

1,4-Palladium Migration via C–H Activation, Followed by Arylation: Synthesis of Fused Polycycles

Marino A. Campo, Qinhua Huang, Tuanli Yao, Qingping Tian, and Richard C. Larock*

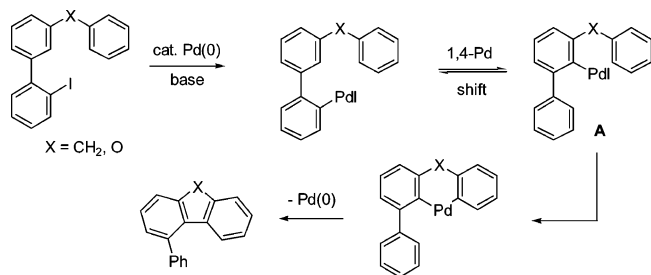
Department of Chemistry, Iowa State University, Ames, Iowa 50011

Received March 12, 2003; E-mail: larock@iastate.edu

The ability of palladium to activate C–H bonds has been used extensively in organic synthesis.¹ In recent years, palladium-catalyzed C–H activation has received considerable attention due to the wide variety of reactions this metal will catalyze.² For instance, catalytic amounts of Pd salts have been used to activate the addition of C–H bonds of electron-rich arenes to alkenes and alkynes, and to effect carbonylation.^{3,4}

We have previously reported that intramolecular C–H activation in organopalladium intermediates derived from *o*-halobiaryls leads to a 1,4-palladium migration and have shown that such intermediates can be trapped by Heck reactions.⁵ We have recently explored sequential migration/arylation via through-space C–H activation and its synthetic potential, and we now wish to report a convenient synthesis of fused polycycles using this novel rearrangement. Our strategy involves the use of palladium C–H activation to catalyze a 1,4-palladium migration within biaryls generating key arylpalladium intermediates such as **A**, which subsequently undergo C–C bond formation by intramolecular arylation producing fused polycycles (Scheme 1). This through-space migration of the metal

Scheme 1



moiety between the *ortho* positions of biaryls amounts to an overall 1,4-palladium shift, which could possibly involve an intermediate hydridopallada(IV)cycle generated by insertion of palladium into a neighboring C–H bond. This process represents a very powerful new tool for the preparation of complex molecules, which might be difficult to prepare by any other present methodology.

By using our previously developed optimal migration conditions [0.25 mmol of aryl halide, 5 mol % Pd(OAc)₂, 5 mol % diphenylphosphinomethane (dppm), and 2 equiv of CsO₂CCMe₃ in DMF (4 mL) at 100 °C],⁵ we have explored this 1,4-palladium migration/arylation process using a variety of substrates carefully selected to study the generality of the process, to understand the migration behavior, and to establish its applicability to commonly encountered synthetic problems (Table 1). We began by allowing 3'-benzyl-2-iodobiphenyl (**1**) to react under our standard reaction conditions at 100 °C, but after 2 d this substrate failed to react. However, by simply increasing the reaction temperature to 110 °C, we were able to obtain the desired compound **2** in a 40% isolated yield (entry 1). The disappointingly low yield obtained with this substrate might be explained by the poor reactivity of the benzyl moiety as an intramolecular trap. To test this idea, we carried out a reaction with the

Table 1. Synthesis of Polycycles via Pd-Catalyzed Migration/Arylation^a

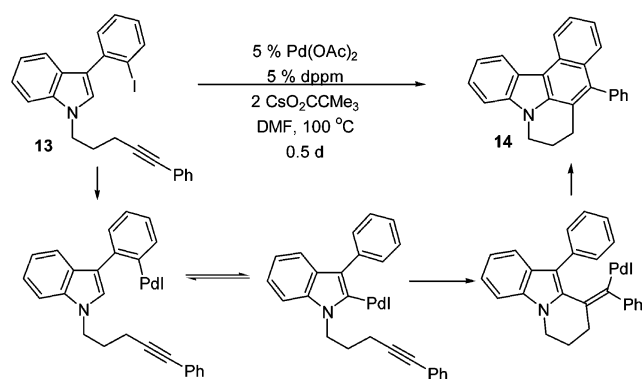
entry	substrate	product	time (d)	% yield ^b
1			3 ^c	40
2			1	89
3			1 ^c	81
4			2 ^c	78 (18)
5			2 ^c	56 (37)
6			1	92 ^d
7			0.5	65
8			1	88 (5)

^a The reaction was carried out under our standard reaction conditions employing 0.25 mmol of the aryl halide, 5 mol % Pd(OAc)₂, 5 mol % dppm, and 2 equiv of CsO₂CCMe₃ in DMF (4 mL) at 100 °C unless otherwise noted. ^b The yield in parentheses corresponds to a GC yield of product in which the C–I bond has been reduced to a C–H bond. ^c The reaction temperature was increased to 110 °C. ^d The yield was determined by ¹H NMR spectroscopy.

more electron-rich 2-iodo-3'-phenoxybiphenyl (**3**) and obtained the desired 4-phenyldibenzofuran (**4**) in an impressive 89% isolated yield (entry 2). Clearly, these results indicate that the electron-rich oxygen-substituted phenyl ring is superior as an arylating agent. Our finding that electron-rich arenes are superior to electron-neutral arene traps is consistent with literature reports indicating that the ease of C–H activation by palladium parallels electrophilic aromatic substitution.⁶

We proceeded to investigate the sequential migration/arylation reaction of more complex polyaromatic compounds. In theory,

Scheme 2



2-iodo-1-phenylnaphthalene (**5**) should afford fluoranthene (**6**) using our methodology. Mechanistically, the palladium must undergo a 1,4-palladium migration from the 2-position of the naphthalene to the *o*-position of the phenyl substituent, followed by arylation at the 8-position of the naphthalene. Although the reaction did not proceed at 100 °C, at 110 °C the desired compound **6** was produced in an 81% yield (entry 3).

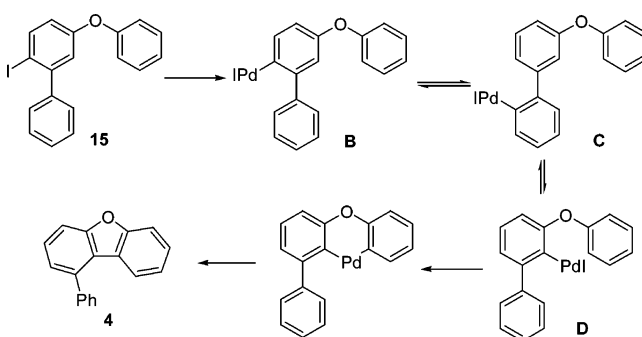
An interesting example of this migration involves the rearrangement of easily prepared 9-iodo-10-phenylphenanthrene (**7**) to benz[*e*]acephenanthrylene (**8**), and the reaction proceeded at 110 °C to generate the desired migration product in a 78% yield (entry 4). We have also studied the regioselectivity of this migration by using an *m*-tolyl moiety in the 10-position of the 9-iodophenanthrene (entry 5). Compound **9** has two available positions for palladium migration, the more sterically congested neighboring 2-position or the remote 6-position of the phenyl ring. The palladium-catalyzed cyclization of compound **9** generated compound **10** exclusively in a 56% yield. This result indicates that palladium migration/arylation occurs exclusively at the less sterically congested 6-position of the phenyl moiety and that either the presence of a methyl group apparently completely inhibited migration to the more hindered 2-position or else ring closure at that more hindered position is completely inhibited.

To confirm our suspicion that the palladium prefers to migrate to a more electron-rich position, because of the relatively easy activation of an electron-rich C–H bond,^{5,6} compound **11** was allowed to react under our migration conditions, and indole **12** was produced in a 92% yield in 1 d at 100 °C (entry 6). From the results of entries 1 and 6, it appears that the high efficiency of palladium migration to a relatively electron-rich position allows the sequential migration/arylation to proceed smoothly at a lower temperature and in a shorter reaction time, although the benzyl group is not a particularly good arylating agent.

We have also carried out the palladium-catalyzed sequential migration/alkyne insertion/arylation of aryl halide **13** in the hope that the arylpalladium intermediate generated by a 1,4-Pd shift via through-space C–H activation could be trapped by alkyne insertion-annulation chemistry described earlier by us (Scheme 2).⁷ The reaction was carried out under our standard migration conditions, and carbazole **14** was isolated in a 65% yield (entry 7). It is important to note that this reaction was complete in 0.5 d at 100 °C, consistent with the particularly facile migration of Pd to the electron-rich indole ring system. This successful alkyne insertion chemistry suggests that there is the exciting possibility of trapping aryl- and other organopalladium intermediates generated by a 1,4-Pd shift by many other synthetically useful palladium methodologies, such as amination and annulation. We are currently examining this possibility.

A mechanistically interesting question is whether the arylpalladium intermediate can migrate more than once and still effect synthetically useful chemistry. To examine this possibility, 2-iodo-

Scheme 3



5-iodobiphenyl (**15**) was allowed to react under our migration conditions, and an 88% yield of double migration product **4** was isolated (entry 8, Scheme 3). Mechanistically, the palladium first inserts into the aryl iodide bond to form intermediate **B**, which migrates to the phenyl unit by through-space C–H activation. The metal moiety in the first migration intermediate **C** can return to the original aromatic ring in either the position from which it originally migrated (**B**) or the position *ortho* to the phenoxy group (**D**), where it can be trapped by arylation. Note that the yield for this double migration chemistry is very similar to that from the single migration chemistry (entry 2) and the success of this double palladium migration indicates that multiple migration processes are entirely feasible.

In conclusion, we have developed a novel palladium migration/arylation methodology for the synthesis of complex fused polycycles, which employs one or more sequential Pd-catalyzed intramolecular migration processes involving C–H activation. 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 a wide variety of palladium migration processes and their synthetic applications.

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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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