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# High-Yielding Palladium-Catalyzed Intramolecular Alkane Arylation: Reaction Development and Mechanistic Studies

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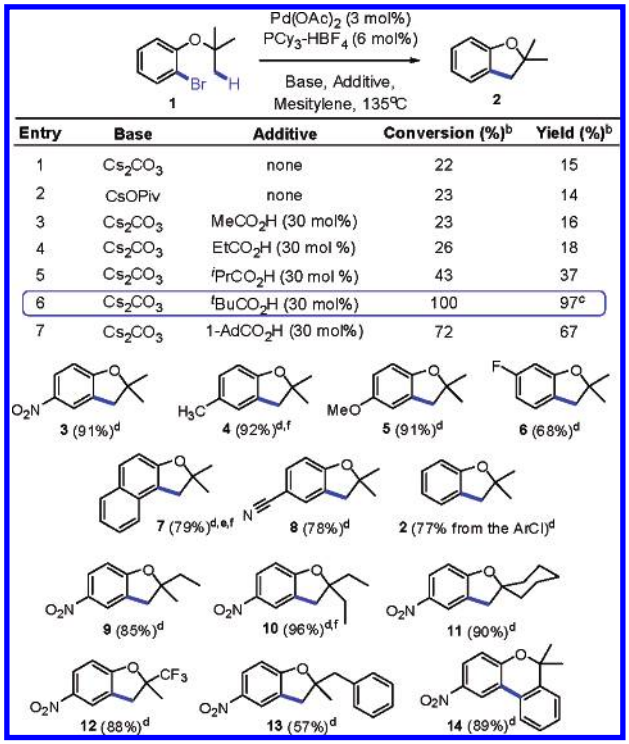
Catalytic hydrocarbon functionalization has undergone rapid growth over the past decade, especially through the application of transition-metal catalysis.[1] In the context of C−C bond formation, reactions occurring at $sp^2$ C−H bonds are more prevalent and widespread than those at $sp^3$ C−H bonds.[1−3] Transformations at $sp^2$ C−H bonds benefit from catalyst interactions with the $\pi$-electrons that enable catalyst−substrate binding and C−H bond cleavage via electrophilic aromatic metalation,[4] concerted metalation−deprotonation[5] or other pathways.[6] Since this type of interaction cannot occur with unactivated $sp^3$ centers, they must rely on other, less clearly defined, substrate−catalyst interactions.[7] Furthermore, while the growing mechanistic understanding of reactions at $sp^2$ bonds can inspire methodological development, the relative lack of similar insight for C−C bond forming processes at corresponding $sp^3$ C−H bonds makes a rational approach to this class of reaction challenging.[7,8]

Herein, we describe the development of Pd-catalyzed alkylation reactions of aryl bromides and chlorides including rare examples of $sp^3$ C−H bond cleavage/functionalization occurring in near quantitative yield. These reactions provide a novel and complementary route to medicinally important 2,2-dialkyldihydrobenzofurans.[9] Mechanistic studies point to the involvement of a concerted, inner-sphere palladation−deprotonation pathway enabled by the presence of three-center agostic interactions at the transition state. This mechanism accurately predicts the preference for reaction at methyl groups over other secondary $sp^3$ C−H bonds at the same proximity, a feature which has also been observed in other classes of alkane functionalization.[10]

Following a similar strategy to that previously employed in the development of benzene arylation reactions,[11] a variety of bases were evaluated in the presence and absence of catalytic quantities of carboxylic acid additives. These studies led to the finding that the reaction of **1** in the presence of $Pd(OAc)_2$ (3 mol %) and $PCy_3 \cdot HBF_4$ (6 mol %) in conjunction with $Cs_2CO_3$ (1.1 equiv) and 2,2-dimethylpropionic acid (pivalic acid, 30 mol %) in mesitylene at 135 °C results in complete and clean conversion to **2** which can be isolated in 97% yield. The superior reactivity associated with the combined use of an insoluble carbonate base and a catalytic quantity of soluble carboxylate base (in this case via deprotonation of the pivalic acid in situ) is illustrated by the lower conversions and yields that are obtained when either component is used as the stoichiometric base alone (entry 6 vs entries 1 and 2). Additional examples are included in Scheme 1. When different aliphatic groups are present that may undergo reaction, high selectivity is observed for reaction at a methyl substituent over a secondary carbon atom as illustrated by the clean formation of **9**, **10**, **11**, and **13**. Trifluoromethyl substituents are inert under the reaction conditions enabling the preparation of $CF_3$ substituted dihydrobenzofuran compounds such as **12** which would be difficult to prepare via the more commonly employed cationic cyclization routes to this class of molecule.[12] Ring closure at a methyl group may still compete with reaction at an aromatic substituent so long as a six-membered ring closure is not accessible as illustrated in the formation of **13** and **14**. The preferential reaction at the aromatic ring over the methyl substituent in the formation of **14** illustrates the greater ease with which the reaction at $sp^2$ positions can occur. The diminished yield of **13** is due to a competitive reaction at the aromatic ring to close the seven-membered ring.[13] An aryl chloride may also be employed as in the formation of **2**. In this case, a slightly lower yield is observed compared to the aryl bromide (77% versus 97%) as a consequence of incomplete conversion.

***Scheme 1.*** Palladium-Catalyzed Alkane Arylation[a]




| Entry | Base | Additive | Conversion (%)[b] | Yield (%)[b] |
|---|---|---|---|---|
| 1 | $Cs_2CO_3$ | none | 22 | 15 |
| 2 | CsOPiv | none | 23 | 14 |
| 3 | $Cs_2CO_3$ | $MeCO_2H$ (30 mol%) | 23 | 16 |
| 4 | $Cs_2CO_3$ | $EtCO_2H$ (30 mol %) | 26 | 18 |
| 5 | $Cs_2CO_3$ | $^iPrCO_2H$ (30 mol %) | 43 | 37 |
| 6 | $Cs_2CO_3$ | $^tBuCO_2H$ (30 mol%) | 100 | 97[c] |
| 7 | $Cs_2CO_3$ | 1-$AdCO_2H$ (30 mol%) | 72 | 67 |

[a] Conditions: $Pd(OAc)_2$ (3 mol %), $PCy_3 \cdot HBF_4$ (6 mol %), the base (1.1 equiv) and 2,2-dimethylpropionic acid (30 mol % if added) and the aryl halide were heated to 135 °C in mesitylene 10 to 15 h (overnight). [b] Determined by GC−MS. [c] Isolated yield. [d] Isolated yield using the conditions from entry 6 with 5 mol % catalyst. [e] Performed at 150 °C. [f] Isolated with 4−6% of the hydrodebromination byproduct.

To further understand the important reaction parameters leading to high yield and selectivity, the mechanism of C−H bond cleavage was examined by density functional theory (DFT) calculations.[13] Both $Pd^{II}$ and $Pd^{IV}$ pathways were explored. The $Pd^{IV}$ pathway involving an oxidative insertion into the methyl C−H bond was ruled out based on the high energy of the $Pd^{IV}$ alkyl−hydride intermediate (Figure S1, $\Delta G_{298K} = 47.7$ kcal/mol) calculated at the B3LYP/DZVP level of theory, and because re-optimization of this intermediate at the B3LYP/TZVP level fails to locate the corresponding energy minimum. On the other hand, a transition state (TS) corresponding to a concerted palladation−deprotonation pathway (Figure 1) was found to have a $\Delta G^{\ddagger}_{298K}$ of 29.4 kcal/mol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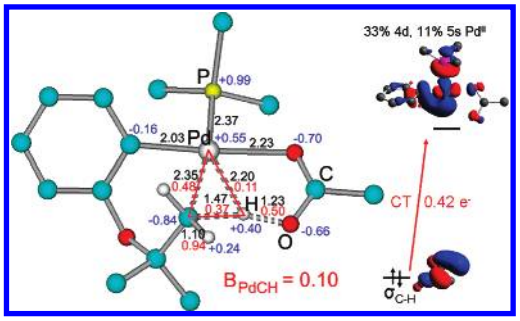
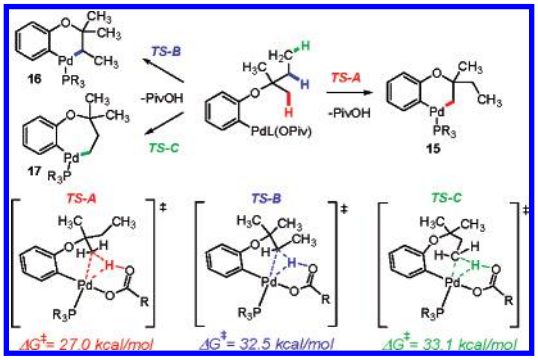



***Figure 1.*** Calculated TS for concerted palladation−deprotonation. Select H atoms have been removed for clarity. Relevant two- and three-center bond orders (red), distances (Å) (black), and NPA-derived atomic charges (blue) are shown. The three-center covalent interaction and charge transferred (CT) from the C−H bond to the metal-based acceptor orbital are shown at right.[13]

***Scheme 2.*** Mechanistic Rationale for Site Selectivity




in the gas phase and 27.7 kcal/mol in benzene (Supporting Information, Table S1). At the TS, agostic, three-center two-electron interactions occur[14] between the C−H $\sigma$ bond and the $Pd^{II}$ atom (the three-center bond order $B_{PdCH}$[15] is 0.10) resulting in a significant weakening of the C−H bond (the Mayer bond order[16] for the C−H bond is 0.37 vs 0.94 for the nonbroken C−H bond). Thus, the energetic cost of C−H bond cleavage is compensated for by the Pd−C and Pd−H interactions that involve electron donation (~0.42 $e^-$) from both the C−H bond to the $Pd^{II}$ atom, and the simultaneous formation of the O−H bond (Figures 1, S2−S4).

The computed value of the deuterium kinetic isotope effect ($k_H/k_D$) via this pathway was found to be 3.6 at 115 °C (Table S1). Considering that this calculation does not include any rate enhancement due to quantum mechanical tunneling,[17] the calculated $k_H/k_D$ is consistent with the experimentally determined value of 5.4 ± 0.3. Furthermore, the reaction barrier at a secondary carbon to give intermediate **16** (-$\underline{CH_2}CH_3$) was found to be 5.5 kcal $mol^{-1}$ higher than the $\Delta G^{\ddagger}$ for reaction at the -$CH_3$ group to give **15**, correlating very well with the experimentally observed selectivity for reaction at methyl groups (Scheme 2, Table S1, Figure S2). Similarly, the reaction at more remote positions, as in the formation of **17**, is also less kinetically and thermodynamically favored (Table S1).

These results point to new opportunities in the catalytic formation of C−C bonds that are less reliant on stoichiometric and wasteful substrate pre-activation, particularly with palladium(0)/(II) catalysis. The mechanistic insights regarding the intimate role of the base and the 3-center agostic interactions at the $sp^3$ C−H bond cleaving TS should also facilitate the development of new catalysts and transformations.

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**Supporting Information Available:** Experimental procedures and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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