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Graphical Abstract

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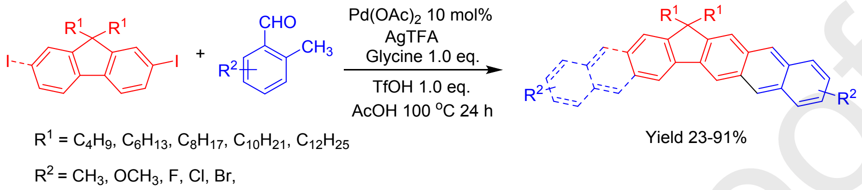

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One-pot synthesis of benzofluorene fused aromatic hydrocarbons

Wendan Dong[a,†], Zhun Hu[b,†], Ziqi Wang[a], Bing Sun[a], Xueqiong Zhang[a, ∗], and Fang-Lin Zhang[a, ∗]

[a]School of Chemistry, Chemical Engineering and Life Sciences, Wuhan University of Technology, Wuhan 430070, PR China
[b]Wuhan Huabenhui Medical Development Co., Ltd., Wuhan 430075, PR China.

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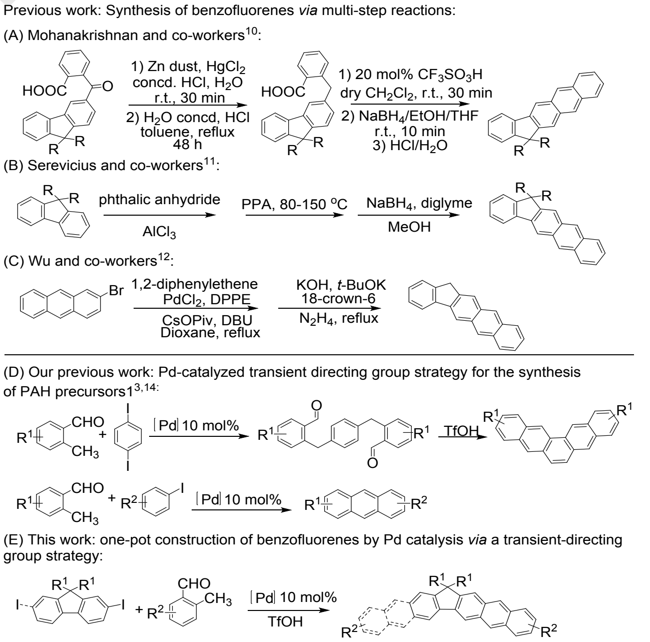
ABSTRACT

A new and efficient synthetic approach for the one-pot construction of benzofluorene fused aromatic hydrocarbons was developed *via* a transient-directing group strategy. The palladium-catalyzed cascade reaction proceeded *via* consecutive arylation, cyclization and aromatization steps. Moderate to good yields along with broad functional group tolerance were achieved under mild reaction conditions.

1. Introduction

Benzofluorenes, an important class of polycyclic aromatic hydrocarbons (PAHs) with rigid planar biphenyl structures, constitute the core of a variety of biologically active compounds,[1] such as secondary metabolites[2] which were isolated from *Streptomyces murayamaensis*. Moreover, the stable organic radical containing benzofluorene structure can be used as ligands in the fields of organometallic and coordination chemistry[3] as well as organic semiconductors.[4] Meanwhile, their unique optical and electronic properties as well as electron-rich structures[5] endow them with extensive applications in organic light-emitting diodes (OLEDs),[6, 8] organic field-effect transistors (OFETs)[7] and organic solar cells.[8] Due to their widespread applications, significant efforts have been devoted to the development of new and efficient synthetic methods for benzofluorenes.[9] Mohanakrishnanet reported the synthesis of benzofluorenes involving cyclization-reductive-dehydration reactions, where 2-arylmethylnaphthoic acids underwent triflic acid-mediated cyclization followed by reductive dehydration to give annulated anthracenes (Scheme 1A).[10] Serevičius reported a new synthetic route to unsymmetrical 2-phenylanthracene and its derivatives with bridging carbons, as well as the thermal, optical and electrical properties of these materials (Scheme 1B).[11] Wu reported an efficient preparation of fluorenes and methylene-bridged polyarenes from haloarenes (or aryl triflates) and diarylethynes *via* a one-pot, two-step procedure. This protocol involved palladium-catalyzed cycloisomerization and subsequent base-mediated retro-aldol condensation (Scheme 1C).[12] However, all the above known methods typically require multiple steps and harsh reaction conditions, and generate stoichiometric amounts of waste. Recently, we reported the palladium-catalyzed *ortho*-C(sp^3)–H arylation of benzaldehydes with aryl diiodides for the synthesis of PAHs precursors *via* a transient directing group. However, a two-step procedure was required to access the final target product.[13] Subsequently, we reported the one-pot Pd(II)-



Scheme 1. Previous synthesis methods (A-D) and the present synthesis method (E).

∗ Corresponding author. Tel.: +86-27-87859019; fax: +86-27-87859019; e-mail: zhangxq@whut.edu.cn

∗ Corresponding author. Tel.: +86-27-87859019; fax: +86-27-87859019; e-mail: fanglinzhang@whut.edu.cn

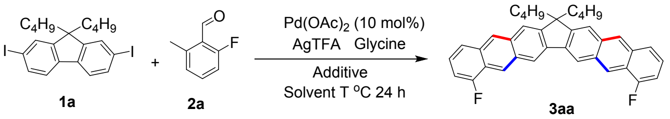
† These authors contributed equally.

cata directing group strategy and further accessed anthracene and tetraphenylene *via* cyclization and aromatization.[14] Nevertheless, the above one-pot approach is restricted to the functionalization of aryl monoiodides, which limits its further application (Scheme 1D). Herein, we report a new and efficient strategy for the synthesis of benzofluorenes with a fused ring structure *via* a one-step cascade reaction sequence (Scheme 1E).

2. Results and Discussion

To explore the feasibility of this strategy, 9,9-dibutyl-2,7-diiodo-9*H*-fluorene (**1a**) and 2-fluoro-6-methylbenzaldehyde (**2a**) were used as model reactants to explore the optimal reaction conditions (Table 1). After extensive screening, we found that the reaction conditions must include the followings: 10 mol% $Pd(OAc)_2$, 1.0 equiv. glycine and TfOH in AcOH with 3.0 equiv. AgTFA. This reaction was sensitive to the amount of glycine and AgTFA (Table 1, entries 1-6). The best result was obtained in the presence of 1.0 equiv. glycine and 3.0 equiv. AgTFA (Table 1, entry 2). As an essential additive, TfOH was a key factor leading to the intramolecular aromatization to afford the arylation product. The optimized amount of TfOH was found to be 1.0 equiv., showing superior yield than the cases of a higher or less amount of TfOH (Table 1, entries 7-8). Systematic screening of the solvents revealed that the reaction proceeded only when AcOH was used (Table 1, entries 9-13). No reaction occurred with either 1.0 equiv. or 5.0 equiv. of TFA (Table 1, entries 14-15). Meanwhile, a minimum temperature was required for this reaction. When the temperature was lower than 50 °C, only trace amounts of products were observed. Additionally, there was no significant improvement at 120 °C. Therefore, the optimum

Table 1. Optimization of the reaction conditions.[a]



Entry	Glycine (equiv.)	AgTFA (equiv.)	Additive (equiv.)	Solvent	Yield **3aa**
1	0.5	3.0	TfOH 1.0	AcOH	33%
2	**1.0**	**3.0**	**TfOH 1.0**	**AcOH**	**80%**
3	1.5	3.0	TfOH 1.0	AcOH	81%
4	2.0	3.0	TfOH 1.0	AcOH	82%
5	1.0	1.5	TfOH 1.0	AcOH	65%
6	1.0	4.0	TfOH 1.0	AcOH	81%
7	1.0	3.0	TfOH 1.5	AcOH	79%
8	1.0	3.0	TfOH 0.5	AcOH	31%
9	1.0	3.0	-	AcOH	trace
10	1.0	3.0	-	TFA	N.R.
11	1.0	3.0	TfOH 1.0	DCE	N.R.
12	1.0	3.0	TfOH 1.0	DCM	N.R.
13	1.0	3.0	TfOH 1.0	THF	N.R.
14	1.0	3.0	TFA 1.0	AcOH	N.R.
15	1.0	3.0	TFA 5.0	AcOH	N.R.
16[b]	1.0	3.0	TfOH 1.0	AcOH	81%
17[c]	1.0	3.0	TfOH 1.0	AcOH	67%
18	1.0	3.0	TfOH 1.0	AcOH	trace

[a] Reagents and conditions: **1a** (0.1 mmol, 1.0 equiv.), **2a** (0.25 mmol, 2.5 equiv.), $Pd(OAc)_2$ (10 mol%), solvent (1.0 mL), 100 °C, 24 h. Isolated yields.

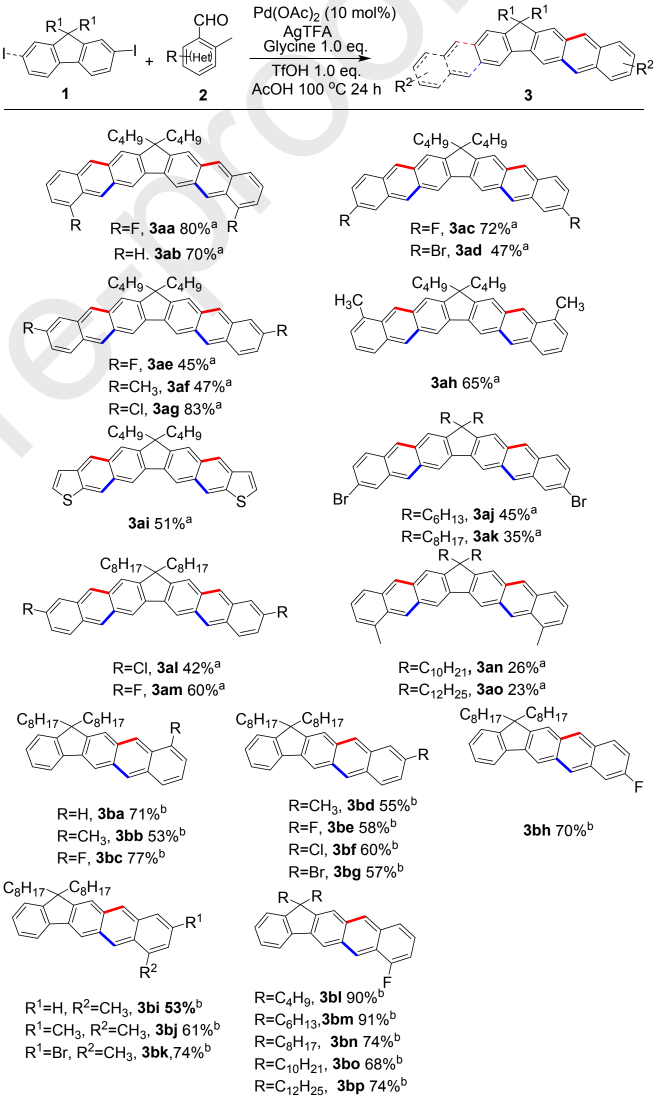
[b] 120 °C.

[c] 80 °C.

1, entries 16-18).

With the optimized procedure in hand, the reaction of a broad scope of benzaldehydes with various diiodobenzenes was probed (Table 2). When *o*-methylbenzaldehyde is substituted with electron-donating groups, the yields were significantly reduced (**3af, 3ah**). To our delight, a series of halogenated products were all transformed into the corresponding products in moderate to good yields (**3aa, 3ac-3ae** and **3ag**). Moreover, the heterocyclic aldehyde **3ai** also reacted well to provide the expected product in moderate yield (**3ai**). To improve the substrate solubility in organic solvents, a series of straight chain alkyl groups were introduced at the C9-position of the iodofluorenes. The length of the alkyl chain on 2,7-diiodoindole did not exert an obvious effect on the yields (**3an**, **3ao**). The X-ray crystal structure of compound **3ag** is shown in Figure 1.[15]

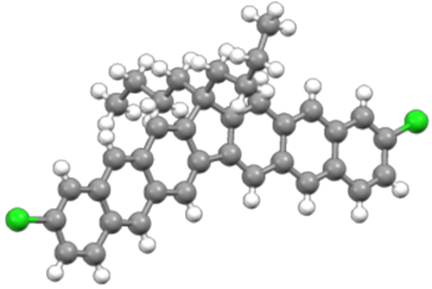
Table 2. Substrate scope investigation.



[a] Reagents and conditions: **1** (0.2 mmol, 1.0 equiv.), **2** (0.5 mmol, 2.5 equiv.), $Pd(OAc)_2$ (10 mol %), AgTFA (3.0 equiv.), glycine (1.0 equiv.), TfOH (1.0 equiv.), AcOH (1.0 mL), 100 °C, 24 h. Isolated yields.

[b] **2** (0.3 mmol, 1.5 equiv.), AgTFA (1.5 equiv.).

Figure 1. X-ray structure of **3ag.**



The above success led us to continue to explore the reaction of 2-iodo-9*H*-fluorene and *o*-methylbenzaldehyde. Surprisingly, when the amount of AgTFA was decreased to 1.5 equiv., the reaction of benzaldehydes with 9,9-dialkyl-2-iodofluorene proceeded successfully, giving **3ba-3bp** in 53-90% yield. The substrate scope of the benzaldehydes was then verified and good to excellent yields were generally achieved, whether substituted by electron-donating (**3bb**, **3bd**, **3bi**, **3bj**) or electron-withdrawing groups (**3bc**, **3be-3bh**). We then studied the effect of the alkyl chain length on the reaction of 2-iodoindole with 2-methyl-6-fluorobenzaldehyde (**2a**). The solubility of the product was improved with the increase of the alkyl carbon chain length (**3bl-3bp**). In contrast, the yield decreased with shorter alkyl carbon chains (**3bl-3bp**).

3. Conclusion

In summary, benzofluorenes were easily constructed in one-pot from *o*-methylbenzaldehyde and 9*H*-fluorene *via* palladium-catalyzed C(sp^3)–H arylation and subsequent acid-mediated dehydration condensation. Moderate to excellent yields were obtained under mild conditions, proving the wide practicality and functional group compatibility.

Acknowledgments

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15. CCDC 1942414 (**3ag**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

Supplementary data

Supplementary data associated with this article can be found in the online version containing experimental procedures and characterization data for all new compounds.

Highlights

- An efficient method for one-pot synthesis of benzofluorenes was developed.
- Glycine was used as the optimal transient directing group.
- Mild reaction conditions and wide substrate range were also highlighted.