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Ortho vs Ipso: Site-Selective Pd and Norbornene-Catalyzed Arene C–H Amination Using Aryl Halides

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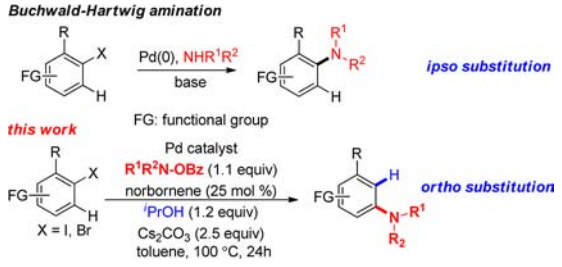
Supporting Information

ABSTRACT: A Pd and norbornene-catalyzed *ortho*-arene amination via Catellani-type C–H functionalization is reported. Aryl halides are used as substrates; *N*-benzoyloxyamines and isopropanol are employed as the amine source (oxidant) and reductant respectively. Examples are provided in 50–99% yields with high functional group tolerance. This method gives complementary site selectivity at the *ortho*- instead of *ipso*-position of aryl halides.

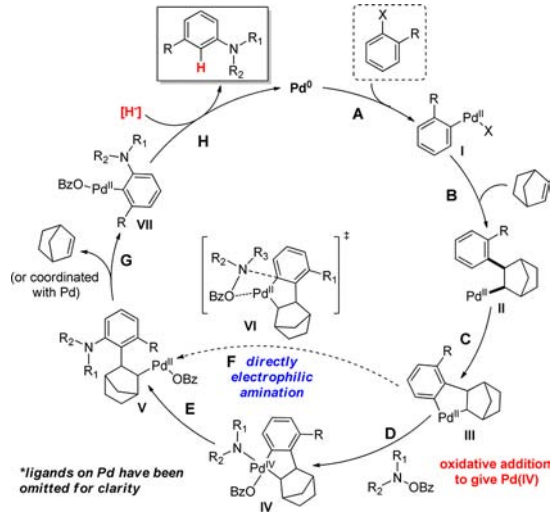
Given the broad application of aromatic amines found in pharmaceutical, agrochemical, and materials industries,[1] arene amination holds a pivotal position in organic synthesis. To date, numerous arene amination approaches have been developed,[2] whereas the Buchwald–Hartwig amination[3] (a Pd-catalyzed direct substitution of aryl halides with amine groups) represents one of the most widely utilized methods to synthesize aromatic amines. This is likely due to its use of readily available aryl halides, broad functional group tolerance, and controlled site selectivity (compared to the aryne-mediated amination[2d]). It is well-known that Buchwald–Hartwig reaction forms C–N bonds at the *ipso*-carbon of aryl halides;[4] thus, the type of amine products is limited by the position of the halogen that can be introduced (Scheme 1). Hence, site-selective arene amination at

Scheme 1. Amination with Aryl Halides



different (other than *ipso*) positions of aryl halides would be significant and complementary to the Buchwald–Hartwig reaction. Undoubtedly, direct amination of aryl C–H bonds would be an ideal alternative solution; however, control of the site selectivity is nontrivial and largely relies on the use of sterically/electronically biased substrates[5] or employing directing groups.[6] Considering the wide availability of aryl halides, herein, we describe our development of a Pd and norbornene (NBE) cocatalyzed *ortho*-amination strategy with aryl halides based on a reductive Catellani reaction pathway (Scheme 2).

Scheme 2. Proposed Reaction Design



The Catellani reaction[7] offers a unique approach to activate the *ortho* C–H bonds of aryl halides and to provide dual functionalizations at both the *ipso*- and *ortho*-positions.[8] A key for this transformation is capture of the aryl-Pd intermediate (**I**, Scheme 2) with NBE via a *syn* migratory insertion (step B) followed by an intramolecular palladation at the *ortho*-position (step C).[9] Seminal work by Catellani and Lautens show that a variety of functional groups, including hydrogen,[10] can be introduced at the *ipso*-carbon using different nucleophiles.[8d,e,11] However, to our knowledge, functionalization at the *ortho*-position via this approach has only been restricted to carbon substituents (using alkyl or aryl halides) to date.[7,8]

Our proposed strategy for the *ortho*-amination (Scheme 2) is focused on developing a new *ortho*-C–N bond forming transformation. We hypothesize that if a proper N-based oxidant can be employed through either a Pd(IV) intermediate (**IV**) or direct electrophilic substitution of the palladacycle (**III**),[12] C–N bond formation at the *ortho*-position would be realized. Also, if a proper reductant can be employed to quench the aryl-Pd intermediate **VII** (after β-C elimination of NBE), the desired *ortho*-amination product would be afforded and the Pd(0) catalyst would be regenerated (step H). Nevertheless, two challenges must be met: (1) the oxidant not only needs to provide the amine group but also has to be stronger than aryl halides (to avoid homo-Catellani coupling[8e,10a,e]) for oxidizing

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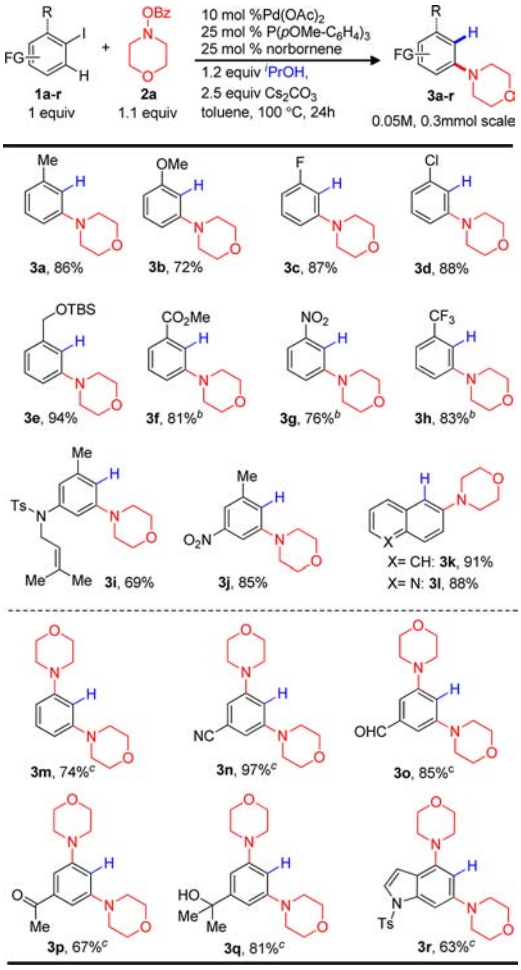
III. However, it cannot be too strong to destroy the labile NBE or the Pd(0) catalyst. (2) A reductant needs to be orthogonal to the oxidant and capable of introducing a hydrogen at the *ipso*-position, but not too strong to reduce the aryl Pd **I** (direct arene reduction) or the alkyl Pd **II** intermediate (reductive Heck reaction).[13]

Stimulated by the aforementioned challenges, 2-iodotoluene (**1a**) was used as the model substrate, and a number of Pd precatalysts, ligands, oxidants, reductants, additives, and solvents were extensively examined. Ultimately, *N*-benzoyloxyamine (**2a**)[14] and isopropanol[15] were found to be the optimal oxidant and reductant combination. For example, use of *N*-chloromorpholine[16] gave a complex mixture of products; use of benzyl alcohol or ethyl formate gave significant over-reduction.[17] To our delight, when 10 mol % $Pd(OAc)_2$ with 25 mol % tris(4-methoxyphenyl)phosphine and 25 mol % NBE were employed as the catalysts, the *ortho*-C−H amination product was obtained in 89% yield in the presence of only 1.1 equiv of 4-(benzoyloxy)morpholine (**2a**), 1.2 equiv of isopropanol, and 2.5 equiv of cesium carbonate (Table S1, entry 1). It is worthy to note that previous Catellani reaction conditions often used stoichiometric to superstoichiometric NBE,[7] while here only 25 mol % NBE is needed. In addition, the oxidant (*N*-benzoyloxyamine) and the reductant (isopropanol) are well compatible, as no large excess of either reagent or slow addition is required for this transformation.

Control experiments were subsequently conducted to understand the role of each reactant (Table S1). In the absence of either Pd precatalyst, phosphine ligand, NBE, or the base, no desired product was observed (entries 2−4 and 6). Interestingly, without isopropanol the desired amination product was still obtained in 29% yield (entry 5).[18] Using a Pd(0) precatalyst instead of $Pd(OAc)_2$ resulted in a lower yield (entry 7). From a number of mono- and bidentate phosphine ligands (entries 8−11), tris(4-methoxyphenyl)phosphine was found to be most efficient. Weaker bases such as potassium carbonate dramatically decreased the yield (entry 12). Use of norbornadiene (NBD) instead of NBE still gave the desired product, albeit in 23% yield (entry 13). Increasing the polarity of solvents from toluene to 1,4-dioxane to DMF led to decreased yields (entries 14 and 15), likely due to more polar solvents enhancing the background reactions between the base and *N*-benzoyloxyamine.[19] When the reaction was diluted from 0.1 to 0.05 M, a slightly higher yield (91%) was observed (entry 16). Lowering the Pd catalyst loading to 5 mol % resulted in an 80% yield (entry 17).

The substrate scope is shown in the Table 1. First, we examined different substitutions at the *ortho*-position of the aryl halides using **2a** as the amine partner. Substrates containing electron-donating and -withdrawing groups worked well providing meta-substituted aromatic amines in good to excellent yields. When electron-deficient arenes were used, the more electron-poor tri(2-furyl)phosphine was found to be a better ligand to prevent homodimerization of the arene.[8e,10a,e,20] One important feature of this method is that many functional groups, including methoxy ethers, fluorides, chlorides, TBS-silyl protected benzyl alcohols, methyl esters, sulfonamides, nitro, and trifluoromethyl groups, are all compatible. Amination of the *ortho*, *para*-disubstituted aryl iodides also proceeded smoothly affording 1,3,5-trisubstituted arenes (**3i**, **3j**). Note that electron-rich trisubstituted olefins, which are generally sensitive to oxidants, were tolerated under the reaction conditions (**3i**). Moreover, high yields were obtained with naphthalene- and quinoline-derived substrates (**3k** and **3l**). Next, aryl iodides

Table 1. Substrate Scope with Different Aryl Iodides[a]



[a]All yields are isolated yields. [b]25 mol % tri(2-furyl)phosphine and 2.0 equiv of **2a** and 3.0 equiv of Cs_2CO_3 were used. [c]50 mol % norbornene and 2.5 equiv of **2a** and 4.0 equiv of Cs_2CO_3 were used.

without an *ortho*-substituent were tested. Although selectively forming the monoaminated products is difficult,[21] the 1,3-diaminated arenes can be obtained in good to excellent yields. It is encouraging to note that sensitive functional groups, such as nitriles, aldehydes, methyl ketones, free tertiary alcohols, and protected indoles, are all compatible.

The scope of the amine coupling partner was investigated next (Table 2). Piperidine, azepane, diethylamine, pyrrolidine, and Boc-protected piperazine all provided the desired amination products in moderate to excellent yields. Primary amine derivatives (e.g., ^{n}BuNHOBz) do not couple under these conditions; however, the benzyl-protected *N*-benzoyloxyamines reacted uneventfully (**3u**), which may serve as an alternative way to access the secondary aryl amine products.[22]

In comparison with aryl iodides, aryl bromides are known to be the more challenging substrates for Catellani reaction because they are weaker oxidants and often less competitive toward Pd(0) oxidative addition than other oxidants.[8e,f] Our preliminary study shows that, simply by adding a silver salt (Ag_2CO_3) and using dppe as the ligand, aryl bromide **4** can be coupled providing the desired *ortho*-amination product (eq 1). In addition, this protocol is also readily scalable, and when operated on a gram scale, the Pd loading can be lowered to 4 mol % (eq 2). Furthermore, to gain mechanistic insights into this reaction, a

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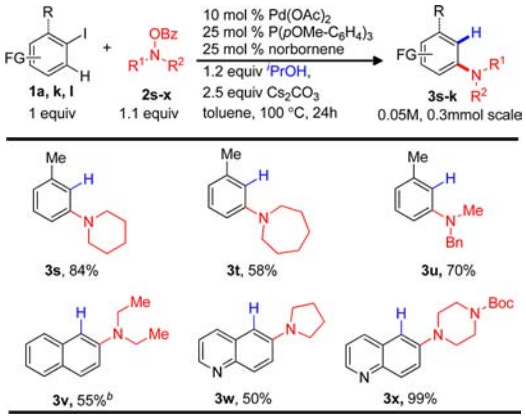
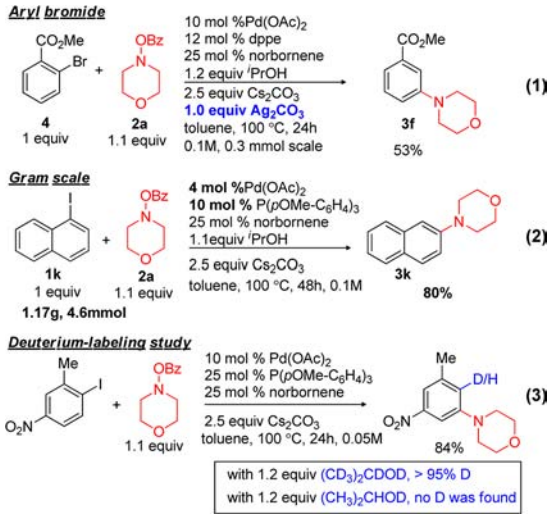
Table 2. Substrate Scope with Different Amines[a]



[a]All yields are isolated yields. [b]2.0 equiv of BzO−NEt_2 and 4.0 equiv of Cs_2CO_3 were used.

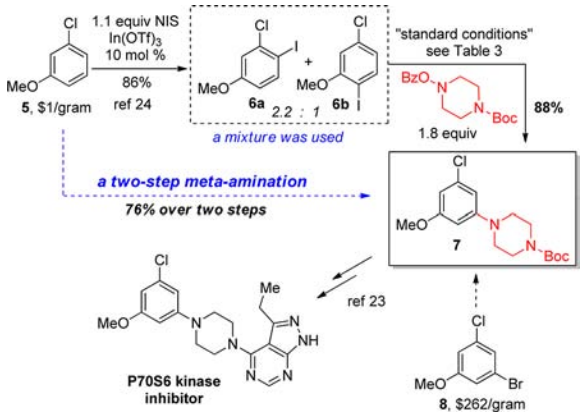


deuterium-labeling study was performed (eq 3). When d_8-isopropanol was used as the reductant, >95% deuterium was incorporated at the *ipso*-position. In contrast, when d_1-$(CH_3)_2CHOD$ was employed, no deuterium incorporation was observed (confirmed by HRMS and ^1H NMR). This study supports our proposed hydride-transfer mechanism (step H, Scheme 2) instead of a proton-transfer mechanism.

To fully demonstrate the applicability of this methodology, we prepared a key aryl amine intermediate (**7**), which was used in a synthesis of a P70S6 kinase inhibitor (Scheme 3).[23] Our strategy employed the inexpensive 3-chloroanisole (**5**) ($1.0/gram) as the starting material. Iodination gave an inseparable mixture of regioisomers (**6a**/**6b**);[24] nevertheless, this mixture can be directly subjected to the *ortho*-amination reaction offering a single regioisomer of amine **7** in 88% yield. It is worth noting that this approach provided a unique *net meta-amination of arenes* (from **5**). In contrast, the corresponding 3-chloro-5-bromoanisole (**8**), a potential precursor for the direct amination, costs $262/gram due to the difficulty in its preparation.[25] Therefore, this Pd and NBE cocatalyzed *ortho*-amination reaction is synthetically useful and complementary to the existing amination methods.

In summary, we have developed a distinct arene-amination strategy with aryl halides using Pd and NBE as the cocatalysts. Compared to the Buchwald−Hartwig reaction, this approach

Scheme 3. Synthetic Application



provides amination products exclusively at the *ortho*-position instead of *ipso*. In addition, this method represents the first example of forming C−N bonds at the *ortho*-carbon via Catellani-type C−H activation which provides broad implications for developing various dual functionalizations of arenes that involve *ortho*-C−X (X≠C) bond formation. While the efficiency of the catalytic system (e.g., Pd and NBE loading) remains to be further improved, this method is scalable and chemoselective with good functional group tolerance. Efforts toward expanding the reaction scope (e.g., generalization with aryl bromides) and detailed mechanistic studies to understand the C−N bond formation step are underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures; 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 no competing financial interest.

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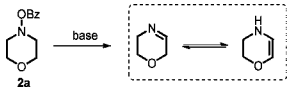
(17) Although the direct aryl halide reduction product (toluene) cannot be quantified, the reductive Heck product (with NBE) was observed.

(18) We hypothesized that the imine or enamine generated from the reaction of **2a** with a base may serve as the reductant.



(19) In the absence of Pd (entry 2), **2a** was found fully consumed by the base; also see: Li, G.; Qian, S.; Wang, C.; You, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 7837.

(20) See Supporting Information, pages 9-10 for details.

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(22) For deprotection of benzylamines, see: (a) Kroutil, J.; Trnka, T.; Cerny, M. *Org. Lett.* **2000**, *2*, 1681. (b) Cheng, C.; Sun, J.; Xing, L.; Xu, J.; Wang, X.; Hu, Y. *J. Org. Chem.* **2009**, *74*, 5671.

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(25) For selective synthesis of **8**, see: Murphy, J. M.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 15434.