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Highly Selective Palladium-Catalyzed Cross-Coupling of Secondary Alkylzinc Reagents with Heteroaryl Halides

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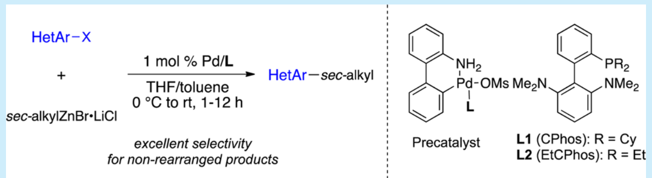
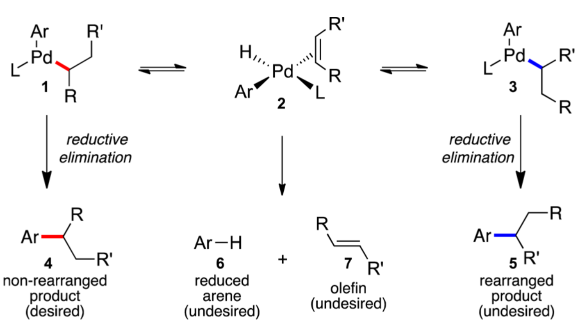
Supporting Information

ABSTRACT: The highly selective palladium-catalyzed Negishi coupling of secondary alkylzinc reagents with heteroaryl halides is described. The development of a series of biarylphosphine ligands has led to the identification of an improved catalyst for the coupling of electron-deficient heterocyclic substrates. Preparation and characterization of oxidative addition complex (**L**)(Ar)PdBr provided insight into the unique reactivity of catalysts based on CPhos-type ligands in facilitating challenging reductive elimination processes.



Aromatic compounds bearing one or multiple alkyl components represent ubiquitous structural motifs among pharmaceuticals and natural products.[1] Consequently, extensive efforts have been devoted to the rapid and direct construction of sp^2−sp^3 carbon−carbon bonds in both industrial and academic settings. One of the most frequently practiced methods to form sp^2−sp^3 carbon−carbon bonds relies on transition-metal-catalyzed coupling reactions.[2] However, the cross-coupling involving *secondary* alkyl nucleophiles remains challenging, owing to the competitive β-hydride elimination and migratory reinsertion that results in the formation of undesired isomerized products (**5**) (Scheme 1).

Scheme 1. Major Side Reactions Associated with Pd-Catalyzed Cross-Coupling Involving Secondary Alkyl Nucleophiles



To overcome this challenge, the development of catalyst systems to facilitate reductive elimination while suppressing competitive β-hydride elimination is of central importance. Since the pioneering work of Kumada and Hayashi[3] in the area of Ni- and Pd-catalyzed selective cross-coupling of secondary alkyl nucleophiles, several key advances have been achieved in the past decade.[4−8] In 2009, our group described a catalyst system based on a diakylbiarylphosphine ligand (CPhos, **L1**), which allowed for the coupling of secondary alkylzinc reagents with aryl bromides and activated aryl chlorides to deliver a range of coupling products with good selectivity.[4] Organ also developed a well-engineered NHC-based PEPPSI precatalyst (Pd-PEPPSI-IPent^{Cl}), enabling the selective preparation of functionalized arenes bearing secondary alkyl substituents.[5]

Despite these advances, significant challenges still remain. While the coupling of relatively simple aromatic substrates and secondary alkyl nucleophiles can be accomplished with good regioisomeric retention, efforts to combine heteroaryl electrophiles with secondary alkyl organometallic reagents have been met with considerably less success. Because of the altered electronic properties of heterocylic compounds, poor selectivity for the desired coupling products (**4**) is usually obtained. In addition, the presence of heteroatoms capable of coordinating to the Pd center can lead to catalyst inhibition and deactivation, thereby rendering the coupling of these heterocycles particularly challenging.[9] Given the importance of heterocyclic compounds in medicinal chemistry and materials science,[10] a general, practical, and selective protocol for the coupling of heteroaryl halides with secondary alkyl nucleophiles is highly desirable. Herein we report our efforts in catalyst development for such coupling reactions. With these monodentate biarylphosphine-based catalysts, a diverse array of heteroaryl halides, including those that were unsuccessful substrates with our previously reported catalyst system, can be combined with secondary alkylzinc reagents with high levels of regiochemical fidelity.

Our initial studies focused on the coupling of various types of heteroaryl halides with isopropylzinc bromide prepared using Knochel's procedure (Scheme 2).[11] It was found that through the use of our easily activated palladacycle precatalyst[12] (**11**) ligated by CPhos[13] (**L1**), a wide range of heteroaryl halides, including 3-chlorobenzosisothiazole (**10a**), 4-chloroquinazoline (**10b**), 4- and 5-halopyrimidine (**10c** and **10d**), and 3-

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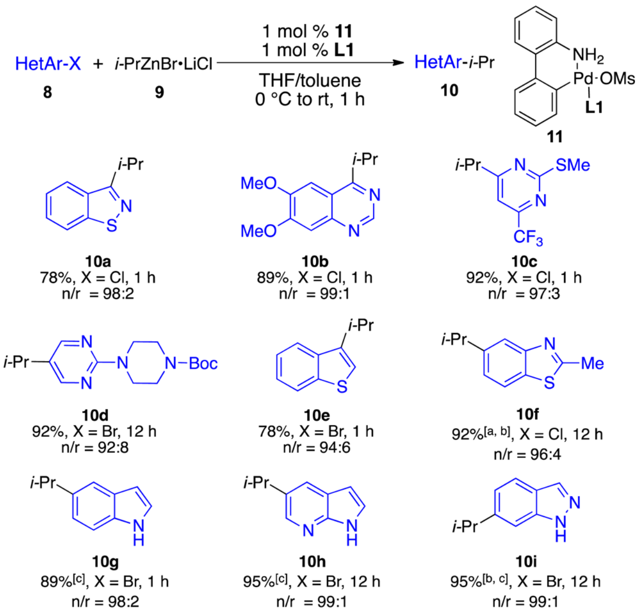
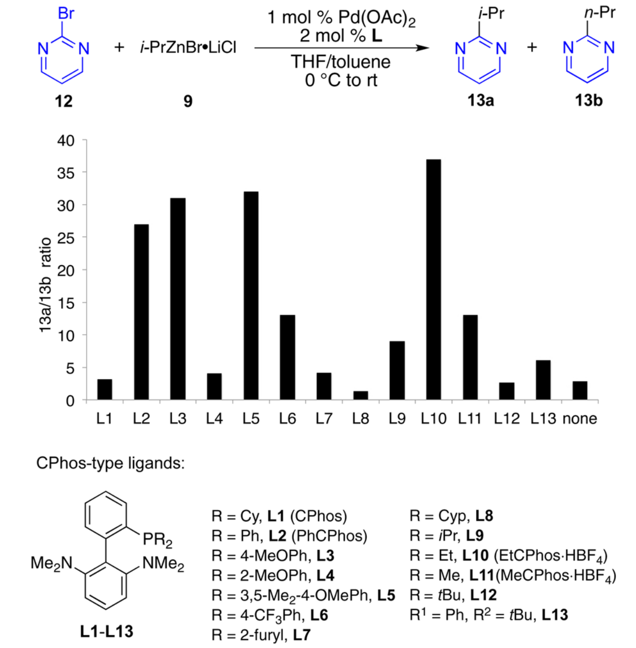
Scheme 2. Cross-Coupling of Heteroaryl Halides with Isopropylzinc Bromide[a]



[a]Reaction conditions: HetAr-X (1.0 mmol), *i*-PrZnBr·LiCl (1.3 mmol), 0 °C to rt, 1−12 h. Yields are isolated yields on average of two runs. [b]1 equiv of LiCl was used; THF was used as the sole solvent; 2 mol % of **15** and 2 mol % of **L1** was used. [c]2.3 equiv of iPrZnBr·LiCl was used. n = normal product, r = rearranged product. n/r ratio was determined by GC and/or ^{1}H NMR spectroscopy analysis of the crude reaction mixture.

Scheme 3. Ligand Effect on the Coupling of 2-Bromopyrimidine and *i*-PrZnBr·LiCl[a,b]



[a]Catalyst derived from **L12** afforded 15% conversion after 2 h. [b]Only 30% conversion was achieved in the absence of phosphine ligands; no reaction in the absence of $Pd(OAc)_2$. **13a**/**13b** ratio was determined by GC analysis of the crude reaction mixture.

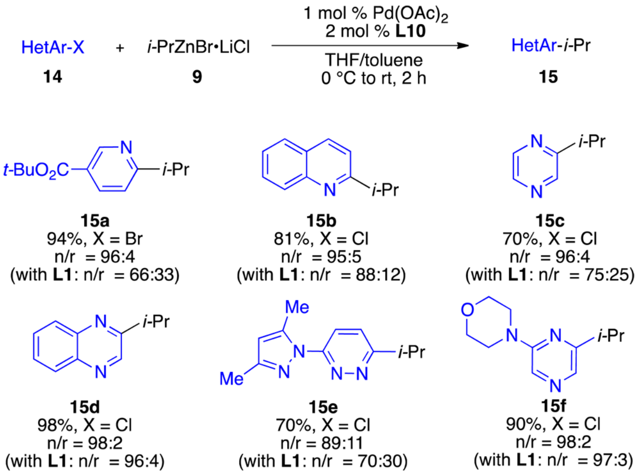
bromobenzothiazole (**10e**) could be effectively transformed in good yields with high level of selectivity. The coupling of 5-chlorobenzothiazole (**10f**) proved to be more difficult with this catalyst system, and we found that the addition of 1 equiv of LiCl allowed these processes to occur with excellent yields.[14] Finally, nitrogen heterocycles with unprotected NH groups such as 5-bromoindole (**10g**), 5-bromo-7-azaindole (**10h**), and 6-bromoindazole (**10i**) also represented compatible substrates under our conditions.

The catalyst derived from CPhos (**L1**) was not effective with electron-deficient six-membered nitrogen heterocycles. For example, using the CPhos-based catalyst, Negishi coupling of 2-bromopyrimidine (**12**) and isopropylzinc bromide (**9**) furnished a 75:25 mixture of 2-isopropylpyrimidine (**13a**) and 2-propylpyrimidine (**13b**) as determined by GC analysis (Scheme 3). To overcome this limitation, we set out to further facilitate the reductive elimination process by preparing and examining a new series of biarylphosphine ligands (**L2**−**L13**). We decided to preserve the biaryl framework of CPhos as a key design element for creating more effective ligands, as mechanistic studies suggested that the dimethylamino (Me_2N-) groups present in the CPhos biaryl backbone are critical to accelerate reductive elimination and discourage β-hydride elimination (vide infra). Since electron-deficient ligands have been demonstrated to accelerate the reductive elimination step,[15] we prepared ligands **L2**−**L7** wherein the cyclohexyl groups on the phosphine were replaced with less electron-donating aryl groups. Indeed, a catalyst composed of **L3** (PhCPhos) furnished improved selectivity than the original **L1**-based catalyst, as demonstrated by a 10-fold increase in the **13a**/**13b** ratio. However, adding additional electron-withdrawing substituents to the P-bound Ar- groups did not provide improved results (**L6**), and the **L5**-based catalyst bearing P-bound 3,5-dimethyl-4-methoxyphenyl groups exhibited the best selectivity for the nonrearranged product. We next replaced the P-bound cyclohexyl group in **L1** by other alkyl groups. Eventually, **L10** (EtCPhos) possessing two less electron-donating P-bound ethyl substituents[16] was identified to as the most effective ligand for this transformation.

With the new set of reaction conditions in hand, we set out to explore the substrate scope of electron-deficient six-membered nitrogen heterocycles (Scheme 4). It was found that the catalyst based on EtCPhos (**L10**) accommodated a wide variety of nitrogen heterocycles including 2-chloropyridine (**15a**), 2-chloroquinoline (**15b**), 2-chloropyrazine (**15c**), 2-chloroquinoxaline (**15d**), 3-chloropyridazine (**15e**), delivering the corresponding coupling products in excellent yields. Moreover, in most cases (**15a**−**e**), improved selectivity for the nonrearranged product was achieved as compared with the **L1**-based catalyst that we previously developed.

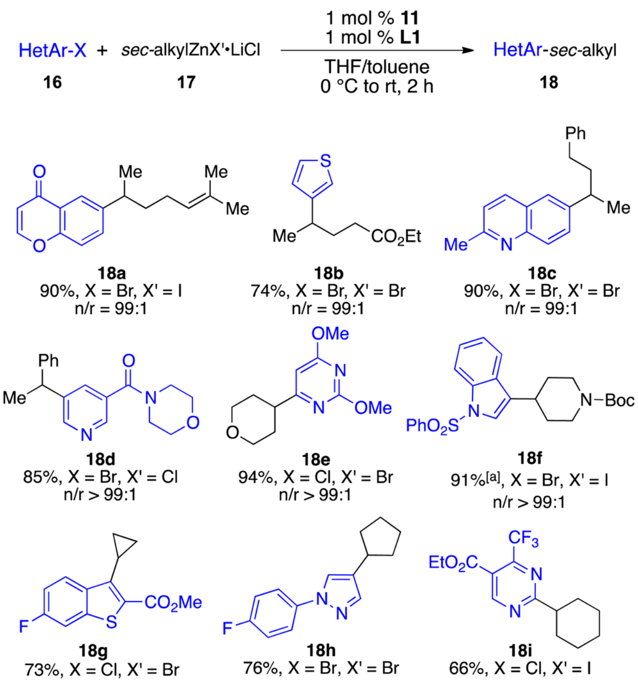
To further demonstrate the utility of catalysts based on CPhos-type ligands, a series of secondary alkylzinc halides were prepared and coupled with a wide range of heteroaryl halides (Scheme 5). Coupling of acyclic secondary alkylzinc halides proceeded with excellent selectivity for the desired product (**18a**−**c**). Notably, rearrangement of the alkyl content was not observed during the coupling event when benzylzinc reagents (**18d**) and cyclic alkylzinc reagents (**18e** and **18f**) were used. Other cyclic secondary alkylzinc reagents ranging from cyclopropyl to cyclohexylzinc halides (**18g**−**i**) could also be effectively coupled. We note, however, that haloimidazoles afforded low yields under the current reaction conditions due to the competitive reduction of these heteroaromatic substrates.

Scheme 4. Cross-Coupling of Electron-Deficient Six-Membered Heteroaryl Halides with Isopropylzinc Bromide[a]



[a]Reaction conditions: HetAr-X (1.0 mmol), *i*-PrZnBr·LiCl (1.3 mmol), $Pd(OAc)_2$ (1 mol %), **L10** (2 mol %), 0 °C to rt, 12 h. n = normal product, r = rearranged product. n/r ratio was determined by GC or ^{1}H NMR spectroscopy analysis of the crude reaction mixture. Yields are isolated yields on average of two runs. In most cases, the rearranged product and the nonrearranged product are chromatographically inseparable.

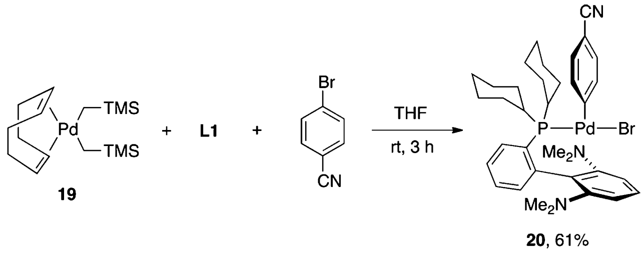
Scheme 5. Substrate Scope of Secondary Alkylzinc Reagents[a]



[a]Reaction conditions: HetAr-X (1.0 mmol), *sec*-alkylZnBr·LiCl (1.3 mmol), **15** (1 mol %), **L1** (1 mol %), 0 °C to rt, 2 h. a. 60 °C. n = normal product, r = rearranged product. n/r ratio was determined by GC and/or ^{1}H NMR analysis of the crude reaction mixture.

To gain further insight into the unique reactivity of Pd-based catalyst system featuring CPhos-type ligands, we prepared oxidative addition complex [**L1**·ArPdBr] (Ar = 4-cyanophenyl) (**20**) as an air-stable bright yellow solid by treating (COD)-$Pd(CH_2TMS)_2$ with 4-bromobenzonitrile and **L1** in THF (Scheme 6). Reaction of methyl 4-chlorobenzoate and isopropylzinc bromide employing catalytic amount (1 mol %)

Scheme 6. Synthesis of Oxidative Addition Complex 20



of **20** afforded the same mixture of rearranged and non-rearranged products (45:1) as when palladacycle precatalyst **11** was used, demonstrating the catalytic competence of **20** for the coupling of secondary alkylzinc halides. Single-crystal X-ray diffraction analysis (Figure 1) of **20** revealed a nearly square-

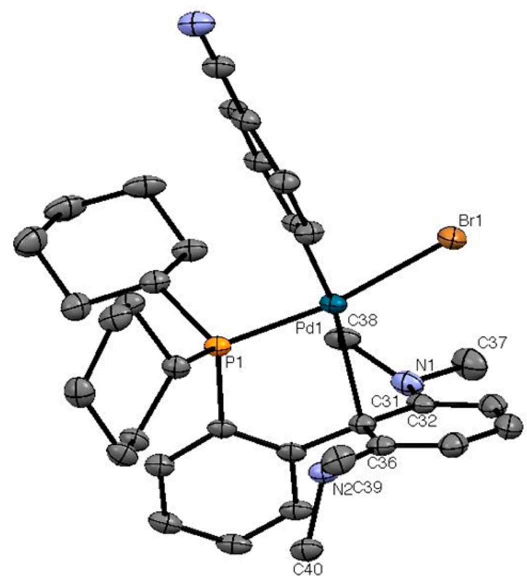


Figure 1. ORTEP representation drawing of oxidative addition complex **20**. Hydrogen atoms omitted for clarity; thermal ellipsoids set at 50% probability.

planar Pd(II) center featuring κ^2 bound CPhos ligand through P atom and *ipso*-C moiety of the bottom aromatic ring (*ipso*-C−Pd bond length = 2.478(3) Å). The solid-state structure of **20** indicates that neither of the dimethylamino substituents of **L1** coordinates to the Pd(II) center, indicating the monodentate nature of **L1**. Further examination of **20** suggests that neither of the dimethylamino groups lies in the plane of the bottom ring of **L1**, with the dihedral angles C38−N1−C32−C31 and C40−N2−C36−C31 being 39.12° and 82.24°, respectively. This observation is suggestive that the lone pair of the Me_2N- group is not in conjugation with the lower ring of **L1** and the Me_2N groups presented in the ligand biaryl backbone could likely serve as electron-withdrawing substituents, thereby rendering the bottom ring of the phosphine less electron-donating. In light of this effect, we believe that the use of CPhos-type ligands may facilitate reductive elimination and carefully balancing the electron-donating ability of P-bound

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substituents and the biaryl backbone is critical to the success of selective coupling of secondary alkyl nucleophiles.

In summary, we have developed general catalyst systems allowing for the highly selective cross-coupling of secondary alkylzinc reagents and heteroaryl halides under mild conditions. Our protocol is effective with a broad spectrum of heteroaryl halides, delivering an array of complex heterocycles possessing secondary alkyl substituents that are frequently found in biologically active compounds. Furthermore, design and evaluation of a series of biarylphosphine ligands bearing a 2,6-bis(dimethylamino)phenyl group proximal to the phosphine have led to a new catalyst that demonstrated superior selectivity for the coupling of electron-deficient heteroaryl halides. Application of these newly developed catalysts in cross-coupling reactions where transmetalation or reductive elimination remains challenging is topic of onging investigation in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization, and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare the following competing financial interest(s): MIT has patents on some of the ligands and precatalysts described in this work from which S.L.B. as well as former or current co-workers receive royalty payments.

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