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Pd(II)-Catalyzed Cross-Coupling of C(sp²)-H Bonds and Alkyl-, Aryl- and Vinyl-Boron Reagents *via* Pd(II)/Pd(0) Catalysis

Masayuki Wasa, Kelvin S. L. Chan, and Jin-Quan Yu

The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla CA 92037 United States

Jin-Quan Yu: yu200@scripps.edu

Abstract

Pd(II)-catalyzed cross-coupling of *ortho*-C–H bonds in benzoic acid and phenylacetic acid amides with alkyl-, aryl- and vinyl-boron reagents have been achieved *via* Pd(II)/Pd(0) catalysis, demonstrating the unprecedented versatility of C–H activation reactions.

The past decade has witnessed a renaissance in Pd(II)-catalyzed C–H activation/C–C bond forming reactions.¹ Among the various catalytic platforms such as Pd(0)/Pd(II) and Pd(II)/Pd(IV) catalysis for forging C–C bonds *via* C–H activation, the Pd(II)/Pd(0) manifold to cross-couple C–H bonds with organometallic reagents is potentially one of the most versatile in terms of the scope of both substrate and coupling partner. More importantly, this catalysis mirrors the highly enabling cross-coupling reactions using organohalides in the forging of new C–C bonds; its potential utility in modern organic synthesis is therefore self-explanatory.² In particular, this catalysis begins with C–H activation by a Pd(II) catalyst (rather than oxidative addition of the aryl, alkyl or vinyl halide to Pd(0)) as a means of entering the catalytic cycle (Scheme 1). Since our initial report on Pd(II)-catalyzed cross-coupling of unactivated C(sp²)-H bonds with alkyl-tin reagents in 2006,³ our group⁴ and others^{5,6} have sought to expand the synthetic utility of the C–C cross-coupling reactions *via* C–H activation by exploiting synthetically useful directing groups, and nontoxic and abundant organo-boron and organo-silane reagents as the coupling partners.

Despite these efforts, the development in Pd(II)-catalyzed C–H activation/C–C cross-coupling reactions still remains at an early stage compared to the state of the art in cross-coupling reactions using organohalides. Modern cross-coupling reactions rely upon bulky, electron-rich phosphine and *N*-heterocyclic carbene (NHC) ligands to promote oxidative addition of the organohalides and subsequent reductive elimination while suppressing undesired side reactions;² however, these ligands are known to be detrimental in Pd(II)-catalyzed C–H activation reactions. In the absence of appropriate ligands, each step of the catalytic cycle could be derailed by undesired side reaction pathways such as homo-coupling and β -hydride elimination. Although aryl-boron reagents have been successfully coupled to the C–H bonds in previous reports,^{3,4,5,6} the cross-coupling of alkyl-boron reagents has remained elusive due to the following reasons: alkyl-boron reagents are generally less stable, transmetalation proceeds at a slower rate, and β -hydride elimination is a competitive pathway upon transmetalation.^{2n,7} In addition, Pd(II)-catalyzed cross-coupling of C–H bonds with vinyl-boron reagents has not been achieved because the olefin moiety competitively coordinates to the Pd catalyst and initiates undesired Wacker-type oxidation chemistry.

With these considerations in mind, we initiated our study on cross-coupling of C(*sp*²)-H bonds with alkyl-, aryl- and vinyl-boron reagents using a highly versatile *N*-arylamide directing group recently developed by our group (Scheme 2). Using this directing group, we have reported a wide range of Pd(0)- and Pd(II)-catalyzed functionalization protocols of both unactivated C(*sp*³)-H and C(*sp*²)-H bonds, which includes arylation, olefination, carbonylation, amination and fluorination reactions.⁸ Based on the remarkable versatility observed, we conjectured that it is possible to devise reaction conditions that enable the cross-coupling of diverse organo-boron reagents with the *ortho*-C(*sp*²)-H bonds of the synthetically and pharmaceutically valuable benzoic acid and phenylacetic acid derivatives.

We began systematic screening of the reaction conditions using *N*-arylamide substrate **1** and phenylboronic acid pinacol ester (Ph-BPin) as the coupling partner. Gratifyingly, we found that the cross-coupling product **1a** was obtained using Pd(OAc)₂ (10 mol%) as the catalyst, Ag₂CO₃ as the terminal oxidant, and NaHCO₃ as the base in *t*AmylOH. The use of other aryl-boron reagents such as Ph-B(OH)₂, phenylboroxine and Ph-BF₃K resulted in inferior yields. The addition of 0.5 equiv of 1,4-benzoquinone (BQ) was crucial as a promoter for the reductive elimination to fashion the C-C bonds: no product was obtained in its absence. Addition of 5 equiv of H₂O aids the transmetallation of Ph-BPin and improves the conversion by 15–20%. The addition of DMSO stabilizes the Pd(0) species by suppressing the formation of Pd black, thus further improving the yield by 5–10%. A mixture of mono- and di-arylation products was obtained for substrates **2**, **3**, **6** and **7**. Chloro- and bromo-substituted substrates **4** and **5** were also tolerated to selectively arylate the C-H bonds *para* to the halides. The amide derivatives of commercial drugs Ibuprofen **7** and Naproxen **8** were also functionalized in good yields. For the Ibuprofen derivative **7**, β-C(*sp*³)-H arylation also took place to give **7b** as a minor side product.

Encouraged by the successful development of the arylation protocol, we further screened the reaction conditions for the cross-coupling of the alkyl- and vinyl-boron reagents (Scheme 3). For the alkylation protocol, the choice of alkyl-trifluoroborate salts was essential, as it provides facile transmetallation relative to the other alkyl-boron reagents and better stability under the reaction conditions.²ⁿ Under the optimized conditions, 74% of the *n*-butylation product **1b** was obtained using *n*Bu-BF₃K as the coupling partner. The use of Li₂CO₃ as the base and THF as solvent was found to be optimal. Subsequently, we also established the *ortho*-vinylation protocol of substrate **1** using cyclohexene-1-boronic acid pinacol ester. To our delight, we obtained the vinylation product **1c** in 70% yield. The product was isolated as a δ-lactam formed *via* a tandem intramolecular Pd-mediated oxidative amination between the amide directing group and the newly installed olefin: a mixture of **1c** and the uncyclized product was obtained with a shorter reaction time. To our knowledge, this is the first example of Pd(II)-catalyzed cross-coupling of vinyl-boron reagents and C(*sp*²)-H bonds.⁹

To summarize, we have developed a versatile Pd(II)-catalyzed protocol for the cross-coupling of C(*sp*²)-H bonds with a diverse range of organo-boron reagents including aryl-, alkyl- and vinyl-boron reagents. The *N*-arylamide directing group could be hydrolyzed under basic conditions to give the corresponding carboxylic acid in excellent yield (Scheme 4). Studies to expand the scope of the cross-coupling protocol to aliphatic acid amide substrates are underway in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1. Simplified cross-coupling catalytic cycles

Scheme 2. Proposed transformations

Scheme 3. Alkylation and vinylation of C(sp²)-H bonds

Scheme 4. Amide hydrolysis

Table 1
Cross-coupling of Ph-BPin and C(sp²)-H bonds^{a,b}

^aReaction conditions: 0.2mmol of substrate, 10 mol% Pd(OAc)₂, 1.5 equiv of Ph-BPin, 3 equiv of NaHCO₃, 1.5 equiv of Ag₂CO₃, 0.5 equiv of BQ, 5 equiv of H₂O, 0.4 equiv DMSO, 1 mL *t*AmylOH, 100 °C, N₂, 12 h.

^bIsolated yields.

^cFormation of di-arylated product was observed by ¹H NMR.