

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

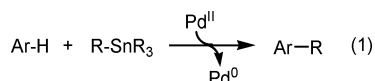
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The direct coupling of C–H bonds with organometallic reagents is an attractive C–C bond-forming method that complements the widely used cross-coupling reactions of Ar–X bonds (X = halide, OTf, OMs, OP(O)(OR)₂, OR, SR, and N₂BF₄) (eq 1).¹ Pyridine- and carbonyl-directed arylation of *o*-aryl C–H bonds using RhCl(PPh₃)₃/Ph₄Sn and RuH₂(CO)(PPh₃)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 Ph₂Si(OH)Me as a coupling partner represents an important step forward in developing this strategy.³

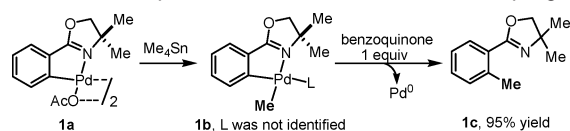
In contrast to the remarkable progress in the Pd⁰-catalyzed cross-coupling reactions of aryl or alkyl halides with organometallic reagents,⁴ the development of Pd^{II}-catalyzed coupling of C–H bonds with organotin still faces the following two challenges:^{5–7} (a) the Pd^{II} species required for C–H 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 Pd⁰ 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 reagents using a combination of directed C–H activation and batch-wise addition of the organotin reagent.



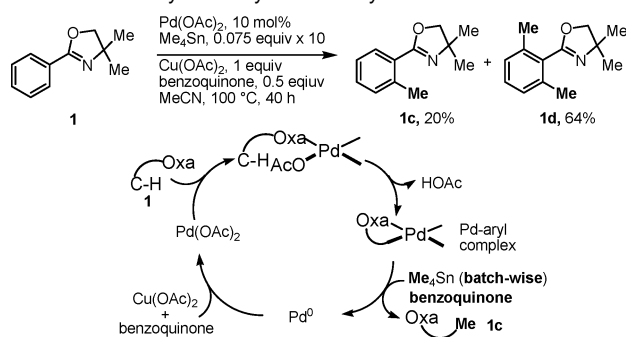
Recently, we reported the palladium-catalyzed 2-oxazoline directed stereoselective iodination and oxygenation of unactivated C–H bonds.⁹ Inspired by the early observation of a stoichiometric phenylation reaction of a tri-*o*-tolylphosphane-bound palladium complex with Me₃SnPh by Hartwig,¹⁰ we decided 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 Pd⁰ 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 CH₂Cl₂ 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 Me₄Sn 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 ¹H NMR revealed that benzoquinone promotes the reductive elimination step* (see Supporting Information).¹²

We next sought to identify a suitable oxidant to reoxidize Pd⁰ 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 Me₄Sn was added every 4 h to allow the C–H activation

Scheme 1. Benzoquinone-Promoted Stoichiometric Coupling



Scheme 2. Catalytic Methylation of Aryl C–H Bonds



and the reoxidation step to complete. After 10 batches of Me₄Sn (0.75 equiv in total) were added, the reaction mixture was subjected to a workup procedure and analyzed by ¹H NMR.

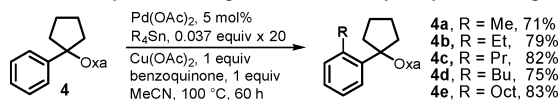
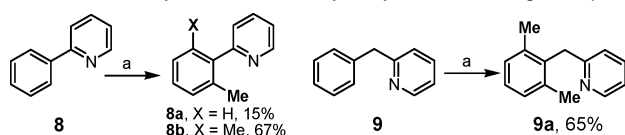
Various protocols for the reoxidation of Pd⁰ to Pd^{II} in catalysis have been developed;¹³ however, most of the conditions involving the use of acetic acid, DMF, and DMSO are not compatible with either the C–H activation or the transmetalation step in our experiments. It was decided to focus on the 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 CH₂Cl₂ 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-benzylloxazolines **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 [Cu₂Pd(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.*

Table 1. Pd-catalyzed Alkylation of Aryl C–H Bonds^a

Entry	Substrate	Methylation product	Yield%	Entry	Product	Yield%
1			84	8		89
			(64%)			(74%)
2			87	9		86
			(17%)			(17%)
3			62	10		60
4			88	11		84
5			76	12		90
6			78	13		85
7			86	14		78

^a Oxa = 4,4-dimethyl-2-oxazoline-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.

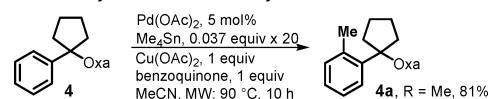
Scheme 3. Alkylation Using Various Primary Alkyl Tin Reagents**Scheme 4.** Methylation Assisted by a Pyridine Directing Group^a

^a Reaction conditions: Pd(OAc)₂ (5 mol %), Me₄Sn (0.037 equiv × 20), Cu(OAc)₂ (1 equiv), benzoquinone (1 equiv), MeCN, 100 °C, 40 h.

We further tested Et₄Sn 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

Scheme 5. Methylation Assisted by Microwave Irradiation

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).

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 sp³ 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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- Fifteen percent of the alkylated product was obtained when substrate **4** and (*i*-Pr)₄Sn were used.

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