Heterocycles

International Edition: DOI: 10.1002/anie.201507128
German Edition: DOI: 10.1002/ange.201507128

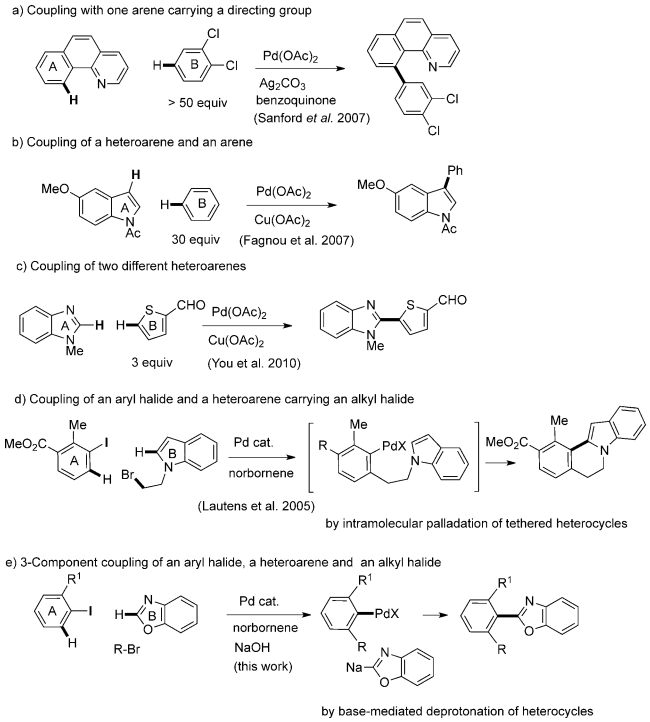
Palladium-Catalyzed Heteroarylation and Concomitant *ortho*-Alkylation of Aryl Iodides

*Chuanhu Lei, Xiaojia Jin, and Jianrong (Steve) Zhou**

Abstract: *Three-component couplings were achieved from common aryl halides, alkyl halides, and heteroarenes under palladium and norbornene co-catalysis. The reaction forges hindered aryl–heteroaryl bonds and introduces ortho-alkyl groups to aryl rings. Various heterocycles such as oxazoles, thiazoles and thiophenes underwent efficient coupling. The heteroarenes were deprotonated in situ by bases without the assistance of palladium catalysts.*

2-Arylated oxazoles and related 1,3-azoles are present in many drug candidates, and have interesting activities against a diverse set of targets including cancers, Alzheimer's disease, anemia, and type-II diabetes.[1] We report herein a new reaction manifold that allows quick construction of hindered aryl–heteroaryl bonds from three common reagents. The products are difficult to access from other synthetic methods. For instance, both cross-couplings[2] and direct heteroarylation[3] of hindered aryl halides require tedious preparation of the aryl halides, especially when two different *o*,*o*′-substituents are present on aryl rings.

In recent years, direct couplings of (hetero)arenes have emerged as an efficient and step-economic way to form aryl–heteroaryl bonds.[4] These reactions avoid prior synthesis of (hetero)aryl halides and (hetero)arylmetal reagents. To control regioselectivity in (hetero)arenes, directing groups were installed,[5] or the innate electrophilicity and acidity of certain C–H bonds on the heteroarenes were exploited (Scheme 1 a,b).[6] Elegant regioselective couplings of two different heteroarenes have been disclosed by the groups of Hirano and Miura, You, and Yamaguchi and Itami, as well as others (Scheme 1 c).[7] Catalyst control of regioselectivity is more challenging and examples of this kind emerged recently, wherein couplings at unconventional sites were allowed.[8] It should be pointed out that in the examples above, the sites of C–H activation are the sites of aryl–heteroaryl bond formation. As a distinct variant, Lautens et al. reported intramolecular heteroarylation of aryl halides with heterocycles carrying tethered alkyl halides by using palladium/norbornene cocatalysis (Scheme 1 d).[9] The covalent linkage was essential for fast cleavage of heteroaryl C–H bonds by electrophilic palladation, but the tethers were retained as extra rings in the products. Without tethers, very little product was obtained.



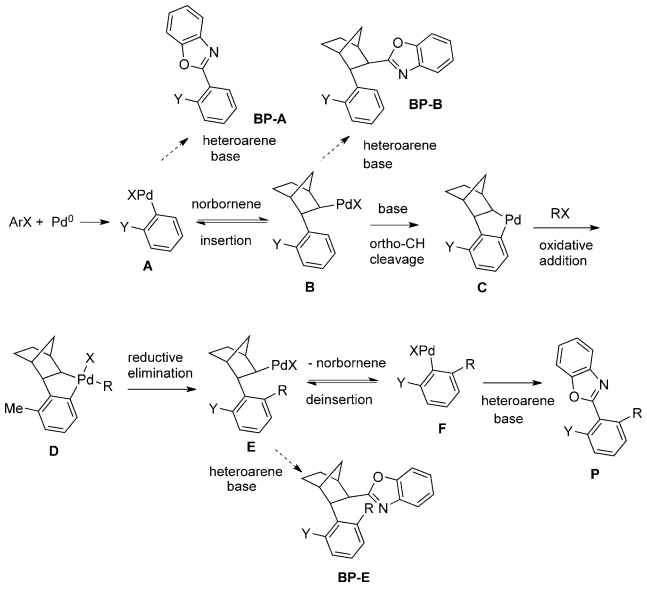
Scheme 1. Representative types of heteroarylation.

Herein, we report a three-component coupling of aryl halides, alkyl halides and oxazoles (Scheme 1 e). Some other heteroarenes such as thiophenes can also react efficiently. The reaction enables arylation of heteroarenes and simultaneous *ortho*-alkylation. In a typical Catellani-type pathway (Scheme 2), insertion of 2-norbornene into **A** and *ortho*-palladation results in the key palladacycle **C**. Subsequent oxidative addition of an alkyl halide[10] and C–C reductive elimination allows *ortho*-alkylation in **E**. After deinsertion of norbornene, an arylpalladium species (**F**) is generated and it can be trapped by various nucleophiles and olefins[11] as reported by the groups of Catellani,[12] Lautens,[13] and others.[14] We hypothesized that trapping **F** intermolecularly with heteroarenes, for example, oxazoles, would lead to the coupling product **P** with very hindered aryl rings. In this pathway, many side-reactions are foreseeable from premature coupling of the upstream species **A**, **B**, or **E** with heteroarenes.

We first attempted a model coupling of *o*-tolyl iodide, 1-bromohexane and 1,3-benzoxazole (Scheme 3).[15] A small, weakly electron-donating tri-2-furylphosphine[16] was essential to achieve the desired reaction and gave good yield of the desired product (76 %). Under optimized reaction conditions, no direct alkylation of benzoxazole was detected. If PPh_3 was

[*] Dr. C. Lei, X. Jin, Prof. Dr. J. Zhou
Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University
21 Nanyang Link, Singapore 637371 (Singapore)
E-mail: jrzhou@ntu.edu.sg

Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under http://dx.doi.org/10.1002/anie.201507128.



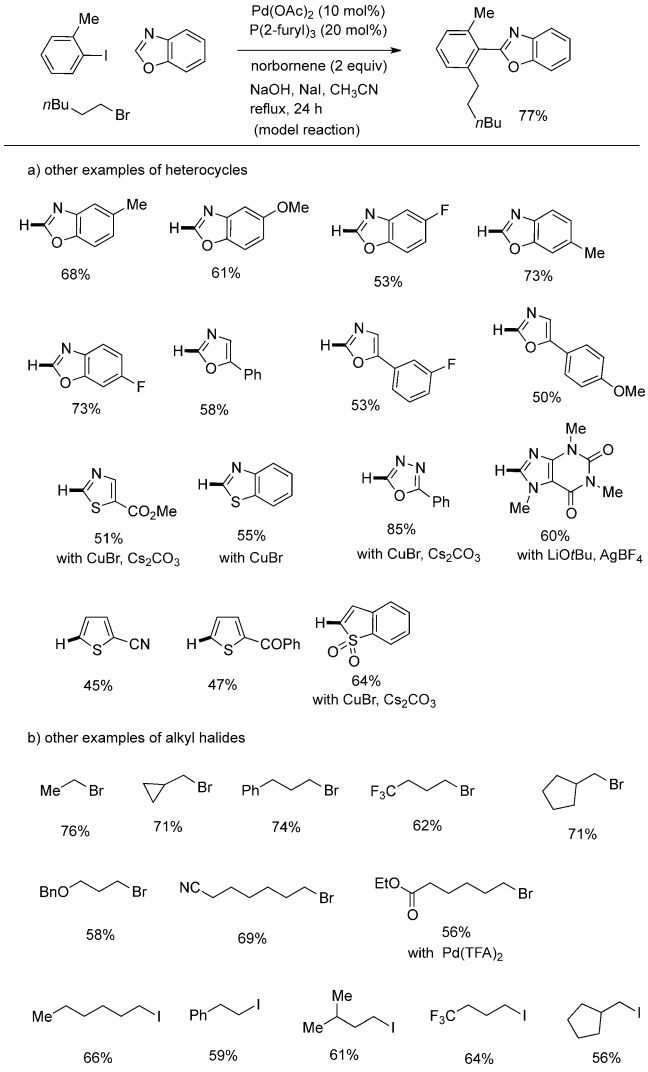
Scheme 2. A proposed pathway and possible byproducts.

used as a ligand, the product yield fell to 21% and premature heteroarylation of **B** became predominant to give 42% yield of **BP-B** (see Scheme 2). When dppp, dppf, and other bis(phosphine)s were used, coordinative saturation by the bis(phosphine)s prevented insertion of norbornene and led to significant premature coupling of **A** with benzoxazole. Without any added phosphine, no product **P** was formed. When the palladium loading was reduced to 5 mol%, the product yield fell slightly to 60%.

The choice of bases proved to be critical. Among many inorganic bases, only NaOH gave a good yield of the desired product. Thus, NaOH efficiently removed two types of C–H hydrogen atoms: the *ortho*-C–H bond of **B** and the relatively acidic hydrogen atom on C2 of benzoxazole, in a later stage of the catalytic cycle (Scheme 2). Other inorganic bases and trialkylamines led to very poor yields. NaI in situ converted alkyl bromides into more reactive alkyl iodides. In reactions of alkyl iodides, NaI was not added. We also tried reaction conditions prescribed by Lautens et al. in which Cs_2CO_3 and tri(2-furyl)phosphine were used as the base and supporting ligand, respectively. Only less than 20% of **P** was detected (see the Supporting Information).

The heterocycles were not restricted to benzoxazoles, oxazoles, and thiazoles (Scheme 3a). For example, selective heteroarylation also took place selectively at the C8-position of caffeine. Interestingly, oxadiazoles and electron-poor thiophenes also coupled in reasonable yields. Thiophenes have relatively acidic hydrogen atoms at the C2-position with pK_a values of below 30 in DMSO.[17] In some cases, Cs_2CO_3 and CuBr were used as a base and additive to improve yields. We believe the copper salt assisted in both deprotonation of the C–H bonds and subsequent transmetalation to arylpalladium species. Pyridine *N*-oxides did not couple, unfortunately.

Both primary alkyl bromides and iodides coupled efficiently (Scheme 3b). Polar groups of esters and nitriles survived well under the basic conditions. Notably, from cyclopropylmethyl bromide, ring opening was not detected.

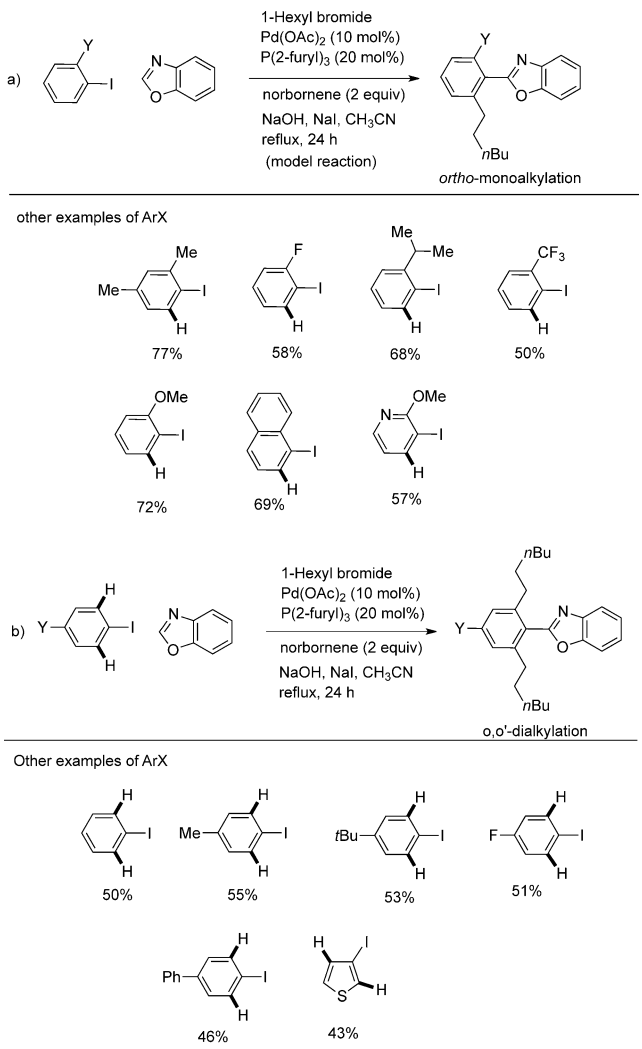


Scheme 3. Examples of heterocycles and alkyl halides. The yields are those for products isolated from reactions using aryl iodide (0.3 mmol), alkyl halide (4 equiv), heterocycle (1.2 equiv), norbornene (2 equiv), NaOH (2 equiv), NaI (2 equiv), and 10 mol% Pd catalyst in dry acetonitrile (3 mL). 90°C, 24 h.

Thus, oxidative addition of alkyl halides was most likely of the S_N2-type and did not engage a cyclopropylmethyl radical. Both primary alkyl chlorides and isopropyl iodide gave low yields.

With regard to the scope of the aryl iodides, both electron-withdrawing trifluoromethyl and electron-donating methoxy groups were tolerated at the *ortho* position (Scheme 4a). 3-iodopyridine also coupled smoothly. From phenyl iodide and *para*-substituted aryl iodides, the main products were 2,6-dilakylated ones (Scheme 4b). The yields of the products isolated from the dialkylation were reasonable, considering that three new C–C bonds were formed in one operation in a congested environment. Curiously, *meta*-substituted aryl iodides led to **BP-E** as major products, which retained the norbornene fragment.

We prepared a putative palladacycle **A**[18] of the catalytic cycle (Scheme 2) and then subjected it to the coupling conditions with benzoxazole (Scheme 5a). In the presence

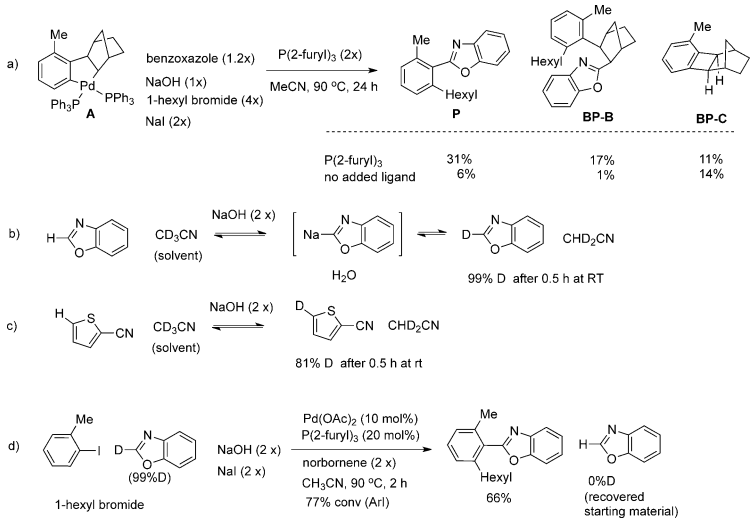


Scheme 4. Examples of *ortho*- and *para*-substituted aryl iodides in couplings. The yields are for products isolated from reactions using the aryl iodide (0.3 mmol).

of tri-2-furylphosphine, the coupling product **P** was formed in 31 % yield, along with 17 % of **BP**-**B**, 11 % of **BP**-**C**, and some unidentified products. Notably, extensive exchange of furyl and phenyl groups between two phosphines was detected by GC and GCMS. This exchange may have caused the moderate yield of **P** in this study and illustrated the importance of tri-2-furylphosphine in promoting the desired coupling process on palladium. The small, weakly donating monophosphine probably slowed down reductive elimination of upstream organopalladium species (Scheme 2). Without added trifurylphosphine, very little **P** was formed.

When 1,3-benzoxazole was vigorously stirred in a suspension of NaOH powder in [D_3]acetonitrile, almost complete H/D exchange was detected at the C2-position after 0.5 hours at room temperature, as monitored by both ^{1}H and ^{2}H NMR spectroscopy (Scheme 5 b).[19] Importantly, no decomposition of benzoxazole by ring opening occurred in [D_3]acetonitrile, even at 90 °C. In comparison, 80 % of the benzoxazole underwent ring opening in [D_4]methanol.[20] We also observed fast H/D exchange at the C5-position of 2-cyanothiophenes at room temperature under similar reaction conditions, as shown in Scheme 5 c. When [D_1]benzoxazole was subjected to the coupling condition in MeCN for 2 hours at 90 °C, the recovered benzoxazole lost almost all deuterium (Scheme 5 d).[21] This loss is consistent with fast and reversible deprotonation of benzoxazole by NaOH to form an anionic benzoxazole in a low concentration.

In summary, we report an intermolecular heteroarylation reaction of aryl iodides with concomitant *o*-alkylation of aryl rings from three common reagents. Hindered aryl–heteroaryl bonds were constructed in a single operation and such bond constructions usually require tedious multistep synthesis. As a key reaction design, norbornene was used to assist *ortho*-C–H activation of the aryl rings, by following a Catellani-type pathway. Importantly, this reaction is distinct from previous procedures by Lautens et al. with respect to the activation of the heteroaryl C–H bonds (Scheme 1 d). Herein, NaOH caused direct deprotonation of the heterocycles without the assistance of palladium catalysts.



Scheme 5. Mechanistic studies.

Acknowledgements

We thank the Singapore Ministry of Education Academic Research Fund (MOE2013-T2-2-057 and MOE2014-T1-001-021) and Nanyang Technological University for financial support.

Keywords: C–H activation · cross-coupling · heterocycles · palladium · synthetic method

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 13397–13400
Angew. Chem. **2015**, *127*, 13595–13598

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Received: July 31, 2015
Published online: September 11, 2015

