C–H Functionalization

DOI: 10.1002/anie.201005990

Palladium(II)-Catalyzed C–H Bond Arylation of Electron-Deficient Arenes at Room Temperature**

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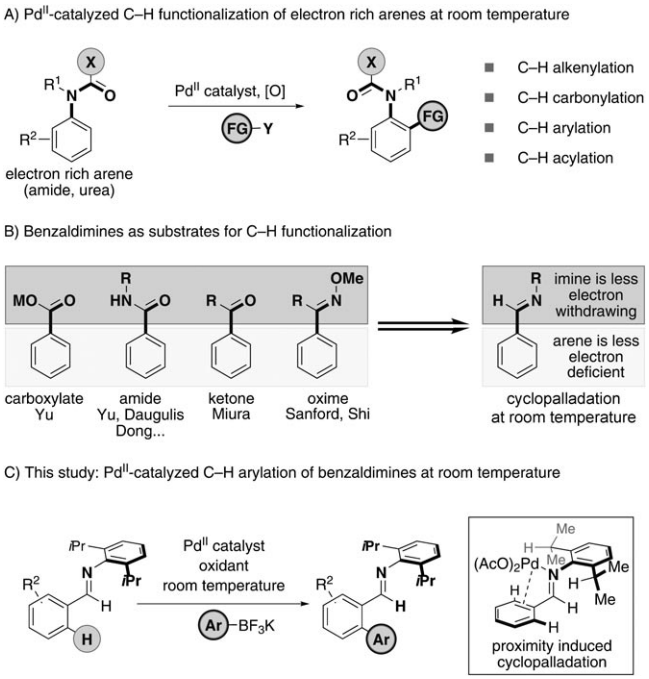
Despite the impressive array of metal-catalyzed C–H bond functionalization processes,[1] significant challenges remain before their full potential as general strategies in complex molecule synthesis can be realized. In relation to this, a key goal in our laboratory is the development of Pd^{II}-catalyzed site-selective C–H bond functionalization reactions that proceed at room temperature,[2] facilitating the assembly of the architectures that define complex natural products, medicines, and functionalized materials. Recent advances have identified that Pd^{II}-catalysts are capable of performing arene C–H functionalization transformations at room temperature, and these examples include the olefination,[3a] arylation,[3b–g] carbonylation,[3h] and acylation[3i] of electron-rich aromatic compounds (Scheme 1 A).[3] The continued advancement of this field would benefit from the development of new processes that facilitate Pd^{II}-catalyzed C–H bond functionalization of the complimentary and versatile electron-deficient arenes at room temperature.

Arenes substituted with carbonyl-related groups provide an effective handle for cyclometalation.[1,4–8] With respect to Pd catalysis, Yu and co-workers have pioneered the use of carboxylate groups as effective promoters of Pd-catalyzed selective C–H functionalization,[5] which has led to seminal developments in cross-coupling with arylorganometallic reagents;[5a,b,6] further developments have led to carbonylation,[5c] alkylation,[5d] olefination,[5e,f] oxygenation,[5g] and iodination[5h,i] reactions. Related to this, other carbonyl-based directing groups such as amide derivatives,[7] ketones,[8] and oximes[9] have also resulted in developments in catalytic C–H bond functionalization. However, many of these groups impart a strong electron withdrawing effect on the parent aromatic nucleus, and hence the C–H bond palladation event often requires forcing reaction conditions that may not always be compatible with more delicate molecular architecture. With this in mind, we envisaged a design plan wherein an arene bearing an imine directing group would be less electron withdrawing than other carbonyl directing groups, thereby enhancing the cyclopalladation capacity at room temperature and still providing easy access to the versatile aldehyde functional group (Scheme 1 B).



Scheme 1. Concepts for room temperature C–H functionalization.

Herein, we report that the C–H bond arylation of benzaldimines with aryl-BF_3K salts can be catalyzed by $Pd(OAc)_2$ at room temperature (Scheme 1 C); the mild reaction conditions enable the functionalization of substrates displaying sensitive functionality.

The cyclopalladation of benzaldimines at room temperature is well documented,[10] however, the paucity of catalytic Pd^{II} reactions on this class of molecule[11] contrasts with the extensive number of Rh^{I}- and Ru^{II}-catalyzed imine directed C–H bond functionalization processes that have been reported.[12] A common feature of oxidative Pd^{II}-catalyzed C–H bond functionalization processes is the generation of acid in the oxidation step that returns the Pd^{0} species formed at the end of a catalytic cycle back to the active catalyst. Imines may display poor stability under such oxidative conditions and are prone to hydrolysis; the release of a primary amine would trap the catalyst in an inactive bis-(amino)–Pd^{II} complex.[13] Despite these potential problems,

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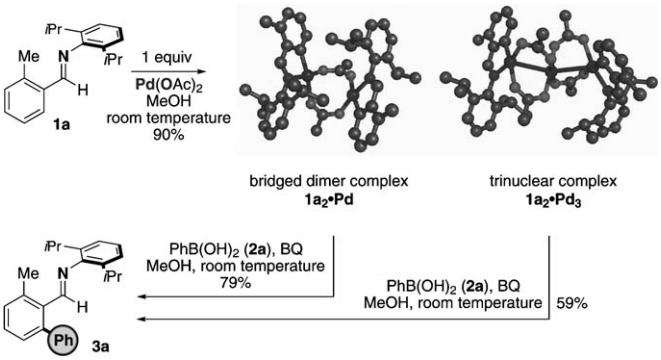
[**] We gratefully acknowledge the Leverhulme Trust (M.J.T. and N.G.B.), the Marie Curie Foundation (M.G.), the EPSRC (C.C.C.J.), the University of Cambridge (B.S.L.C.), the Royal Society, and Philip and Patricia Brown (M.J.G.) for funding, and the EPSRC Mass Spectrometry Service (University of Swansea).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201005990.

we were attracted by the apparent ease of cyclopalladation on the intrinsically electron-deficient benzaldimine nucleus.[10] We deemed that benzaldimines derived from aniline would be unsuitable for our needs due to the likely instability towards the mildly acidic conditions of the oxidative catalytic cycle, and we proposed that increased steric bulk around the aniline component would stabilize the imine towards hydrolytic cleavage. In light of this hypothesis, we selected 2,6-diisopropylaniline as an ideal source of sterically demanding amine to form the benzaldimine substrate for our catalytic C–H bond functionalization strategy (Scheme 1 C).[8,14]

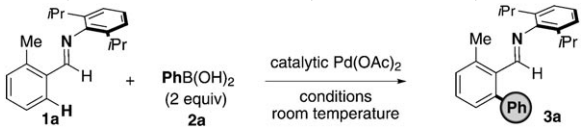
We focused our initial studies on benzaldimine **1a**, and upon treatment of **1a** with 1 equivalent of $Pd(OAc)_2$ at room temperature in methanol, a cyclopalladated complex was formed and subsequently identified as comprising a bridged dimer **$1a_2$·Pd** and a trinuclear architecture **$1a_2$·Pd_3**, whose structures were confirmed by X-ray diffraction following recrystallization (Scheme 2). Making use of the C–H cross-coupling tactic introduced by Yu et al.,[5a,b,6] we determined that **$1a_2$·Pd** underwent arylation when treated with $PhB(OH)_2$ (**2a**) in methanol to give the *ortho*-arylated benzaldimine **3a** in excellent yields. Importantly, the aryl transfer only proceeded in the presence of benzoquinone (BQ), a reliance also identified by others.[6,15] We also confirmed that trinuclear complex **$1a_2$·Pd_3** underwent arylation to **3a**, albeit in lower yield.



Scheme 2. Cyclopalladation and functionalization of **1a**.

Encouraged by these initial results, we next investigated the reaction parameters towards a mild catalytic arylation process and commenced screening by varying the nature of the oxidant in the presence of 20 mol% of $Pd(OAc)_2$ in methanol and benzoquinone (2 equiv) (Table 1). Optimized conditions were established which entailed the treatment of **1a** with 10 mol% $Pd(OAc)_2$, 2 equiv of $PhB(OH)_2$ (**2a**), 2 equiv of BQ, 2 equiv of $tBuO_2H$ as oxidant, 1 equiv of Ac_2O and 4 Å molecular sieves in a CH_2Cl_2/*i*PrOH (4:1) solvent mixture to provide a 95% yield of the arylated imine **3a** after 24 h at room temperature (Table 1, entry 7). We believe that the presence of acetic anhydride ensures reformation of $Pd(OAc)_2$ during the oxidation step with $tBuO_2H$.[16] Control experiments ensured that no arylation took place on the parent *o*-tolualdehyde[8] under the optimized conditions, or in the absence of $Pd(OAc)_2$. We also tested the benzaldimine derived from aniline in the catalytic reaction and no arylation was observed, supporting the suspected decomposition of the imine.

Table 1: Optimization of the Pd^{II}-catalyzed C–H bond arylation.[a]

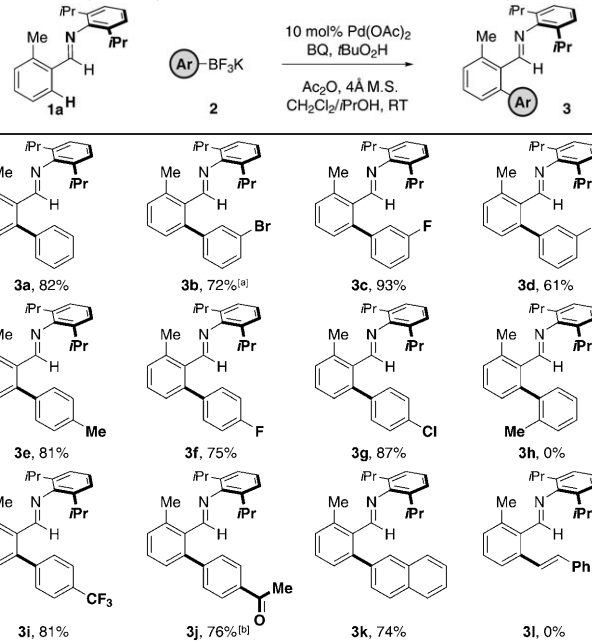


Entry	$Pd(OAc)_2$	Additive	Oxidant	Solvent	Conv. [%][b]
1	20 mol%	–	–	MeOH	18
2	20 mol%	–	oxone	MeOH	–
3	20 mol%	–	$Cu(OAc)_2$	MeOH	–
4	20 mol%	–	$PhI(OAc)_2$	MeOH	–
5	20 mol%	–	$tBuO_2Bz$	MeOH	50
6	20 mol%	–	$tBuO_2H$	MeOH	50
7	10 mol%	Ac_2O, 4 Å M.S.	$tBuO_2H$	CH_2Cl_2/IPA	100 (95)

[a] BQ = benzoquinone, Bz = benzoyl, IPA = *i*PrOH. [b] Conversion determined by ^1H NMR spectroscopy. Yield of isolated product in brackets.

The capacity of the arylation process was assessed through variation of the arylboronic acid component. We noticed a strong reliance on the quality of arylboronic acid, in particular the source of the reagent.[17] However, following the precedent first identified by Yu and co-workers, we found that the reaction proved superior and worked reliably with aryl-BF_3K salts (Table 2, **3a**).[5b] Accordingly, a range of aryl groups can be transferred in excellent yields, displaying electron-donating (**3c**, **3e**, **3f**, **3k**), and electron-withdrawing properties (**3i**, **3j**). Unfortunately, aryl-BF_3K salts displaying *ortho*-substituents and styryl-BF_3K salts did not result in the desired products (**3h**, **3l**). Aryl groups containing halogens (**3b–d**, **3g**)

Table 2: Scope of aryl transfer in the *ortho*-selective C–H arylation.

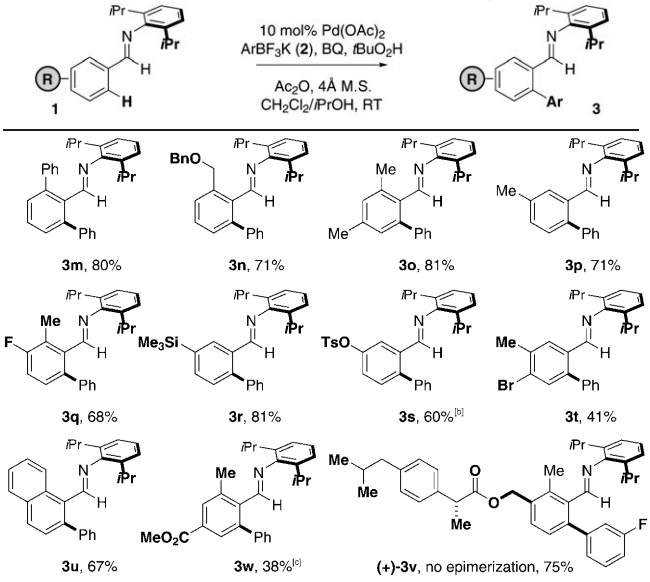


[a] 12 mol% $Pd(OAc)_2$ used. [b] Acetone/*i*PrOH used as solvent.

were transferred in excellent yields, demonstrating that the C–H arylation process is compatible with functionality required for conventional Pd^0-catalyzed cross-coupling reactions.

Benzaldimines that display a variety of functional and structural motifs are also compatible with the catalytic arylation process (Table 3). The process readily transformed

Table 3: Scope of *ortho*-selective benzaldimine C–H arylation.[a]

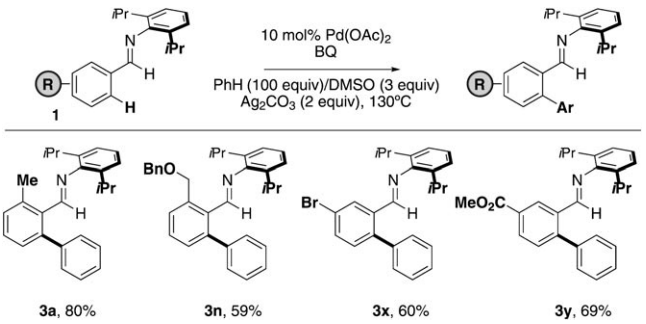


[a] Bn = benzyl, Ts = *p*-toluenesulfonate. [b] 20 mol% $Pd(OAc)_2$. [c] 40 °C.

benzaldimines bearing halogens, (**3q**, **3t**), tosyl (**3s**), silyl (**3r**), aryl and alkyl substituents (**3m–p**, **3u**) in good to excellent yields. The significant advantage of this mild method is the ability to arylate structurally complex molecules bearing labile stereogenic centers. For example, an ibruprofen derived benzaldimine could be arylated under our standard conditions in good yield to give **3v** without loss of chiral integrity. Even when an additional electron-withdrawing group is displayed on the benzaldimine, the arylation of this electron deficient arene still proceeds in moderate yield at 40 °C (**3w**).

The enhanced stability that the isopropyl groups impart on benzaldimine **1a** suggested that it may also be possible to use this reaction manifold in C–H bond functionalization reactions that require more forcing conditions. We were particularly attracted by the possibility of a dehydrogenative cross-coupling reaction[6b,18] along similar lines to those published by Sanford[18c] and Dong.[6b] Pleasingly, we found that benzaldimine **1a** could be phenylated to **3a** in good yield using benzene as a source of the aryl group in place of the phenylboronic acid (Scheme 3).[18c] Moreover, we were delighted to find that in addition to obtaining benzaldimines that display alkyl (**3a**, **3n**) and bromide (**3x**) functionalities in good yields, we could further expand the scope of the transformation by facilitating *ortho*-selective arylation of highly electron deficient arenes like **3y**.[19]

In summary, we have developed a Pd^{II}-catalyzed C–H arylation for benzaldimines. A broad range of substrates are



Scheme 3. Dehydrogenative cross-coupling of benzaldimines.

compatible with this process, and to the best of our knowledge this represents the first example of a Pd^{II}-catalyzed direct C–H bond arylation on electron-deficient arenes that proceeds at room temperature. Using modified conditions we were also able to demonstrate a dehydrogenative C–H to C–H cross-coupling that even works on benzaldimines that display further electron-withdrawing functional groups. We are currently investigating aspects of the mechanistic pathway of these processes to develop additional novel reactions based on this room temperature C–H activation, and these studies will be reported in due course.

Received: September 24, 2010
Published online: December 22, 2010

Keywords: arylation · C–H functionalization · palladium catalysis · site-selective reactions · synthetic methods

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[19] The benzaldimine can be cleaved under a variety of acidic conditions, however we favored reaction with acetyl chloride in tetrahydrofuran or ether to afford the corresponding aldehyde in excellent yield.

