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Palladium-Catalyzed Cyclization of Alkenes with Organohalides

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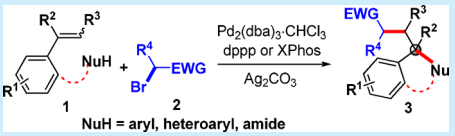
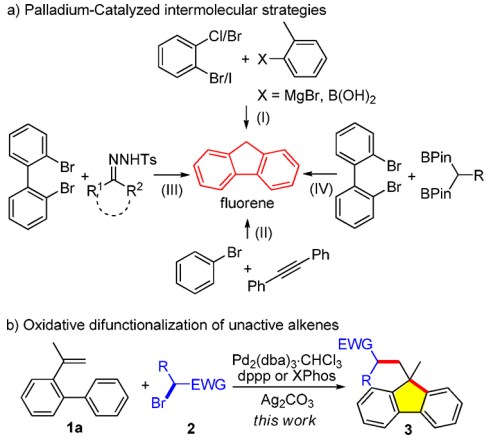
Supporting Information

ABSTRACT: A palladium-catalyzed tandem C−Br/C−H functionalization and cyclization of alkenes with organohalides is reported. This reaction provides an operationally simple method for the synthesis of various fluorene, pyrroloindole, and benzoxazine derivatives, which are useful pharmaceutical framework and photoelectronic devices. Two new C−C/O bonds, a quaternary carbon center and a new ring, are simultaneously formed in this one-pot reaction.



Polycyclic aromatic hydrocarbons (PAHs) have attracted a great deal of attention over the last decades because of their special physical and chemical properties.[1] Fluorene, one of the most important diverse PAH structures, is widely employed in the manufacture of advanced materials,[2] biological and pharmaceutical relevant compounds,[3] as well as effective ligands[4] and unique protecting groups.[5] As such, intense research interest has been paid to explore some practical synthetic strategies,[6] including Brønsted or Lewis acid promoted intramolecular Friedel−Crafts alkylation,[7] transition-metal-catalyzed/mediated cyclization utilizing C−H bond activation[8] or carbene C−H insertion,[9] and even radical reactions.[10] Among them, palladium-catalyzed tandem reaction, which allows efficient access to substituted fluorene derivatives, leads to major progress (Scheme 1, a).[11−14] For example, Hu and co-workers disclosed the cascade coupling of dihalobenzenes with methylphenylmagnesium bromide[11a] or 2-tolylboronic acid to fluorenes (Scheme 1, **I**).[11b] Wu et al. merged the Pd-catalyzed cycloisomerization and subsequent retro-aldol condensation in this manner (Scheme 1, **II**).[12] Recently, tosylhydrazones[13] and 1,1-diboronates[14] were used in the construction of ring systems through a suitable design (Scheme 1, **III** and **IV**). However, most of these reactions suffer drawbacks of harsh conditions, limited starting materials (*ortho*-disubstituted arenes), and low functional group tolerance. The fast assembly of versatile aromatic skeletons commencing from readily available substrates is highly desirable due to the simple operation and atom economy.

Scheme 1. Pd-Catalyzed Strategies for the Synthesis of Fluorene Derivatives



Direct alkene difunctionalization represents an extremely powerful approach for bond formations.[15] Few methods utilizing a palladium-catalyzed Heck insertion are available for the oxidative difunctionalization of alkenes with alkyl halides.[16−18] The main challenge is avoiding the rapid β-hydride elimination[19] and assisting another nucleophilic addition during the domino processes. A recent advance is the catalytic dicarbonation of *N*-arylacrylamides with α-carbonyl alkyl bromides through a tandem C−Br/C−H activation reported by Li's group.[17] Another elegant example is allylic alcohols coupled with organohalides with concomitant 1,2-migration.[18] However, further ingenious synthetic applications are considerably less established. As part of our recent interest in alkenes functionalization,[20] herein we present a palladium(0)-catalyzed transformation of 2-aryl styrene with alkyl halides through a Heck insertion and trapped by an *o*-aryl C(sp^2)−H bond (Scheme 1, b).

Initially, our investigation was carried out by treating 2-(prop-1-en-2-yl)biphenyl (**1a**) with 2-bromoacetonitrile (**2b**) in the presence of $Pd(MeCN)_2Cl_2$ (10 mol %), dppp (20 mmol %), and Ag_2CO_3 as additives in acetonitrile under reflux for 17h (Table S1; see the Supporting Information). Gratifyingly, the desired cyanomethylated product **3aa** was obtained in 15% GC yield (entry 1). After several solvents, palladium species, and ligands were examined, the optimal reaction conditions were then quickly established by elevating the temperature time to 24 h, which provided **3aa** in 84% GC yield and along with 78% isolated yield (entry 22). Lower yields and lower selectivity

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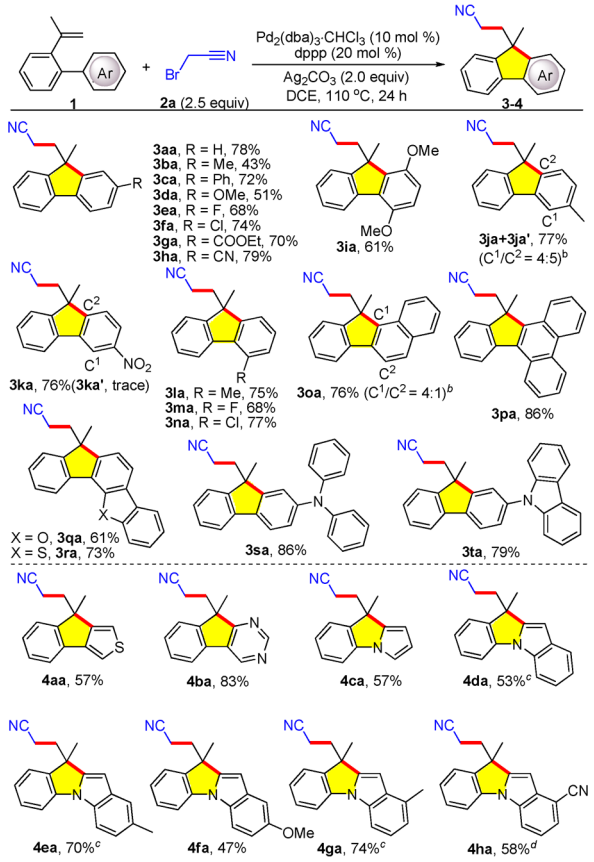
were obtained when other transition-metal salts, which were previously demonstrated to be efficient for the single-electron reduction of C−Br bonds,[21] were used (entries 15 and 16).

Under the optimal reaction conditions, a series of 2-arylalkenes were tested to demonstrate the reaction scope, and the results are listed in Scheme 2. Generally, substrates

Scheme 2. Synthesis of Fluorenes and Heterofluorenes from Alkenes 1 with 2a[a]

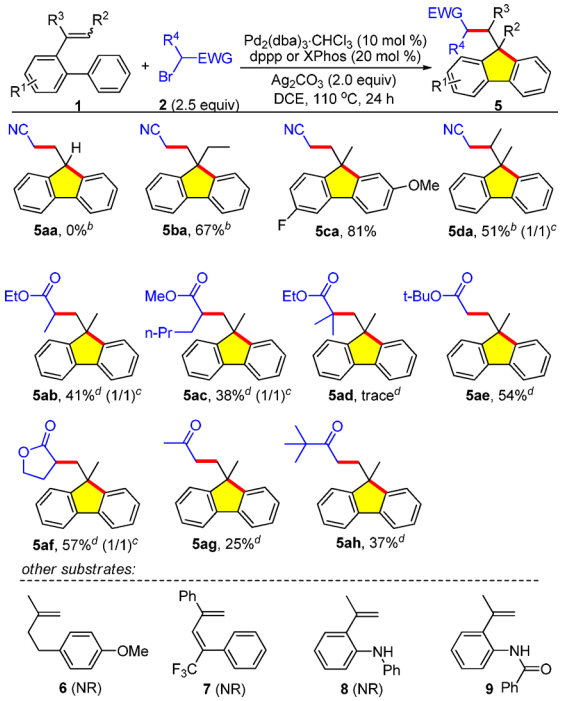


[a]Standard conditions; yields of isolated products. [b]Determined by ^{1}H NMR analysis; only major products are shown. [c]2 mmol scale. [d]0.15 mmol scale.

containing substituents of varying electronic character (donating or withdrawing) and steric demand (*para*-, *meta*-, as well as *ortho*-) for the aromatic ring were smoothly cyclized to afford the desired fluorene derivatives **3aa**−**na** with moderate to good yields. It was found that functionalities such as halogen (F, Cl), ethoxycarbonyl, and cyano groups were satisfactorily compatible with the reaction, furnishing products **3ea**−**ha** and **3ma**−**na** in 68−79% yields, which facilitated a chance for further modifications. A mixture of two anticipated regioisomers **3ja**/**3ja**′ (C^1/C^2 = 4/5) was obtained for *meta*-substituted alkene **1j**. Notably, the cleavage of the C−H bond at the C^2-position of **1k** occurred preferentially, and **3ka** was isolated as the major product. Considering that π-conjugated fluorene derivatives are important structural constituents of optoelectronic materials and pharmaceutical molecules, we then proceeded to explore the generality of this novel cascade reaction to alkenes with fused rings and heterocycles. When the *o*-aryl part of **1** was used instead of naphthalene (**1o**) and phenanthrene (**1p**), the reaction could smoothly convert into the alkylarylated products in 76% and 86% yields, respectively (**3oa**−**pa**). The substrates, featuring the functionalized polycyclic motifs such as dibenzo[*b*,*d*]furan (**1q**), dibenzo[*b*,*d*]thiophene (**1r**), triphenylamine (**1s**), and 9-phenyl-9*H*-carbazole (**1t**), also participated in the process (**3qa**−**ta**). Furthermore, alkenes bearing heterocycles including thiophene and pyrimidine were proven to be appropriate candidates, thus providing an opportunity for potential applications in medicinal chemistry (**4aa**−**ba**). More importantly, pyrrole and indole could be facilely incorporated into the family of these compounds, which greatly streamlined access to fused pyrroloindoles (used as electroluminescence materials[22]) (**4ca**−**ha**). Photophysical properties of the prepared polycyclics **3qa**,**sa** and **4da**,**ha** were measured by UV−vis absorption photoluminescence measurements at room temperature in CH_2Cl_2 (Figure S1−2; see the SI).

Encouraged by the above results, we turned our attention to various alkenes and organohalides (Scheme 3). Fluorene **5ba**

Scheme 3. Synthesis of Fluorenes from 1 and Organohalides 2[a]



[a]Standard conditions; yields of isolated products. [b]0.2 mmol scale. [c]Diastereomeric ratio. [d]20 mol % of XPhos was used.

with an ethyl group at the methylene moiety was synthesized in 67% yield, whereas simple styrene failed to generate the corresponding product (**5aa**). Remarkably, 2-vinylbiphenyls with a halogen atom (F) or derived from 1-(biphenyl-2-yl)propan-1-one gave tricyclic **5ca** and **5da** in 66% and 57% yield, respectively. To our delight, both primary and secondary α-bromoalkyl esters could undergo the protocol in the presence of $Pd_2(dba)_3$, XPhos, and Ag_2CO_3 in relatively lower yields (**5ab**−**ac** and **5ae**, 38%−54%). In contrast, only a trace amount of product was detected when tertiary ethyl 2-bromo-2-methylpropanoate was applied, possibly due to negative steric effects (**5ad**). In addition, cyclic α-bromo-γ-butyrolatone transferred to **5af** in 57% yield. α-Bromo ketones such as propan-2-one and 3,3-dimethylbutan-2-one were inferior to ethers; their reactivity was slightly lower (**5ag**−**ah**). Unfortunately, other types of alkenes having an aliphatic chain (**6**),

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double bond (**7**), or heteroatom (**8**) as the tether were not suitable substrates. Interestingly, the presented methodology can be conveniently used in the synthesis of complicated benzoxazines from olefinic amides (**9**) in moderate yields (Figure 1).[20f]

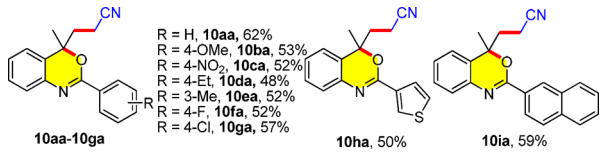
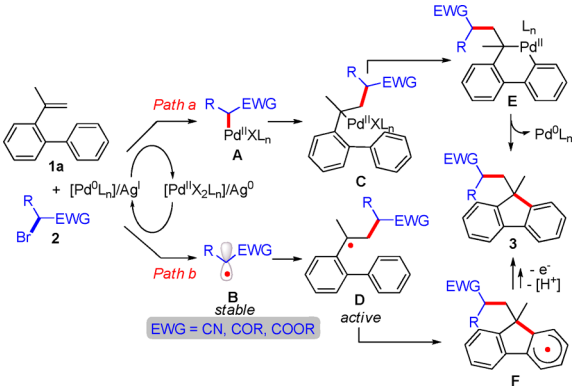


Figure 1. Synthesis of benzoxazine derivatives.

In order to clarify the mechanism of this transformation, radical-trapping experiments were carried out (Figure S3; See SI). The reactions were completely inhibited in the presence of a radical scavenger 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO, 3.0 equiv), and only the TEMPO adduct **11** was observed (Figure S3, a). Furthermore, a major product methyl 2-methyl-4,4-diphenylbut-3-enoate (**12**) was provided when 2-(prop-1-en-2-yl)biphenyl (**1a**) was treated with **2a** in the presence of 1,1-diphenylalkene under standard reaction conditions (Figure S3, b). These results suggested that a free cyanomethyl radical was most likely involved. The intramolecular cyclization occurred before β-hydride elimination[19] through a radical pathway.[17]

On the basis of the above results, two plausible reaction mechanisms are proposed in Scheme 4. The reaction is initiated

Scheme 4. Plausible Reaction Mechanism



with the aid of a Ag^I oxidant by a $[Pd^0(L_n)]$-promoted SET pathway to generate acetonitrile radical **B** and $Pd^{II}X_2(L_n)$ (Scheme 4, path b).[17] The thermodynamically stable **B** (SOMO-π delocalized) adds to the C=C bond in alkene **1a** to form radical intermediate **D**. Subsequently, an intramolecular cyclization from **D** to intermediate **E** occurs (the former is kinetically competitive with TEMPO trapping; thus, TEMPO adduct of **D** was not observed). The direct β-hydride elimination may be inferior to compete with cyclization under this conditions. Finally, radical **E** was oxidized by $Pd^{II}X_2(L_n)$ species and followed by deprotonation to furnish fluorene **3**.[16h,17,18] However, an alternative pathway through a palladium-catalyzed Heck-type mechanism cannot be ruled out (Scheme 4, path a). The alkene **1a** inserts itself in the palladium−carbon bond of organopalladium species **A** to provide palladium(II) intermediate **C**, which would be further carbopalladation with *ortho*-aryl group with the aid of Ag^I to yield Pd(II) species **E**. Species **E** then undergoes reductive elimination to afford the desired product **3** and regenerate the Pd(0) catalyst.

In conclusion, we have reported (1) a palladium-catalyzed difunctionalization reaction for rapid assembly of fluorene, pyrroloindole, and benzoxazine derivatives from unactivated alkenes with organohalides; (2) an autotandem radical sequence via a Heck-type insertion and trapped by an *o*-aryl $C(sp^2)$−H bond; and (3) in one reaction, two new C−X bonds, a quaternary carbon center, and a new ring that simultaneously formed. More importantly, this methodology provides chemists an alternative method for designing various condensed carbo- or heterocycles as a promising scaffold for synthetic intermediates, pharmacophores, and organic photoelectronic materials.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00035.

Experimental procedures and full spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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