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Palladium-Catalyzed Alkylation of sp² and sp³ C−H Bonds with Methylboroxine and Alkylboronic Acids: Two Distinct C−H Activation Pathways

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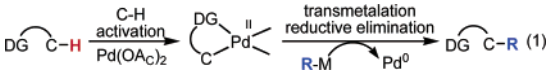
The development of C−H activation/C−C bond forming reactions catalyzed by transition metals has received much attention recently.[1] A wide range of efficient Ru- and Rh-catalyzed alkylations and arylations of aryl C−H bonds have been achieved with olefins or aryl organometallic reagents.[2,3] Pd-catalyzed alkenylation of aryl C−H bonds via Pd^{II}/Pd^{0} catalysis has been reported.[4] Significant results have also been obtained using $Ar_2I^+X^-$ or ArX as the arylating reagents for sp² [5a,b] and sp³ C−H bonds[5c−e] involving Pd^{II}/Pd^{IV} catalysis. An alternative strategy involving C−H activation by an intramolecular ArPdX moiety has been developed.[6] In this context, an impressive example of arylation of sp³ C−H bonds via Suzuki−Miyaura coupling has been achieved.[7]

We have recently initiated efforts to develop protocols for the coupling of C−H bonds with organometallic reagents assisted by a directing group (DG) (eq 1), which provided the first example for Pd-catalyzed alkylation of sp² C−H bonds.[8] In this alkylation reaction, the organotin reagents were added batch-wise to minimize the undesired homocoupling reaction, which constitutes a practical drawback. The toxicity of organotin reagents also limits the applications. Furthermore, catalytic coupling of sp³ C−H bonds with organotin reagents could not be achieved. Herein, we describe a one-pot procedure for the coupling of sp² and sp³ C−H bonds with nontoxic and readily available methylboroxine and alkylboronic acids using pyridine (Py) as a directing group.

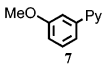
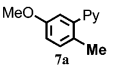
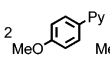
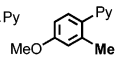
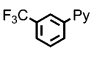
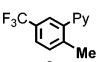
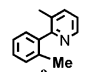
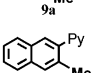
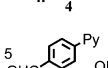
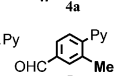
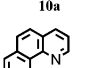
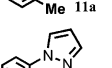


The remarkable progress made in Pd-catalyzed alkyl−alkyl Suzuki cross-coupling reactions with boronic acids[9] indicates that a C−H activation/C−C coupling sequence with organoboron reagents outlined in eq 1 is plausible in principle.[10] However, the execution of the sequential steps in a catalytic cycle represents a formidable challenge for the following reasons: (1) Pd^{II}-catalyzed homocoupling[11a] of organometallic reagents is faster than C−H activation; (2) the palladacycle formed from the C−H activation step catalyzes homocoupling of the organometallic reagents[11b] if the subsequent transmetalation and reductive elimination is not sufficiently fast. Our strategy is to identify promoters for each step to overcome the undesired homocoupling of the organoboron reagents.

Screening of coupling partners and reaction conditions using 2-phenylpyridine **1** as the substrate established that the combination of $Pd(OAc)_2$, methylboroxine (see eq 4), $Cu(OAc)_2$, and benzoquinone provided a promising solution to this challenging problem (Table 1). Functional groups attached to the aryl rings, such as MeO, vinyl, and CF_3, were tolerated (entries 2, 4, and 6), while a CHO group decreased the yield (entry 5). Methylated product **12a** was also isolated in 36% yield using pyrazole as a directing group (entry 12).

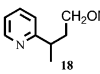
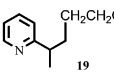
Importantly, the coupling of sp³ C−H bonds with methylboroxine was also achieved by running the reaction in acetic acid/O_2 (1 atm) rather than CH_2Cl_2/air (Table 2). Ether, alcohol, and ester substrates (entries 6−8) are compatible with this reaction. It is worth noting that alkylation of the methylene group was also shown to be possible (entry 9), albeit in lower yield. Unfortunately, the coupling of either substrate **1** or **13** with ethyl- or butylboroxines as coupling partners failed to give any desired alkylation products under various conditions.

Table 1. Methylation of sp² C−H Bonds with Methylboroxine[a]

entry	substrate	product	yield(%)	entry	substrate	product	yield(%)
1			72[b]	7			82
2			66	8			65
3			64	9			84
4			62	10			78
5			38	11			93
6			50	12			38

[a] 10 mol % of $Pd(OAc)_2$, 1 equiv of benzoquinone, 1 equiv of $Cu(OAc)_2$, 2 equiv of methylboroxine, 100 °C, 24 h, CH_2Cl_2, air. [b] 10% dimethylated product was isolated.

Table 2. Methylation of sp³ C−H Bonds with Methylboroxine[a]

entry	substrate	product	yield(%)	entry	substrate	product	yield(%)
1		 	79 / 11	5			60
2		 	50 / 20	6			50
3			33	7			51
4			70	8			70
				9			22
				10			80

[a] 10 mol % of $Pd(OAc)_2$, 2 equiv of benzoquinone, 2 equiv of $Cu(OAc)_2$, 2 equiv of methylboroxine, 100 °C, 24 h, HOAc, O_2.

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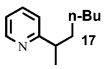
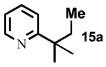
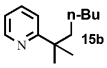
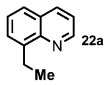
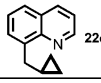
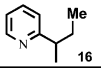
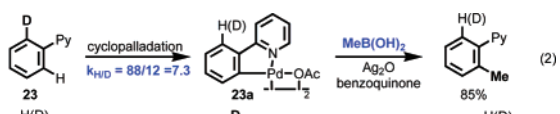
Table 3. Alkylation of C−H Bonds with Boronic Acids[a]

entry	RB(OH)$_2$	product	yield(%)	entry	RB(OH)$_2$	product	yield(%)
1	Me-B(OH)$_2$	 **1a**	67	8	n-Bu-B(OH)$_2$	 **17**	55
2	Et-B(OH)$_2$	 **1b**	64	9	Me-B(OH)$_2$	 **15a**	40
3	n-Bu-B(OH)$_2$	 **1c**	75	10	n-Bu-B(OH)$_2$	 **15b**	43
4	n-Hex-B(OH)$_2$	 **1d**	51	11	Me-B(OH)$_2$	 **22a**	48
5	Ph(CH$_2$)$_2$B(OH)$_2$	 **1e**	53	12	n-Bu-B(OH)$_2$	 **22b**	56
6		 **1f**	52	13		 **22c**	35
7	Me-B(OH)$_2$	 **16**	48				

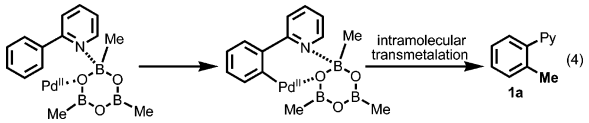
[a] 10 mol % of Pd(OAc)$_2$, 1 equiv of Ag$_2$O, 0.5 equiv of benzoquinone, 3 equiv of boronic acid, 100 °C, 6 h, *tert*-amyl alcohol, air.

To solve this problem, we turned to boronic acids. The reaction of **1** with ethylboronic acids under the conditions described in Table 1 resulted in full recovery of the starting material. The stoichiometric reaction of the dimeric palladacycle prepared from **1** with ethylboronic acid gives **1b** in less than 5% yield, indicating that transmetalation is problematic. Screening a wide range of bases, oxidants, and solvents established that the alkylation reaction proceeds smoothly in the presence of Ag_2O (or Ag_2CO_3) and benzoquinone using *t*-amyl alcohol as the solvent (see Supporting Information). Ag_2O plays a dual role as an efficient promoter for the transmetalation[12] and co-oxidant[13] with benzoquinone. Benzoquinone is crucial for the reductive elimination step.[8] We were pleased to find that this new protocol allowed the coupling of both sp^2 and sp^3 C−H bonds with other boronic acids, including cyclopropylboronic acid, thereby substantially expanding the scope of C−H activation/C−C coupling reactions (Table 3). It should be noted that the formation of dialkylated products was not observed in entries 1−10. Interestingly, while Cu(OAc)$_2$ is an efficient oxidant with methylboroxine, the coupling reactions with boronic acids were severely suppressed.[14]

Mechanistic observations were made with methylboroxine and MeB(OH)$_2$. First, the intramolecular kinetic isotope effects ($k_{H/D}$) in the cyclopalladation of **23** are 7.3. Second, the dimeric palladacycle **23a** reacts with MeB(OH)$_2$ under the conditions in Table 3 to give the methylated product (eq 2), but does not react with methylboroxine under the conditions in Table 1. Third, the intramolecular kinetic isotope effects ($k_{H/D}$) in the methylation of **23** with MeB(OH)$_2$ and methylboroxine are 6.7 and 3.0, respectively (eq 3), with the former being approximately the same as the isotope effects observed for the cyclopalladation step (within the error of NMR measurement). Fourth, the intermolecular kinetic isotope effects with MeB(OH)$_2$ and methylboroxine are 4.0 and 3.5, respectively, suggesting that C−H cleavage is the rate-limiting step in both reactions (see Supporting Information).



On the basis of these observations, the coupling reaction with boronic acids most likely involves a conventional cyclopalladation process (eq 2). For the reaction with methylboroxine, we propose that the methylboroxine coordinates with the pyridyl group first, and the chelation of the oxygen atom in the methylboroxine with Pd(OAc)$_2$ directs the C−H cleavage (eq 4).[15] The subsequent intramolecular transmetalation is highly efficient, not requiring a promoter (eq 4).



In summary, we have developed the first protocol for Pd^{II}-catalyzed alkylations of sp^2 and sp^3 C−H bonds with either methylboroxine or alkylboronic acids. Mechanistic investigations alluded to an unusual methylboroxine-assisted C−H activation pathway. We are currently exploring this new C−H activation pathway.

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Supporting Information Available: Experimental procedure and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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