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ARTICLE TYPE

# Copper-mediated radical alkylarylation of unactivated alkenes with acetonitrile leading to fluorenes and pyrroloindoles†

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A Cu-mediated/catalyzed oxidative selective oxidative dual C-H bonds cleavage of an arene and alkylnitrile or acetone is reported. This method provides a novel approach to highly functionalized fluorene and pyrroloindole derivatives, which are useful in pharmaceutical and photoelectronic areas. In this reaction, two new C(sp<sup>3</sup>)-C(sp<sup>3</sup>) and C(Ar)-C(sp<sup>3</sup>) bonds, a quaternary center and a five-membered ring are simultaneously formed.

Polycyclic aromatic hydrocarbons (PAHs) are playing increasingly important roles in organic, medicinal and material chemistry during the past decades.<sup>[1]</sup> Representative examples are fluorene and pyrroloindole derivatives (Figure 1, I and II), which have excellent anti-inflammatory (III),<sup>[2]</sup> antitumor (VII),<sup>[3]</sup> anticancer (VIII) activities<sup>[4]</sup> and were confirmed as cholesterol acyltransferase (ACAT) inhibitor (IV),<sup>[5]</sup> cyclophilin A inhibitor (V)<sup>[6]</sup> or S1P1 receptor agonist (VI),<sup>[7]</sup> etc. In addition, while these structural motifs are privileged in naturally occurring and biological active molecules, they also exhibit unique electrical and optical properties.<sup>[8]</sup> As such, development of practical and efficient methods for the synthesis of functionalized PAHs is urgently demanded.

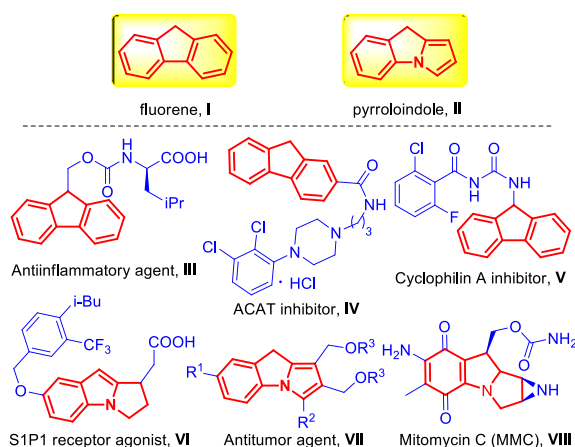
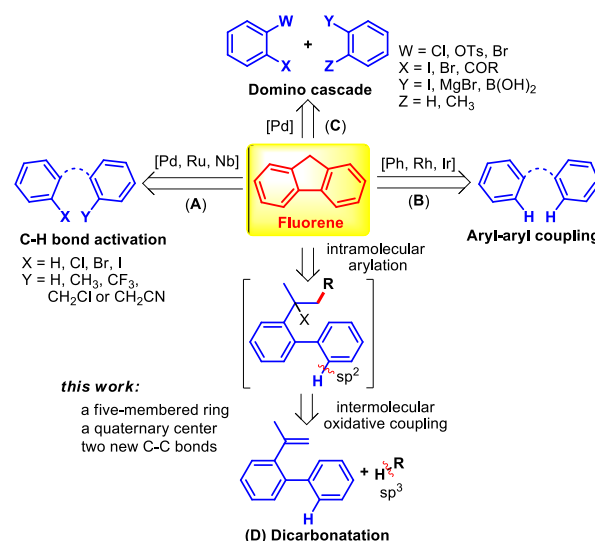


Figure 1 Representative bioactive related compounds exhibiting the fluorene or pyrroloindole motifs

Several synthetic procedures to build fused cyclic compounds which suffered from limitations, such as tedious multistep synthesis, harsh reaction conditions, lack of regioselectivity, and

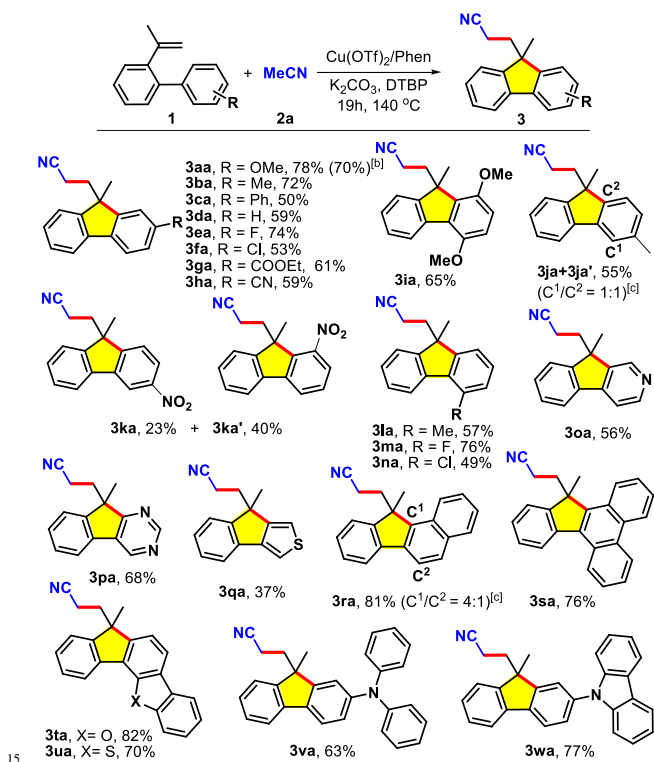


Scheme 1 Metal-mediated routes to fluorenes

poor functional group tolerance, were reported.<sup>[9-10]</sup> Recently, extensive research attention have been paid on transition-metal-mediated cyclizations utilizing a C-H bond activation (Scheme 1, A)<sup>[11]</sup> or direct dehydrogenative aryl-aryl coupling strategy (Scheme 1, B).<sup>[12]</sup> Although intermolecular catalytic reactions were also reported (Scheme 1, C),<sup>[13]</sup> the fast assembly of diverse fluorenes commencing from properly functionalized starting materials is still an exciting goal because of its simple operation and atom economy.<sup>[14]</sup> In this account we report: (1) an autotandem radical process for the construction of polycyclic aromatic compounds through a oxidative C-C/C-C cross-coupling sequence with participation of unactivated alkenes (It should be noted that the documented intermolecular dicarboxylation was still restricted to oxindoles<sup>[15]</sup> and related heterocycles<sup>[16]</sup> using activated substrates); (2) an inexpensive Cu-mediated/catalyzed<sup>[17]</sup> selective oxidative C-H bond cleavage of an arene and alkylnitrile; (3) two new C-C bonds, a quaternary center and a five-membered ring are simultaneously formed in one reaction; (4) an operationally simple and air benign catalyst system allowing access to various condensed carbo- or heterocycles as a promising scaffold for synthetic intermediates, pharmacophores, and organic photoelectronic materials (Scheme 1, D).

The sequence of domino oxidative coupling of alkene **1a** with acetonitrile (**2a**) and subsequent aryl intramolecular incorporation was established after conducting a variety of reactions (for detailed information on the optimization of the reaction conditions, see the Table S1, ESI†). It was found that the presence of nitrogen-containing ligand (1,10-phenanthroline) was critical to obtaining high yields of the target product. A reasonable explanation is that the cyano group of acetonitrile might coordinate strongly to metal leading to catalyst poisoning.<sup>[18]</sup> Screening of other parameters (ligand, base, catalyst, oxidant, *etc.*) substantially increased the yield of **3aa** to 78%. In addition, this one-pot reaction can be scaled up to 2 mmol (70% yield) under air atmosphere (Table 1, product **3aa**).

**Table 1** Rapid assembly of fluorenes from alkenes **1** and acetonitrile **2a**<sup>a</sup>

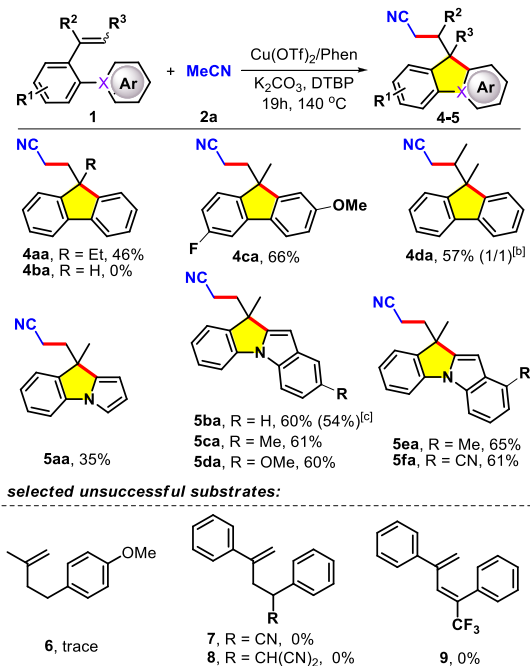


<sup>a</sup>Reaction conditions: alkene **1** (0.2 mmol), **2a** (2 mL),  $\text{Cu}(\text{OTf})_2$  (0.1 mmol), 1,10-phenanthroline (0.2 mmol),  $\text{K}_2\text{CO}_3$  (0.6 mmol) and di-*tert*-butyl peroxide (0.5 mmol) at  $140^\circ\text{C}$  under air for 19 h; yields of isolated products. <sup>b</sup>2 mmol scale. <sup>c</sup>Determined by  $^1\text{H}$  NMR analysis of the isolated products; only major products were showed.

Encouraged by this results, next we set out to investigate the scope of various alkenes **1** in acetonitrile (Tables 1-2). As shown in Table 1, the substrates bearing electron-withdrawing or electron-donating group always afforded the desired products in moderate to good yields (**3aa-3na**). The functionalities such as halogen, cyano, and ester groups at the *p*-(**3aa-3ha**), *m*-(**3ia-3ka**), or *o*-position (**3la-3na**) of the aryl rings have no significant influence on the efficiency, thereby facilitating a chance for further modifications of the embedded functional groups. Notably, the use of substrates containing *meta*-substituents gave a mixture of two regioselective products (**3ja/3ja'** and **3ka/3ka'**). Moreover, substrates bearing heterocyclic rings including pyridine (**1o**), pyrimidine (**1p**) and thiophene (**1q**) were proven to

be appropriate candidates, delivering the corresponding products **3oa-3qa** in 37-68% yields. To our delight, when the benzene ring of **1** was changed to naphthalene (**1r**), phenanthrene (**1s**), dibenzo[*b,d*]furan (**1t**), dibenzo[*b,d*]thiophene (**1u**), triphenylamine (**1v**), and 9-phenyl-9*H*-carbazole (**1w**), the substrates were also successfully converted into the alkylarylated products **3ra-3wa**. This methodology provides a concise entry to methylene-disubstituted fluorenes which are not easily accessed by reported methods. More importantly, these new members of the family of  $\pi$ -conjugated polycyclic derivatives could be used as potential optoelectronic materials.<sup>[1h,8d]</sup>

**Table 2** Substrate scope for the reaction of various alkenes **1** with **2a**<sup>a</sup>

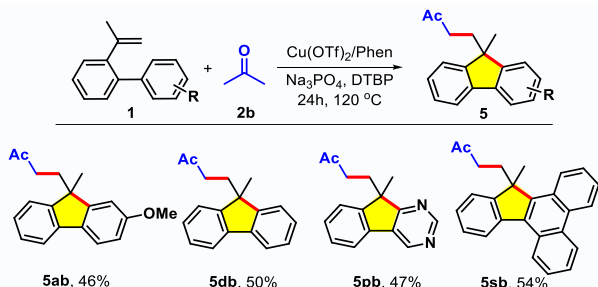


<sup>a</sup>Reaction conditions: alkene **1** (0.2 mmol), **2a** (2 mL),  $\text{Cu}(\text{OTf})_2$  (0.1 mmol), 1,10-phenanthroline (0.2 mmol),  $\text{K}_2\text{CO}_3$  (0.6 mmol) and di-*tert*-butyl peroxide (0.5 mmol) at  $140^\circ\text{C}$  under air for 19 h; yields of isolated products. <sup>b</sup>Diastereomeric ratio was determined by  $^1\text{H}$  NMR spectroscopy of the isolated products. <sup>c</sup>30 mol% of  $\text{Cu}(\text{OTf})_2$  was used.

The synthesis of fluorene **4aa** with ethyl group at the methylene moiety proceeded smoothly under optimal conditions, whereas simple styrene failed to afford the product **4ba** (Table 2, **4aa-4ba**). In addition, it was found that 2-vinylbiphenyls containing halogen atom or derived from 1-(biphenyl-2-yl)propan-1-one were also compatible with the reaction conditions, leading to the tricyclic products **4ca** and **4da** in 66% and 57%, respectively. Interestingly, pyrroles and indoles could be readily incorporated into these skeletons, which greatly streamlined accesses to such fused pyrroloindoles (as electroluminescence materials<sup>[8b]</sup> and pharmaceutically relevant molecules<sup>[3,4,7]</sup>). Unfortunately, a series of other type of alkenes having an aliphatic chain (**6-7**) or double bonds (**8**) as the tether were not suitable. Apart from acetonitrile **2a**, acetone **2b** could also act as effective substrate in this system with alkenes **1** (Table 3).<sup>[19]</sup> The aryl-substituted alkenes **1** also worked well and mainly offered the desired products **5ab**, **5db** and **5sb** in medium yield.

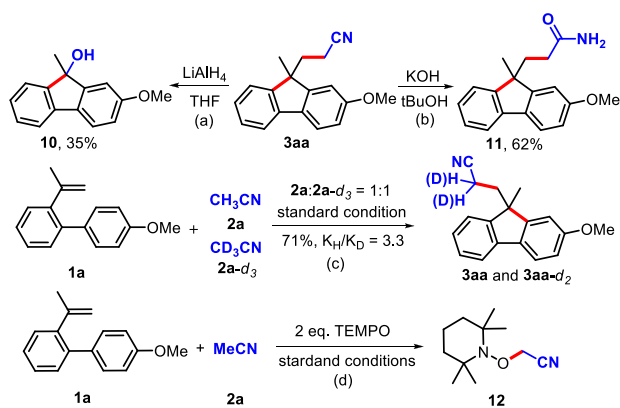
Gratifyingly, the reaction was applicable to 5-(2-(prop-1-en-2-yl)phenyl)pyrimidine (**1s**), furnishing the product **5pb** in 47% yield.

**Table 3** Rapid assembly of fluorenes from alkenes **1** and acetone **2b**<sup>a</sup>

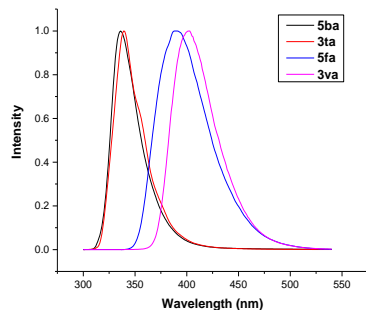


<sup>a</sup>Reaction conditions: alkene **1** (0.3 mmol), **2a** (2 mL), Cu(OTf)<sub>2</sub> (0.03 mmol), 1,10-phenanthroline (0.06 mmol), Na<sub>3</sub>PO<sub>4</sub> (0.3 mmol) and di-*tert*-butyl peroxide (0.75 mmol) at 120 °C under air for 24 h; yields of isolated products.

It is noteworthy that the cyanomethylated products were widely applied in synthetic transformations (Scheme 2).<sup>[20]</sup> For instance, an unexpected product of 9*H*-fluoren-9-ol **10** was synthesized from **3aa** with the reduction of lithium aluminium hydride (Scheme 2, a). In addition, the cyano group can be easily hydrolyzed to amide in the KOH/*t*BuOH system (Scheme 2, b). Moreover, photophysical properties of the prepared polycyclics were measured by UV-Vis absorption photoluminescence measurements at room temperature in CH<sub>2</sub>Cl<sub>2</sub> (Figure 2).

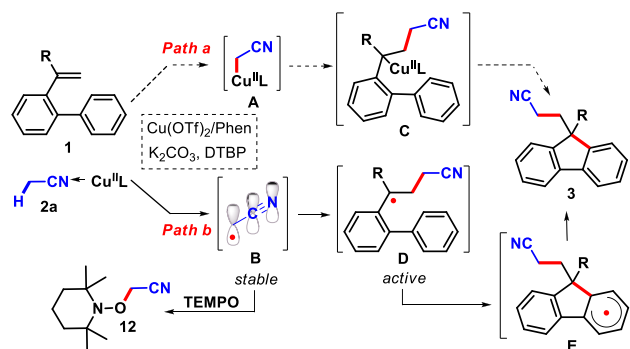


**Scheme 2** Further synthetic transformations and mechanism studies



**Figure 2** The fluorescence spectra of prepared polycyclic compounds

To get insight into the mechanism, a kinetic isotopic effect (KIE) study was conducted. The intermolecular  $k_H/k_D$  (3.3) indicated that C(sp<sup>3</sup>)-H bond cleavage of acetonitrile should be the rate-determining step (Scheme 2, c). Furthermore, the reactions were completely inhibited in the presence of a radical scavenger 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) (Scheme 2, d), implying that a radical process might be involved in this transformation (for detailed information, see the Figure S2 and S3, ESI<sup>†</sup>). Initial mechanistic studies suggested a free radical pathway (Scheme 3, path b) was more likely than a process involving the formation of an organocopper species (path a).<sup>[17]</sup> Thus, initially acetonitrile radical **B** (SOMO- $\pi$  delocalization)<sup>[17g]</sup> which is thermodynamically stable, adds to alkene **1** to form a free radical **D**. Subsequently, an intramolecular cyclization from active alkyl radical **D** to intermediate **E** occurs; the former is kinetically competitive with TEMPO trapping, thus TEMPO adduct of **D** was not observed.<sup>[21]</sup> Finally, radical **E** was oxidized and followed by deprotonation to furnish fluorene **3**.<sup>[15-16]</sup>



**Scheme 3** Proposed reaction mechanism

In conclusion, we have developed a copper-mediated/catalyzed selective oxidative C-H bonds functionalization reaction for rapid assembly of fluorene and pyrroloindole derivatives from unactivated alkenes and acetonitrile. The reaction is general and practical because of its high reaction efficiency, broad substrate scope, the use of inexpensive Cu-catalyst, and simple operation under air. More importantly, this methodology provides chemists an alternative method for designing new pharmaceutical framework and photoelectronic devices. Further studies to elucidate the detailed reaction mechanism and its application to the synthesis of complex products are ongoing in our group and will be disclosed in the near future.

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## Notes and references

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