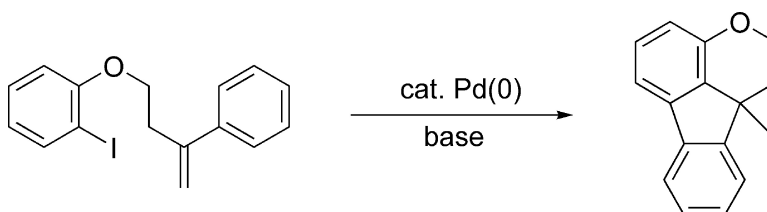Communication

Pd-Catalyzed Alkyl to Aryl Migration and Cyclization: An Efficient Synthesis of Fused Polycycles via Multiple C–H Activation

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Pd-Catalyzed Alkyl to Aryl Migration and Cyclization: An Efficient Synthesis of Fused Polycycles via Multiple C−H Activation

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Metal-catalyzed C−H bond activation is an area of considerable current interest.[1] In particular, the ability of palladium to activate C−H bonds has been used extensively in organic synthesis.[1b,2] Furthermore, the cyclopalladation of a pendant aromatic ring, a process that constitutes a good model for C−H activation, has led to many useful synthetic applications.[3,4] For example, Lautens,[5] Catellani,[6] and Cámpora[7] have previously reported interesting transformations that proceed through alkyl/aryl palladacycles. To date, only a couple of examples of complete alkyl to aryl palladium rearrangements via intramolecular C−H activation have been reported.[4c,8]

We have previously reported that intramolecular C−H activation in organopalladium intermediates derived from o-halobiaryls leads to a 1,4-palladium aryl to aryl migration and shown that such intermediates can be trapped by Heck reactions and intramolecular arylation.[9] Herein, we wish to report 1,4-palladium alkyl to aryl migrations via through-space C−H activation, followed by intramolecular arylation or an intermolecular Heck reaction, which provide a very efficient way to synthesize fused ring systems.

Our first attempts to effect 1,4-palladium alkyl to aryl migration employed compound 1. Under our usual palladium migration conditions reported earlier[9] [0.25 mmol of aryl halide, 5 mol % Pd(OAc)$_2$, 5 mol % bis(diphenylphosphino)methane (dppm), and 2 equiv of CsO$_2$CCMe$_3$ in DMF (4 mL)], aryl iodide 1 afforded an 88% yield of chromene 2 (entry 1, Table 1).[10] This reaction appears to proceed as shown in Scheme 1 by a process that involves

Scheme 1
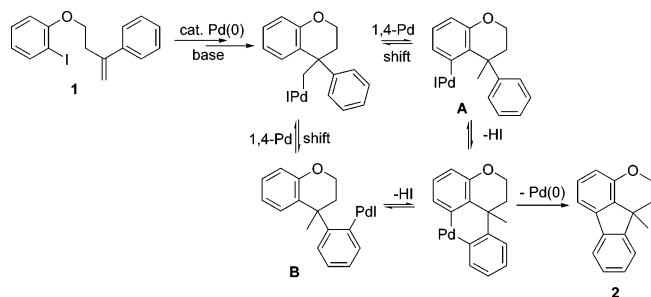
palladium C−H activation with simultaneous 1,4-palladium alkyl to aryl migration via key arylpalladium intermediate **A** or **B** and subsequent intramolecular arylation by another Pd-catalyzed C−H activation. This through-space migration of a metal moiety between an alkyl and an aryl position amounts to an overall 1,4-palladium alkyl to aryl shift, which may involve an intermediate hydridopallada-(IV)cycle[4c,d] generated by insertion of palladium into a neighboring C−H bond. Alternatively, Pd migration may proceed by generation of a pallada(II)cycle and subsequent protonation,[7] although this seems unlikely in the present base and should proceed by cleavage of the arylpalladium bond. This process represents a very powerful new tool for the preparation of complex molecules, which may be difficult to prepare by any other present methodology.

To test the effect of the linkage between the carbon−carbon double bond and the halide-substituted arene on this 1,4-palladium alkyl to aryl migration chemistry, aryl halides **3** and **5** were allowed

Table 1. Synthesis of Fused Polycycles via 1,4-Palladium Alkyl to Aryl Migration, Followed by Intramolecular Arylation[a]

entry	substrate	product	time (h)	% yield[b]
1	X = O 1	2	4	88
2	X = NMs 3	4	1	95
3	5	6	5	82[c]
4	X = H 7	8	4	84
5	X = OMe 9	10	3	91
6	X = NO$_2$ 11	12	4	21
7	13	14	2	95
8	15	16	4	76
9	17	18	4	83[d]

[a] The reaction was carried out under our standard reaction conditions employing 0.25 mmol of aryl halide, 5 mol % Pd(OAc)$_2$, 5 mol % dppm, and 2 equiv of CsO$_2$CCMe$_3$ in DMF (4 mL) at 100 °C unless otherwise noted. [b] Isolated yield. [c] The seven-membered Heck reaction product was obtained in a 5−10% yield. [d] The reaction was carried out at 90 °C.

to react under our standard migration conditions. The results indicate that this migration/arylation process proceeds well with either an N or a C linkage (entries 2 and 3). We have also studied the regioselectivity of this migration by employing naphthalene derivatives **7**, **9**, and **11** (entries 4−6). The palladium migration/arylation occurs exclusively at the less sterically congested 3-position of these naphthalenes. The data in entries 4−6 indicate that the substituents on the aryl halide ring have a strong influence on the yield in this migration/arylation process. This migration process works best with electron-rich aromatics. Our finding that electron-rich arenes are superior to electron-deficient arenes in this alkyl to aryl migration via C−H activation is consistent with literature reports indicating that the ease of C−H activation by palladium parallels that of electrophilic aromatic substitution.[11] It is important to note that this sequential migration/arylation reaction works well with more complex polycyclic aromatic compounds. For example, the reaction of compound **13** afforded pentacycle **14** in a 95% yield (entry 7), and tetrahydroquinoline **16** containing a 5,5-ring juncture has been successfully synthesized by this process in a 76% yield (entry 8).

An interesting example of this migration involves the rearrangement of diaryl ether **17** to dibenzofuran **18** (entry 9). Mechanistically, the palladium must undergo a 1,4-palladium shift from an alkyl position to the 2-position of the diaryl ether, followed by arylation at the 2′-position of the diaryl ether (Scheme 2). This unique high yielding migration/arylation process provides a very powerful and efficient way to prepare complex fused benzofurans, carbazoles, and indenes.

Scheme 2
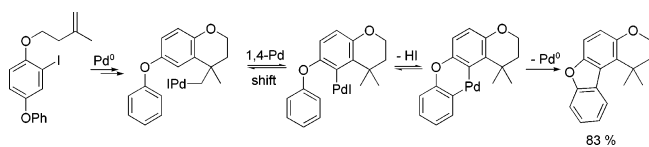
We have also carried out the Pd-catalyzed double migration/arylation of easily prepared aryl halide **19** and the complex fused dioxarubicenes **20** and **21** have been obtained in good yields (eq 1). This example further illustrates the efficiency of this migration/
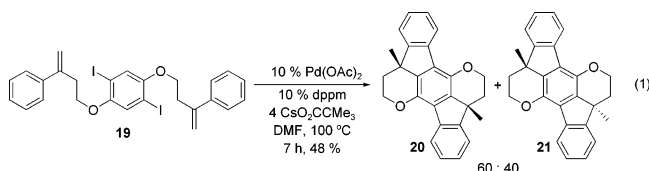

arylation process for the construction of complex heterocycles and carbocycles using easily prepared starting materials.

Another example of a reaction involving an alkyl to aryl palladium migration to generate a functionalized polycycle has been obtained from the reaction of 3-iodo-1-*p*-tosylindole (**22**) with norbornene under our standard Pd migration conditions (Scheme 3). The first step of this reaction involves the cis addition of an indol-3-ylpalladium iodide to norbornene,[5−7] generating a stable alkylpalladium intermediate lacking cis β-hydrogens properly aligned for β-hydride elimination. This intermediate in turn undergoes a 1,4-palladium alkyl to aryl shift to the 2-position of the indole, followed by intramolecular cyclization onto the *p*-toluenesulfonyl moiety.[12] This successful migration/arylation process indicates that the incorporated carbon−carbon double bonds can be introduced from external sources, which broadens the scope of this alkyl to aryl migration chemistry.

Scheme 3
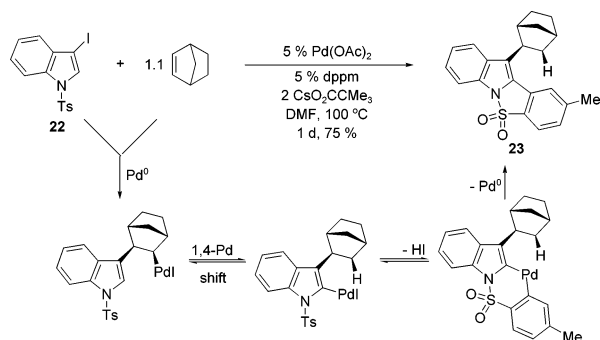
A mechanistically interesting question is whether the migrated arylpalladium(II) intermediate can be trapped by other traditional organopalladium chemistry and still affect synthetically useful chemistry. Thus, aryl halide **24** was allowed to react with ethyl acrylate and methyl vinyl ketone, and olefinated chromenes have been generated in good yields (eq 2). It appears that the intermolecular trapping of migrated arylpalladium intermediates by olefins
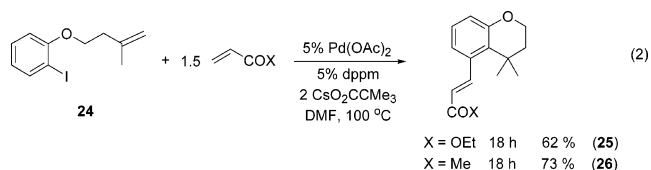
is much slower and less efficient than intramolecular arylation of the migrated arylpalladium intermediates.

In conclusion, we have developed novel palladium alkyl to aryl migration methodology for the synthesis of complex fused polycycles, which employs sequential Pd-catalyzed C−H activation processes. The chemistry developed here works best with electron-rich aromatics, which is in agreement with the idea that these palladium-catalyzed C−H activation reactions parallel electrophilic aromatic substitution. We are presently examining more closely the mechanism of this 1,4-palladium alkyl to aryl shift and further synthetic applications.

Supporting Information Available: General experimental procedures and spectroscopic characterization of all new products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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