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Three-Component Pd/Cu-Catalyzed Cascade Reactions of Cyclic Iodoniums, Alkynes, and Boronic Acids: An Approach to Methylidenefluorenes

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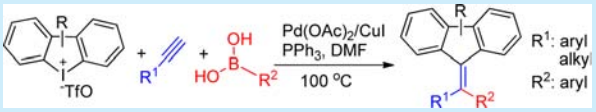
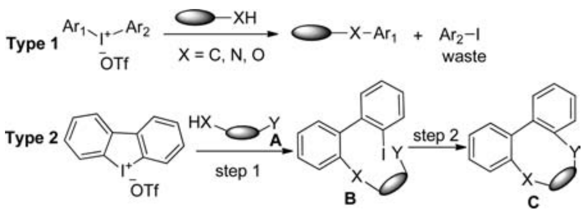
Supporting Information



ABSTRACT: Linear diaryliodonium salts are widely used as arylating reagents for C−C and C−X bond formation. Meanwhile, synthetic applications of cyclic iodoniums are relatively rare although they offer the opportunity to set up reaction cascades. We demonstrate an atom and step economical three-component reaction involving cyclic diphenyleneiodoniums, alkynes, and boronic acids, resulting in the construction of methylidenefluorenes in a single operation. Our route enables facile access to both symmetrical and unsymmetrical methylidenefluorene derivatives, compounds that have attracted interest due to their optical properties.

Linear diaryliodonium salts have been broadly studied as arylating agents to construct C−C[1] and C−X bonds.[2] In the arylation reactions with linear diaryliodoniums, the formation of an iodoarene Ar_2−I (Type 1 reaction, Scheme 1) is usually ignored and accepted as an unwanted byproduct. With cyclic iodoniums, the iodoarene remains as a part of the arylated product **B**. Thus, the reaction is more atom economical compared to linear iodoniums. Moreover, if the reaction partner **A** contains a second functional group that is able to react with iodoarenes, **B** will undergo further transformation to provide more structurally complicated molecules **C** (Type 2 reaction). However, there are few reports that focus on the cyclic iodoniums although they are potentially valuable synthons. One major reason could be that cyclic iodoniums have a rigid geometry in regards to the tricoordinate iodine complex and a concomitant tendency to homolytical decomposition compared to linear iodoniums.[3] Recently, the groups of Detert and Nachtsheim reported the synthesis of carbazole derivatives from cyclic diphenyleneiodoniums with anilines using Pd catalysts.[4] We have also discovered that a variety of carbazoles could be obtained easily from cyclic diphenyleneiodoniums with anilines, amines, and sulphonamides, mediated by $Cu(OAc)_2$.[5] In the construction of carbazoles with cyclic iodoniums, the amino group reacts twice as a bis-nucleophile. We envisioned that other scaffolds could be accessed from cyclic iodoniums by reaction with compounds that contain two different intercepting functional groups XH and Y.

Scheme 1. Arylation Reactions with Linear and Cyclic Iodonium Salts



Fluorene-based derivatives are present in a number of biologically active compounds[6] and advanced materials.[7] The subfamily of methylidenefluorenes have attracted attention due to their unique structure and interesting optical properties.[8] A series of de novo synthetic methods have been developed to construct these fused aromatic rings. The Larock group synthesized 9-alkylidene-9*H*-fluorenes by a Pd-catalyzed coupling of aryl iodides and 1-aryl-1-alkynes.[9] Later, they reported an alternative method to access 9-fluorenylidenes through Pd-catalyzed annulation of *ortho*-halogen substituted styrenes with in situ generated arynes.[10] Gevorgyan et al. took advantage of a C−H activation strategy to construct the methylidenefluorene frame.[11] In addition to these representative synthetic strategies, miscellaneous methods have also contributed to the development of methylidenefluorene synthetic chemistry.[12]

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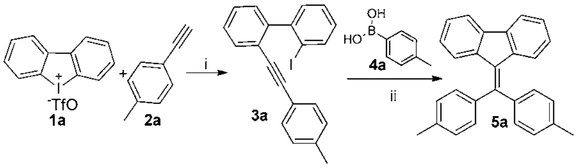
Multicomponent reactions represent an important approach to aromatic skeletons, as they construct a complex product by formation of multiple bonds between several substrates in one single operation.[13] Chen et al. have achieved a multicomponent reaction involving linear iodoniums to prepare quinolines[14] and quinazolines[15] with linear iodoniums. However, one problem remains, as byproduct iodoarenes were ignored. Based on literature precedents that alkynes can be arylated by linear diaryliodoniums,[16] we envisaged that **3a** resulting from the arylation of alkyne **2a** with cyclic iodoniums **1a** could undergo an intramolecular cyclization catalyzed by Pd species. A subsequential incorporation of a nucleophile such as a boronic acid **4a** will lead to a rapid formation of fluorene derivatives (Scheme 2).

Scheme 2. A Proposed Multicomponent Route to methylidenefluorenes



Here, we report this novel multicomponent cascade reaction to construct methylidenefluorenes by Pd/Cu-catalyzed alkynylation/annulation of cyclic diphenyleneiodoniums, alkynes, and boronic acids.

Table 1. Optimization of Reaction Conditions for 3a from 1a and 2a[a]

entry	catalysts	base	solvent	yield
1	CuI	Na_2CO_3	DMF	17
2	$Pd(PPh)_2Cl_2$, CuI	Na_2CO_3	DMF	23
3	$PdCl_2$, CuI, PPh_3	Na_2CO_3	DMF	1
4	$Pd(OAc)_2$, PPh_3	Na_2CO_3	DMF	43
5	$Pd(PPh_3)_4$, CuI	Na_2CO_3	DMF	51
6	$Pd(OAc)_2$, CuI, PPh_3	Na_2CO_3	DMF	89
7	$Pd(OAc)_2$, CuI, PPh_3	K_2CO_3	DMF	38
8	$Pd(OAc)_2$, CuI, PPh_3	K_3PO_4	DMF	20
9	$Pd(OAc)_2$, CuI, PPh_3	Et_3N	DMF	33
10	$Pd(OAc)_2$, CuI, PPh_3	Cs_2CO_3	DMF	10
11	$Pd(OAc)_2$, CuI, PPh_3	Na_2CO_3	toluene	59
12	$Pd(OAc)_2$, CuI, PPh_3	Na_2CO_3	dioxane	21
13	$Pd(OAc)_2$, CuI, PPh_3	Na_2CO_3	DCE	29

[a] Conditions: **1a** (0.23 mmol), **2a** (1.2 equiv), Pd catalyst (10 mol %), CuI (20 mol %), PPh_3 (30 mol %) when used, base (3.0 equiv), solvent (2 mL), rt, 3 h, Ar. DCE: 1,2-dichloroethane.

To test our hypothesis, we initially investigated the arylation of *p*-tolylacetylene **2a** with cyclic iodonium **1a** using CuI as a catalyst and Na_2CO_3 as the base in DMF under an argon atmosphere at rt (Table 1). The reaction gave the desired compound **3a** albeit in 17% yield (entry 1). To further optimize the reaction conditions, various Pd catalyst systems were examined (entries 2−6), and $Pd(OAc)_2$/CuI in the presence of the PPh_3 ligand was discovered to be optimal (entry 6). Next, different bases including K_2CO_3, K_3PO_4, Et_3N, and Cs_2CO_3 were screened, and Na_2CO_3 was found to be the best in promoting the reaction (entries 7−10). Finally, solvents were found to play an important role in the efficiency of the reaction, with DMF giving the highest yields (entries 11−13). Thus, the optimal catalytic system for this transformation was $Pd(OAc)_2$/CuI/PPh_3 in DMF.

Since 2-iodo-1,1′-biphenyl **3a** was obtained, we envisaged that the same catalyst system should be suitable for further cyclization followed by the interception of nucleophiles by the vinylpalladium intermediate. Indeed, methylidenefluorene **5a** was obtained when *p*-tolylboronic acid **4a** was added as a nucleophile when the reaction was performed at a higher temperature (Table S1, Supporting Information (SI)), with the highest yield (91%) achieved at 100 °C.

Next, we investigated whether these two stepwise reactions could be coupled as a cascade whereby **1a**, **2a**, and **4a** react in an atom and step economical fashion to form the methylidenefluorene in a single operation. To our delight, **5a** was obtained in an excellent yield (93%) by stirring the three components at 100 °C (Figure 1). To explore the general utility of our method, a variety of boronic acids were investigated for this transformation. Phenylboronic acids with substituents regardless of electron-withdrawing or -donating properties were suitable substrates. It appears that the strong electron deficiency of the substituted groups on phenylboronic acids resulted in lower yields (**5e**, **5i**). It is noteworthy that the heterocyclic furan boronic acid also gave the expected methylidenefluorene in a good yield (**5k**).

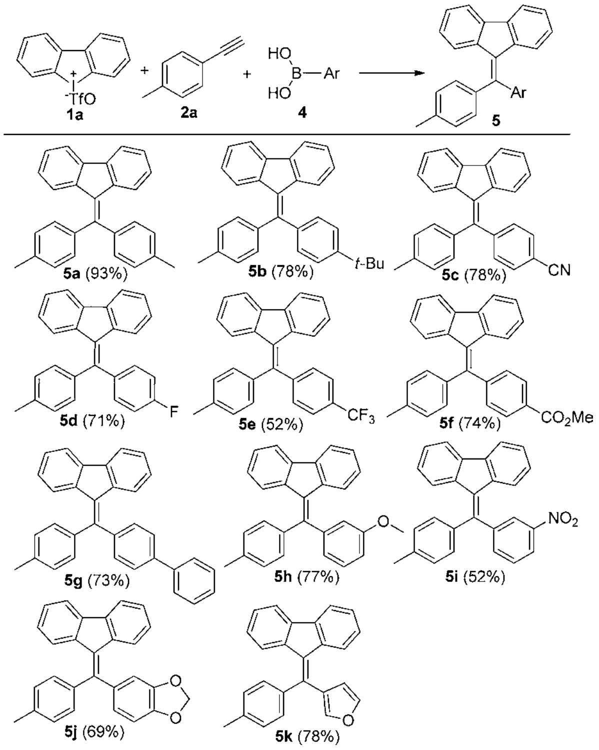


Figure 1. Scope of boronic acids. Conditions: **1a** (0.23 mmol), **2a** (1.1 equiv), **4** (1.2 equiv), $Pd(OAc)_2$ (10 mol %), CuI (20 mol %), PPh_3 (30 mol %), Na_2CO_3 (3.0 equiv), DMF (2.0 mL), 100 °C, 12 h, Ar.

To further explore the synthetic versatility of the multicomponent reactions, we examined the scope of alkynes in this process (Figure 2). Not only terminal aryl but also alkyl alkynes (for **6i**, **6j**) were found to perform well in the reactions. Among the aryl alkynes, those with electron-deficient groups gave methylidenefluorenes in lower yields (**6e−6h** vs **6a−d**). It is notable that halogens including fluorine and chlorine were well tolerated in the reactions, providing an opportunity for further functionalization of the products.

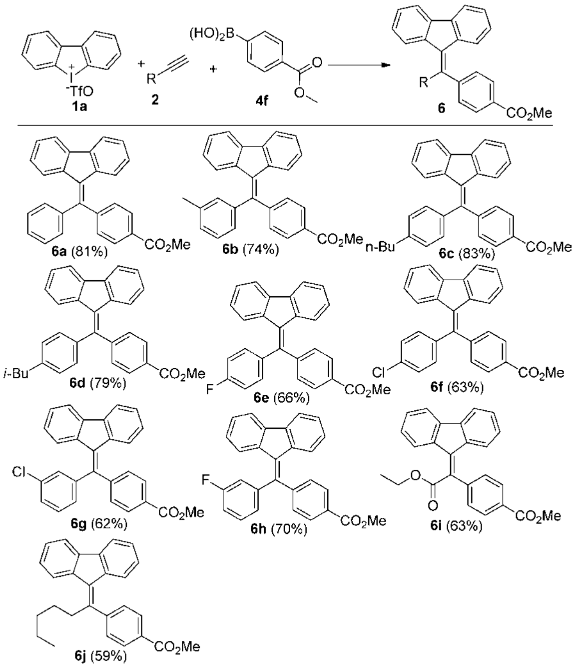


Figure 2. Scope of alkynes. Conditions: **1a** (0.23 mmol), **2** (1.1 equiv), **4f** (1.2 equiv), $Pd(OAc)_2$ (10 mol %), CuI (20 mol %), PPh_3 (30 mol %), Na_2CO_3 (3.0 equiv), DMF (2.0 mL), 100 °C, 12 h, Ar.

Finally, a variety of unsymmetrical cyclic diphenyleneiodoniums were tried to generate more diverse methylidenefluorenes (Figure 3). In the first trials with *p*-tolylacetylene **2a** and *p*-tolylboronic acid **4a**, the iodoniums with different substitutions regardless of their electron property provided the expected methylidenefluorenes (**7a**−**f**), demonstrating the generality of this three-component cascade reaction. To our knowledge, chemoselective arylation with unsymmetrical linear iodoniums are not well solved except for cases influenced by large differences in steric and electronic effects.[17] In this work, it was also of interest to investigate the chemoselectivity of our multicomponent reactions with unsymmetrical cyclic diphenyleneiodoniums to give isomeric methylidenefluorenes (**7g**−**7j**). Under our conditions, it seemed that the electronic effect had an influence on chemoselectivity in the reactions. Electronically poor substituted unsymmetrical cyclic diphenyliodoniums gave **7h** (−CN) in high chemoselectivity (1/4) while electronically rich diphenyliodoniums gave **7g** (−OMe) in a mixture of 65/35. Meanwhile, the steric effect of the 3-*tert*-butyl substituent was not significant, and the chemoselectivity was 61/39 (**7i**). Based on our observations, we envisaged that the chemoselectivity should be synergistically enhanced if one side of cyclic diphenyleneiodoniums was electron-rich and the other side electron-poor. Thus, compound **7j**, as predicted by our hypothesis, was indeed obtained in higher chemoselectivity (1/9). Further investigations to enhance the chemoselectivity of unsymmetrical iodoniums are underway.

Since all possible pairwise combinations of iodonium, acetylene, and boronic acid are able to react together,[18,19] it was of importance to investigate the mechanism by which the three components underwent cascade reactions under our conditions. Three control reactions were then performed, in which two of the three components, cyclic diphenyleneiodonium **1a**, *p*-tolylacetylene **2a**, and (4-(methoxycarbonyl)phenyl)boronic acid **4a**, were mixed together under the same conditions for the synthesis of methylidenefluorenes (Figure S1, SI). A mixture of **3a** and the unexpected 9-(4-methylbenzylidene)-9*H*-fluorene **8** was obtained when the iodonium **1a** was treated with alkyne **2a**. In the other two control experiments involving boronic acid **4a**, they unexpectedly provided dimethyl [1,1′-biphenyl]-4,4′-dicarboxylate **9** exclusively, likely resulting from self-coupling of *p*-tolylboronic acid.[20] The findings further confirmed that the reactivity of cyclic iodoniums is different from that of linear iodoniums.[3] Also, the coupling reaction of boronic acid and the alkyne was surprisingly suppressed under our conditions. Based on these observations, a mechanism was thus proposed (Scheme 3). Initially, Pd(0) resulting from the reduction of Pd(II) undergoes oxidative addition with the iodonium to form organopalladium(II) **D**. Then, a transmetalation between **D**

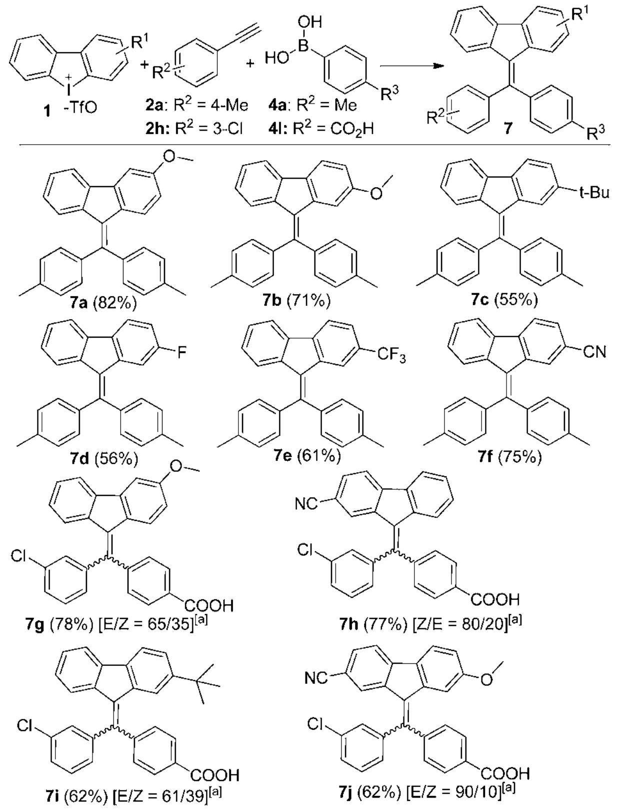
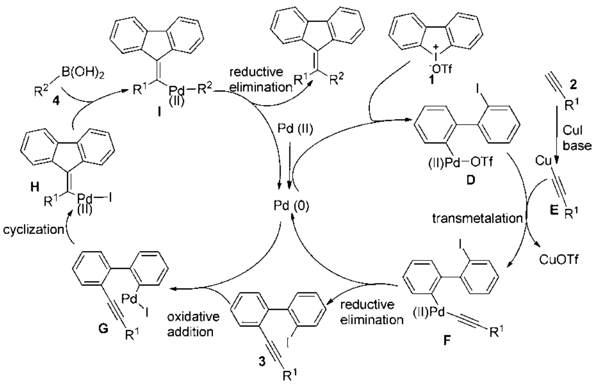


Figure 3. Scope of cyclic iodoniums. Conditions: **1** (0.23 mmol), **2** (1.1 equiv), **4** (1.2 equiv), $Pd(OAc)_2$ (10 mol %), CuI (20 mol %), PPh_3 (30 mol %), Na_2CO_3 (3.0 equiv), DMF (2.0 mL),100 °C, 12 h, Ar. [a] The ratio was determined by HPLC; for details, see SI.

Scheme 3. Proposed Mechanism for the Multicomponent Synthesis of Fluorenes



and Cu(I) activated alkyne species **E** generates intermediate **F**, followed by a reductive elimination to form **3**. Our results implied that the electron-deficient ring side of cyclic iodoniums is favorable in this alkynylation step (**7g**−**7j**). A further oxidative addition of **3** produces Pd species **G**, which undergoes an intramolecular insertion into the neighboring alkyne, leading to the formation of **H**. Subsequently, Pd species **H** was intercepted through transmetalation by boronic acid **4**, and the final product methylidenefluorene is obtained from **I** after a second reductive elimination. It is noteworthy that in situ formation of a similar Cu species substituting for Pd species **D** is possible since the formation of **3** was obtained with CuI albeit only in a low yield (entry 1, Table 1).

In summary, structurally diverse methylidenefluorene derivatives can be conveniently obtained via three-component cascade alkynylation/annulation with cyclic diphenyleneiodoniums, alkynes, and boronic acids under our method. Arylboronic acids with substituents regardless of their electronic properties are well tolerated in the reactions. Both aryl and alkyl alkynes are compatible, providing an opportunity to further functionalize the product methylidenefluorenes by subsequent transformations. We have demonstrated that the method can be applied to the synthesis of unsymmetrical fluorenes in cases where the cyclic diphenyleneiodoniums are markedly different in the electronic properties of the two aryl rings.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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