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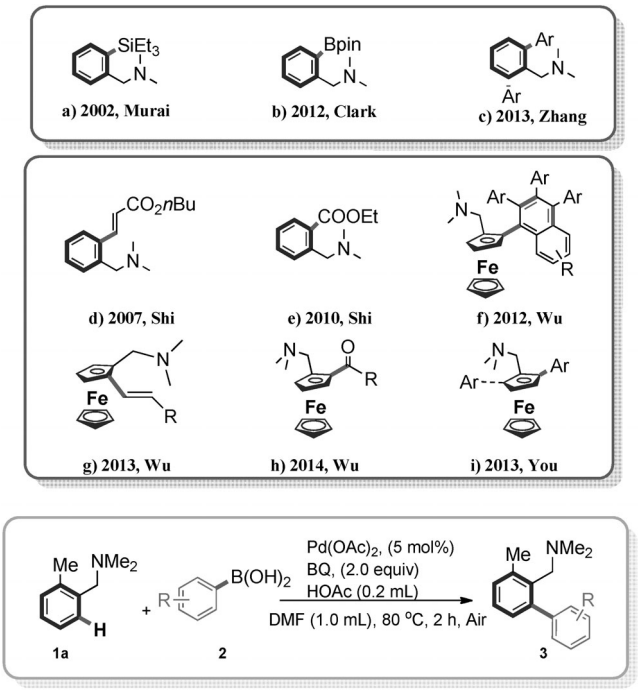
C–H Activation

Direct Oxidative Arylation of Aryl C–H Bonds with Aryl Boronic Acids via Pd Catalysis Directed by the *N,N*-Dimethylaminomethyl Group

Ji-Cheng Zhang,[a] Jiang-Ling Shi,[b] Bi-Qin Wang,[b] Ping Hu,[b] Ke-Qing Zhao,[b] and Zhang-Jie Shi*[a, c]

Abstract: Biaryl skeletons were directly constructed via palladium-catalyzed *ortho*-arylation of *N,N*-dimethyl benzylamine with aryl boronic acids with high efficiency and high regioselectivity under open-flask conditions. The *N,N*-dimethylaminomethyl group was first applied as a directing group in such an oxidative coupling. Various substrates proved to be efficient coupling partners, furnishing the corresponding *ortho*-monoarylated or -diarylated arenes in moderate to good yields under mild conditions.

C–H bond functionalization is the most sustainable, straightforward and attractive strategy to construct C–X bonds (X = C, O, N, B, Si, etc.) and has received significant attention in the past several decades.[1,2] Since biarylskeletons extensively exist in natural products, pharmaceuticals, agrochemicals, and functional materials,[3] transition-metal-catalyzed C–H arylation of aromatic compounds is an indispensable and desirable mode to construct such skeletones. In this research field, the directing strategy has been demonstrated to promote both efficiency and regioselectivity.[4] A variety of heteroatom-containing functional groups, such as benzamido,[5] pyridyl,[6] anilides,[7] amides,[8] imines,[9] nitriles,[10] benzylamines,[11] and carboxylic acids,[12] have been broadly utilized as *ortho*-metalation directing groups. *N,N*-Dimethylaminomethyl as a directing group in C–H activation has received increasing attention in recent years, attributing to its easy transformation to different and useful functional groups, such as a methyl,[13] aldehyde,[14] and alkene.[15] In 2002, Murai and co-workers reported for the first time Ru^0-catalyzed aromatic C–H bond silylation of benzylamine, proving the possibility of using the *N,N*-dimethylaminomethyl group as a directing group (Scheme 1 a).[16] Later on,



Scheme 1. Direct *ortho*-functionalizations of *N,N*-dimethylbenzylamines under different conditions.

Clark and co-workers reported iridium(I)-catalyzed C(sp^2)–H bond borylation (Scheme 1 b).[17] Different from such Ru^0 or Ir^I catalysis that probably occurs through C–H oxidative addition, we reported the Pd^{II}-catalyzed C–H bond oxidative alkenylation through electrophilic metalation (Scheme 1 d).[18] The key point for this reaction to take place smoothly is to tune the concentration of free amine by adjusting the amount of HOAc. We also expanded this system to the carbonylation reaction in 2009 (Scheme 1 e).[19] With this success, other oxidative cou-

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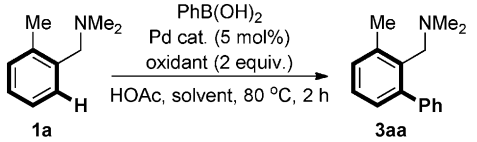
pling directed by the *N,N*-dimethylaminomethyl group has been well applied such as *ortho*-oxidative arylation of ferrocenes by Wu (Scheme 1 f)[20] and Zhang (Scheme 1 c)[24] Later on, this chemistry was further extended to the asymmetric version, although it only worked for ferrocene derivatives[21–23] (Scheme 1 g,h,i). Due to the lack of studies on oxidative coupling of simple *N,N*-dimethyl benzylamines with organometallic compounds, we intended to explore such a chemistry and herein present a Pd^{II}-catalyzed *ortho*-arylation of *N,N*-dimethylbenzylamines via oxidative arylation with arylboronic acids.

Screening of reaction conditions for *ortho* arylation of *N,N*-dimethyl-1-(*o*-tolyl)methanamines

In our previous work, we successfully controlled the reactivity and binding ability of *N,N*-dimethylbenzylamine by tuning the acidity of the reaction system.[18,19] Initially, we tested the use of $Pd(OAc)_2$/BQ (BQ = 1,4-benzoquinone) instead of $PdCl_2$/$Cu(OAc)_2$ in DMSO/HOAc, which resulted in a small amount of arylation product (Table 1, entry 2). Such a result encouraged us to further optimize this transformation. Based on the conventional Suzuki–Miyaura coupling, we envisaged that polar solvents may promote this reaction. In fact, we observed an increase in the GC yield from 12% to 53% with the replacement of 1,2-dichloroethane (DCE) to DMF (Table 1, entries 1–6). Luckily, when we reduced the reaction time to 2 h, the isolated yield was increased to 87% (Table 1, entry7), which may arise from the decomposition of the product under the reaction conditions. Different oxidants were further explored, and $tBuO_2tBu$, O_2, and $Cu(OAc)_2$ showed reduced yields compared with BQ (Table 1, entries 10–12). Further studies indicated that the palladium catalyst affected the efficiency, and $Pd(OAc)_2$ was found to work best (Table 1, entries 14–17). Undoubtedly, both catalyst and oxidant were essential for this reaction since no desired product was obtained in the absence of either one (Table 1, entries 9 and 13).

Table 1. *ortho*-Phenylation of **1a** under different conditions.[a]



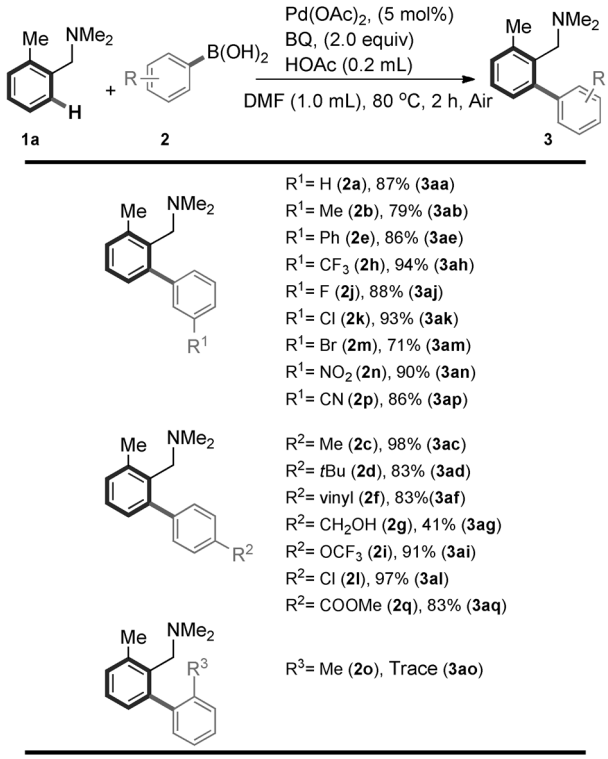
1a **3aa**

Entry[a]	Solvent	Oxidant	Pd cat.	Yield of **3aa**[b]
1[c]	Toluene	BQ	$Pd(OAc)_2$	–
2[c]	DCE	BQ	$Pd(OAc)_2$	12%
3[c]	C_2H_5OH	BQ	$Pd(OAc)_2$	36%
4[c]	HOAc	BQ	$Pd(OAc)_2$	67%
5[c,d]	DMF	BQ	$Pd(OAc)_2$	40%
6[c,e]	DMF	BQ	$Pd(OAc)_2$	53%
7[f]	DMF	BQ	$Pd(OAc)_2$	93% (87%)
8	DMSO	BQ	$Pd(OAc)_2$	90%
9[g]	DMF	–	$Pd(OAc)_2$	–
10	DMF	$tBuOOtBu$	$Pd(OAc)_2$	–
11	DMF	$Cu(OAc)_2$	$Pd(OAc)_2$	8%
12[h]	DMF	O_2	$Pd(OAc)_2$	<5%
13	DMF	BQ	–	–
14	DMF	BQ	$PdCl_2$	84%
15	DMF	BQ	$PdCl_2$(dppe)	–
16	DMF	BQ	$PdCl_2(PPh_3)_2$	11%
17[i]	DMF	BQ	$Pd_2(dba)_3$	37%

[a] Table 1 conditions: [a] **1a**, 0.2 mmol; $PhB(OH)_3$, 3 equiv; HOAc, 0.2 mL; solvent, 1.0 mL. [b] GC yield with *n*-decane as an internal standard. [c] 24 h. [d] without HOAc added. [e] HOAc, 1 equiv [f] isolated yield in parentheses. [g] under N_2. [h] O_2 balloon was used. [i] 2.5 mol% of $Pd_2(dba)_3$ was used.

Evaluation of various arylboronic acids

On the basis of the optimization studies, we evaluated the scope and generality of arylboric acid **2** by using *N,N*-dimethyl-1-(*o*-tolyl)methanamines **1a** as one partner (Scheme 2). We found that this transformation had good functional group tolerance with regard to arylboronic acids containing a substituent at the *meta*-position of the phenyl ring. Fluoride, chloride, bromide, trifluoromethyl, nitryl, cyano, methyl, or phenyl groups were well tolerated to give good to excellent yields ranging from 71% to 94% (**2a**, **2b**, **2e**, **2h**, **2j**, **2k**, **2m**, **2n**, **2p**, Scheme 2). In addition, substituents such as methyl, tertiary butyl, trifluoromethoxyl, chloride, ester, and vinyl at the *para*-position of arylboronic acids (**2c**, **2d**, **2f**, **2g**, **2i**, **2l**, **2q**, Scheme 2) could also be employed in this transformation to give the corresponding products in moderate to good yields. This reaction afforded excellent yields for electron-rich or elec-



Scheme 2. *ortho*-Phenylation of **1a** with different phenyl boronic acids.[a,b] Conditions: [a] **1a**, 0.2 mmol; **2**, 3 equiv; [b] isolated yield.

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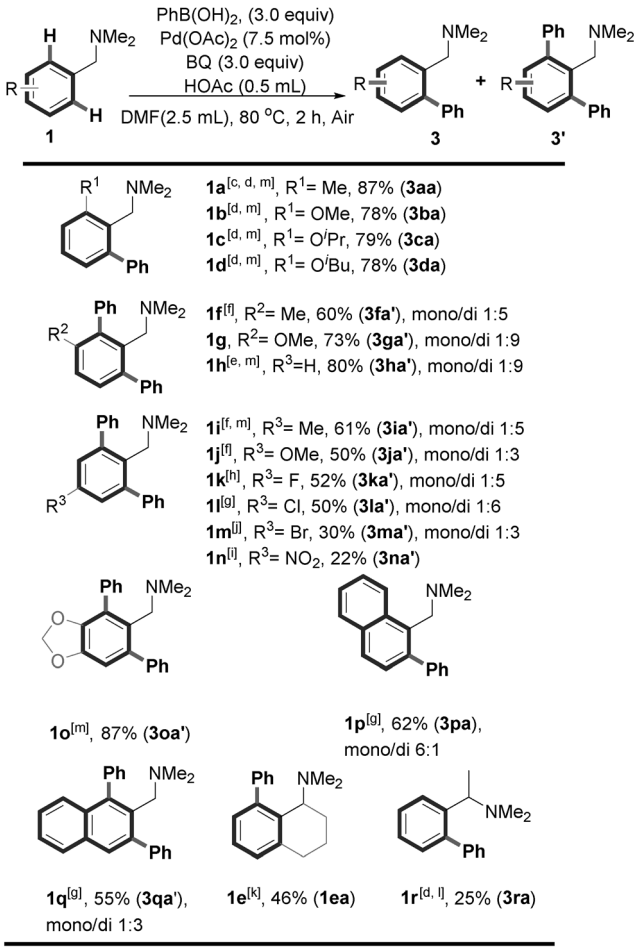
tron-deficient *para* or *meta* substituents under the standard conditions. Furthermore, we explored the steric effect of this reaction with *ortho*-substituted phenylboronic acid as substrates. We found that the transformation was sensitive to steric effects, for example, *ortho*-methyl substitution only gave a trace of desired product (**2o**, Scheme 2). Unfortunately, other heteroaryl and alkyl substituents on boronic acids were inactive and the starting material was recovered.

Screening of different substituted benzylamines

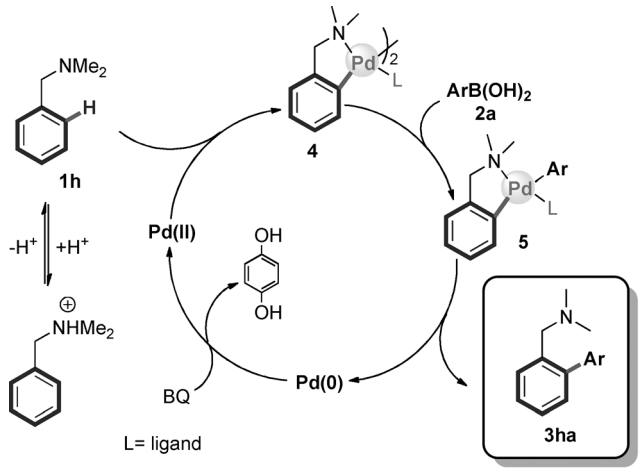
We next examined the reactivity of other benzylamines. As shown in Scheme 3, various benzylamines reacted smoothly with diarylation products **3** as the main product, if both *ortho*



Scheme 3. *ortho*-Phenylation of *N,N*-dimethyl benzylamines.[a] Conditions: [a] **1**, 0.5 mmol; [b] isolated yield; [c] **1a**, 0.2 mmol; HOAc, 0.2 mL; DMF, 1 mL; [d] 2.0 equiv. BQ; [e] 0.5 h; [f] 4 h; [g] 5 h; [h] 19 h; [i] 21 h; [j] 22 h; [k] 24 h; [l] 26 h; [m] 5 mol% $Pd(OAc)_2$.

positions were unoccupied. Generally, no matter of the location of substitution, electron-rich substituents showed higher reactivity, such as *o*-Me, *o*-OMe, *o*-*i*Pr, *o*-*i*Bu (Scheme 3, **1a–1d**, **1f–1j**, **1o**). Arenes containing an electron-withdrawing substituent, such as NO_2 or F, gave much lower yields of *ortho* diarylation product, even at a prolonged reaction time and increased temperature (Scheme 3, **1n**). This electronic effect provided additional proof to support the potential electrophilic palladation pathway for this transformation. It is worth noting that *p*-F, *p*-Cl, and *p*-Br also were well tolerated to form the corresponding *ortho*-diarylation products, thus providing opportunities for further transformations to make more complex molecules (Scheme 3, **1k**, **1l**, **1m**). The *ortho*-methyl substituted benzylamine produced exclusively the monoarylation product in a lower yield, owing to the steric effect (Scheme 3, **1r**). *N,N*-Dimethyl-8-phenyl-1,2,3,4-tetrahydronaphthalen-1-amine (Scheme 3, **1e**) was also obtained through such arylation in a good yield. Furthermore, 1- or 2-substituted naphthalene also gave mono- or biarylation products in moderate to good yield (Scheme 3, **1p**, **1q**).

On the basis of the above results and previous studies, the mechanism of the arylation reaction is proposed as shown in Scheme 4. As we have reported previously, the proper acidic



Scheme 4. Proposed mechanism.

conditions are critical for tuning the concentration of free tertiary amine. Chelation-assisted *ortho* palladation of free tertiary amine **2** by the Pd^{II} cation formed the key five-membered palladacycle **5**. Transmetalation with arylboronic acids and subsequent reductive elimination released the target molecules. The produced Pd^0 was then reoxidized by BQ to Pd^{II} and entered another catalytic cycle.

In summary, we developed a Pd^{II}-catalyzed directed *ortho*-arylation of *N,N*-dimethylbenzylamine derivatives via selective aryl C–H activation to construct biaryl skeletons. These transformations also offer an efficient method to construct C–C bonds in organic synthesis under air and mild conditions. Resulting from further easy transformation of the amine group, *ortho*-functionalized toluene and its derivatives could be synthesized from other simple transformations as reported.

Experimental Section

Physical Methods. ^1H NMR (200, 300, or 400 MHz) and ^{13}C NMR (50, 75, or 100 MHz) spectra were registered on Varian 300M spectrometers with $CDCl_3$ as solvent and tetramethylsilane (TMS) as an

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internal standard. Chemical shifts were reported in units (ppm) by assigning the TMS resonance in the ^1H spectrum as 0.00 ppm and the $CDCl_3$ resonance in the ^{13}C spectrum as 77.0 ppm. All coupling constants (*J* values) are reported in Hertz (Hz). Column chromatography was performed on silica gel 200–300 mesh. IR, GC, and MS data were obtained by the state-authorized Analytical Center at Peking University.

N,N-Dimethylbenzylamines **1** were synthesized according to the reported methods.[25]

General procedure for the arylation of *N,N*-dimethylbenzylamines with arylboronic acids.

$Pd(OAc)_2$ (5.6 mg, 0.05 mmol), BQ (162.3 mg, 1.5 mmol), and arylboronic acid (2.0 mmol) were added into a Schlenk tube. Then DMF(2.5 mL), HOAc (0.5 mL), and *N,N*-dimethylbenzylamine **1** (0.5 mmol) were added. The mixture was stirred at 80 °C in an oil bath for 2 h under air. After the reaction was finished, the mixture was cooled, neutralized to slightly alkaline condition with a saturated Na_2CO_3 solution (5 mL), and stirred for 10 min. Then the suspension was filtered through a Celite pad and extracted with Et_2O for three times. The combined organic layer was washed with saturated NaCl (3×30 mL) and dried over anhydrous Na_2SO_4.The desired products **3** were obtained in the corresponding yields after purification by flash chromatography on silica gel (petroleum ether (PE)/EtOAc/NEt_3 10:1:0.5).

The characterization data of compounds **3** are shown in the Supporting Information.

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Keywords: biaryls · boronic acid · C–H activation · *N,N*-dimethylbenzylamine · oxidative coupling

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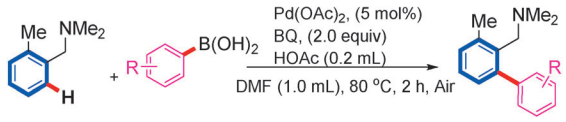

Getting the skeleton right: Biaryl skeletons were directly constructed via palladium-catalyzed *ortho*-arylation of *N*,*N*-dimethyl benzylamine with aryl boronic acids under open-flask conditions. The *N*,*N*-dimethylaminomethyl group was first applied as a directing group in such an oxidative coupling. Various substrates proved to be efficient coupling partners, furnishing the corresponding *ortho*-monoarylated or -diarylated arenes in moderate to good yields under mild conditions.

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