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Palladium-catalyzed Catellani-type couplings using methylating reagents for the synthesis of highly substituted *ortho*-methyl-arenes and heteroarenes

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ABSTRACT

The incorporation of a methyl group into a small molecule can have a profound impact on its biological activity, pharmacokinetic profile, and physical properties. As part of an ongoing effort to develop novel methods for methylation of small molecule drug candidates, a three-component coupling of aryliodides, *O*-benzoylamines, and methylboronic acid that proceeds via a Catellani-type mechanism has been developed. The methodology allows for the *ortho*-amination/*ipso*-methylation of aryl- and heteroaryliodides with a wide variety of cyclic *O*-benzoylamines including pyrrolidines, piperidines, piperazines, morpholines, azepines, diazepines, and azocanes in a single step. A preliminary result for an *ortho*-methylation/*ipso*-olefination Catellani-type three component-coupling reaction is also described.

During the course of a recent medicinal chemistry program we became interested in the synthesis of a variety of tetra- and penta-substituted pyridines and benzenes in which one substituent was a methyl group and the adjacent position was occupied by a heterocyclic moiety. This type of array is commonly utilized in medicinal chemistry to accomplish one or more of the following; (1) to block positions of oxidative-metabolism, (2) to promote oxidative-metabolism through introduction of a benzylic C–H bond, and/or (3) to change the conformation of the heterocyclic moiety at the adjacent position from a coplanar arrangement with the attached aromatic group, as in compounds with a hydrogen atom at the *ortho*-position, to a perpendicular arrangement, as in compounds with an methyl group at the *ortho*-position (Fig. 1).[1,2] Thus, the introduction of a methyl group can have a profound impact on the biological activity, pharmacokinetic profile, and physical properties of a drug candidate.

We were drawn to strategies that utilize the Catellani reaction, a palladium-catalyzed three-component coupling whereby an aryl iodide may be coupled to an electrophilic reagent at the *ortho*-position and a nucleophilic reagent at the *ipso*-position, to accomplish this goal because the process has the capacity to introduce multiple substituents in a single synthetic step. The unique reactivity observed in Catellani-type processes is promoted by the inclusion of norbornene which enables the transposition of palladium from the *ipso*-position to *ortho*-position. This is thought to occur via sequential insertion of the Pd(II)-oxidative addition adduct, A, into norbornene followed by a C–H activation reaction at a vacant *ortho*-position to give rise to intermediate B. Intermediate B then reacts with an electrophilic reagent via oxidative addition to furnish intermediate C. Subsequent reductive elimination and β-elimination results in functionalization of the *ortho*-position to produce intermediate D. β-Elimination of the norbornene ligand and subsequent reaction with a nucleophilic reagent lead to functionalization of the *ipso*-position to afford the Catellani product and concurrent regeneration of the Pd(0)-catalyst (Fig. 2).[3–9]

Many combinations of electrophilic and nucleophilic partners have been incorporated into this reaction manifold allowing for the synthesis of a vast array of highly substituted aromatic compounds.[10–16] However the variants of the reaction in which we were most interested, those that introduce a methyl group by employing methylboronic acid as the nucleophile reagent or iodomethane as the electrophile reagent, had not at the time been described in the literature. Herein, we describe the development and scope of a variant of the Catellani reaction that employs *O*-benzoyl amines as the electrophilic reagent[17–20] and methyl boronic acid as the nucleophilic reagent. Furthermore, we show that iodomethane is a competent electrophilic reagent for the *ortho*-methylation/*ipso*-olefination variant of the Catellani reaction.

At the outset of this effort, we were aware of Ritter's methodology which provides access to the 1-heteroaryl-2-methyl-(hetero) aromatic target compounds via a two-step sequence consisting of: (1) palladium-catalyzed *ortho*-amination/*ipso*-borylation using an *O*-benzoyl amine as the electrophilic reagent and bis(pinacolato)diboron as the nucleophilic reagent and (2) subsequent Suzuki

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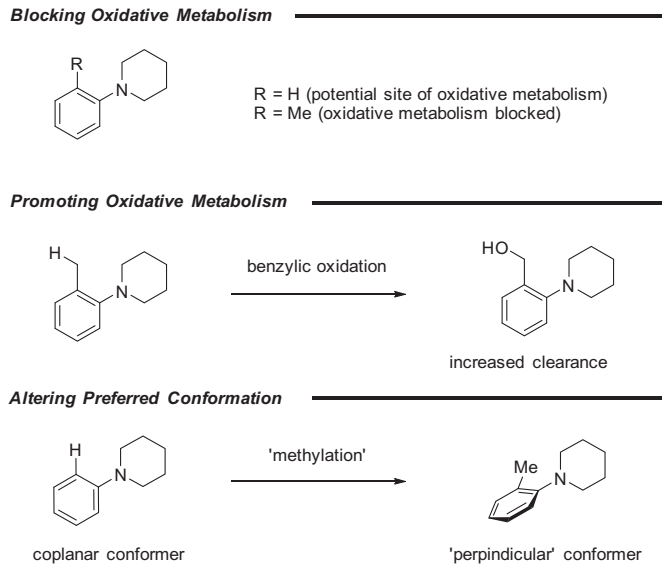


Figure 1. Tactical uses of *ortho*-methyl groups in medicinal chemistry.

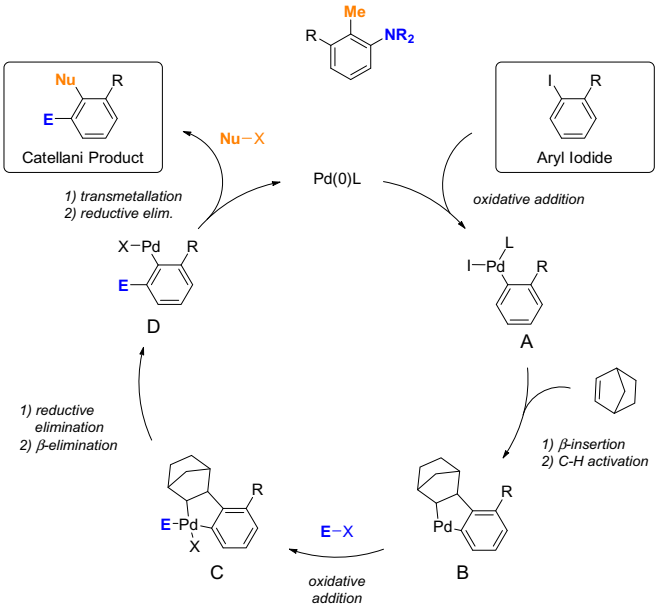


Figure 2. Proposed mechanism for Catellani-type reactions.

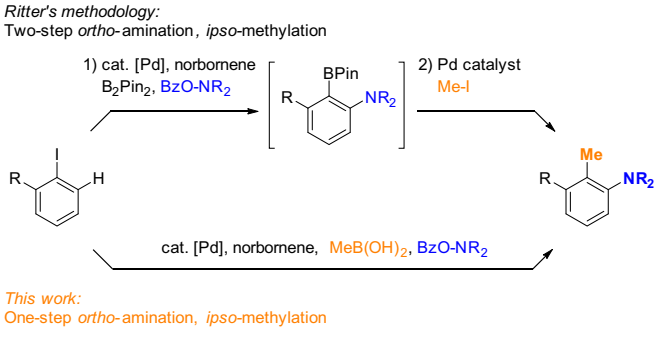


Figure 3. Synthesis of 1-heterocyclic-2-methyl-(hetero)aromatic derivatives via Catellani-type reactions.

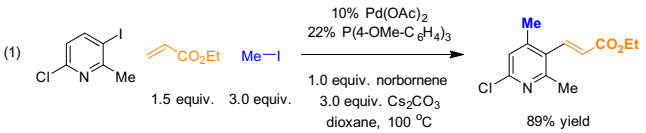
coupling with iodomethane (Fig. 3).[21] In contrast, we envisioned directly accessing the 1-heterocyclic-2-methyl-(hetero)aromatic derivatives in a single step by substituting methylboronic acid for bis(pinacolato)diboron.

After screening several typical Catellani reaction conditions, we were pleased to find that Ritter's catalyst system was suitable for this transformation with some minor modifications: (1) substitution of $MeB(OH)_2$ for B_2Pin_2 and (2) substitution of dioxane for toluene to simplify the reaction set-up by promoting rapid dissolution of $MeB(OH)_2$. The scope of the reaction with respect to the aryl iodide is broad. Both electron-rich and electron-deficient aromatic iodides are good substrates for the reaction (Table 1, entries 1–4). Additionally, the bicyclic compounds 1-iodonaphthalene and 4-iodoquinoline are good coupling partners and deliver both the disubstituted-naphthalene and -quinoline derivatives in good yield (Table 1, entries 5 and 6). An iodobenzamide and a methyl iodobenzoate participate in the reaction to afford the tetrasubstituted-benzamide and tetrasubstituted-benzoate ester (Table 1, entries 7 and 8). Furthermore, we have successfully employed a variety of substituted iodopyridines in the reaction for the synthesis of tri- and tetra-substituted pyridines (Table 1, entries 9–12).

The scope of the *O*-benzoylamine coupling partner encompasses an array of saturated amine heterocycles including piperazines, piperidines, tetrahydroisoquinolines, morpholines, diazepines, diazepinones, pyrrolidines, and azocanes (Table 2). Some of the compounds prepared in Table 2 2 contain highly complex, druglike amine fragments (Table 2, examples 2, 5, 6, and 7). Example 5 is of particular note as it contains a molecular fragment of our dual orexin receptor antagonist, suvorexant. One current limitation of the methodology is reactions of acyclic *O*-benzoylamines. Products from these couplings are observed in the crude reaction mixture but only in trace amounts.

The yields for the process are generally modest but are comparable to the overall yield for the two-step process that has been reported by Ritter's group.[21] The major side-product observed is the *ipso*-H-aniline which is the result of reduction of intermediate D instead of the desired Suzuki coupling.[23] Dong and coworkers have suggested that the imine or enamine that results from elimination of the *N*-benzoyloxyamine may serve as a reductant.[17] This is likely the reductant in this process as well, although we have not observed the imine or enamine as a byproduct. More experimentation would be needed to verify this hypothesis.

Having successfully developed an *ortho*-amination/*ipso*-methylation Catellani-type reaction we next turned our attention to variants that employ iodomethane as the methylating reagent. As an initial foray into this area, we chose to explore an *ortho*-methylation/*ipso*-olefination Catellani-type reaction. We were pleased to find that the same catalyst system employed for the *ortho*-amination/*ipso*-methylation reaction was suitable for this variant. A preliminary example of this coupling reaction is shown in Eq. 1.



(1)

In conclusion, we have developed a palladium-catalyzed one-step *ortho*-amination/*ipso*-methylation of aryl iodides. This chemistry represents the first example of a Catellani-type process that employs methyl boronic acid as the nucleophilic coupling partner. The scope of the reaction is broad encompassing a wide variety of aryl- and heteroaryliodides as well as wide array of cyclic *O*-benzoylamines. Furthermore, we have shown that iodomethane is a good substrate for Catellani-type reactions by utilizing it in a related *ortho*-methylation/*ipso*-olefination reaction of a heteroaro-