OL | Organic Letters

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

Letter

pubs.acs.org/OrgLett

# Intramolecular Remote C−H Activation via Sequential 1,4-Palladium Migration To Access Fused Polycycles

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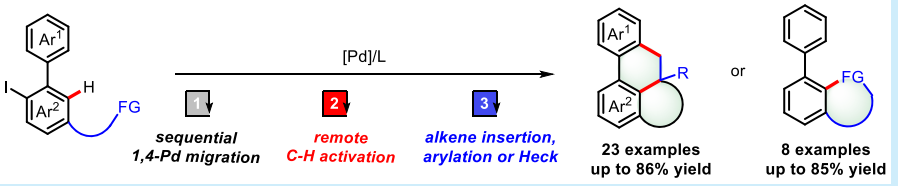
Supporting Information




**ABSTRACT:** An unprecedented intramolecular remote C−H activation via sequential 1,4-palladium migration with an aromatic ring as a conveyor has been described. This reaction provides an efficient route to construct diverse polycyclic frameworks in moderate to good yield via palladium-catalyzed remote C−H activation/alkene insertion, arylation, alkenylation, and the Heck reaction. The preliminary mechanistic studies revealed that the 1,4-palladium migration process was reversible.



In the past two decades, palladium-catalyzed C−H functionalization has provided an efficient method for constructing carbon−carbon or carbon−heteroatom bonds,[1] which has been widely employed to the rapid synthesis of natural products and biologically active compounds.[2] In this context, σ-chelation-directed *ortho*-C−H activation of aromatic compounds via a conformationally rigid five- or six-membered palladacycle intermediate has been substantially explored;[3] however, the selective activation of remote C−H bonds (meta or para position) of arenes is still a difficult task due to the distance and geometry within the substrates. With the aid of the innate steric or electronic bias of substrates, Yu[4a] and Hartwig[4b] independently achieved the palladium-catalyzed *meta*-C−H functionalization of aromatic compounds (Figure 1a). In 2012, Yu and coworkers innovatively developed a U-shaped template that could well overcome the constraint of spatial geometry and accomplished the *meta*-C−H functionalization of arenes (Figure 1b).[5a] Subsequently, Yu,[5b−i] Tan,[6] Maiti,[7] Li,[8] Jin,[9] and Kong[10] further established the versatility of this U-shaped template in the *meta*-C−H functionalization of arenes. In addition, Maiti and coworkers described a palladium-catalyzed remote *para*-C−H functionalization of arenes with a D-shaped biphenyl template-based assembly (Figure 1b).[11] In 2015, Yu and coworkers creatively disclosed a palladium-catalyzed, ligand-enabled *meta*-C−H activation employing norbornene as a transient mediator (Figure 1c).[12] Almost simultaneously, Dong and coworkers reported a simple amine-directed *meta*-C−H arylation via Pd/norbornene catalysis with $Ph_3As$ as the ligand (Figure 1c).[13] The use of norbornene as a mediator was then extensively applied in the palladium-catalyzed *meta*-C−H functionalization of arenes.[14] These foregoing and remarkable works have inspired chemists to unremittingly explore other more strategies or models to achieve the remote C−H functionalization of aromatic compounds. Herein we describe an unprecedented intramolecular remote C−H activation via sequential 1,4-palladium

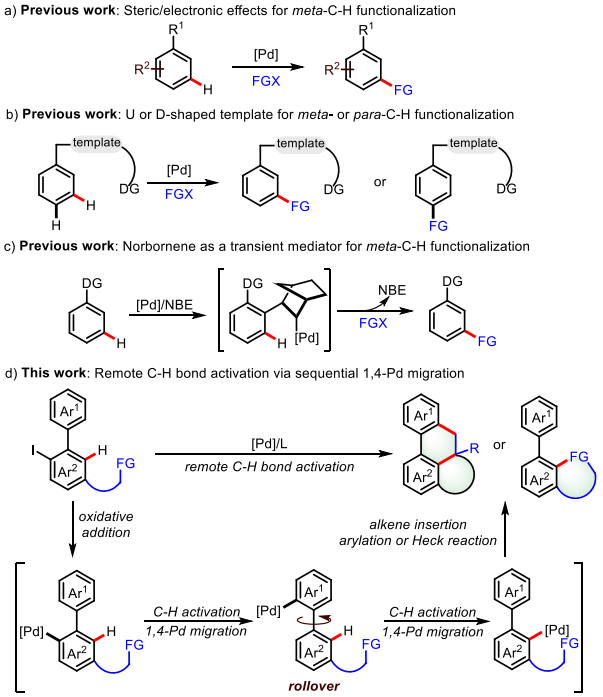


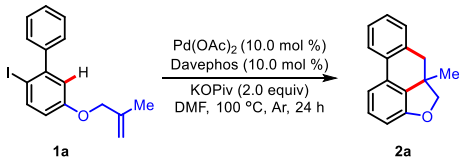

**Figure 1.** Palladium-catalyzed remote C−H functionalization of arenes. DG = directing group. FG = functional group.

**Received:** July 11, 2019




DOI: 10.1021/acs.orglett.9b02392
Org. Lett. XXXX, XXX, XXX−XXX

**Table 1. Optimization of the Reaction Conditions**[a]




| entry | deviation from standard conditions | yield (%)[b] |
|---|---|---|
| 1 | none | 84 |
| 2 | without $Pd(OAc)_2$ | n.d. |
| 3 | without KOPiv | n.d. |
| 4 | $PdCl_2$ instead of $Pd(OAc)_2$ | 71 |
| 5 | $Pd(dba)_2$ instead of $Pd(OAc)_2$ | 62 |
| 6 | $Pd(PPh_3)_4$ instead of $Pd(OAc)_2$ | 51 |
| 7 | $PPh_3$ instead of Davephos | 74 |
| 8 | TFP instead of Davephos | 70 |
| 9 | $PCy_3$ instead of Davephos | 77 |
| 10 | Xantphos instead of Davephos | 33 |
| 11 | DPPE instead of Davephos | 49 |
| 12 | CsOPiv instead of KOPiv | 73 |
| 13 | KOAc instead of KOPiv | 75 |
| 14 | reducing the temperature to 80 °C | n.d. |

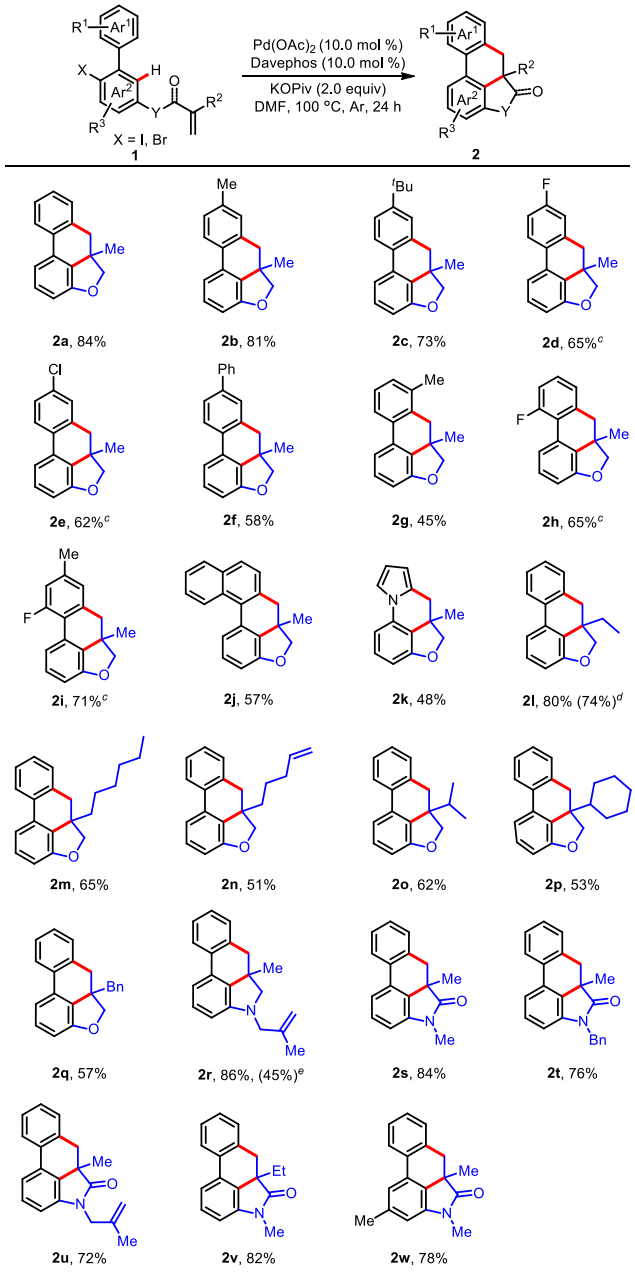
[a]Standard reaction conditions: **1a** (0.2 mmol), $Pd(OAc)_2$ (10.0 mol %), Davephos (10.0 mol %), KOPiv (0.4 mmol), DMF (2.0 mL), 100 °C, 24 h, Ar atmosphere, sealed tube. [b]Yield of isolated **2a**. TFP: tri(2-furyl)phosphine.

migration[15] with an aromatic ring as a conveyor to construct fused polycyclic compounds (Figure 1d).

Initially, we commenced our study with 2-iodo-5-((2-methylallyl)oxy)-1,1′-biphenyl **1a** as the model substrate for the palladium-catalyzed remote C−H activation/alkene insertion reaction. After an intensive investigation (see the Supporting Information (SI) for details), we found that the dihydrophenanthrofuran **2a** could be ultimately obtained in 84% yield in the presence of $Pd(OAc)_2$ (10.0 mol %), Davephos (10.0 mol %), and KOPiv (2.0 equiv) as the base in DMF at 100 °C under an argon atmosphere (Table 1, entry 1). Without the palladium catalyst or the base, no desired product was detected (Table 1, entries 2 and 3). Employing $PdCl_2$, $Pd(dba)_2$, or $Pd(PPh_3)_4$ to replace $Pd(OAc)_2$ resulted in a low transformation of **1a** (Table 1, entries 4−6). A range of phosphine ligands were also tested, delivering **2a** in a diminished yield (Table 1, entries 7−11). Other bases, such as CsOPiv and KOAc, slightly impacted the yield of **2a** (Table 1, entries 12 and 13). Reducing the reaction temperature to 80 °C, no reaction occurred (Table 1, entry 14).

With the optimized conditions established, we then explored the substrate scope of this palladium-catalyzed remote C−H activation/alkene insertion reaction, and the results are shown in Scheme 1. Decorated 2-iodobiaryls **1** bearing electron-donating or electron-withdrawing substituents at the para position of the **Ar1** ring offered the corresponding products **2a−f** in moderate to good yield. The substrate with a methyl group at the meta position of the **Ar1** ring gave **2g** as a single regioisomer in 45% yield, and the structure was determined by heteronuclear multiple bond correlation (HMBC) analysis. (See the SI for details.) The ortho-substituted **Ar1** substrates (**1h** and **1i**) were also compatible candidates, delivering **2h** and **2i** in good yield. The substrates **1j** and **1k** with naphthalene and pyrrole ring occurred smoothly in this sequential 1,4-Pd migration process. The tethered alkenes with various substituents were then investigated, and the products **2l−q**

**Scheme 1. Substrate Scope of Palladium-Catalyzed Remote C−H Activation/Alkene Insertion Reaction**[a,b]




[a]Reaction conditions: X = I, **1** (0.2 mmol), $Pd(OAc)_2$ (10.0 mol %), Davephos (10.0 mol %), KOPiv (0.4 mmol), DMF (2.0 mL), 100 °C, 24 h, Ar atmosphere, sealed tube. [b]Isolated yields. [c]48 h. [d]1.0 mmol. [e]X = Br, 48 h.

were achieved in 51−80% yield. Substrates **1r−w** with the nitrogen atom as a linker delivered tetrahydronaphthoindole **2r** in 86% yield and dihydronaphthoindolones **2s−w** in 72−84% yield. The 2-brombiaryl **1r′** provided **2r** in 45% yield, even when the reaction time was extended to 48 h. Two additional isomers of **1s**, such as *N*-(2-iodo-[1,1′-biphenyl]-3-yl)-*N*-methylmethacrylamide and *N*-(2′-iodo-[1,1′-biphenyl]-3-yl)-*N*-methylmethacrylamide, were also synthesized to explore the reactivity, and the product **2s** was achieved in 8 and 81% yield under our standard reaction conditions, respectively. (See the SI for details.) It should be noted that when *N*-ally and *N*-



DOI: 10.1021/acs.orglett.9b02392
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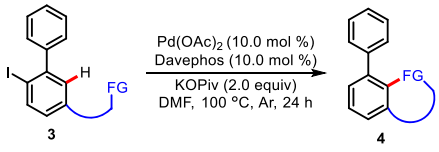
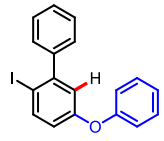
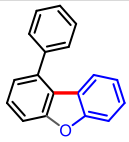
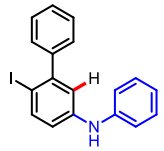
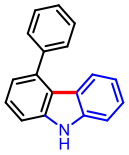
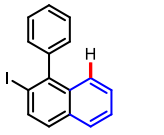
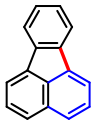
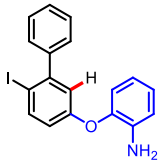
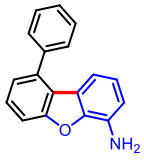
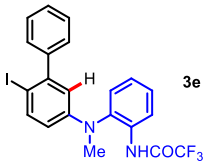
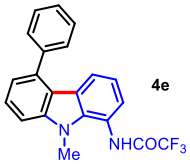
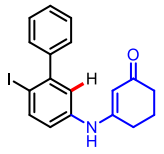
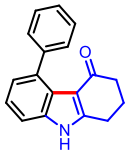
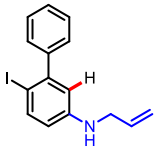
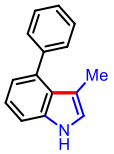
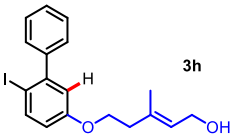
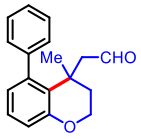
**Table 2. Palladium-Catalyzed Remote C−H Activation/Arylation, Alkenylation, and Heck Reaction**[a,b]



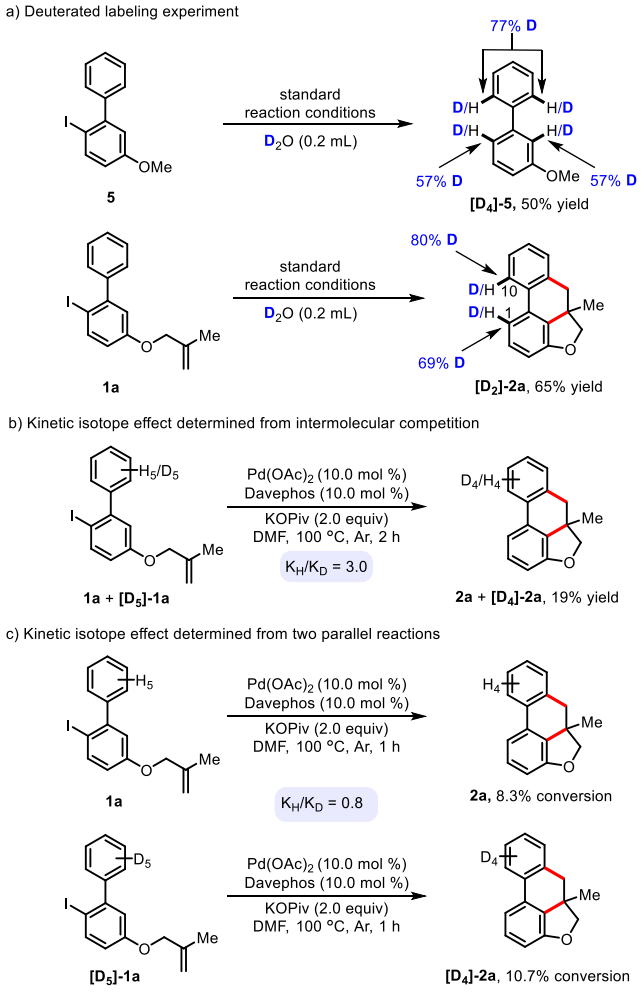

| entry | substrate | | product | | yield[%][b] |
|---|---|---|---|---|---|
| 1 |  | 3a |  | 4a | 82 |
| 2 |  | 3b |  | 4b | 85 |
| 3 |  | 3c |  | 4c | 70 |
| 4 |  | 3d |  | 4d | 57 |
| 5 |  | 3e |  | 4e | 47 |
| 6 |  | 3f |  | 4f | 44 |
| 7 |  | 3g |  | 4g | 45 |
| 8 |  | 3h |  | 4h | 30 |

[a]Reaction conditions: **3** (0.2 mmol), $Pd(OAc)_2$ (10.0 mol %), Davephos (10.0 mol %), KOPiv (0.4 mmol), DMF (2.0 mL), 100 °C, 24 h, Ar atmosphere, sealed tube. [b]Isolated yields.

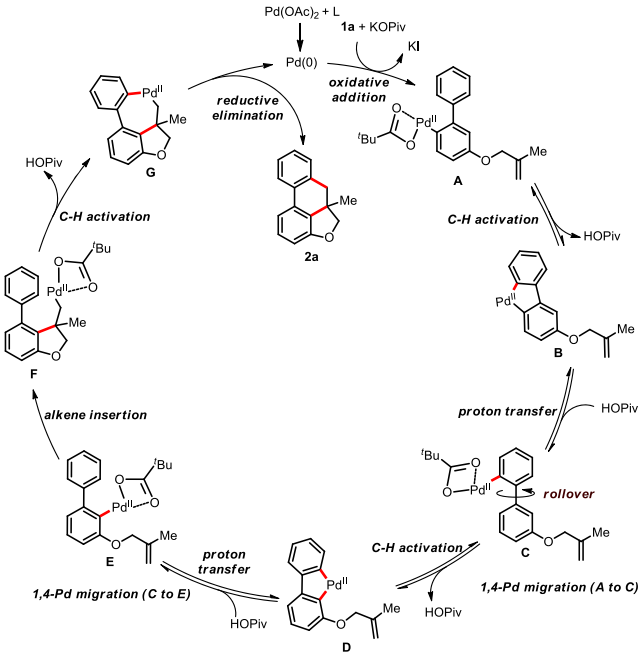
methacrylamide existed simultaneously, product **2u** was preferentially generated with the allyl group untouched.

After exploring the palladium-catalyzed remote C−H activation/alkene insertion reaction, we then turned our attention to expand this strategy in the remote C−H activation/arylation process. The products 1-phenyldibenzo-

**Scheme 2. Mechanistic Experiments**




**Scheme 3. Proposed Mechanism**




[b,d]furan **4a**, 4-phenyl-9*H*-carbazole **4b**, and fluoranthene **4c** could be obtained in good yield (Table 2, entries 1−3).



DOI: 10.1021/acs.orglett.9b02392
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Substrates **3d** and **3e** delivered the products **4d** and **4e** in moderate yield (Table 2, entries 4 and 5). The potential C−N coupling side reaction to offer phenoxazine and phenazine did not occur. A remote C−H activation/alkenylation was also explored, and the dihydrocarbazolone **4f** was isolated in 44% yield (see the SI for the detailed reaction pathway) (Table 2, entry 6). The palladium-catalyzed remote C−H activation/Heck reaction provided indole derivative **4g** in moderate yield (see the SI for the detailed reaction pathway) (Table 2, entry 7). Product **4h** was also acquired in an acceptable yield via a complicated palladium-catalyzed remote C−H activation/redox-relay Heck cascade process (see the SI for the detailed reaction pathway) (Table 2, entry 8).[16]

To elucidate some mechanistic insight into this reaction, the H/D exchange and kinetic isotope experiments were conducted. The reversibility of the C−H cleavage was determined by running the reaction in the presence of $D_2O$ (Scheme 2a). $^1$H NMR analysis of the product [**$D_4$**]-**5** indicated that the deuteration occurred at four different positions. The analysis of the product [**$D_2$**]-**2a** revealed that the deuteration occurred at both the C1 and C10 positions. These results demonstrated that the 1,4-palladium migration process was reversible. The $K_H/K_D$ value was determined to be 3.0 by the intermolecular kinetic isotope effect (KIE) competition experiment (Scheme 2b), whereas a $K_H/K_D$ value of 0.8 was observed when two parallel reactions were conducted (Scheme 2c). These two inconsistent KIE results revealed that the C−H activation or the cleavage of the C−H bond might occur after the rate-limiting step, and the oxidative addition might be involved in the rate-limiting step.[17]

On the basis of the above mechanistic study and literature precedents,[15] a plausible catalytic cycle was proposed, as shown in Scheme 3. The in situ formed Pd(0) undergoes oxidative addition to the carbon−iodine bond of **1a**, followed by iodine−carboxylate exchange, leading to the intermediate **A**. The subsequent C−H activation generates the five-membered palladacycle intermediate **B** through the carboxylate-mediated concerted metalation−deprotonation (CMD) pathway.[15n,18] First, 1,4-palladium migration takes place to furnish the arylpalladium intermediate **C**. Subsequently, the intermediate **C** undergoes a rollover pathway and the C−H activation to deliver a five-membered palladacycle intermediate **D**. The 1,4-palladium migration occurs again to give the arylpalladium intermediate **E**. The intramolecular alkene insertion affords the transient alkylpalladium intermediate **F**; then, the C−H activation occurs to form a seven-membered palladacycle intermediate **G**.[19] The reductive elimination of **G** provides the product **2a**.

In summary, we have developed a palladium-catalyzed intramolecular remote C−H activation for the construction of diverse polycyclic frameworks in good efficiency. This reaction involves sequential 1,4-palladium migration and multiple C−H activation processes. The preliminary mechanistic studies revealed that the 1,4-palladium migration process was reversible. Further investigations into remote C−H activation are currently underway in our laboratory.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02392.

Experimental procedures, characterization data for all new compounds, and copies of $^1$H and $^{13}$C NMR spectra (PDF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (NSFC21572272) and the Innovation Team of "the Double-First Class" Disciplines (CPU2018GY04 and CPU2018GY35) for the financial support.

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DOI: 10.1021/acs.orglett.9b02392
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DOI: 10.1021/acs.orglett.9b02392
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