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Pd(II)-catalyzed Cross-coupling of C(sp^2)–H Bonds and Alkyl–, Aryl–, and Vinyl–Boron Reagents via Pd(II)/Pd(0) Catalysis

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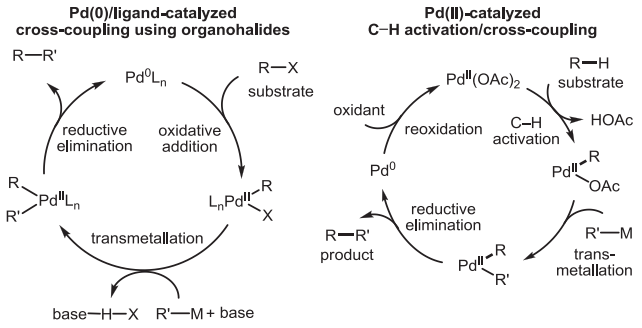
Pd(II)-catalyzed cross-coupling of *ortho*-C–H bonds in benzoic acid and phenylacetic acid amides with alkyl–, aryl–, and vinyl–boron reagents have been achieved via Pd(II)/Pd(0) catalysis, demonstrating the unprecedented versatility of C–H activation reactions.

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 scope of 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 report on Pd(II)-catalyzed cross-coupling of unactivated C(sp^2)–H bonds with alkyl–tin reagents in 2006,[3] our group[4] and others[5] 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 organoboron and organosilane reagents as the coupling partners. It is worth noting that early studies by the groups of Oi and Murai have independently demonstrated C(sp^2)–H activation/C–C cross-coupling reactions catalyzed by Rh and Ru, respectively,[5] although Pd-catalyzed C–H/R–M coupling represent a distinct challenge involving completely different redox chemistry.

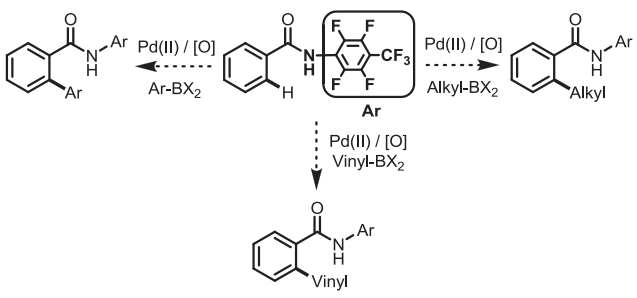
Despite these efforts, the development in Pd(II)-catalyzed C–H activation/C–C cross-coupling reactions still remains at an early stage compared to the state of the art in cross-coupling reactions using organohalides. Modern cross-coupling reactions rely upon bulky, electron-rich phosphine and *N*-heterocyclic carbene (NHC) ligands to promote oxidative addition of the organohalides and subsequent reductive elimination while suppressing undesired side reactions;[2] however, these ligands have been incompatible in Pd(II)-catalyzed oxidative C–H activation reactions based on our previous reports.[3,4] In the absence of appropriate ligands, each step of the catalytic cycle could be derailed by undesired side reaction pathways such as homocoupling and β-hydride elimination. Although aryl–boron reagents have been successfully coupled to the C–H bonds in previous reports,[3,4,6] the cross-coupling of alkyl–boron reagents has remained elusive[3,4a–4c] due to the following reasons: alkyl–boron reagents are generally less stable, transmetallation proceeds at a slower rate, and β-hydride elimination is a competitive pathway upon transmetallation.[2n,7]

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 organoboron 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 (Table 1). Gratifyingly, we found that the cross-coupling product **1a** was obtained using $Pd(OAc)_2$ (10 mol %) as the catalyst, Ag_2CO_3 as the terminal oxidant, and $NaHCO_3$ as the base in *t*AmylOH(*tert*-pentyl alcohol). The use of other aryl–boron reagents such as Ph–$B(OH)_2$, phenylboroxine and Ph–BF_3K resulted in reduced 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-

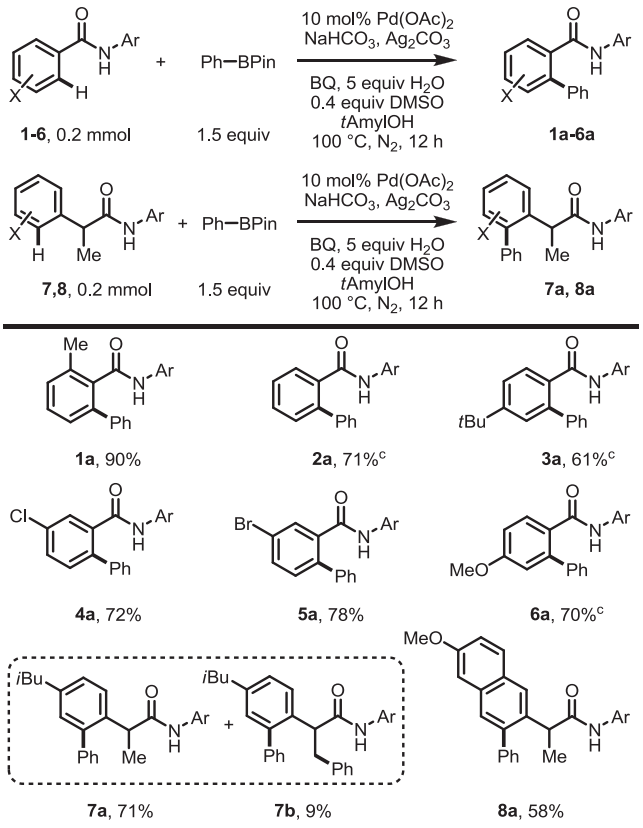


Scheme 1. General cross-coupling catalytic cycles.



Scheme 2. Proposed transformation.

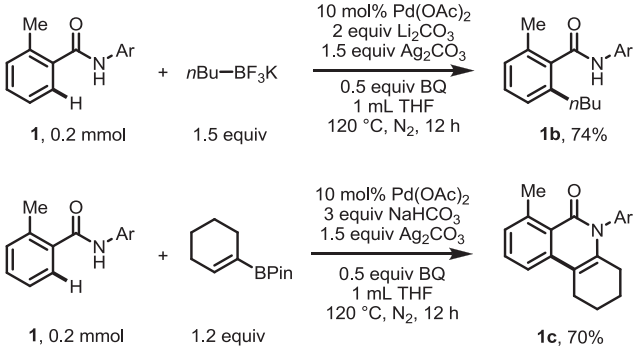
Table 1. Cross-coupling of Ph–BPin and C(sp^2)–H bonds[a,b]



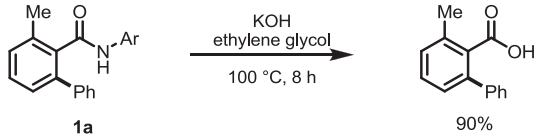
[a]Reaction conditions: 0.2 mmol of substrate, 10 mol % $Pd(OAc)_2$, 1.5 equiv of Ph–BPin, 3 equiv of $NaHCO_3$, 1.5 equiv of Ag_2CO_3, 0.5 equiv of BQ, 5 equiv of H_2O, 0.4 equiv DMSO, 1 mL *t*AmylOH, 100 °C, N_2, 12 h.[13] [b]Isolated yields. [c]Formation of diarylated product was observed by ^1H NMR.

ally, the introduction of 5 equiv of H_2O to the reaction improves conversion (15–20%) by facilitating transmetallation of Ph–BPin.[9] The addition of DMSO stabilizes the Pd(0) species by suppressing catalyst decomposition, thus further improving the yield by 5–10%.[10] Substrates **2**, **3**, **6**, and **7** provide a mixture of mono- and diarylation products under the optimized reaction conditions, however, substitution in the meta position with an electron-withdrawing group (**4** and **5**) provides selective arylation in the para position respective to the halide. 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 takes place to provide **7b** as a minor side product.

Encouraged by the successful development of the arylation protocol, we further investigated the cross-coupling of alkyl– and vinyl–boron reagents (Scheme 3). The successful development of the alkylation protocol relied on utilizing alkyl–trifluoroborates as the coupling partner as they undergo facile transmetallation relative to the other alkyl–boron reagents and display better stability under the reaction conditions.[2n] Under the optimized conditions, 74% of the *n*-butylation product **1b** was obtained using *n*-Bu–BF_3K as the coupling partner. The use of Li_2CO_3 as the base and THF as solvent was found to be optimal.



Scheme 3. Alkylation and vinylation of C(sp^2)–H bonds.[13]



Scheme 4. Amide hydrolysis.[13]

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.[11,12]

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 organoboron 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.

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