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Synthesis of Fluorenes Starting from 2-Iodobiphenyls and CH_2Br_2 through Palladium-Catalyzed Dual C−C Bond Formation

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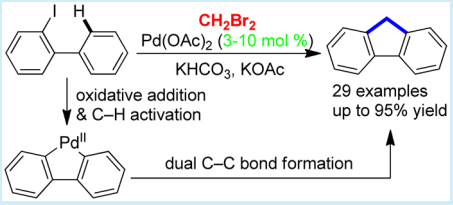
Supporting Information

ABSTRACT: A facile and efficient approach is developed for the synthesis of fluorene and its derivatives starting from 2-iodobiphenyls and CH_2Br_2. A range of fluorene derivatives can be synthesized under relatively mild conditions. The reaction proceeds via a tandem palladium-catalyzed dual C−C bond formation sequence through the key dibenzopalladacyclopentadiene intermediates, which are obtained from 2-iodobiphenyls through palladium-catalyzed C−H activation.



Fluorene is one of the simplest motifs in polycyclic aromatic hydrocarbons, and its derivatives have found broad applications in materials science,[1] pharmaceutical chemistry,[2] and organic synthesis.[3] While traditional methods for the synthesis of fluorenes suffer from harsh conditions or complicated procedures,[4] an efficient strategy via C−H functionalization has gained considerable interest. This novel strategy involves transition-metal-mediated C−H activation and subsequent cyclization. Currently, a variety of great reactions of this type have been developed.[5] All the reactions rely on the use of substrates in which the methylene carbon is preinstalled (Figure 1).

Metallacycles are one of the most popular classes of organometallic compounds and have been extensively investigated over the past several years.[6] Dibenzometallacyclopentadiene (metal 2,2′-biphenyl complex) (Figure 1, **DBM**), a particularly intriguing metallacycle, remains comparatively underexploited.[7] Recently, we initiated a program to exploit the unique reactivity of **DBM**, aiming to develop novel organic reactions and shed light on the mechanism of reactions

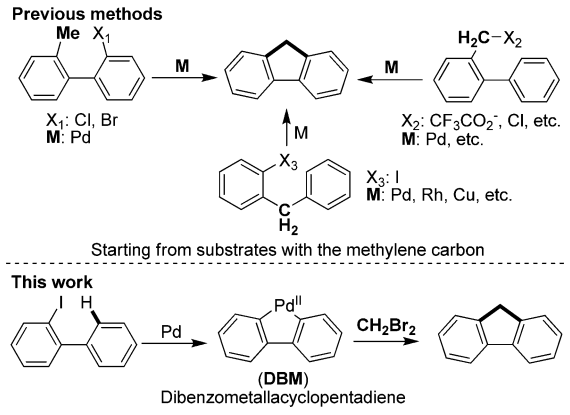
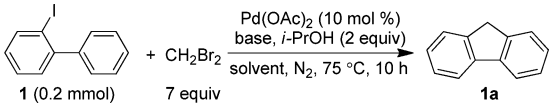


Figure 1. Synthesis of fluorenes via C−H functionalization.

Table 1. Optimization of the Reaction Conditions for the Synthesis of Fluorene from 2-Iodobiphenyl and CH_2Br_2



entry	base (equiv)	solvent (mL)	yield/%[a]
1	K_2CO_3/KOAc (5/6)	DMF (1.2)	52
2	$KHCO_3$/KOAc (5/6)	DMF (1.2)	60
3	$KHCO_3$/KOAc (5/6)	DMF/DMA (1.2/0.4)	63
4	$KHCO_3$/KOAc (5/6)	DMF/DMA/H_2O[b]	73
5	$KHCO_3$/KOAc (3/4)	DMF/DMA/H_2O[b]	57
6	**$KHCO_3$/KOAc (8/9)**	**DMF/DMA/H_2O[b]**	**85 (81[c])**
7[d]	$KHCO_3$/KOAc (8/9)	DMF/DMA/H_2O[b]	71
8[e]	$KHCO_3$/KOAc (8/9)	DMF/DMA/H_2O[b]	60
9[f]	$KHCO_3$/KOAc (8/9)	DMF/DMA/H_2O[b]	75
10[g]	$KHCO_3$/KOAc (8/9)	DMF/DMA/H_2O[b]	22
11[h]	$KHCO_3$/KOAc (5/6)	DMF/DMA/H_2O[b]	57
12[i]	$KHCO_3$/KOAc (8/9)	DMF/DMA/H_2O[b]	81
13[j]	$KHCO_3$/KOAc (5/6)	DMF/DMA/H_2O[b]	–
14[k]	**$KHCO_3$/KOAc (8/9)**	**DMF/DMA/H_2O (12/4/2)**	**78[c]**

[a]The yields were determined by ^{1}H NMR analysis of crude reaction mixture using $CHCl_2CHCl_2$ as the internal standard. [b]DMF/DMA/H_2O (1.2 mL/0.4 mL/0.2 mL). [c]Isolated yield. [d]2 equiv of MeOH were used instead of *i*-PrOH. [e]No *i*-PrOH. [f]4 equiv of CH_2Br_2. [g]7 equiv of CH_2Cl_2 were used instead of CH_2Br_2. [h]Under an air atmosphere. [i]3 mol % $Pd(OAc)_2$. [j]No $Pd(OAc)_2$. [k]2.0 mmol of **1**.

involving other metallacycles.[8] We found that **DBM** exhibited novel reactivity that is distinct from that of other common arylmetal complexes. **DBM** can selectively react with alkyl halides,[9] which are not reactive toward open-chain arylmetal complexes.[8a] Furthermore, one of the advantages of **DBM** is that the presence of two carbon−metal bonds in the complex

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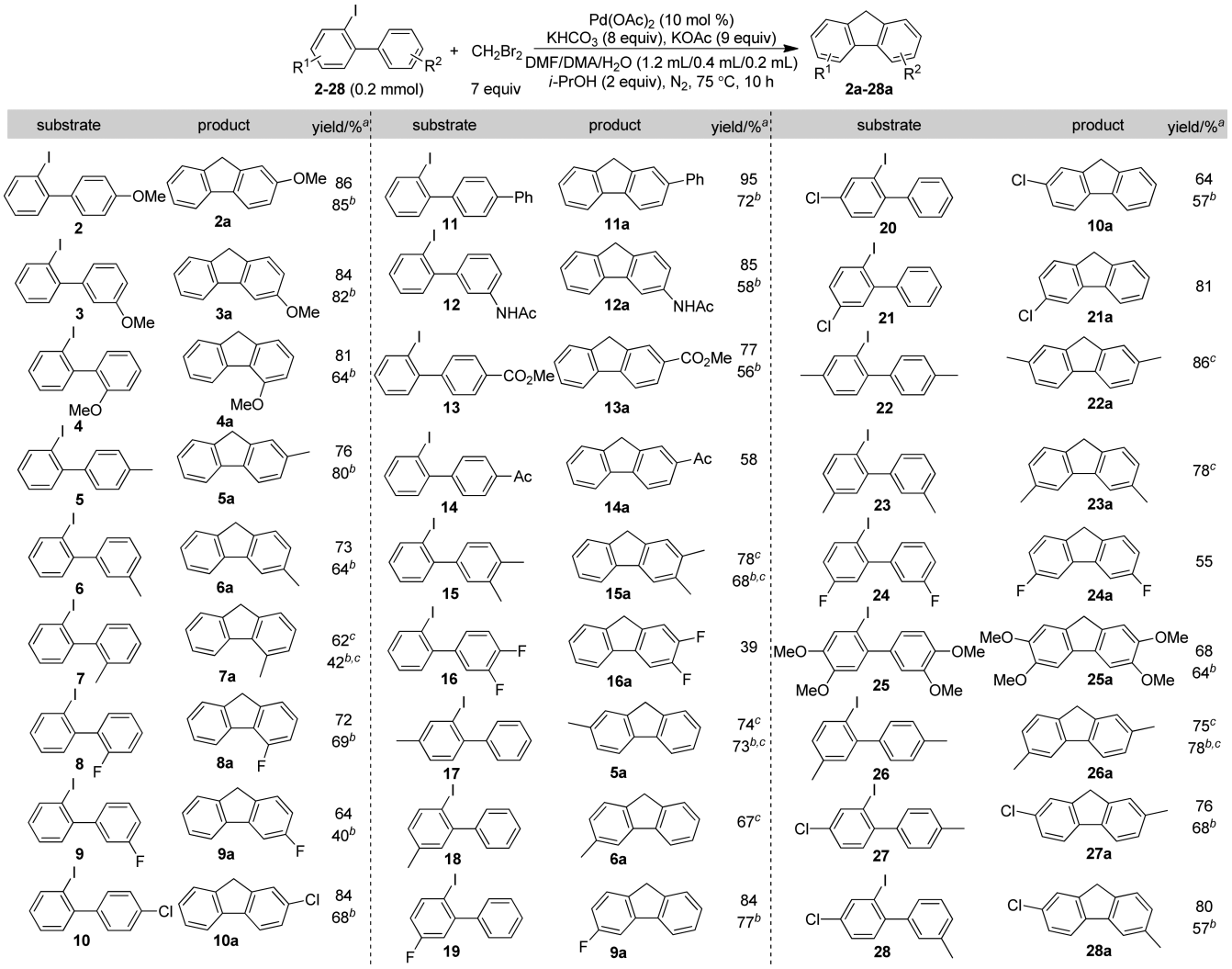
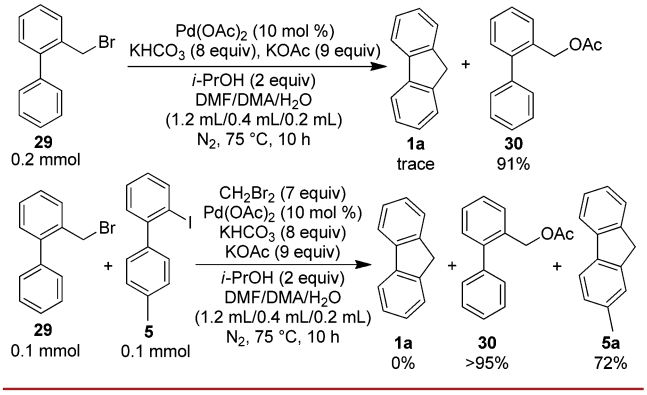
Scheme 1. Substrate Scope for Pd-Catalyzed Coupling of 2-Iodophenyls and CH_2Br_2



[a]Isolated yield. [b]3 mol % $Pd(OAc)_2$. [c]90 °C.

Scheme 2. Mechanistic Studies for the Dual Alkylation of 2-Iodobiphenyl with CH_2Br_2



offers opportunities to difunctionalize biphenyl at the 2- and 2′-positions. Inspired by this advantage and their unique reactivity toward alkyl halides, we envisioned that the reaction of **DBM** with dihaloalkanes would offer efficient access to dibenzocycloalkanes via a tandem palladium-catalyzed dual C−C bond-forming reaction.

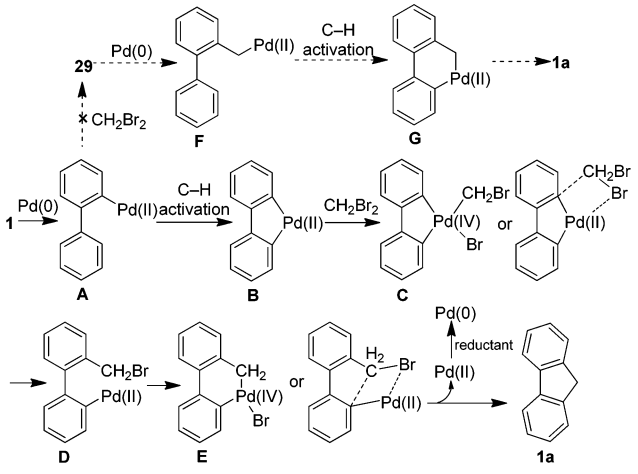


Figure 2. Proposed mechanism for the dual alkylation of 2-iodobiphenyl with CH_2Br_2.

Herein, we report the Pd-catalyzed coupling reaction of 2-iodobiphenyls with dibromomethane, which provides a convenient and efficient method for the synthesis of fluorenes starting from substrates without a preinstalled methylene group.

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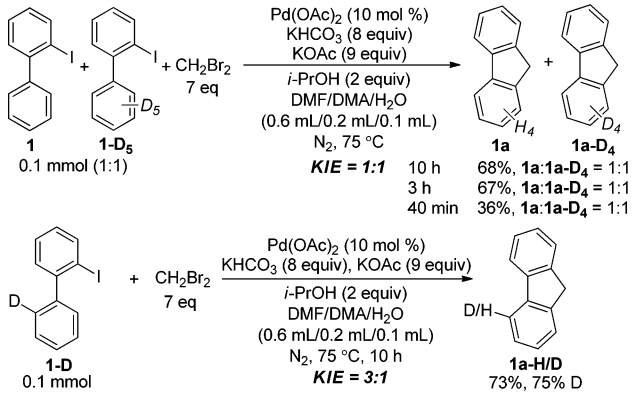
Scheme 3. Kinetic Isotope Effect Studies for the Dual Alkylation of 2-Iodobiphenyl with CH_2Br_2



The research was commenced by investigating the reaction of 2-iodobiphenyl with CH_2Br_2. Gratefully, the reaction formed the desired fluorene product **1a** in 52% yield in the presence of 10 mol % $Pd(OAc)_2$, 5 equiv of K_2CO_3, 6 equiv of KOAc, and 2 equiv of *i*-PrOH (Table 1, entry 1). The yield further increased to 60% in the presence of a mixture of $KHCO_3$ and KOAc (entry 2) and was improved to 73% when the reaction was carried out in a mixture of DMF, DMA, and H_2O (entry 4). The yield was optimized to 85% by increasing the amounts of $KHCO_3$ and KOAc (entry 6). The use of CH_3OH as the reductant led to a lower yield (entry 7), and the yield decreased to 60% in the absence of an alcohol (entry 8), demonstrating the positive effect of an alcohol on the reaction. The reaction afforded the desired product in good yield even when the amount of CH_2Br_2 was reduced to 4 equiv (entry 9). CH_2Cl_2 was also reactive, albeit in a far lower yield (entry 10). When the reaction was carried out under an atmosphere of air, **1a** was formed in a lower yield (entry 11). One possible explanation for this observation is that O_2 could oxidize catalytically active Pd(0) and thereby suppress the reaction. Notably, the yield remained almost unchanged when the amount of $Pd(OAc)_2$ was reduced from 10 to 3 mol % (entry 12). A control experiment in the absence of $Pd(OAc)_2$ confirmed that it was necessary for formation of **1a** (entry 13). Notably, the product could be obtained in 78% yield even on 2.0 mmol scale (entry 14), demonstrating the practical utility of this method.

Having developed an efficient protocol for palladium-catalyzed coupling of 2-iodobiphenyl with CH_2Br_2, we next investigated the substrate scope of this transformation. We first examined the compatibility of different functional groups on the phenyl ring opposite to the iodo group. As shown in Scheme 1, substrates bearing a substituent (either methoxy or methyl group) at the 2′, 3′, or 4′ positions underwent the coupling reaction with CH_2Br_2 efficiently under the optimal conditions. Both fluoro and chloro groups were similarly well-tolerated in the reaction, giving the desired fluorene derivatives in moderate to high yields. A range of other common functional groups were compatible, including phenyl, acetylamino, alkoxycarbonyl, and acetyl groups. 2-Iodobiphenyl substrates bearing two substituents were also reacitve, albeit in a poor yield for 3′,4′-difluoro-2-iodobiphenyl. Next, we investigated the coupling reaction of 2-iodobiphenyl derivatives with a subtituent on the phenyl ring containing the iodo group. 2-Iodobiphenyls substituted at 4 or 5 positions were transformed into corresponding fluorenes in high yields. Finally, the reactivity of multiply substituted 2-iodobiphenyls was also examined. A variety of symmetrically or asymmetrically substituted 2-iodobiphenyls were found to be compatible with the reaction conditions, affording multiply functionalized fluorenes as the products. Notably, for several representative substrates, the yield was the same or only slightly diminished when the catalyst loading was lowered to 3 mol % $Pd(OAc)_2$.

To gain insight into the mechanism involved in the formation of fluorene, additional experiments were conducted (Scheme 2). The formation of fluorene could involve intermediate **29**, which is formed via the reaction of complex **A** and CH_2Br_2 (Figure 2, dashed arrows). To rule out this possible pathway, we subjected **29** to the standard reaction conditions. Only a negligible amount of fluorene was observed, and **29** was converted into its acetoxy analogue in 91% yield. Furthermore, when 0.5 equiv of **29** was added into the reaction mixture of 0.5 equiv of **5**, fluorene was not observed, and the fluorene derivative **5a** was formed in 72% yield. Based on these experimental outcomes, the pathway involving **29** can be ruled out. Therefore, a mechanism involving the dibenzometallacyclopentadiene complex appears plausible. As shown in Figure 2, the catalytic cycle starts with the oxidative addition of 2-iodobiphenyl to Pd(0). The resulting Pd(II) species **A** cleaves the 2′-C−H bond to form the key palladacycle **B**. The oxidative addition of the CH_2Br_2 to the Pd(II) in **B** forms Pd(IV) complex **C**, which then undergoes reductive elimination to afford intermediate **D**. It should be mentioned that a metathesis pathway cannot be ruled out for the formation of **D**.[10] **D** undergoes intramolecular oxidative addition to give **E**, and the subsequent reductive elimination affords fluorene as the final product. Likewise, a metathesis pathway cannot be excluded.

In addition, the kinetic isotope effect in the reaction was investigated. Therefore, a mixture of **1** and 2′,3′,4′,5′,6′-pentadeutero-2-iodo-biphenyl (**1-D$_5$**) (1:1) or 2′-deutero-2-iodobiphenyl (**1-D**) was subjected to the standard conditions (Scheme 3). Intriguingly, whereas the intermolecular KIE was 1 to 1, the intramolecular KIE was 3 to 1. These results are consistent with a mechanism in which the first oxidative addition of the aryl iodide to Pd(0) or reduction of Pd(II) to Pd(0) is the slowest step. Subsequently, after complex **A** is formed C−H activation is the next slowest step, and subsequent steps should be comparatively fast.

In conclusion, we have developed a facile and efficient approach for the synthesis of fluorene and its derivatives starting from 2-iodobiphenyls and CH_2Br_2. This strategy represents the first synthesis of fluorenes via C−H activation utilizing substrates without a preinstalled methylene group and provides convenient access to a variety of fluorene derivatives. Mechanistic studies provided evidence to support the intermediacy of a dibenzopalladacyclopentadiene in the reaction, and the reaction proceeds via a tandem Pd-catalyzed dual C−C bond formation sequence.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01300.

Detailed experimental procedures, spectroscopic data and characterization of starting materials and products (PDF)

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Notes

The authors declare no competing financial interest.

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