium loadings.[22] Taken together, these studies suggest that a catalyst system based on L3 exhibits the highest activity for Negishi couplings.

In light of the importance of heterocyclic compounds in medicinal chemistry and materials chemistry,[23] we focused on the Negishi cross-coupling of heteroarylzinc reagents with heterocyclic halides and pseudohalides (Table 1). We were interested in the Negishi coupling of five-membered 2-heteroaromatic zinc chlorides (i.e., 2-furyl, 2-thienyl, 2-benzofuranyl, 2-benzothiophenyl and 2-indolyl zinc chlorides) and 2-pyridylzinc chlorides, as the corresponding organoboron reagents are difficult substrates for Suzuki-Miyaura coupling due to the rapid protodeboronation,[17] and, in the case of 2-pyridylboronate,[24] the relatively slow rate of transmetallation.[25] We found that by using 0.25–4 mol% of **3c**,

these heteroaryl zinc reagents (**7a–7j**) could be efficiently coupled at room temperature to furnish heterobiaryls in excellent yield. 3-Furyl, 3-thienyl, 3-pyrroryl, 3-indolyl and 3-pyridylzinc chlorides were equally effective under the current protocol (**7k–7o**). Azole coupling partners were also evaluated with the current catalyst system. 4-Iodo-1-tritylimidazole (**7p**), 2- and 4-bromothiazoles (**7q** and **7r**) proved to be more challenging substrates, requiring higher reaction temperatures to obtain appreciable amounts of coupled product. Benzo-fused azole (**7s**) and *N*-substituted pyrazole (**7t**) electrophiles were excellent substrates for this methodology and could be converted to the desired products in excellent yields at room temperature.[26] Azole containing nucleophilic coupling partners such as pyrazolyl (**7u, 7v, 7w** and **7z**), 4-isoxazolyl (**7x**), 2-thiazolyl (**7y**) and 2-imidazolyl (**7a’**) zinc chlorides can also be smoothly cross-coupled using our protocol. Finally, different types of halides and pseudohalides can all be effectively coupled with organozinc reagents under our conditions.

To further demonstrate the utility of our methodology, we sought to extend the scope of our catalyst system to reactions of polyfluorophenylzinc reagents (Table 2). We were particularly intrigued by the coupling of fluorinated arylzinc reagents because methods for the preparation of polyfluorinated biaryls remain underdeveloped. Reactions of corresponding polyfluorophenyl boronic acids constitute a challenging family of nucleophiles for Suzuki-Miyaura coupling due to rapid protodeboronation.[17] For example, the half-life time of 2,3,6-trifluorophenylboronic acid under our most recently developed conditions for Suzuki-Miyaura coupling is only 2 min,[17] rendering the Suzuki-Miyaura coupling of this boronic acid a formidable task. We therefore reasoned that Negishi coupling could serve as an important alternative to achieve this type of transformation.[27] Subjecting various types of polyfluorophenylzinc reagents to the current protocol furnished coupling products in uniformly good yields (**8a-8j**). Moreover, by increasing the reaction temperature to 40 °C, perfluoro-4-pyridylzinc chloride reacted well with an aryl triflate derived from estrone (**8k**).[28,29]

Encouraged by the high level of reactivity of our catalyst system, we set out to examine the scope of this system at extremely low levels of catalyst loading (Table 3). We were able to lower the catalyst loading to 0.025-0.05 mol% (turnover number = 2,000-4,000) while tolerating a variety of functional groups, including an acetal (**9e**), a tertiary amine (**9f**), an amide (**9f**) as well as heterocycles (**9c** and **9d**). These results clearly demonstrate the ability of our catalyst to operate at low concentrations of catalyst for a range of functionalized substrates. However, we note that with the current catalyst system, substrates bearing an *ortho* coordinating substituent such as an ester or a ketone usually require catalyst loadings higher than 0.1 mol% to achieve full conversion.

In summary, through the use of our recently developed palladacycle precatalysts, we have identified a highly active catalyst system based on **L3** for the Negishi cross-coupling of heteroarylzinc reagents and polyfluoroaryl zinc reagents under mild reaction conditions. Our method is effective with a broad scope of heteroaryl halides, pseudohalides and other types of challenging substrates, delivering a wide range of heterobiaryls that represent structural motifs frequently found in biologically active compounds.

Supplementary Material

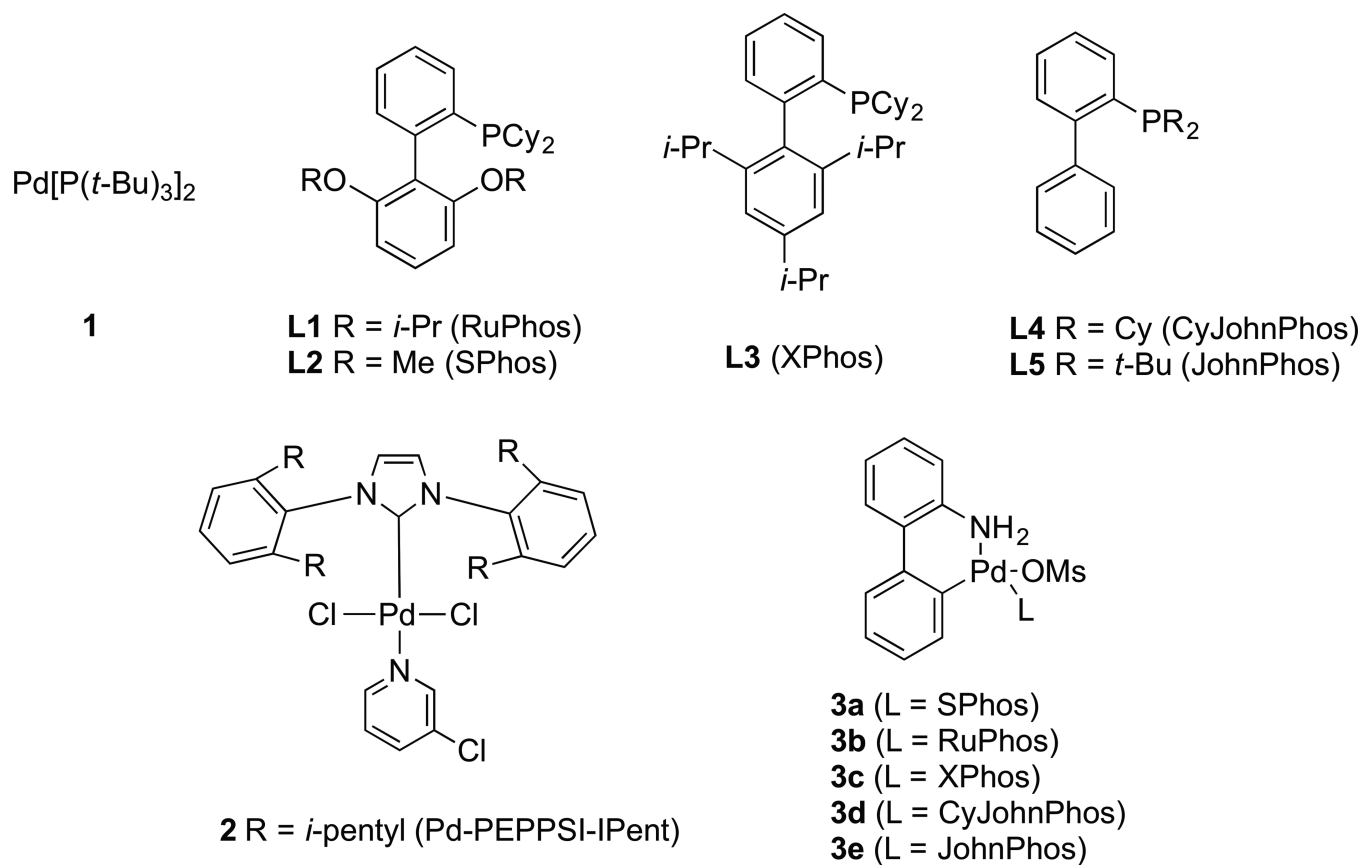Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Pd[P(*t*-Bu)₃]₂

1

L1 R = *i*-Pr (RuPhos)
L2 R = Me (SPhos)

L3 (XPhos)

L4 R = Cy (CyJohnPhos)
L5 R = *t*-Bu (JohnPhos)

2 R = *i*-pentyl (Pd-PEPPSI-IPent)

3a (L = SPhos)
3b (L = RuPhos)
3c (L = XPhos)
3d (L = CyJohnPhos)
3e (L = JohnPhos)

Scheme 1.
Precatalysts and Ligands Employed for Negishi Cross-Coupling Reactions.
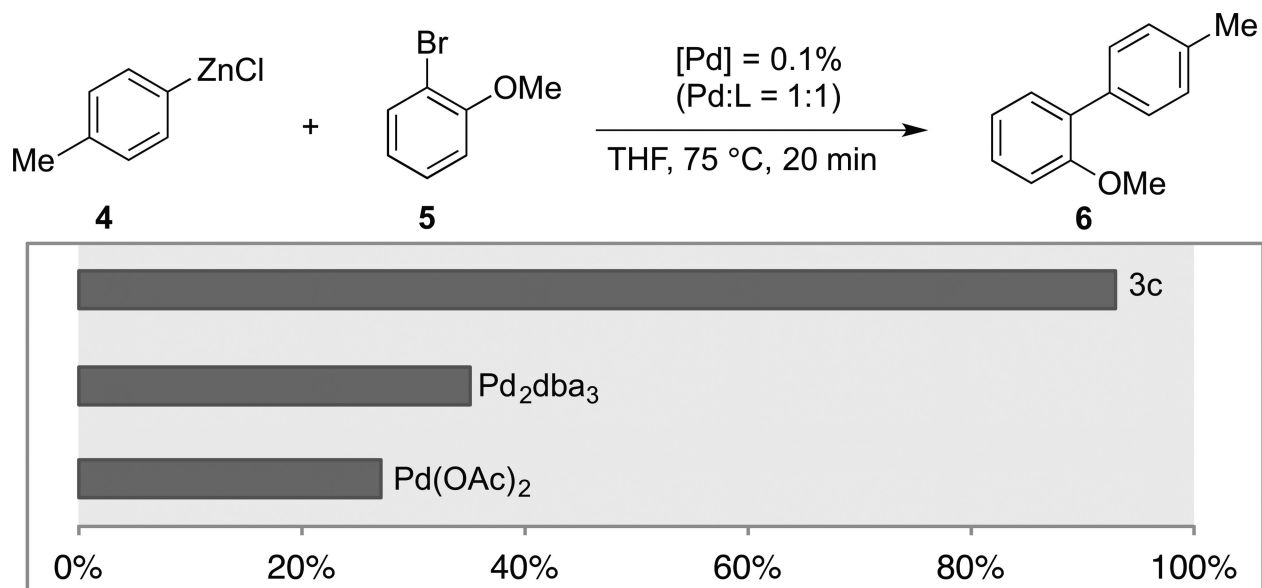
Figure 1.
Comparison of precatalyst **3c** with several other palladium sources. Conditions: *p*-tolylzinc chloride (0.65 mmol), 2-bromoanisole (0.5 mmol), Pd (0.1%, Pd:L = 1:1), L = **L3**, THF, 75 °C, 20 min; yields were determined by GC analysis of the crude reaction mixture.
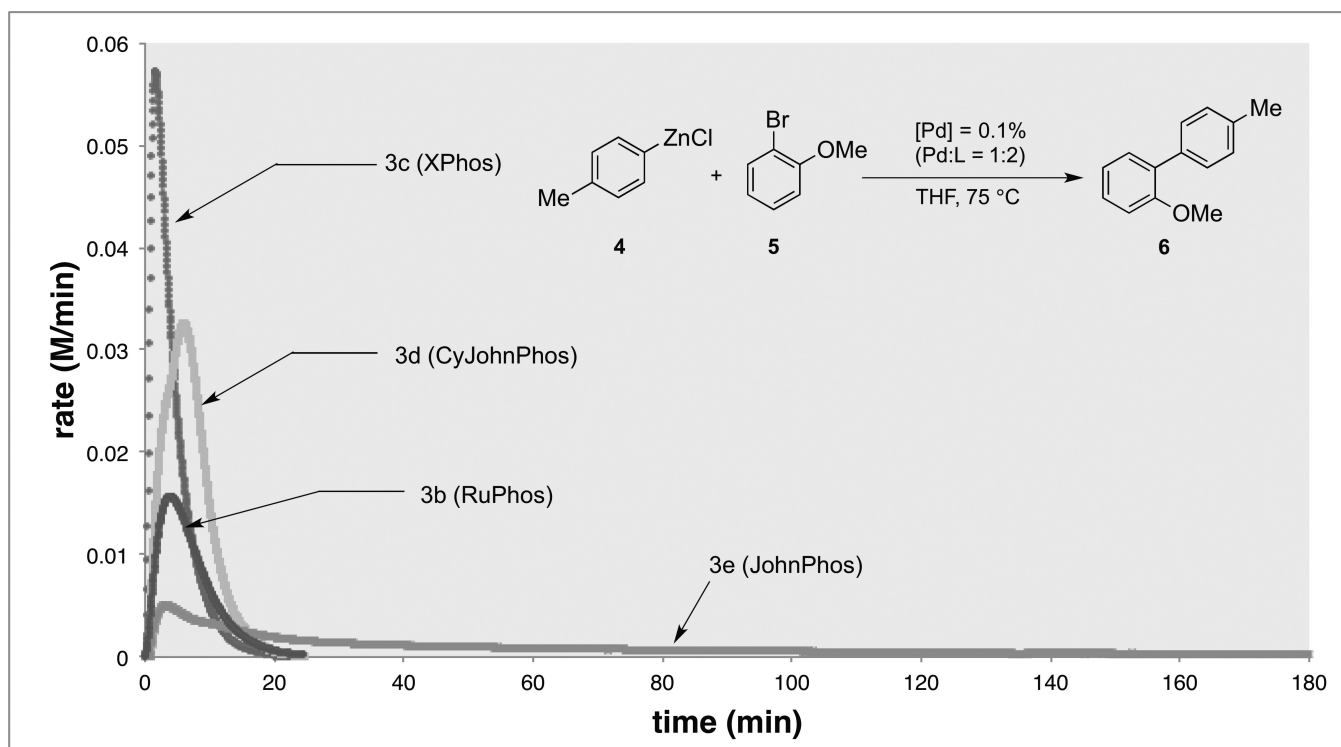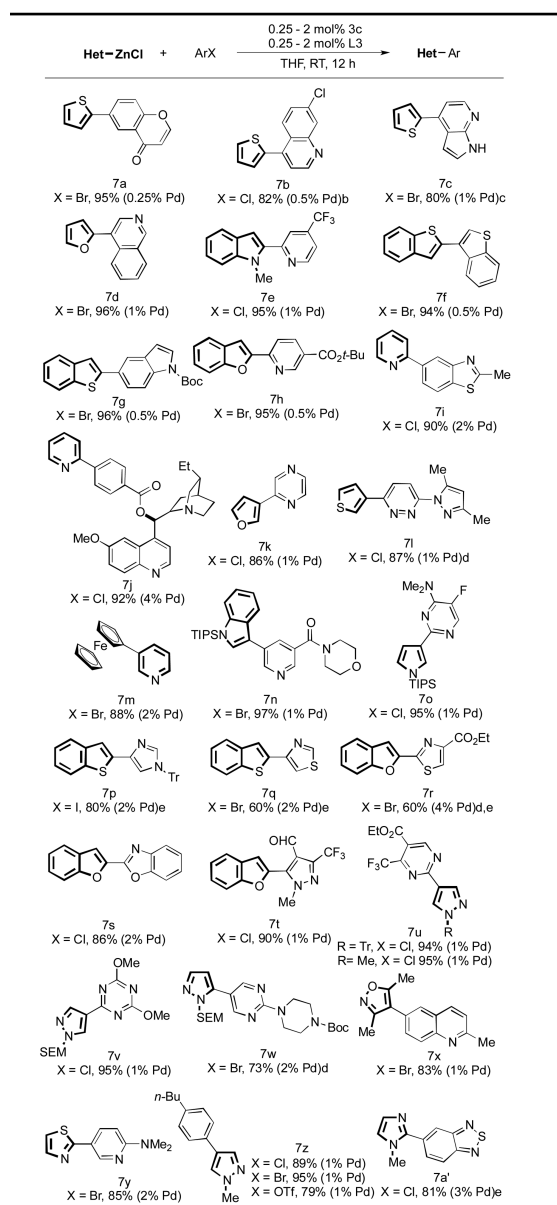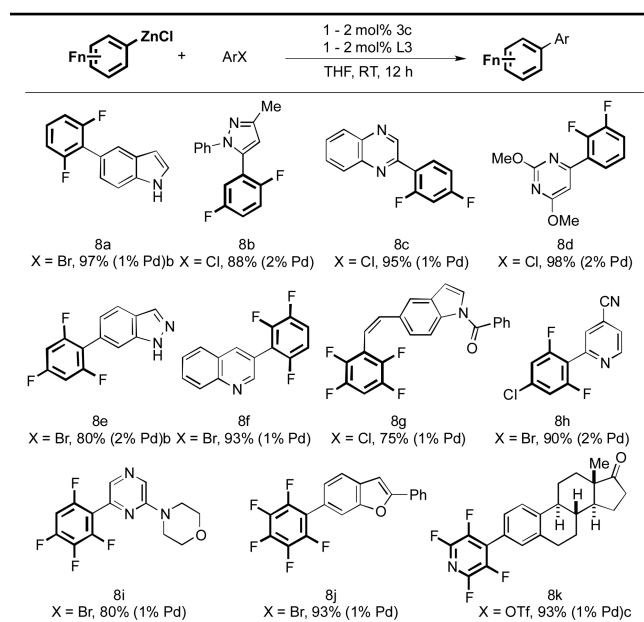
Figure 2.
Comparison of precatalysts with different dialkylbiarylphosphine ligands. Conditions: *p*-tolylzinc chloride (0.65 mmol), 2-bromoanisole (0.5 mmol), **3** (0.1%), L = **L2-5** (0.1%), THF, 75 °C.

Table 1

Cross-Coupling of Heteroarylzinc Reagents and Heteroaryl Halides[a].
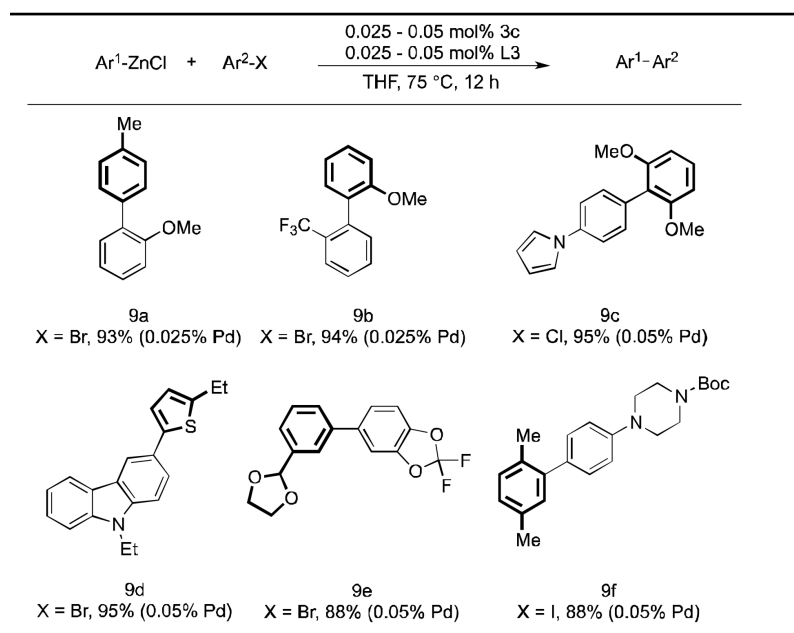

[a] ArZnCl (1.3 mmol), ArX (1.0 mmol), **3c** (0.25-2 mol%), **L3** (0.25-2 mol%), THF, rt, 12 h; [b] ArZnCl (1.2 mmol) was used. [c] ArZnCl (2.3 mmol), ArX (1.0 mmol), **3c** (1 mol%), **L3** (1 mol%), THF, 12 h; [d] **3b** and **L1** instead of **3c** and **L3**; [e] ArZnCl (1.3 mmol), ArX (1.0 mmol), **3c** (2 mol%), **L3** (2 mol%), THF, 80 °C, 12 h; isolated yields, average of two runs.

Table 2

Cross-Coupling of Polyfluoroarylzinc Reagents and Heteroaryl Halides at Room Temperature[a].

8a	8b	8c	8d
X = Br, 97% (1% Pd)b	X = Cl, 88% (2% Pd)	X = Cl, 95% (1% Pd)	X = Cl, 98% (2% Pd)
8e	8f	8g	8h
X = Br, 80% (2% Pd)b	X = Br, 93% (1% Pd)	X = Cl, 75% (1% Pd)	X = Br, 90% (2% Pd)
8i	8j	8k	
X = Br, 80% (1% Pd)	X = Br, 93% (1% Pd)	X = OTf, 93% (1% Pd)c	

[a] ArZnCl (1.3 mmol), ArX (1.0 mmol), **3c** (1-2 mol%), **L3** (1-2 mol%), THF, rt, 12 h; [b] ArZnCl (2.3 mmol), ArX (1.0 mmol), **3c** (1-2 mol%), **L3** (1-2 mol%), THF, rt, 12 h; [c] ArZnCl (1.3 mmol), ArX (1.0 mmol), **3c** (1-2 mol%), **L3** (1-2 mol%), THF, 40 °C, 12 h; isolated yields, average of two runs.

Table 3

Cross-Coupling of Arylzinc Chlorides and Aryl Halides at Low Catalyst Loadings[a].

9a
X = Br, 93% (0.025% Pd)

9b
X = Br, 94% (0.025% Pd)

9c
X = Cl, 95% (0.05% Pd)

9d
X = Br, 95% (0.05% Pd)

9e
X = Br, 88% (0.05% Pd)

9f
X = I, 88% (0.05% Pd)

[a] ArZnCl (1.3 mmol), ArX (1.0 mmol), **3c** (0.025-0.05 mol%), **L3** (0.025-0.05 mol%), THF, 75 $^{\circ}$C, 12 h; isolated yields, average of two runs.