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Modular C–H Functionalization Cascade of Aryl Iodides

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Supporting Information

ABSTRACT: We report the first example of *ipso*-borylation for the modular 1,2-bisfunctionalization of aryl iodides via C–H functionalization. The carbon–boron bond is used as a lynchpin to access *ipso* carbon–carbon, carbon–nitrogen, carbon–oxygen, and carbon–halogen (Cl, Br, I) bonds. The utility of our methodology is illustrated through quick, modular syntheses of the pharmaceuticals Abilify and Flunixin.

Transition-metal-catalyzed cross-coupling reactions of aryl halides are among the most reliable transformations for arene functionalization.[1] Directed transition-metal-catalyzed *ortho*[2] and *meta*[3] C–H activations can functionalize arene C–H bonds directly, but directing groups are often challenging to remove or modify. Combining C–H activation with cross-coupling could (1) form two new bonds in one step and (2) avoid restriction to a particular directing group. However, methods for bisfunctionalization of aryl halides that utilize C–H activation/cross-coupling strategies have limited substrate scope.[4] Most notably, methods for the incorporation of heteroatoms at the *ipso* position by this strategy are absent. Here we report the first *ortho*-amination/*ipso*-functionalization reaction of aryl iodides, which provides direct access to C–B, C–C, C–N, C–O, C–Cl, C–Br, and C–I bonds at the *ipso* position without the remnant of a coordinating directing group (Scheme 1). We demonstrate how our methodology provides quick access to a myriad of 2,3-disubstituted anilines, which can be found in a variety of biologically active molecules (Chart 1).

Scheme 1. Synthesis of 1,2-Heterosubstituted Arenes through C–H Activation

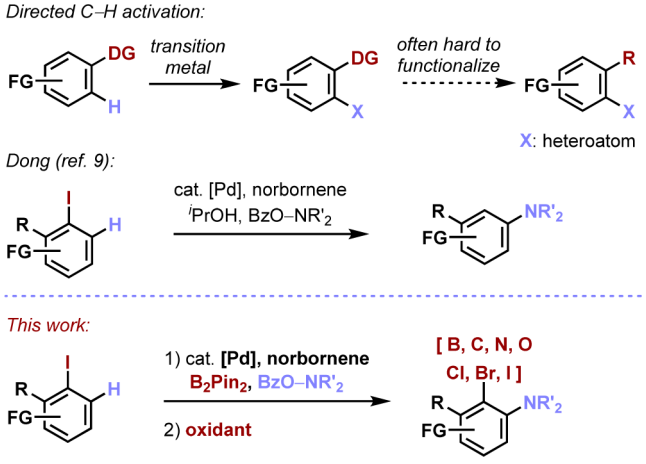
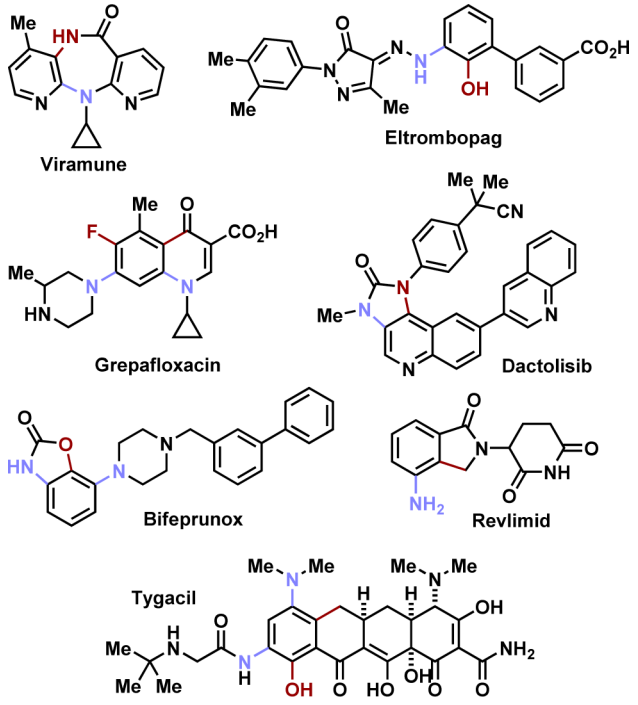


Chart 1. Selected Pharmaceuticals Containing the 2,3-Disubstituted Aniline Structure



The Catellani reaction is a bisfunctionalization of aryl halides through a palladium-catalyzed/norbornene-mediated reaction that proceeds via an initial *ortho*-C–H functionalization.[4] Seminal reports by Catellani[5] and Lautens[6] have demonstrated the utility of this reaction in the formation of C–C bonds.[7] Developments of the norbornene-mediated bisfunctionalization of aryl halides with two distinct coupling partners have been limited to the formation of C–C bonds at the *ortho* position and C–C or C–H bonds at the *ipso* position.[8] While Dong and co-workers have developed a method for the *ortho*-C–H amination/*ipso*-hydrogenation of aryl halides,[9] no method currently exists for the intermolecular incorporation of C–C(sp^3) or C–heteroatom bonds at the *ipso* position in the Pd-catalyzed bisfunctionalization of aryl halides.

Our strategy to achieve a broadly useful, modular 1,2-bisfunctionalization to access 1,2-disubstituted anilines involves

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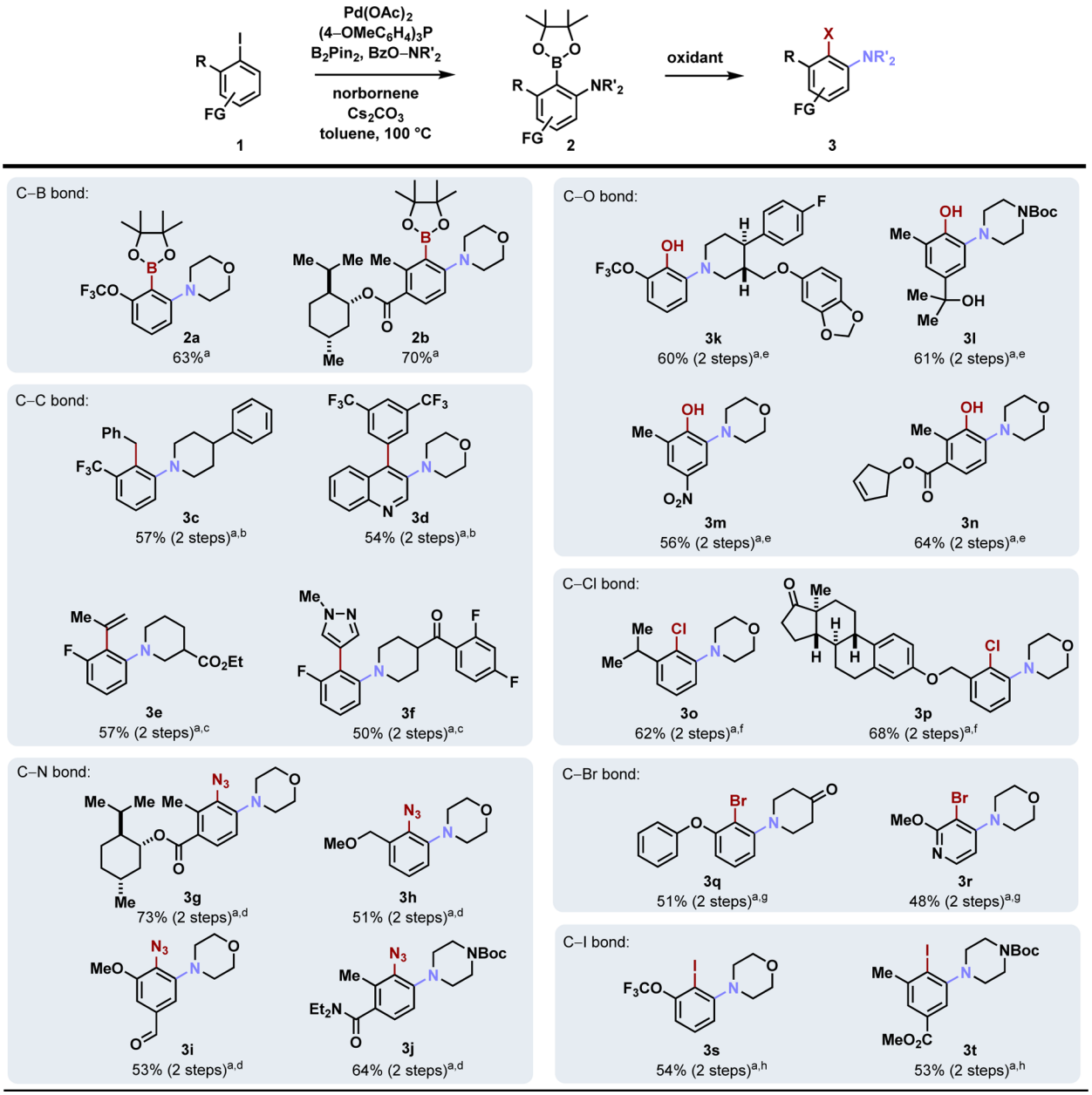
Table 1. ***ortho*-Amination/*ipso*-Borylation and Derivatization**



[a]Aryl iodide (0.3 mmol), $Pd(OAc)_2$ (5 mol % Pd), $(4\text{-}MeOC_6H_4)_3P$ (10.5 mol %), norbornene (1 equiv), BzO-amine (1.05 equiv), B_2Pin_2 (1 equiv), Cs_2CO_3 (2.5 equiv), toluene (0.05 M), 100 °C. [b]Pd_2dba_3 (5 mol % Pd), DavePhos (10 mol %), electrophile (1 equiv), K_2CO_3 (3.75 equiv), toluene/ethanol/water (8/8/1 v/v/v), 100 °C. [c]$Pd(OAc)_2$ (5 mol % Pd), DavePhos (10 mol %), electrophile (1 or 2 equiv), K_3PO_4 (2 equiv), *n*-BuOH/water (5/2 v/v). [d]NaN_3 (1.5 equiv), $Cu(OAc)_2$ (10 mol %), air, methanol, 50 °C. [e]H_2O_2 (2.5 or 5 equiv), NaOH (2.5 or 5 equiv), THF. [f]$CuCl_2$ (3 equiv), methanol/water (1/1 v/v), 80 °C. [g]$CuBr_2$ (3 equiv), methanol/water (1/1 v/v), 80 °C. [h]Chloramine T (1.5 equiv), NaI (1.6 equiv), THF/water (1/1 v/v), 50 °C.

(1) oxidative addition into aryl iodides, (2) norbornene-directed C−H functionalization, and (3) novel conversion to *ortho*-substituted aryl pinacol boronates, which can be used as lynchpins to access a wide variety of 1,2-bisfunctionalized arenes. Treatment of *ortho*-substituted aryl iodides[10] with *N*-benzoyloxyamines (BzO-amines) and bis(pinacolato)diboron in the presence of $Pd(OAc)_2$, $(4\text{-}MeOC_6H_4)_3P$, norbornene,[11] and Cs_2CO_3 in toluene at 100 °C gave the *ortho*-aminated phenyl pinacol boronate esters **2a** and **2b** (Table 1). The results provide the first example of *ipso*-C−B bond formation in *ortho*-C−H activation reactions. Subsequent functionalizations allowed for the direct conversion of the C−B bond to C−C (**3c**–**f**), C−N (**3g**–**j**), C−O (**3k**–**n**), C−Cl (**3o**, **3p**), C−Br (**3q**, **3r**), and C−I (**3s**, **3t**) bonds. Conventional C−C bond formation at the *ipso* position in the norbornene-mediated bisfunctionalization of aryl halides is typically achieved via Heck, Sonogashira, or Suzuki cross-coupling.[6,12] Our approach allows access to additional carbon substituents that cannot be obtained readily with conventional reactions, such as benzyl and isopropenyl groups (**3c**, **3e**), and thereby further provides access to functionality beyond the previous substrate scope.

A variety of BzO-amines derived from six-membered rings were successfully employed in our methodology. BzO-amines derived from complex amines such as paroxetine (**3k**) were

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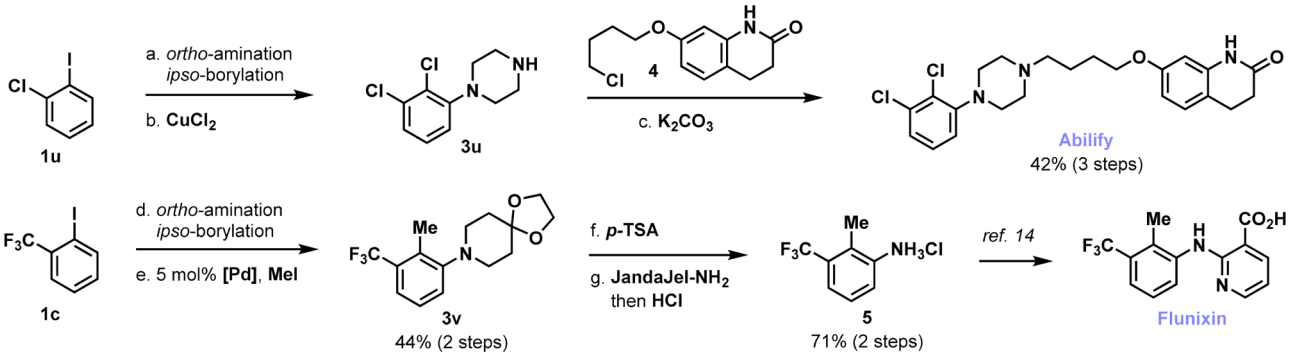
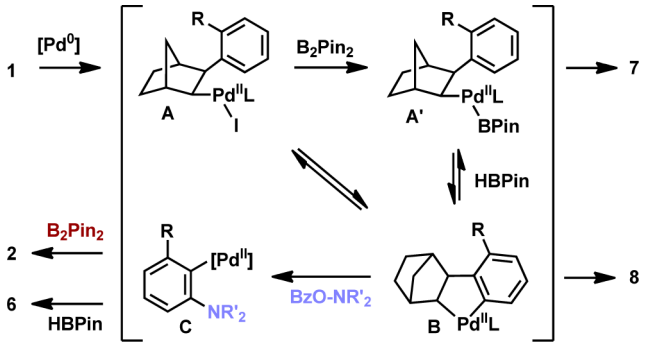
Scheme 2. Application to the Synthesis of Abilify and the Formal Synthesis of Flunixin[a]



[a]Conditions: (a) $Pd(OAc)_2$ (5 mol %), $(4\text{-}MeOC_6H_4)_3P$ (10.5 mol %), 2-chloroiodobenzene (1 equiv), 1-benzoyloxy-4-BOC-piperazine (1.05 equiv), B_2Pin_2 (1 equiv), norbornene (1 equiv), Cs_2CO_3 (2.5 equiv), toluene (0.05 M), 100 °C. (b) $CuCl_2$ (3 equiv), methanol/water (1/1 v/v), 80 °C. (c) **4** (1.05 equiv), K_2CO_3 (1.55 equiv), NaI (1.43 equiv), DMF, rt. (d) $Pd(OAc)_2$ (5 mol %), $(4\text{-}MeOC_6H_4)_3P$ (10.5 mol %), 2-trifluoromethyliodobenzene (1 equiv), 1-benzoyloxy-4-piperidone ethylene ketal (1.05 equiv), B_2Pin_2 (1 equiv), norbornene (1 equiv), Cs_2CO_3 (2.5 equiv), toluene (0.05 M), 100 °C. (e) $Pd(OAc)_2$ (5 mol %), DavePhos (10 mol %), K_3PO_4 (2 equiv), MeI (5 equiv), *n*-BuOH/water (5/2 v/v), 80 °C. (f) *p*-TSA (10 mol %), acetone/water (10/1 v/v), 65 °C. (g) JandaJel-NH_2 (1.5 equiv), NH_4Cl (1 equiv), ethanol, 95 °C.

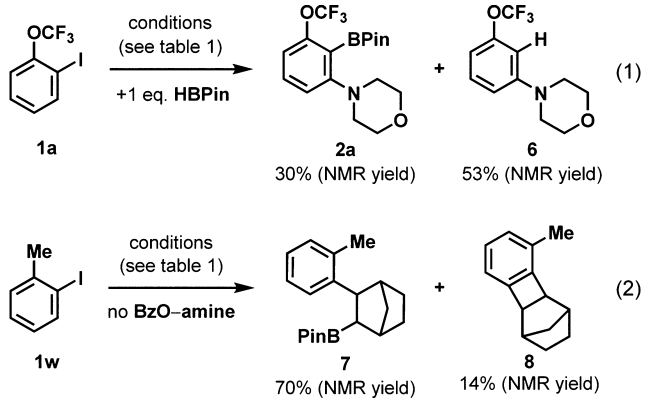
Scheme 3. Simplified Catalytic Cycle



well-tolerated. BzO-amines derived from five-membered rings as well as linear amines, however, are not currently suitable. This limitation can be overcome by accessing 4-piperidone analogues (e.g., **3q**), which can be converted to the corresponding primary anilines (**3v** → **5** in Scheme 2).[13]

The 1,2-bisfunctionalization method presented here could be employed to quickly access the antipsychotic Abilify and the anti-inflammatory Flunixin in only a few steps (Scheme 2). Both examples reveal the potential and modularity of our methodology in diversity-oriented synthesis to quickly generate a wide variety of substituted anilines.

Our strategy was devised on the basis of previous hypotheses of mechanistically related Pd-catalyzed, norbornene-mediated transformations.[15] Under the standard reaction conditions, the *ipso*-H aniline (see, e.g., compound **6** in eq 1) is the major side product. Resubjection of the aminoboronates **2** to the reaction conditions in the presence of benzoic acid did not generate the corresponding *ipso*-hydrogenation product.[16] Therefore, formation of the reduced proteo side product through protodeborylation is unlikely. When HBPin was added to the reaction conditions, *ipso*-H aniline **6** became the major product (eq 1), which suggests that the formation of **6** is due to the reduction of intermediate **C** by HBPin.[17] HBPin may be generated under the standard reaction conditions in the *ortho*-C−H activation step (intermediate **A′** to **B**). In the absence of BzO-amine, boronate **7** was the major product with **8** as the minor product (eq 2). Because compound **7** was observed in only trace amount under the standard reaction conditions, we conclude that *ortho*-C−H activation is reversible.[15a] All of the obtained data are consistent with the mechanism shown in Scheme 3.



In conclusion, we have reported the first general method for the formation of *ipso*-C−heteroatom bonds in the Pd-catalyzed, norbornene-mediated *ortho*-C−H amination of aryl iodides. By trapping Pd(II) intermediates with B_2Pin_2, we have developed a simple, two-step procedure that harnesses the synthetic utility of the C−B bond to access a variety of *ortho*-functionalized anilines and provides the first example of intermolecular C−heteroatom bond formation in Pd-catalyzed, norbornene-mediated C−H functionalization. We believe that the strategy outlined above can be utilized to overcome the functional group limitations at the *ipso* position in current palladium-catalyzed, norbornene-mediated 1,2-bisfunctionalization methodologies and provide a modular strategy for the synthesis of substituted anilines.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data for all new compounds, and crystallographic data (CIF). 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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We thank David Jaramillo for initial reaction development, Heejun Lee for X-ray analysis, and the NSF (CHE-0952753) for financial support.

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(9) Dong, Z.; Dong, G. *J. Am. Chem. Soc.* **2013**, *135*, 18350. For other examples of *ortho*-C−N bond formation in the Catellani reaction, see refs 7b, 7c, and 7f.

(10) Non-*ortho*-substituted aryl iodides gave inferior results. When ethyl 4-iodobenzoate was subjected to the reaction conditions, the desired product was obtained in 34% yield. See the Supporting Information.

(11) The best results were obtained when 1 equiv of norbornene was employed. When 25 mol % was used, the desired products were obtained in lower yields. See the Supporting Information.

(12) Additionally, cyanation (ref 6a) and *N*-tosylhydrazone insertion (refs 7d, 7e, and 7f) have also been employed.

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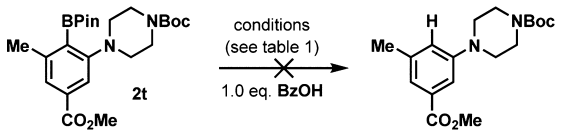
(16) Aminoboronate **2t** was resubjected to the reaction conditions in the presence of benzoic acid. ^{1}H NMR analysis of the reaction mixture revealed no generation of the corresponding *ipso*-hydrogenation product.



(17) Dong and co-workers have hypothesized that under the reaction conditions, the imine or enamine generated upon elimination of benzoate from *N*-benzoyloxyamines may serve as the reductant. See ref 9.

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