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Cyanomethylation of Substituted Fluorenes and Oxindoles with Alkyl Nitriles

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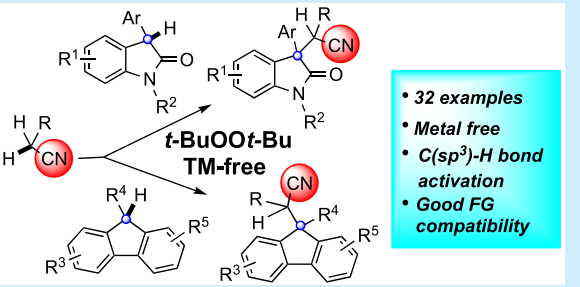
ABSTRACT: The first example of metal-free cyanomethylenation from alkyl nitriles of sp^3 C−H bonds to afford quaternary carbon centers is described. This oxidative protocol is operationally simple and features good functional group compatibility. This method provides a novel approach to highly functionalized fluorene and oxindole derivatives, which are commonly used in material and pharmaceutical areas. Control experiments provide evidence of a radical reaction process.

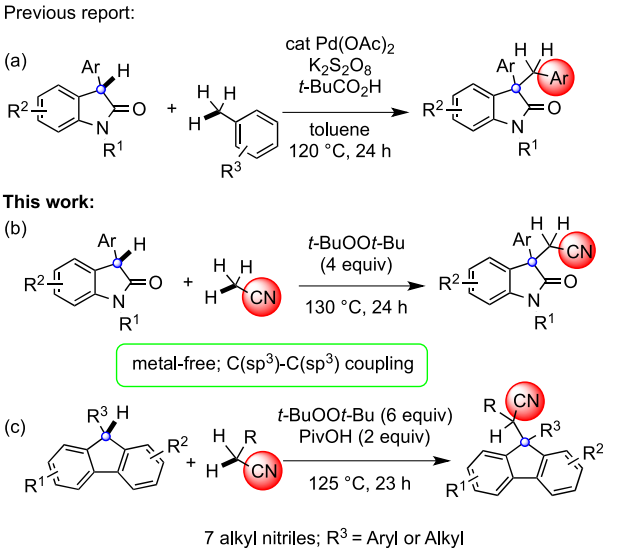


Nitriles are versatile functional groups in organic synthesis. In addition to being a very useful functional group in biologically active compounds, they can be readily converted into amines, carboxylic acids, ketones, and even heterocycles.[1] Compounds containing nitrile groups are frequently employed as building blocks in drug-discovery programs.[2] The introduction of a nitrile group by the activation of the α-hydrogen of simple aliphatic nitriles is one of the most efficient and environmentally benign entries to this class of structure. For example, the generation and reaction of stable α-nitrile anions is well-explored with a range of electrophiles.[3] The nitrile group also stabilizes radicals arising from α-hydrogen atom abstraction, and these radicals permit bond disconnections[4] complementary to those available from the α-nitrile anions. Among these reactions, there are relatively few involving the C−H activation of a second component, that is, oxidative fragment coupling. Building off of our prior efforts in the dual-C−H activation of two components (Scheme 1a),[5] the use of acetonitrile was investigated with oxindoles and fluorenes. To the best of our knowledge, there are no examples of cross-coupling between sp^3 C−H bonds and alkyl nitriles under metal-free conditions. Herein we communicate our efforts, culminating in the facile, metal-free oxidative cyanomethylenation of oxindoles and fluorenes with alkyl nitriles through C(sp^3)−H oxidative radical functionalization using *t*-BuOO*t*-Bu as the oxidant (Scheme 1b,c).

As an important structural unit, 2-oxindoles with a quaternary carbon center at the C3 position are a class of heterocycles existing in many natural products, pharmaceuticals, and drug candidates (Figure 1a).[6] Their importance has prompted considerable interest in developing new construction methods.

Similarly, fluorenes have attracted much attention for a variety of applications involving advanced materials, including

Scheme 1. Dual C−H Activation of Oxindoles and Fluorenes with Toluenes or Alkylnitriles to Generate Quaternary Centers



those used in semiconductors,[7] optoelectronics,[8] and solar cells.[9] In addition, fluorene derivatives have also been playing an increasing role in pharmaceuticals and biochemistry[10] as seen by the incorporation of fluorene moieties into bioactive compounds (Figure 1b).[11] As a consequence, the development

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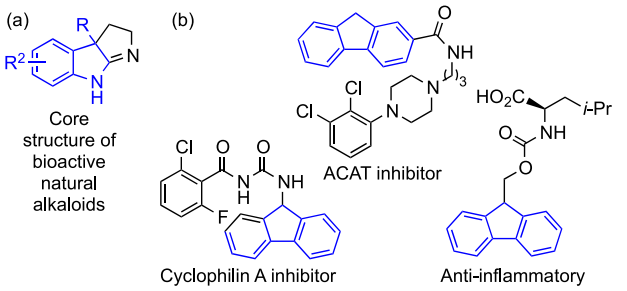
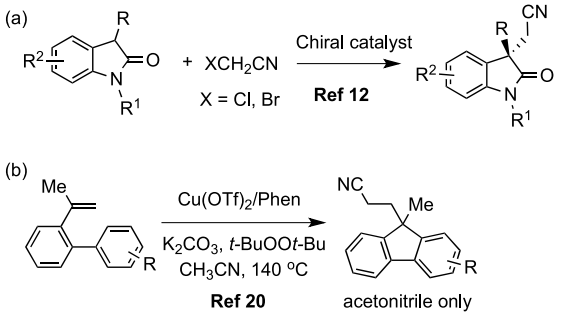


Figure 1. Structures of bioactive compounds with (a) oxindole or (b) fluorene moieties.

of practical synthetic methods for the construction of functionalized fluorenes is in demand.

The asymmetric cyanomethylenation of three-substituted oxindoles using prefunctionalized cyanomethyl halides has been reported by different groups (Scheme 2a).[12] Recently,

Scheme 2. Approaches to Cyanoalkyl Oxindoles and Fluorenes

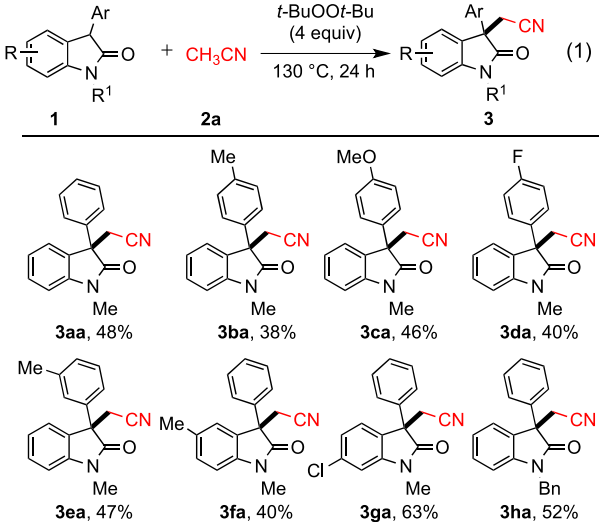


many studies focused on the atom-transfer radical addition reactions of nitriles with olefins.[13] Among them, the Zhu group has made significant contributions to this research field.[14] In 2016, the Ge group reported the first example of the palladium-catalyzed cross-coupling of sp^3 C−H bonds with acetonitrile.[15] Thereafter, Wu[16] and Shen[17] independently reported the direct oxidative cyanomethylenation reactions by adding acetonitrile to 1,3-dicarbonyls and tetrahydroisoquinolines respectively; however, other alkyl nitrile coupling partners were unsuccessful.

In 2015, the Liu group developed a simple and efficient synthesis of 9-arylfluorenes via the metal-free reductive coupling of arylboronic acids and *N*-tosylhydrazones.[18] Also, extensive attention has been paid to generating fluorenes via transition-metal-catalyzed cyclizations or direct dehydrogenative aryl−aryl coupling via C−H bond activation.[19] In 2016, the Ji group developed a copper-mediated radical alkylarylation of unactivated alkenes with acetonitrile, leading to methylene-disubstituted fluorenes, which are not easily accessed by conventional methods (Scheme 2b).[20] Nonetheless, this transformation still suffered from some drawbacks, such as the use of transition metals and ligands, a narrow substrate scope (acetonitrile only), and only access to 9-alkyl-substituted fluorenes, thus limiting its further applications.

With a clear need for alternative strategies to construct highly functionalized oxindoles, we initiated our investigations by screening various metal sources (Cu, Fe, Pd, Co, Mn, and Sc) and reaction conditions (see the Supporting Information (SI)) for the *t*-BuOO*t*-Bu-mediated coupling of three-substituted oxindoles with acetonitrile (Scheme 3, eq 1). Notably, the protocols employed by Zhu and Li[14a,21] involving

Scheme 3. Reaction of 3-Monosubstituted Oxindoles with Acetonitrile[a]



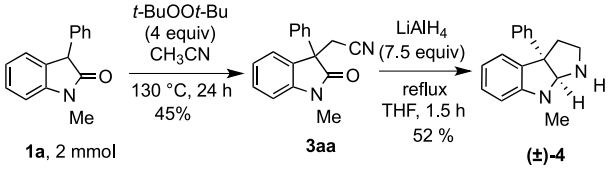
[a]Conditions: **1** (0.15 mmol), **2a** (1.5 mL, 0.1 M), *t*-BuOO*t*-Bu (4 equiv), 130 °C, under Ar, 24 h.

metal catalysts to generate acetonitrile radicals for additions to alkenes were not effective in these couplings. After an extensive investigation of the reaction conditions (see the SI), control reactions revealed that the metal catalyst was unnecessary, leading to a very straightforward oxidative method for introducing the cyanomethylene functionality to an oxindole. The optimum reaction conditions entailed heating a solution of **1a** in acetonitrile (0.1 M) in the presence of *t*-BuOO*t*-Bu (4 equiv) to 130 °C for 24 h, which provided **3aa** in 48% yield.

Subsequently, a range of 3-substituted oxindoles were explored for the cyanomethylenation at the C3 position with acetonitrile (Scheme 3). Electron-neutral (**3aa**), electron-donating (**3ba**, **3ca**, **3ea**, **3fa**), and electron-withdrawing (**3da**) substituents on the phenyl ring were all well tolerated under the optimal reaction conditions. Substituents at the different positions did not affect the yields significantly. The 6-chloro-oxindole also gave the corresponding product **3ga** in 63% yield. The *N*-benzyl-substituted oxindole also exhibited good reactivity, providing **3ha** in 52% yield.

The cyanomethylenated products derived from three-substituted oxindoles are versatile intermediates in organic synthesis and can be readily converted into other important building blocks including phenyl-substituted pyrroloindolines.[22] To show the utility of this method in producing useful precursors, a further transformation was carried out on product **3aa** (Scheme 4). First, the 2-mmol-scale synthesis of product

Scheme 4. Scale-Up and Synthetic Transformation of the Cyanomethylenated Product 3aa



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3aa proceeded successfully, delivering **3aa** in 45% yield. The reductive cyclization of oxindole **3aa** using $LiAlH_4$ provided pyrroloindoline **4** in 52% yield. Overall, this route provides comparable or better efficiencies relative to other routes for generating target **4** with aryl substitution at the angular carbon.[23]

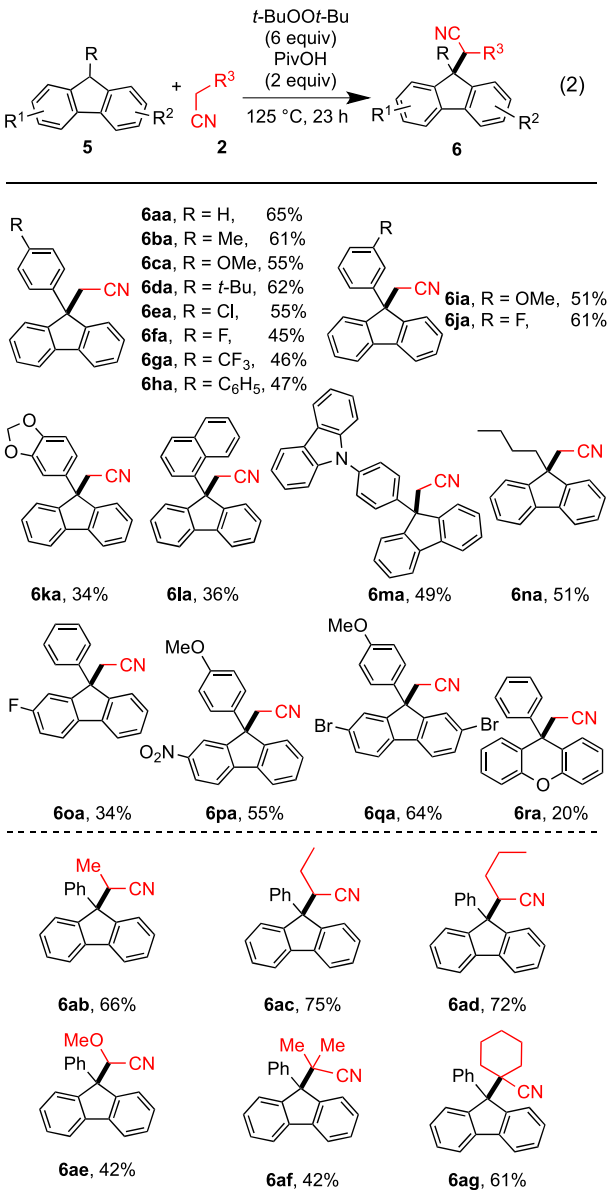
The application of the above conditions to the coupling of 9-phenyl-9*H*-fluorene **5a**[24] and acetonitrile **2a** provided product **6aa** (eq 2) in 49% yield (see the SI). Further experimentation (see the SI) ultimately revealed that carboxylic acid additives enhanced the outcome. The optimum conditions were *t*-BuOO*t*-Bu (6 equiv) with PivOH (2 equiv) at 125 °C for 23 h, which provided **6aa** in 65% yield (Scheme 5).

With these conditions in hand, the scope of the reaction with respect to the fluorene component and alkyl nitrile was evaluated (Scheme 5). First, different para-substituted aryl groups at C9 on the fluorene were explored. With either electron-donating or electron-neutral substituents, the products were formed in good yield (**6aa**–**da**). Those bearing an electron-withdrawing chloro, fluoro, trifluoromethyl, or phenyl group gave the corresponding products in a slightly lower yield (**6ea**–**ha**). C9-Aryl groups with either methoxy or fluoro groups at the meta position reacted smoothly with **2a** to give **6ia** and **6ja** in 51 and 61% yield, respectively. A range of bulkier aryl groups could be tolerated at C9 of the fluorene, including acetal-derived, naphthyl, and *para*-carbazolylphenyl groups, affording the corresponding products in 34–49% yield (**6ka**–**ma**). Of particular note, 9-butylfluorene can also react with acetonitrile to afford **6na** in 51% yield.

Notably, functional groups such as methoxy, halogen, and nitro can be employed in different positions on the fluorene component (**6oa**–**qa**). 9-Phenyl-9*H*-xanthene **5r** also successfully reacted with acetonitrile, albeit with 20% yield (**6ra**). Next, other alkyl nitriles, such as propionitrile, *n*-butyronitrile, *n*-valeronitrile, and 2-methoxyacetonitrile, were discovered to be effective in this reaction, affording the corresponding fluorenes in 42–75% yield (**6ab**–**ae**). The steric hindrance of these compounds is manifest as judged by the proton and carbon NMR spectra, where the phenylfluorene is desymmetrized from hindered rotation. Tertiary nitriles, such as isobutyronitrile **2f** and cyclohexanecarbonitrile **2g**, smoothly underwent oxidative C–H activation at the α-position to give **6af** and **6ag** in 42 and 61% yield, respectively. Notably, these adducts arise from the approach of two hindered tertiary centers and give rise to compounds with two adjacent quaternary centers. However, some other nitriles were unreactive, including cyanocyclopropane, 2-methoxypropionitrile, bromoacetonitrile, and ethyl cyanoacetate.

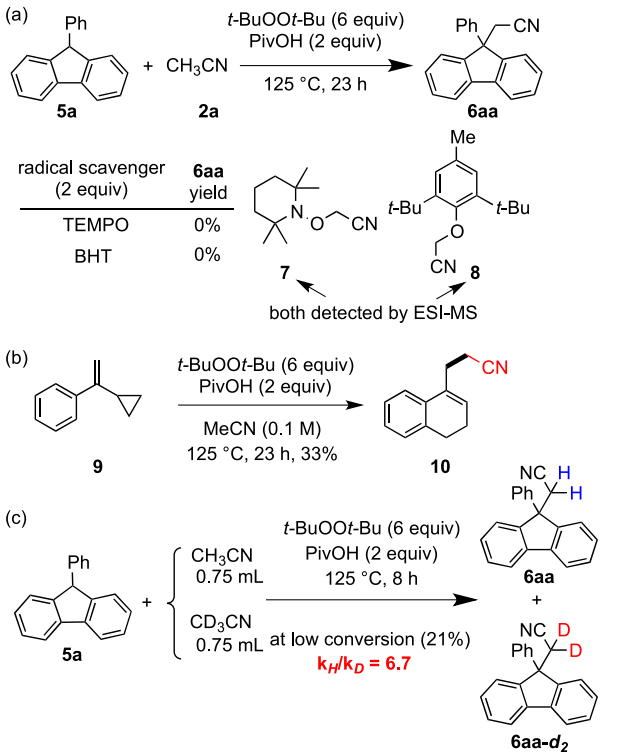
Some control experiments were carried out to gain a better understanding of the mechanism (Scheme 6). The cyanome-

Scheme 5. Reaction of Various 9-Substituted Fluorenes with Alkyl Nitriles[a]



[a]Conditions: **5** (0.15 mmol), **2** (1.5 mL, 0.1 M), *t*-BuOO*t*-Bu (6 equiv) PivOH (2 equiv), 125 °C, under Ar, 23 h.

Scheme 6. Control Experiments



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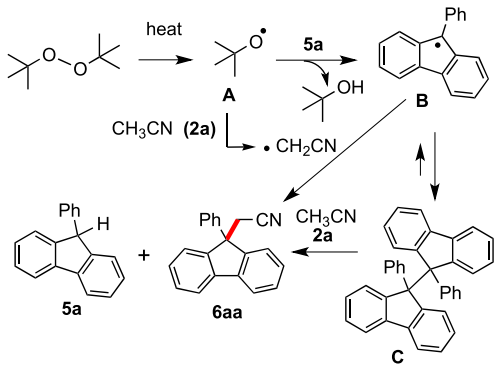
thylenation reaction was completely inhibited when 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,6-di-*tert*-butyl-4-hydroxytoluene (BHT) was added into the reaction system (Scheme 6a). Moreover, the corresponding adducts **7** and **8** were detected in the reaction mixture by ESI-MS (see the SI). In addition, we found that compound **10** was isolated in 33% yield from (1-cyclopropylvinyl)benzene **9** (Scheme 6b). This adduct arises from sequential ring opening of a cyclopropylmethyl radical intermediate and cyclization,[13cb] and this intermediate presumably arises from the addition of a cyanomethylenyl radical to the alkene. Together, the above experiments suggest that the current reaction is triggered by a free-radical process. Moreover, all of the experiments point to formation and reaction of a cyanomethylenyl radical. Next, an intermolecular kinetic isotopic effect (KIE) experiment was performed in a mixture of acetonitrile (0.75 mL) and acetonitrile-d_3 (0.75 mL). As a result, a k_H/k_D = 6.7 was obtained (Scheme 6c), indicating that the acetonitrile C−H bond cleavage is involved in a product-determining step.

The lack of adducts from either the fluorene or the oxindole with any of the radical traps described above (Scheme 6a,b), implies that these stabilized radicals are less reactive than the cyanomethyl radical. It is likely that the resting states of the fluorenyl or oxindole radicals are the dimers, as we[5,25] and others[26] have observed previously under oxidative conditions. Integrating the formation of the dimer with reports of related systems,[13f,16,27] we propose the mechanism outlined in Scheme 7. First, *t*-BuOO*t*-Bu decomposes to give the *tert*-butoxyl

Scheme 7. Proposed Mechanism



radical (**A**) at high temperature. The oxindole[27] or fluorene undergoes facile hydrogen atom abstraction due to the weak C−H bonds (71 and 72 kcal/mol, respectively)[5b] forming *tert*-butanol and the corresponding radical **B**, which is in equilibrium with its dimer **C**. Substrates lacking the 9-phenyl groups (e.g., fluorene) were not reactive, presumably due to the greater barrier to formation of the corresponding radical **C**, consistent with this hypothesis. In addition, the dimers of **1a** (**C′**)[5b] and **5a** (**C**)[28] both gave rise to the product under the reaction conditions (see the SI). At this stage, the excess *t*-BuOO*t*-Bu may cause the alkyl nitrile (CH bond dissociation energy = 96 kcal/mol)[29] to undergo a hydrogen atom abstraction to generate the radical. Subsequent recombination with the oxindole or fluorene radical or dimer would generate the product (e.g., **6aa** in Scheme 7). Alternately, the dimer (**C**) may react directly with the nitrile to generate one equivalent of product (**6aa**) and one equivalent of the starting material (**5a**). Regardless, very hindered forms of the radical **B** are not expected to be able to react, which is supported by the lack of reactivity with 9(2′-methylphenyl)fluorene.

In summary, we have developed a novel and efficient metal-free method to activate the C(sp^3)−H bond of alkyl nitriles for the synthesis of highly functionalized fluorene and oxindole derivatives. On the basis of the control experiments, the transformation is proposed to proceed via a radical process. None of the compounds described herein have been previously reported, illustrating the absence of methods to generate such hindered nitrile-derived structures. In particular, there are few examples in the literature of any nitrile-derived fluorenes.[18−20] Thus this method contributes to new chemical space as well as provides a means to generate highly hindered quaternary centers, including compounds with adjacent quaternary/tertiary or quaternary/quaternary centers.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00160.

Experimental procedures, reaction condition screening, analytical data, and copies of spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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