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Palladium-Catalyzed Alkylation of Aryl C−H Bonds with sp^3 Organotin Reagents Using Benzoquinone as a Crucial Promoter

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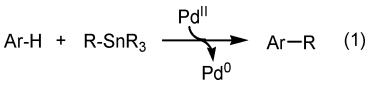
The direct coupling of C−H bonds with organometallic reagents is an attractive C−C bond-forming method that compliments the widely used cross-coupling reactions of Ar−X bonds (X = halide, OTf, OMs, $OP(O)(OR)_2$, OR, SR, and N_2BF_4) (eq 1).[1] Pyridine- and carbonyl-directed arylation of *o*-aryl C−H bonds using $RhCl(PPh_3)_3/Ph_4Sn$ and $RuH_2(CO)(PPh_3)_3$/arylboronates, respectively, illustrate the feasibility of this approach.[2] Sames' $Pd(OAc)_2$-catalyzed arylation of sp^3 C−H bonds in a bisdentate chelating substrate using $Ph_2Si(OH)Me$ as a coupling partner represents an important step forward in developing this strategy.[3]

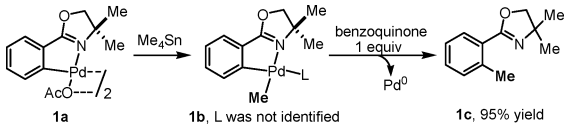
In contrast to the remarkable progress in the Pd^0-catalyzed cross-coupling reactions of aryl or alkyl halides with organometallic reagents,[4] the development of Pd^{II}-catalyzed coupling of C−H bonds with organotin still faces the following two challenges:[5−7] (a) the Pd^{II} species required for C−H activation causes rapid homo-coupling of the organotin reagent,[8] (b) the C−H activation reaction conditions are often not compatible with the transmetalation step or the reoxidation of the Pd^0 in the catalytic cycle (eq 1). In this communication, we disclose the first protocol for Pd^{II}−catalyzed alkylations of aryl C−H bonds with a variety of primary-alkyl tin regents using a combination of directed C−H activation and batch-wise addition of the organotin reagent.



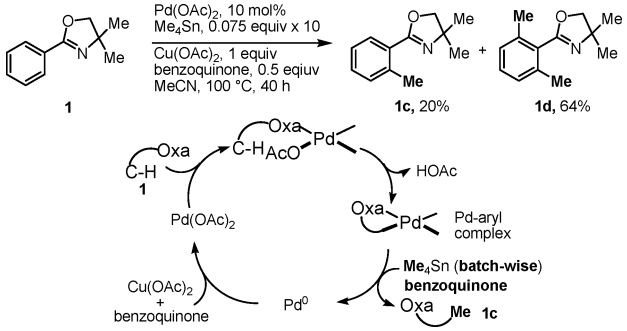
Recently, we reported the palladium-catalyzed 2-oxazoline directed stereoselective iodination and oxygenation of unactivated C−H bonds.[9] Inspired by the early observation of a stoichiometric phenylation reaction of a tri-*o*-tolyphosphane-bound palladium complex with Me_3SnPh by Hartwig,[10] we decided to explore $Pd(OAc)_2$-catalyzed coupling of aryl C−H bonds with sp^3 organotin reagents. We envisioned that the undesired homo-coupling of tin reagents mediated by Pd^{II} could be avoided by adding the organotin coupling partner batch-wise if C−H cleavage and reoxidation of Pd^0 is sufficiently fast. To establish suitable conditions that are compatible with each individual step, oxazoline substrate **1** was stirred with 1 equiv of $Pd(OAc)_2$ in CH_2Cl_2 at 100 °C for 3 h (in a tube sealed with a Teflon cap) to afford the previously reported dimeric complex **1a** in 90% yield.[11] Treatment of complex **1a** with 0.75 equiv of Me_4Sn under the same conditions gives the expected methylation product **1b** in 20% yield (Scheme 1). The use of 1 equiv of benzoquinone was found to improve the yield to 95%. *Monitoring the formation and reductive elimination of* ***1b*** *by* ^{1}*H NMR revealed that benzoquinone promotes the reductive elimination step* (see Supporting Information).[12]

We next sought to identify a suitable oxidant to reoxidize Pd^0 to Pd^{II} to close the catalytic cycle under the same conditions. Reactions were carried out by stirring oxazoline substrates with 10 mol % $Pd(OAc)_2$ in the presence of various oxidants, and 0.075 equiv of Me_4Sn was added every 4 h to allow the C−H activation and the reoxidation step to complete. After 10 batches of Me_4Sn (0.75 equiv in total) were added, the reaction mixture was subjected to a workup procedure and analyzed by ^{1}H NMR.

Scheme 1. Benzoquinone-Promoted Stoichiometric Coupling



Scheme 2. Catalytic Methylation of Aryl C−H Bonds

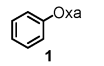
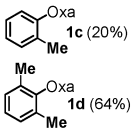
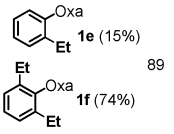
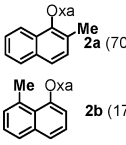
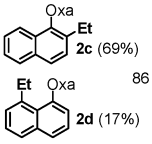
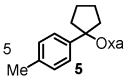
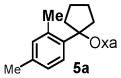
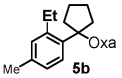


Various protocols for the reoxidation of Pd^0 to Pd^{II} in catalysis have been developed;[13] however, most of the conditions involving the use of acetic acid, DMF, and DMSO are not compatible with either the C−H activation or the transmetalation step in our experiments. It was decided to focus on the most commonly used oxidation system $Cu(OAc)_2$/air/benzoquinone. We found that catalytic alkylation of **1** can be achieved by using 1 equiv of $Cu(OAc)_2$ and 0.5 equiv of benzoquinone in CH_2Cl_2 under air to afford mainly the dialkylated product **1d** (Scheme 2). Further screening of solvents then established that MeCN is the best solvent for this catalytic reaction.

As previously pointed out by Murai and co-workers, directed C−H activation of aryl C−H bonds are favored by a σ-chelating heteroatom that is conjugated to the aryl rings as in **1** and **2**, and the non-π-conjugated chelation-assisted *catalytic* C−H activation/C−C bond-forming reactions are still relatively rare.[14] We were pleased to find that the coupling reactions of 2-benzyloxazolines **3**−**7** containing one carbon atom between the aryl ring and the σ-chelating group proceeded smoothly to give the desired methylation products in the presence of 1 equiv of benzoquinone (Table 1). In contrast to **1** and **2**, the reactions of **3**−**7** give the mono-methylation products **3a**−**7a** exclusively. *Importantly, our experiments showed that the presence of 1 equiv of benzoquinone is essential for C−H activation to occur with this type of substrate (****3****−****7****) (see Supporting Information). Since the formation of a cyclic trinuclear mixed metal acetate* $[Cu_2Pd(OAc)_6]$ *was previously reported,*[15] *it is possible that benzoquinone prevented the formation of this complex which is not reactive for substrates* ***3***−***7****.*

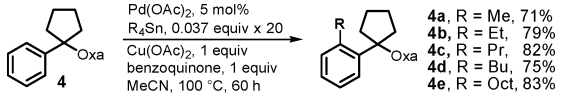
10.1021/ja0570943 CCC: $33.50

Table 1. Pd-catalyzed Alkylation of Aryl C−H Bonds[a]

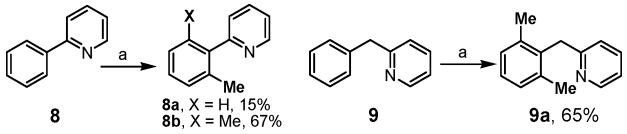
Entry	Substrate	Methylation product	Yield%	Entry	Product	Yield%
1		 **1c** (20%) **1d** (64%)	84	8	 **1e** (15%) **1f** (74%)	89
2		 **2a** (70%) **2b** (17%)	87	9	 **2c** (69%) **2d** (17%)	86
3			62	10		60
4			88	11		84
5			76	12		90
6			78	13		85
7			86	14		78

[a] Oxa = 4,4-dimethyloxazoline-2-, $Pd(OAc)_2$ (10 mol %), organotin reagents (0.075 equiv × 10), $Cu(OAc)_2$ (1 equiv), benzoquinone, 1 equiv, MeCN, 100 °C, 40 h.

Scheme 3. Alkylation Using Various Primary Alkyl Tin Reagents



Scheme 4. Methylation Assisted by a Pyridine Directing Group[a]



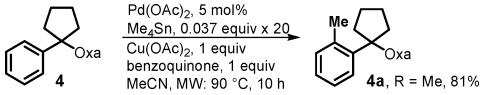
[a] Reaction conditions: $Pd(OAc)_2$ (5 mol %), Me_4Sn (0.037 equiv × 20), $Cu(OAc)_2$ (1 equiv), benzoquinone (1 equiv), MeCN, 100 °C, 40 h.

We further tested Et_4Sn as a coupling partner, and satisfactory yields were obtained, suggesting that the reductive elimination is sufficiently faster than the undesired β-hydride elimination in the presence of benzoquinone (Table 1, entries 8−14). By adding the organotin reagents in 20 batches every 3 h, alkylation reactions proceed smoothly in the presence of 5 mol % of $Pd(OAc)_2$. A variety of primary alkyl tin reagents were tested using these new conditions, and the alkylated products were obtained in good yields consistently (Scheme 3).[16]

These results encouraged us to extend our protocol to the extensively investigated pyridine-directed C−H activation/C−C bond-forming reactions of substrate **8** (Scheme 4).[2,6c] The advantage is again demonstrated by coupling substrate **9** containing a pyridine ring that is not conjugated to the aryl ring.

The necessity for the addition of the tin reagent in batches results in long reaction time, especially when Pd-loading is low. In principle this could be circumvented by shortening the reaction time of the C−H activation and reoxidation steps since the transmetalation is a fast step. By using the microwave conditions, the reaction can be carried out by adding the organotin every 0.5 h, thereby reducing the overall reaction time to 10 h using 5 mol % $Pd(OAc)_2$ (Scheme 5).

Scheme 5. Methylation Assisted by Microwave Irradiation



In summary, we have developed a protocol for Pd^{II}−catalyzed alkylations of aryl C−H bonds. The combination of directed C−H activation, batch-wise addition of tetraalkyltin reagents, and rate enhancement by benzoquinone and microwave irradiation provides a promising strategy for the development of C−C bond-forming reactions via coupling of C−H bonds with organometallic reagents. Future work will concentrate on the coupling of sp^3 C−H bonds and other environmentally benign organometallic reagents.

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Supporting Information Available: Experimental procedures 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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