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Synthesis of Fluorenes with an All-Carbon Quaternary Center *via* Palladium-Catalyzed Dual Arylation using Cyclic Diaryliodonium Triflates

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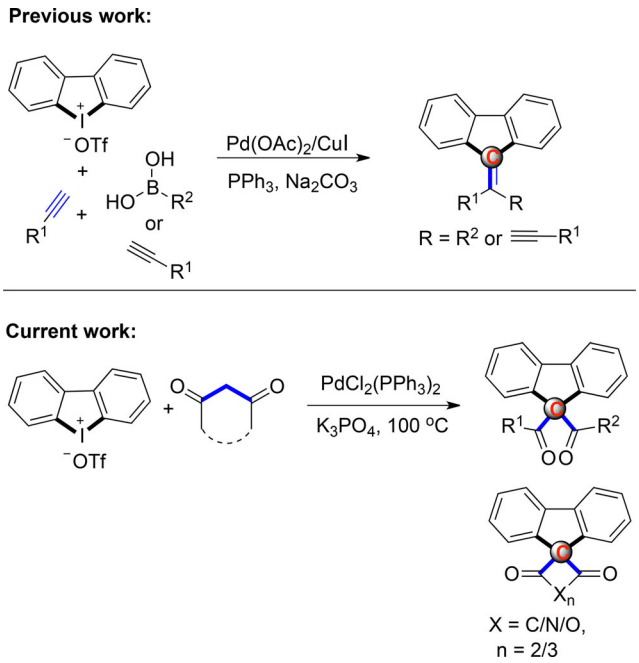
Abstract: Catalyzed by palladium species, cyclic diaryliodonium salts underwent dual C-aryl functionalization smoothly with activated methylene sources. With this new finding, a series of diversified fluorenes with an all-carbon quaternary center was quickly constructed. Moreover, our approach also provided various novel spirofluorenes containing barburate acid or indane motifs which are featured in medicinal drugs and functional materials.

Keywords: arylation; diaryliodonium triflates; fluorenes; palladium; quaternary center

Fluorene is an important structural motif, widely present in a variety of organic functional materials and natural products.[1,2] Thus, the synthesis of fluorene has attracted extensive studies,[3] including traditional Freidel–Crafts reactions,[4] modification of the existing fluorene core structures,[5] and miscellaneous methods.[6] Although the present methods are efficient to prepare various fluorenes, they still suffer from poor accessibility of starting materials, limited substrate scopes, and harsh reaction conditions. Therefore, it is desirable to seek other general and practical strategies to quickly access structurally diversified fluorenes.

Arylation is of high importance in the construction of intricate molecules by installing a variety of aromatic rings on the existing scaffold. Undoubtedly, aryl halides, especially iodoarenes are highly valuable arylating reagents. Recently, hypervalent diaryliodonium compounds have attracted broad research interest as surrogates to aryl iodides due to their high reactivity and environmentally benign nature.[7] In the literature, linear diaryliodoniums have mostly been explored, but the arylation process suffers from an atom economical issue because half of the fragments were often wasted.[8] Cyclic diaryliodonium salts have stood out to overcome these drawbacks due to their synthetic potential to undergo dual arylations. Moreover, these unique species can set up cascade reactions to construct more complicated molecules.[9]

In our previous study, the methylene uniut in terminal alkenes was successfully inserted into cyclic diaryliodonium compounds *via* a multicomponent reaction, finally leading to the formation of fluorenes.[10] However, the method is limited to the synthesis of 9-alkylene-9*H*-fluorenes (Scheme 1). We envisioned that 9,9-disubstituted fluorenes could be accessed if an enolizable methylene (CH_2) unit was employed as an arylation acceptor. It is well known that methylene groups substituted with dual electron withdrawing groups can act as versatile nucleophiles in various chemical transformations under basic conditions.[11] Herein, we report an efficient Pd-catalyzed dual arylation of enolizable compounds with cyclic diaryliodo-

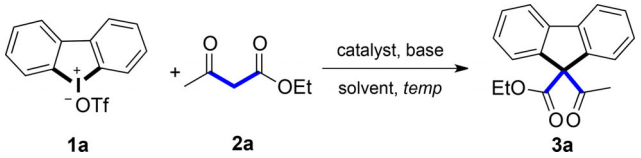


Scheme 1. The strategies to build fluorenes with cyclic diaryliodonium salts.

nium species. The work is able to provide a quick access to a variety of 9,9-dicarbonylfluorenes which have been reported as functional materials.[12] Moreover, with our approach, a series of novel spirofluorenes with potential drug-like properties can be also synthesized. A notable feature of the transformation is the formation of an all-carbon quaternary center which always remains a challenge to be obtained in one-pot operations.[13] Meanwhile, spiro rings are important motifs in bioactive natural products and medicines, and their construction is also highly demanded.[14]

Our current study began with diaryliodonium triflate **1a** and ethyl acetoacetate **2a** to set up a model reaction. Since the arylation of enolizable methylene species mediated by copper salts is reported,[15] a widely used catalyst system, namely CuI/proline,[16] was tried at the beginning. As expected, the desired 9,9-dicarbonylfluorene **3a** was obtained albeit in a low yield (Table 1, entry 1). Meanwhile, a common palladium species available in our lab, $Pd(OAc)_2$ was also investigated, giving a slightly better result (entry 2). The following solvent screening found that the yields with protic solvents were poor while other solvents did not make much difference (entries 2–8). Finally, 1,2-dichloroethane was chosen for the following study (entry 6). The investigation of palladium catalysts selected $PdCl_2(PPh_3)_2$ for further condition optimization (entries 9–13). The subsequent test of bases revealed potassium phosphate to be the best (entry 21). To our delight, **3a** was prepared in 82% yield when the reaction temperature was increased to 100 °C (entry 22). A short reaction time dramatically decreased the yield while a longer time was not necessary (entries 24 and 25). It is worth noting that the reaction did not happen in the absence of either bases or catalysts (data not shown).

Table 1. Optimization of the conditions for the reaction of **1a** and **2a**.[a]



1a **2a** **3a**

Entry	Catalyst	Base	Solvent	T [°C]	Yield [%]
1	CuI/proline	Cs_2CO_3	DMSO	60	16
2	$Pd(OAc)_2$	Na_2CO_3	DMSO	60	23
3	$Pd(OAc)_2$	Na_2CO_3	toluene	60	22
4	$Pd(OAc)_2$	Na_2CO_3	DMF	60	25
5	$Pd(OAc)_2$	Na_2CO_3	DMA	60	17
6	$Pd(OAc)_2$	Na_2CO_3	DCE[d]	60	31
7	$Pd(OAc)_2$	Na_2CO_3	MeOH	60	7
8	$Pd(OAc)_2$	Na_2CO_3	*i*-PrOH	60	9
9	$PdCl_2$	Na_2CO_3	DCE	60	23
10	$Pd_2(dba)_3$	Na_2CO_3	DCE	60	35
11	$Pd(PPh_3)_4$	Na_2CO_3	DCE	60	25
12	$PdCl_2(dppf)_2$	Na_2CO_3	DCE	60	28
13	$PdCl_2(PPh_3)_2$	Na_2CO_3	DCE	60	39
14	$PdCl_2(PPh_3)_2$	K_2CO_3	DCE	60	41
15	$PdCl_2(PPh_3)_2$	Cs_2CO_3	DCE	60	43
16	$PdCl_2(PPh_3)_2$	KO-*t*-Bu	DCE	60	25
17	$PdCl_2(PPh_3)_2$	NaOAc	DCE	60	23
18	$PdCl_2(PPh_3)_2$	Li_2CO_3	DCE	60	27
19	$PdCl_2(PPh_3)_2$	$NaHCO_3$	DCE	60	33
20	$PdCl_2(PPh_3)_2$	DBU[d]	DCE	60	14
21	$PdCl_2(PPh_3)_2$	K_3PO_4	DCE	60	49
22	$PdCl_2(PPh_3)_2$	K_3PO_4	DCE	100	82
23	$PdCl_2(PPh_3)_2$	K_3PO_4	DCE	120	79
24[b]	$PdCl_2(PPh_3)_2$	K_3PO_4	DCE	100	41
25[c]	$PdCl_2(PPh_3)_2$	K_3PO_4	DCE	100	81

[a] Unless otherwise stated, **1a** (1.0 equiv.), **2a** (1.2 equiv.), catalyst (5 mol%), base (3.0 equiv.), 15 h, argon.
[b] For 5 h.
[c] For 24 h.
[d] DBU = 1,5-diazabicyclo[5.4.0]undec-5-ene; DCE = 1,2-dichloroethane.

With the optimal reaction conditions in hand, the scope of enolizable compounds was investigated (Figure 1). Both methyl and *tert*-butyl esters of acetoacetate gave the desired fluorenes **3b** and **3c** in good yields. 1,3-ketomethanes including acetoacetone, hexafluoroacetoacetone, and dibenzoylmethane, that is an ingredient in sunscreen products,[17] also resulted in the corresponding fluorenes **3d–3f** in modest to good yields. With the same strategy, sulfone and phosphate functional groups can be installed in the fluorenes (**3g** and **3h**). Esters of benzoylacetate and malo-

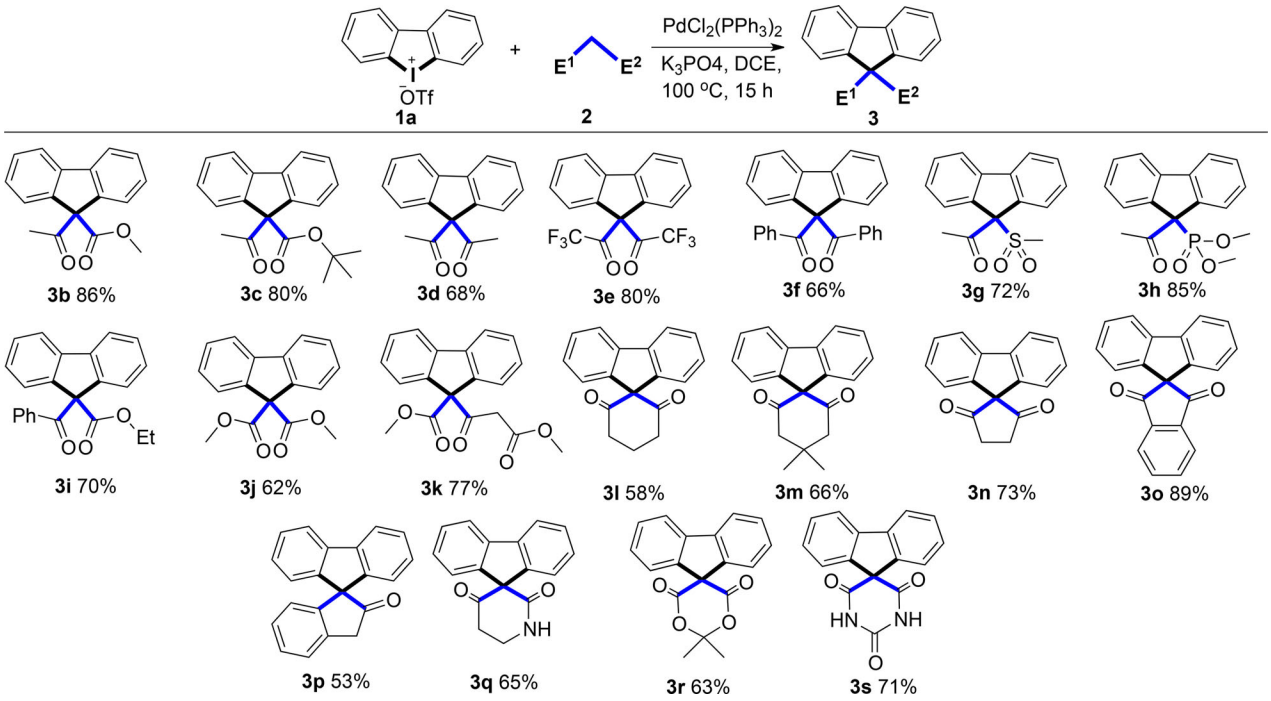


Figure 1. The scope of enolizable methylene nucleophiles. *Conditions*: **1a**, nucleophile (1.2 equiv.), $PdCl_2(PPh_3)_2$ (5 mol%), K_3PO_4 (3.0 equiv.), argon.

nate are suitable substrates to provide fluorenes **3i** and **3j** which could undergo further transformations to build other complex molecular scaffolds. When symmetrical 3-oxopentanedioic ester with two enolizable methylenes was used, only one methylene species was incorporated in the newly formed ring of product **3k**, demonstrating that the preferential formation of the middle-sized five-membered ring is a major driving force in the construction of fluorenes. Moreover, a series of spirofluroenes **3l–3s** was successfully obtained when cyclic diones and other cyclic enolizable species were employed. Especially 2-indanone with only one electron-withdrawing carbonyl group also underwent the transformation smoothly, providing the unique spiro structure in **3p**. Meanwhile, fluorenes **3o** and **3p** contain a special indane unit that is often employed in dyes.[18] Fluorenes **3q–3s** with spiro cyclic lactam, dilactone, and dilactam structures are more drug-like since they resemble the barbituric acids present in nervous system depressant agents and anticancer agents.[19] Our results have demonstrated a broad substrate generality, and a variety of unique fluorenes with an all-carbon quaternary center could be quickly obtained. To the best of our knowledge, α-aryl quaternary centers are present in natural products and pharmacologically important compounds, including diazonamide, physostigmine, and oxindole alkaloids.[20] Our new constructed fluorenes might provide novel structural leads in the discovery of new drugs as well as functional materials.

To further verify the synthetic generality of this transformation, a variety of symmetrical and unsymmetrical cyclic diaryliodonium triflates was then examined (Figure 2). With the ethyl ester of acetoacetate **2a**, fluorenes **4a–4c** were successfully obtained regardless of the electronic properties of the substitutents on the iodoniums. As mentioned above, indane is an important fragment so 1,3-indanedione was employed as an enolizable methylene nucleophile to react with the various cyclic diaryliodoniums. Thus, a broad range of novel fluroenes containing a spiroindane motif was successfully constructed. In our study, cyclic diaryliodoniums with electron-donating substituents gave slightly higher yields than those with electron-withdrawing ones (**4a** *vs.* **4c**, and **5d–5e** *vs.* **5i–5m**).

Considering that the indane motif is important in the dye and solar cell functional material fields,[21] spirofluorenes **3o** and **5** with an indane motif were selected to test their photophysical properties (Figure 3 and Supporting Information, Figure S1). Similar to 1,3-indanedione itself, most of these tested fluorenes displayed two discrete bands in the UV/Vis absorption spectra. However, the second band is red-shifted while the first one has a nearly unchanged peak at 300 nm compared to 1,3-indandione. Moreover, the absorptions of **5d, 5f** and **5l** extend from the visible light region to the ultraviolet light region (Figure 3). More surprisingly, the second absorption band spans a broader wavelength range (from 350 to 550 nm

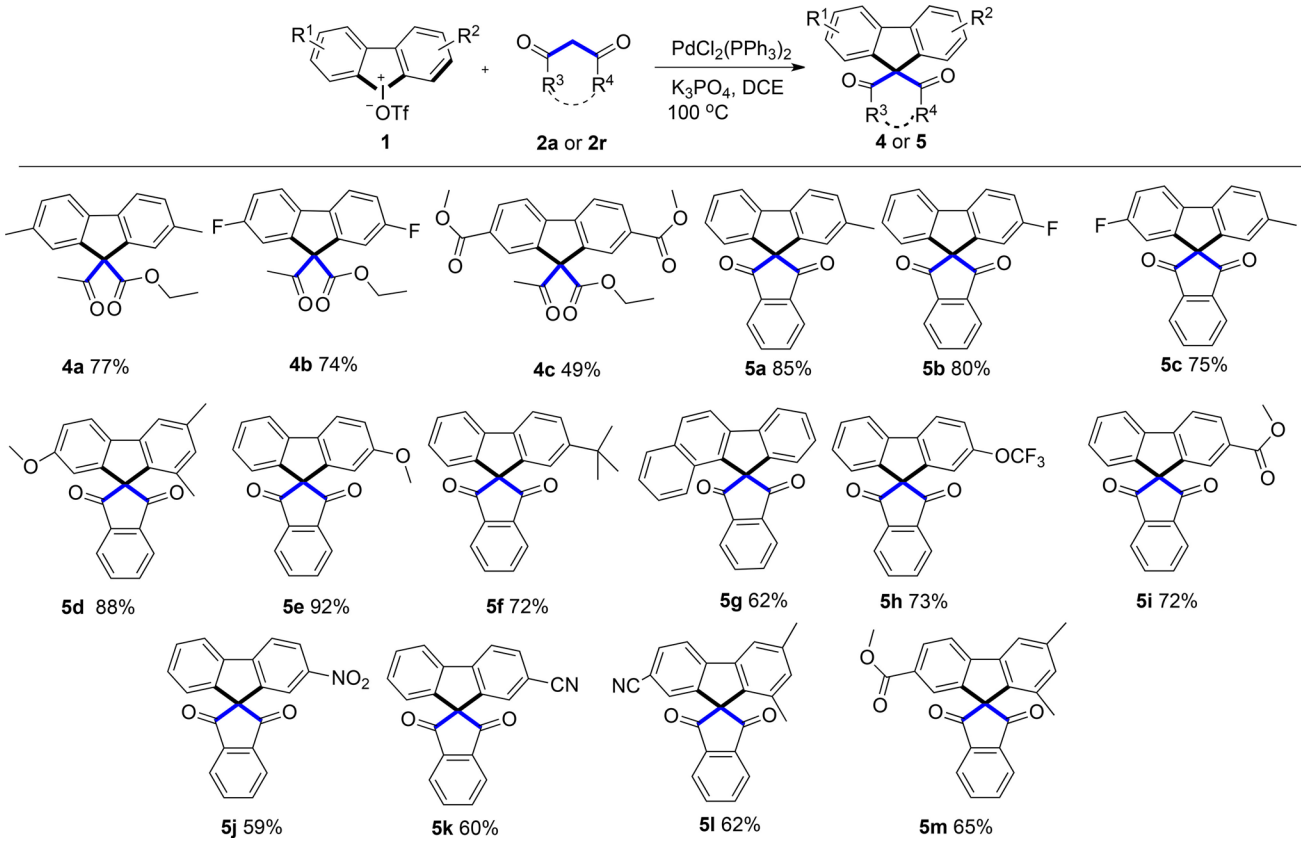


Figure 2. The scope of cyclic diaryliodonium trfilates **1**. *Conditions:* **1** (0.23 mmol), **2a** or **2r** (0.28 mmol), $PdCl_2(PPh_3)_2$ (5 mol%), K_3PO_4 (3.0 equiv.), DCE (3.0 mL), 15 h, argon.

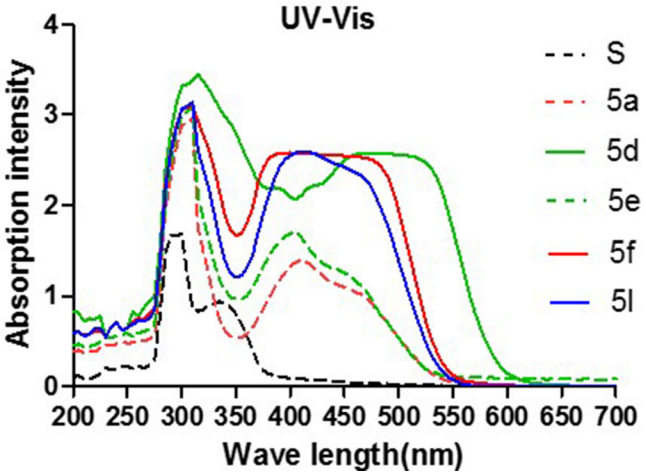
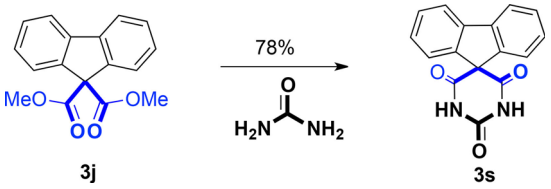


Figure 3. UV/Vis absorption spectra of the selected compounds at 1.0 μM in CH_3CN, 25 °C. Note: S is 1,3-indanedione.

wavelength for **5f** and **5l**, and from 400 to 600 nm for **5d**), which is highly desirable in the development of solar cell functional materials.[22] A further study on their photophysical properties is underway.



Scheme 2. The transformation of **3j** to **3s**.

In the following study, the dimethyl ester fragment of **3j** was reacted with urea under refluxing conditions using ethanol as solvent (Scheme 2), resulting in the formation of spirofluorene **3s**. Although **3s** could be also constructed from a cyclic iodonium in our method, the further transformation of **3j** should provide other novel complex spirofluorenes. The application of such transformations with other synthetic spirofluorenes are under study.

In summary, structurally diverse fluorene derivatives with an all-carbon quaternary center can be concisely conctructed *via* dual C–C arylation using cyclic diaryliodonium salts and enolizable methylene species by our method. Moreover, our method can also provide a series of spirofluorenes containing different heterocyclic motifs that might endow the fluorenes

with potential pharmalogical or photophysical properties. Currently, the biological evaluation and photophysical study of these special spirofluorenes is under way.

Experimental Section

General Procedure for the Construction of Fluorenes 3

A Schlenk tube was charged with cyclic diaryliodonium triflate **1** (100 mg), K_3PO_4 (3 equiv.), and $PdCl_2(PPh_3)_2$ (5 mol%). The tube was evacuated and backfilled with argon three times, and a solution of **2** (1.2 equiv.) in 1,2-dichloroethane (3.0 mL) was added *via* a syringe under argon protection. The tube was sealed and heated to 100 °C in an oil bath. After 15 h, the reaction mixture was diluted with dichloromethane (20 mL), washed with H_2O (2 mL *x* 3), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography on silica gel (petroleum to 1% EtOAc in petroleum) to give fluorene **3**.

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