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$Pd(OAc)_2$-catalyzed domino reactions of 1,2-dihaloarenes and 2-haloaryl arenesulfonates with Grignard reagents: efficient synthesis of substituted fluorenes

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Abstract

$Pd(OAc)_2$-catalyzed domino reactions of 1,2-dihalobenzenes and 2-haloaryl arenesulfonates with hindered Grignard reagents to form substituted fluorenes, which are believed to occur through palladium associated aryne intermediates, are described. Such palladium associated aryne reaction pathway was found to be favored by omitting the use of phosphine and *N*-heterocyclic carbene ligands for palladium catalysts and with better leaving groups. Our study suggested that Pd(leaving group)X associated arynes should be formed first and the sp^3 C–H activation preferentially occurred at benzylic C–(1°)H bonds. The work described here provides a high yield, one-step access to substituted fluorenes from readily available 1,2-dihalobenzenes and 2-haloaryl arenesulfonates and hindered Grignard reagents, and this substituted fluorene-making method may find applications in the preparation of substituted fluorene-containing molecules including polymers.

Keywords: 1,2-Dihalobenzenes; Domino reactions; Grignard reagents; 2-Haloaryl arenesulfonates; Palladium; Substituted fluorenes

1. Introduction

Over the past decades, palladium-catalyzed cross-coupling reactions, e.g., the Suzuki coupling, the Kumada coupling, the Stille coupling, the Sonogashira coupling, and the amination of aryl halides with amines, etc., have become powerful tools for organic synthesis.[1] They have been extensively employed to synthesize a wide variety of organic compounds ranging from small organic molecules to macromolecules.[1,2] Extensive study established that there are three key elementary steps in the catalytic cycles of Pd(0)-catalyzed cross-coupling reactions:[1] oxidative addition of Pd(0) with an aryl halide to form Pd(II) complex; transmetalation of the Pd(II) complex with an organometallic reagent to form an diorganopalladium(II) complex; and reductive elimination of the diorganopalladium(II) complex to form the cross-coupling product and regenerate the Pd(0) catalyst (Fig. 1). Based on our understanding of the general mechanism depicted in Figure 1, we envisioned that the individual elementary steps in each catalytic cycle might be controlled. Such a control, especially combined with other bond forming processes, might provide us excellent opportunities to develop new reactions/processes and thus could make the already powerful transition metal-catalyzed cross-coupling reactions even more powerful for organic synthesis. Toward this end, we have recently documented Pd(0)/*t*-Bu_3P-catalyzed Suzuki cross-coupling of

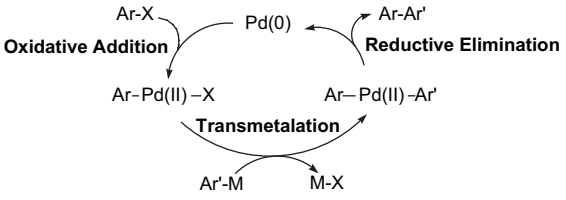

Figure 1. Generalized mechanism for Pd(0)-catalyzed cross-coupling reactions.

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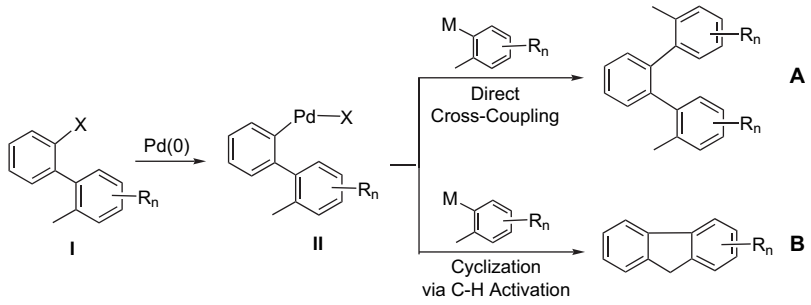
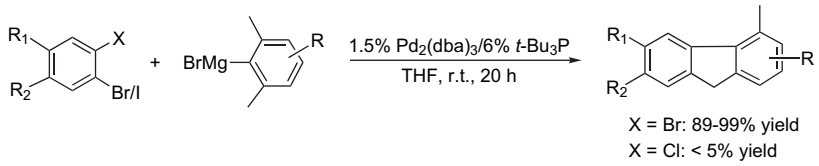


Scheme 1. Controlling competition between direct cross-coupling and cyclization via sp^3 C–H bond activation.



Scheme 2. Pd(0)/*t*-Bu_3P-catalyzed tandem reactions of 1,2-dihalobenzenes with hindered Grignard reagents.

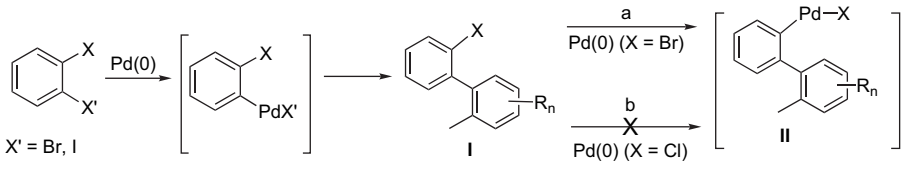
dihaloarenes with arylboronic acids,[3] a process that relies on the control of oxidative addition step. We have also reported Pd(0)/*t*-Bu_3P-catalyzed reaction of 2-bromobiphenyl with hindered Grignard reagents to form substituted fluorenes (Scheme 1),[4–6] a cyclization process that combines the control of the transmetalation step with sp^3 C–H activation (Scheme 1).[7–9] We have further incorporated a cross-coupling step into the latter type of reaction and developed a new type of tandem reaction that combines the cross-coupling strategy and cyclization via sp^3 C–H activation strategy (Scheme 2).[4,10,11] With Pd(0)/*t*-Bu_3P as catalyst, substituted fluorenes could be easily prepared in excellent yields from 1,2-dibromobenzenes and 1-bromo-2-iodobenzene.

Although Pd(0)/*t*-Bu_3P has been demonstrated to be a highly efficient catalyst system for the tandem reaction of 1,2-dibromobenzenes and 1-bromo-2-iodobenzene to form substituted fluorenes, we reasoned that further improvement of this new substituted fluorene-making process could be possible. For example, the air-sensitivity of *t*-Bu_3P makes the handling of the catalyst very stringent. In addition and more importantly, Pd(0)/*t*-Bu_3P catalyst system was ineffective for substrates other than 1,2-dibromobenzenes and 1-bromo-2-iodobenzene, e.g., 1-chloro-2-halobenzenes. To expand the substrate scope and explore more practical catalyst systems, we envisioned a pathway other than the cross-coupling-cyclization (via sp^3 C–H activation) strategy, namely palladium associated aryne forming pathway. We investigated factors that could influence the reaction to proceed via the palladium associated aryne forming pathway including the ligand effect and leaving group effect. We also investigated the substrates other than 1,2-dibromobenzenes and 1-iodo-2-bromobenzene, i.e., 1-chloro-2-halobenzenes, 1-bromo-2-fluorobezene, 2-haloaryl tosylates, and benzenesulfonates for the reaction. Herein, our detailed study is reported.[12]

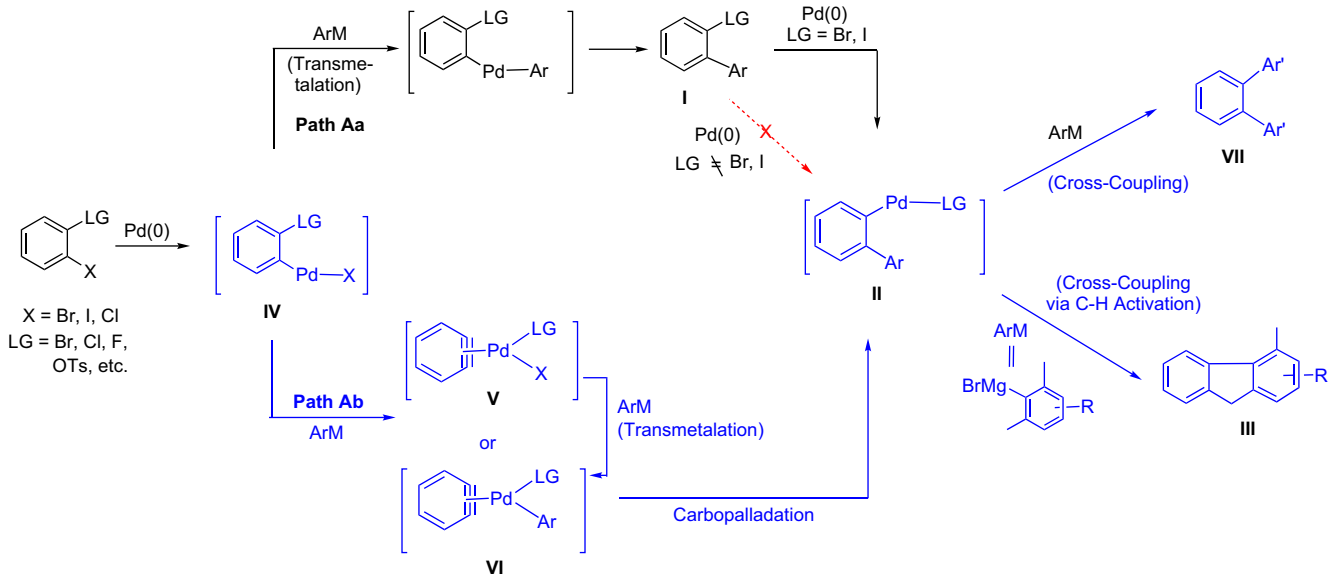
2. Results and discussions

2.1. Palladium associated arynes as intermediates for the reaction of 1,2-dihalobenzenes with Grignard reagents: ligand effect and leaving group effect

Our mechanistic study in Pd(0)/*t*-Bu_3P catalyst system suggested that the key obstacle to employ 1-chloro-2-halobenzenes as substrates for the reaction is the reluctance of the C–Cl bond in **I** to undergo oxidative addition with Pd(0) catalyst (Scheme 3).[4] We thus envisaged that if no oxidative addition of C–Cl bond with Pd(0) was involved in the formation of ArPd(II)Cl (**II**), these substrates could then be suitable substrates for the new type of annulative tandem reactions. Recognizing that halo groups are known to function as leaving groups, we reasoned that this could be possible: as depicted in Scheme 4, *ortho*-leaving group (LG) bearing *o*-aryl(LG)palladium(II) halides (**IV**), in addition to undergoing transmetalation with organometallic reagents to form **I** (Scheme 4, path Aa), could undergo β-LG-elimination to form palladium associated arynes (**V**) (Scheme 4, path Ab). The generated



Scheme 3. Pd(0)/*t*-Bu_3P-catalyzed tandem reactions of 1,2-dihalobenzenes with bulky Grignard reagents.

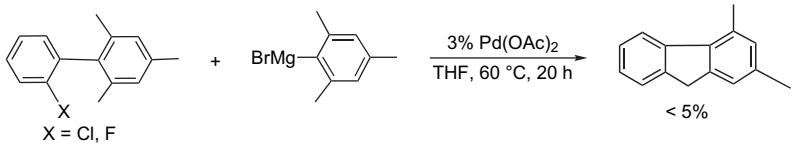


Scheme 4. Outline for 1-halo-2-(leaving group)benzenes for domino reactions via palladium(II)(LG)X associated aryne intermediates.

Pd(II)(LG)X associated arynes could then undergo transmatalation followed by carbopalladation to form intermediate **II**, which could further undergo other transformations (Scheme 4, path Ab). Therefore, through palladium associated aryne intermediates, intermediate **II** could be formed without undergoing the oxidative addition of C–LG bond with Pd(0), thus making it possible to employ 1-chloro-2-halobenzenes as suitable substrates for the domino reaction.

Arynes are very reactive and have recently been demonstrated as useful substrates for palladium-catalyzed carbon–carbon bond forming reactions.[13–17] Careful examination of aryne chemistry showed that the aryne generation strategy in reported reactions, in which arynes were generated in situ from expensive *o*-trimethylsilylaryl triflates, often does not work well with the use of catalytic amount of palladium because short-lived arynes needed to search for inherently unstable palladium intermediates for reactions to occur. Consequently, large excess of *o*-trimethylsilylaryl triflates were often required to achieve good yields. The pathway to generate arynes depicted in Scheme 4 (path Ab) could employ widely available *o*-halo(LG)benzenes including 1,2-dihaloarenes as substrates with the assurance of every generated aryne associated with a palladium. More importantly, in this strategy, because the formation of **II** does not involve the oxidative addition of C-leaving group bond, e.g., C–Cl bond, with Pd(0) species, the overall reactivity of *o*-halo(LG)benzenes would be governed by the reactivity of C-halo bonds that undergo the initial oxidative addition with Pd(0) catalysts. Thus, substrates that bear leaving groups other than Br and I groups might also be suitable substrates for tandem/domino reactions. Therefore, exploration of this palladium associated aryne generation strategy could be fundamentally interesting and synthetically useful.

As depicted in Scheme 4, the direct transmetalation of *o*-aryl(LG)palladium(II) halides (**IV**) to form cross-coupling product **I** (Scheme 4, path Aa) would compete with the formation of Pd(II)(LG)X associated benzynes (path Ab). Therefore, factors that could influence the transmetalation and/or the β-leaving group elimination of *o*-aryl(LG)Pd(II) halides, e.g., the steric hindrance and nucleophilicity of organometallic reagents, LG leaving ability, ligand effect, basicity of the base, and reaction temperature, etc., were expected to affect the generation of Pd-associated arynes. We reasoned that for a given type of *o*-aryl(LG)Pd(II) halides with the same LG and a given type of organometallic regents such as Grignard reagents at a certain reaction temperature, the influential factors could be narrowed down to steric hindrance and ligand effect. Since increasing the steric hindrance of Grignard reagents has been established to slow down the transmetalation process, we thus began our study by examining the ligand influence. The reaction of 1-bromo-2-chlorobenzene with bulky 2-mesitylmagnesium bromide was employed as the model reaction. As the initial oxidative addition was believed to occur at the C–Br bond[18,19] and 2-chloro-2′,4′,6′-trimethylbiphenyl (**Ia**, LG=Cl) was found to be inert under $Pd(OAc)_2$/Grignard reagent condition (Scheme 5), we expected that the domino reaction product 2,4-dimethylfluorene would be expected if the reaction proceeded via benzyne intermediate (path Ab). The reaction product would be 2-chloro-2′,4′,6′-trimethylbiphenyl if the reaction occurred via



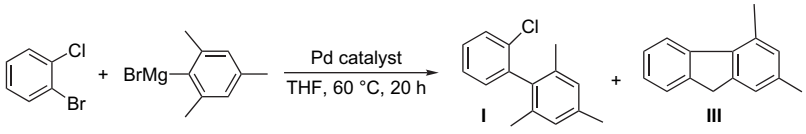
Scheme 5. $Pd(OAc)_2$-catalyzed reactions of 2-halo-2′,4′,6′-trimethylbiphenyls with 2-mesitylmagnesium bromide.

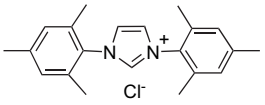
transmetalation followed by reductive elimination (path Aa). We screened a number of ligands and palladium source and our results are listed in Table 1. We found that with monodentate PPh_3, PCy_3, t-Bu_3P, an *N*-heterocyclic carbene (NHC),[20] or bidentate DPPE, DPPB, and BINAP as ligands, 2-chlorobiaryl was obtained as the major product (Table 1, entries 1–8), suggesting the reactions proceeded predominately through path Aa. However, 2,4-dimethylfluorene was observed as the major product with $PdCl_2$, $Pd_2(dba)_3$, $Pd(OAc)_2$, $Pd(PhCN)_2Cl_2$, or Pd/C (10% weight) as catalysts (Table 1, entries 9–13), implying that the reaction proceeded predominately through path Ab and Pd-associated benzynes were involved.

The ligand effect on reaction pathways was further confirmed by the reaction results of 1-bromo-2-chlorobenzene with less sterically hindered *p*-tolylmagnesium bromide. We expected that 4,4″-dimethyl-(1,1′,2′,1″)-terphenyl (**VII**) would be the product if the reaction occurs via palladium associated aryne pathway (path Ab) and 2-chloro-4′-methylbiphenyl (**Ia**, LG=Cl) would be the product via transmetalation followed by reductive elimination (path Aa) (Scheme 4). Our results showed that with t-Bu_3P as ligand, 4,4″-dimethyl-(1,1′,2′,1″)-terphenyl and 2-chloro-4′-methylbiphenyl were formed in a ratio of 7:93 (based on ^{1}H NMR), suggesting that path Aa should be the major pathway. However, with only $Pd(OAc)_2$ as the catalyst, 4,4″-dimethyl-(1,1′,2′,1″)-terphenyl was obtained as the major product (Scheme 6). These results further suggested that the absence of *tert*-butylphosphine favored the reaction occur via palladium associated aryne intermediates. Comparing these results with the reaction result of 1-bromo-2-chlorobenzene with 2-mesitylmagnesium magnesium (Table 1, entry 11) further showed that increasing the steric hindrance of Grignard reagents would slow down the transmetalation process and favor the reaction to proceed via the aryne pathway.

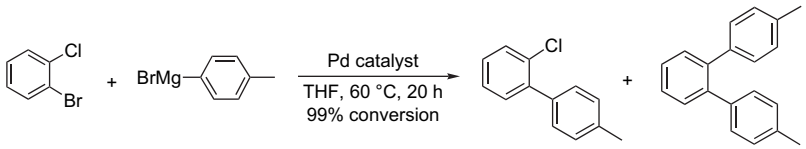
To gage the leaving group effect on the reaction pathways, we chose 2-mesitylmagnesium bromide as the reagent and studied 1,2-dihalobenzenes with different leaving groups. We first examined 1-bromo-2-halobenzenes (halo=F, Cl, Br) as the substrates and found that the better the leaving group,

Table 1
Ligand effect on palladium-catalyzed reactions of 1-bromo-2-chlorobenzene with Grignard reagents[a]



Entry	Catalyst	Conversion (%)	Ratio (%)[b]	
			I	**III**
1	1.5% $Pd_2(dba)_3$+6% Ph_3P	99	69	31
2	1.5% $Pd_2(dba)_3$+6% Cy_3P	99	91	9
3	1.5% $Pd_2(dba)_3$+6% t-Bu_3P	99	90	10
4	3% $Pd(PPh_3)_4$	99	88	12
5	1.5% $Pd_2(dba)_3$+6% 	22	99	<1
6	1.5% $Pd_2(dba)_3$+3% DPPE	5	99	<1
7	1.5% $Pd_2(dba)_3$+3% DPPB	27	99	<1
8	1.5% $Pd_2(dba)_3$+3% BINAP	8	99	<1
9	1.5% $Pd_2(dba)_3$	99	<3	>97
10	3% $Pd(PhCN)_2Cl_2$	99	<3	>97
11	3% $Pd(OAc)_2$	99	<3	>97
12	3% $PdCl_2$	93	<3	>97
13	3% Pd/C (10% weight)	11	<3	>97
14	None	0	—	—

[a] Reaction conditions: 1-bromo-2-chlorobenzene (1.0 equiv), Grignard reagent (2.5 equiv), THF (2 ml).
[b] Ratio based on ^{1}H NMR.



1.5% $Pd_2(dba)_3$ + 6% t-Bu_3P	93	:	7
3% $Pd(OAc)_2$	48	:	52

Scheme 6. $Pd(OAc)_2$-catalyzed reactions of 1-bromo-2-chlorobenzene with *p*-tolylmagnesium bromide.

the higher the ratio of **III**:**I**, suggesting benzyne intermediates formed easier with better leaving group (Table 2, entries 1–4). With 1-fluoro-2-halobenzenes as substrates, as 2-fluoro-2′,4′,6′-trimethylbiphenyl (**Ib**) was found to be also inert under $Pd(OAc)_2$/Grignard reagent condition (Scheme 5),[21] formation of 2,4-dimethylfluorene would be expected if the reaction proceeded via benzyne intermediate (path Ab). With a bromo group as the leaving group, the reaction occurred smoothly at room temperature with exclusive formation of 2,4-dimethylfluorene (for the establishment of palladium associated benzyne pathway, see the section that describes the reactions of 1,2-dibromobenzenes with hindered Grignard reagents (vide infra)). For comparison purpose, room temperature reaction of 1-bromo-2-chlorobenzene with 2-mesitylmagnesium bromide was also tested, a conversion of 61% was observed. As the oxidative addition of C–Br bond with Pd(0) for 1-bromo-2-chlorobenzene is expected to occur at the same rate as or higher than that of 1,2-dibromobenzene because of the more electron-withdrawing nature of Cl group than Br group, the lower conversion for 1-bromo-2-chlorobenzene suggested that the benzyne formation occurred slower with a Cl leaving group than that with a Br leaving group.

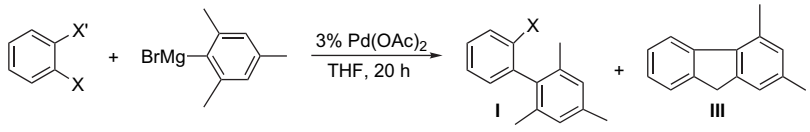
We have also carried out the reactions of 1-chloro-2-fluorobenzene and 1,2-dichlorobenzene with 2-mesitylmagnesium bromide. Our results showed that higher ratio of **III**:**I** was observed for 1,2-dichlorobenzene than that for 1-chloro-2-fluorobenzene (Table 2, entries 5 and 6), and thus further confirmed that benzyne intermediates formed easier with better leaving groups. The higher conversion for 1-chloro-2-fluorobenzene than that of 1,2-dichlorobenzene might be explained by thinking of the C–Cl bond in 1-chloro-2-fluorobenzene being more activated than that in 1,2-dichlorobenzene because a fluoro group is more electron-withdrawing than a Cl group.

2.2. *$Pd(OAc)_2$-catalyzed annulative reactions of 1-chloro-2-haloarenes and 1-bromo-2-fluorobenzene with hindered Grignard reagents via palladium associated arynes*

After establishing $Pd(OAc)_2$, $Pd_2(dba)_3$, and $Pd(PhCN)_2Cl_2$ as excellent catalysts for 1-bromo-2-chlorobenzene to undergo annualtive reaction with 2-mesitylmagnesium bromide, we next examined other 1-chloro-2-halobenzenes and hindered Grignard reagents. Our results are listed in Table 3. We found that all tested 1-chloro-2-halobenzenes including 1,2-dichlorobenzene gave good to excellent yields of substituted fluorene products. For 1,2-dichlorobenzene, higher reaction temperature and longer reaction time are needed to achieve good yield, likely because the initial oxidative addition of C–Cl bond with Pd(0) is more difficulty than C–Br bonds. We have also employed 1-bromo-2-fluorobenzene as substrate and a good yield of 2,4-dimethylfluorene was obtained (Table 3, entry 11).

The palladium associated benzyne intermediates could be formed via several possible pathways, e.g., transmetalation followed by benzyne formation (path A), transmetalation and benzyne formation occurred simultaneously (path B), or benzyne formation first followed by transmetalation (path C) (Scheme 7). We reasoned that the results with unsymmetrical 1-halo-2-chlorobenzenes as substrates could be used to differentiate these pathways as different ratio of isomeric substituted fluorenes would be obtained for these pathways. Both path A and B would give a mixture of fluorene products in a ratio related to oxidative addition rate difference between C–X bond and C–Cl bond. The third pathway, path C, is expected to give the ratio of products related to the transmetalation rates between Pd–Cl and Pd–X. Previous study on the reaction of 1-bromo-4-chlorobenzene with phenylboronic acid showed that the oxidative addition of Pd(0) occurred almost exclusively at C–Br bond (≥97%).[19] Path A or B would yield the two isomeric fluorenes in a ratio of 97:3 or higher for unsymmetrical 1-bromo-2-chlorobenzenes. Our results with 3-bromo-4-chlorotoluene and 3-bromo-4-chloroanisole as substrates showed that the two isomeric fluorenes were formed in about 4:1 ratio (Table 3, entries 6–8),[22] suggesting that the benzyne intermediates formed first followed by transmetalation. Since C–I bond has also been established to have higher oxidative addition rate than C–Br bond,[1,20] *o*-chloroiodobenzenes would yield two isomeric fluorenes in a ratio close to 100:0 if the reaction proceeded via path A or B. Our result with 3-chloro-4-iodotoluene as the substrate showed that the two isomeric fluorenes were formed in about 85:15. This observation was consistent with that the palladium associated benzyne intermediates were formed via path C. Comparison

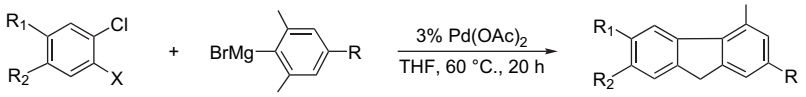
Table 2
$Pd(OAc)_2$-catalyzed reactions of 1,2-dihalobenzenes with 2-mesitylmagnesium bromide[a]

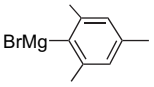
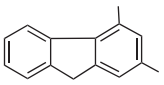
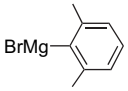
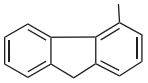
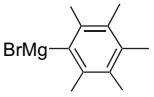
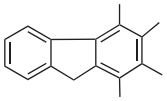
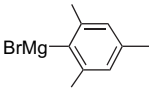
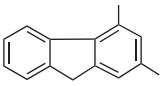
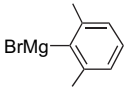
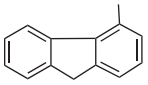
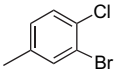
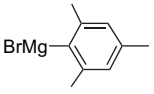
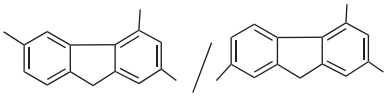
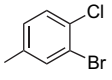
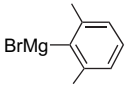
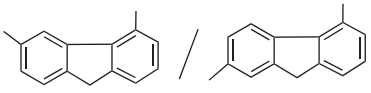
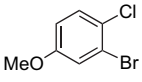
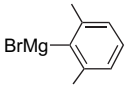
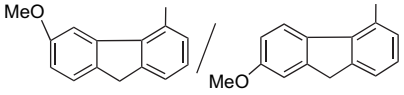
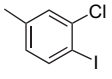
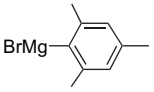
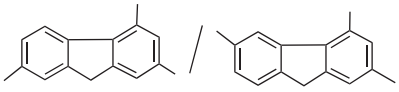
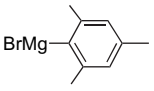
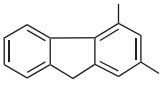
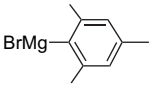
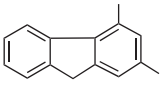


Entry	X	X′	Temperature	Conversion (%)	**I**:**III**[b]
1	F	Br	60 °C	84	17:83
2	Cl	Br	60 °C	99	<3:>97
3	Cl	Br	rt	73	<3:>97
4	Br	Br	rt	99	0:100
5	F	Cl	60 °C	72	63:37
6	Cl	Cl	60 °C	24	3:97

[a] Reaction conditions: 1,2-dihalobenzene (1.0 equiv), Grignard reagent (2.5 equiv), THF (2 ml).
[b] Ratio based on ^1H NMR.

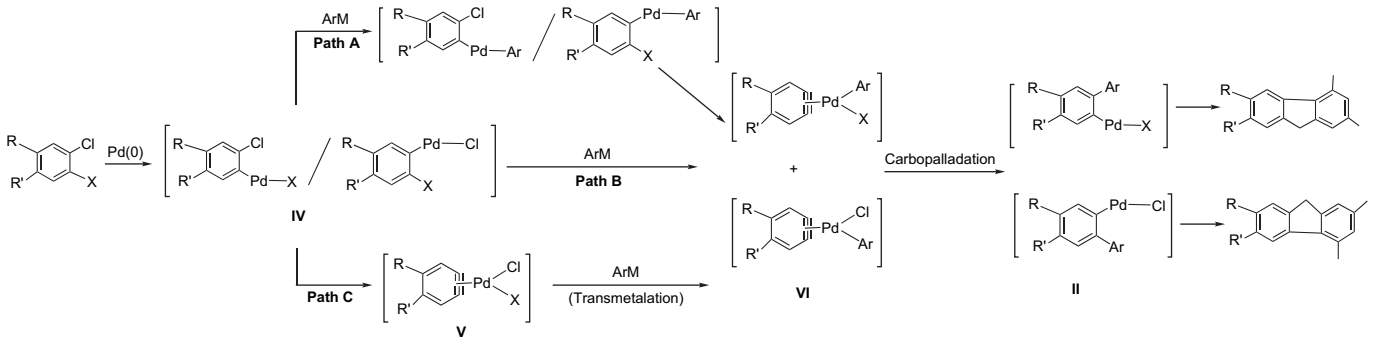
Table 3
$Pd(OAc)_2$-catalyzed cross-couplings of 1-chloro-2-halobenzenes and 1-bromo-2-fluorobenzene with hindered Grignard reagents[a]



Entry	Dihalide	BrMg–R	Product		Yield[b,c] (%)
1					95
2					86
3					89
4					93
5					92
6				(77:23)[e]	84[d]
7				(80:20)[e]	89[d]
8				(78:22)[e]	86
9				(85:15)[e]	82
10					61[f]
11					59[g]

[a] Reaction conditions (not optimized): 1,2-dihalobenzene (1.0 equiv), Grignard reagent (2.5 equiv), $Pd(OAc)_2$ (3%), THF (2 ml).
[b] Isolated yields.
[c] 2-Chlorobiaryls were observed in less than 5% yields.
[d] 1.5% $Pd_2(dba)_3$ as catalyst.
[e] Ratio based on ^1H NMR.
[f] Refluxing in THF, 40 h, 16% 2-chloro-2′,4′,6′-trimethylbiphenyl was observed.
[g] 2-Fluoro-2′,4′,6′-trimethylbiphenyl of 17% was observed.

of results of 3-bromo-4-chlorotoluene with that of 3-chloro-4-iodotoluene indicated that the first C–C bond formed mainly at the more reactive C–Br or C–I bond, suggesting that the formed benzyne species (**VI**) did not undergo coordination flipping (dissociation followed by recoordination in a reversed way). Otherwise, substituted fluorenes with the same ratio would be observed for 3-bromo-4-chlorotoluene and 3-chloro-4-iodotoluene.



Scheme 7. Possible pathways for the formation of palladium(II)ClX associated aryne intermediates.

The observation of the formation of two isomeric fluorenes in a similar ratio (4–5:1) for 3-bromo-4-chlorotoluene, 3-bromo-4-chloroanisole, and 3-chloro-4-iodotoluene (Table 3, entries 6–9) suggested that the transmetalation rates for Pd–Br and Pd–I bonds with hindered Grignard reagents were comparable to each other.

2.3. $Pd(OAc)_2$-catalyzed annulative reactions of 1,2-dibromoarenes and 1-bromo-2-iodobenzene with hindered Grignard reagents

Our study on the leaving group ability effect suggested that 1,2-dibromobenzenes should also be excellent substrates for the $Pd(OAc)_2$-catalyzed annulative reaction. We have thus also employed 1,2-dibromobenzenes as substrates for the reaction and our results are listed in Table 4. We found with $Pd(OAc)_2$ as catalyst, the reaction could proceed at room temperature for 1,2-dibromobenzene and 3,4-dibromotoluene, and excellent yields of substituted fluorenes were obtained. Unsymmetrical 3,4-dibromotoluene gave two isomeric fluorenes in 42:58 ratio, suggesting that the reactivity of two C–Br bonds is close to each other. For 1,2-dibromo-4,5-dimethylbenzene, heating to 60 °C was necessary to achieve high yields, likely because of slower initial oxidative addition of C–Br with Pd(0) species. We have also tested 1-bromo-2-iodobenzene as substrate and found it was also an excellent one for the reaction. Our study showed that $Pd(OAc)_2$ was a highly efficient, operationally convenient catalyst for this reaction.

However, no cyclization product was observed with 2,3-dibromopyridine as the substrate (Table 4, entry 9).

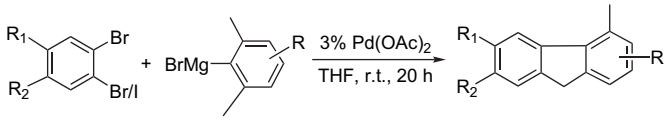
To establish that the $Pd(OAc)_2$-catalyzed annulative reactions of 1,2-dibromobenzenes with hindered Grignard reagents did not proceed via cross-coupling followed by C–H activation pathway, we adopted the same strategy we used for Pd(0)/*t*-Bu_3P catalyst system: to detect the existence of the intermediate **I** by interrupting the reactions before their completion by using limited amount of Grignard reagent. 2-Bromo-2′,4′,6′-trimethylbiphenyl (**I**) was found to be inert under the reaction condition (Scheme 8) and has been established to be detectable by GC–MS.[4] We thus reasoned that it could be detected if it was formed in the reaction as the intermediate. We have thus carried out the reaction of 1,2-dibromobenzene with 0.5 equiv of 2-mesitylmagnesium bromide. Our result showed that no **I** was observed with $Pd(OAc)_2$ as catalyst (Table 5, entry 1). In contrary, 7% of **I** was observed with Pd(0)/*t*-Bu_3P as catalyst (Table 5, entry 2). The reaction of 3,4-dibromotoluene with 0.5 equiv of 2-mesitylmagnesium bromide gave similar results: **I** was not detected with $Pd(OAc)_2$ as catalysts, and 12% **I** observed with Pd(0)/*t*-Bu_3P as catalyst (Table 5, entries 3 and 4). In combination with our results that no reaction was observed when mixing **I** with 2-mesitylmagnesium bromide in the presence of $Pd(OAc)_2$ (Scheme 8), the absence of **I** strongly suggests that the pathway for the $Pd(OAc)_2$-catalyzed reaction of 1,2-dibromobenzenes as well as 1-bromo-2-iodobenzene with bulky Grignard reagents should be benzyne formation pathway, rather than the cross-coupling followed by C–H activation pathway.

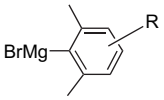
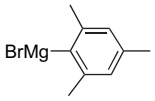
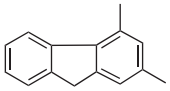
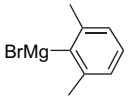
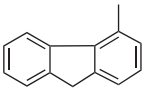
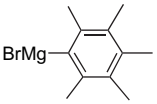
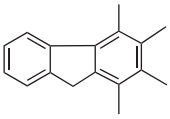
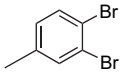
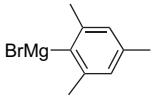
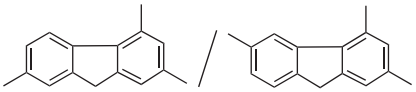
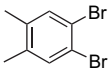
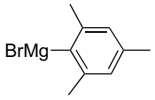
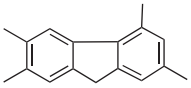
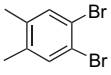
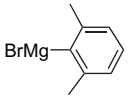
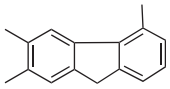
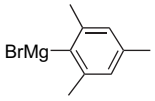
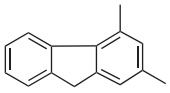
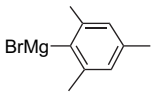
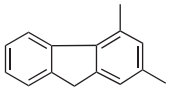
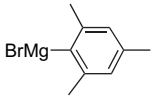
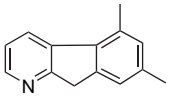
To understand whether other types of carbon–hydrogen bonds (nonbenzylic C–(1°)H bonds, benzylic C–(2°)H bonds, and benzylic C–(3°)H bonds) could also be activated under our condition, we tested 2-ethyl-6-methylphenylmagnesium bromide and 2-isopropyl-6-methylphenylmagnesium bromide for the domino reaction. We found that the reaction with sterically more hindered Grignard reagent underwent slower than that with less sterically hindered Grignard reagent (Table 6, entries 1–3). Such a slower reaction could be improved by raising the reaction temperature (Table 6, entries 3 and 4). We also found that the sp^3 C–H activation occurred at the benzylic methyl groups, suggesting that benzylic C–(1°)H bonds preferentially be activated over nonbenzylic C–(1°)H bonds (nonbenzylic methyl group), benzylic C–(2°)H bonds, and C–(3°)H bonds (Table 4, entry 2, Table 6, entries 1 and 2). This observation was further confirmed by the fact that no reaction was observed for 2,6-diethylphenylmagnesium bromide (Table 6, entry 4).

2.4. $Pd(OAc)_2$-catalyzed annulative reactions of hindered Grignard reagents with 2-haloaryl arenesulfonates

Based on the hypothesis that the reactions of 1,2-dihalobenzenes proceeded with hindered Grignard reagents could proceed via palladium associated aryne intermediates, we found by omitting the use of phosphine and NHC ligands for palladium catalysts, a broad range of 1,2-dihalobenzenes including 1,2-dibromobenzenes, 1-bromo-2-iodobenzene, 1-chloro-2-

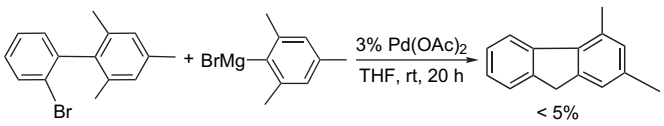
Table 4
Pd-catalyzed cross-couplings of 1,2-dibromobenzenes and 1-bromo-2-iodobenzene with hindered Grignard reagents[a]



Entry	Dihalide		Substituted fluorene	Yield[b] (%)
1				99
2				99
3				92
4				99 (42/58)[c]
5				97[d]
6				94[d]
7				99
8				99
9				0

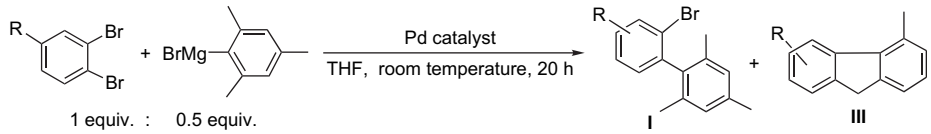
[a] Reaction conditions (not optimized): 1,2-dihalobenzene (1.0 equiv), Grignard reagent (2.5 equiv), 3% Pd catalyst, THF (2 ml), rt.
[b] Isolated yields.
[c] Ratio based on ^{1}H NMR.
[d] Reaction temperature: 60 °C.

halobenzenes, and 1-bromo-2-fluorobenzene could be suitable substrates for the preparation of substituted fluorenes. Our palladium associated aryne hypothesis suggested that other types of *o*-halo(LG)arenes, such as 2-haloaryl tosylates (Ts) and benzenesulfonates (Bs), which contain very inert C–OTs or C–OBs bonds, should also be suitable substrates for the domino reaction because the oxidative addition of Pd(0) with the very inert C–OTs or C–OBs bond would not be involved and the OTs/OBs group would only serve as a leaving group. We thus tested 2-haloaryl tosylates and benzenesulfonates, which are readily available from 2-halophenols,[23] as substrates for the domino reactions (Table 7). We found that with $Pd(OAc)_2$ as catalyst, good to excellent yields of substituted fluorenes were obtained for 2-iodoaryl tosylates/benzenesulfonates and



Scheme 8. Pd-catalyzed reactions of 2-bromo-2′,4′,6′-trimethylbiphenyls with 2-mesitylmagnesium bromide.

Table 5
Pd-catalyzed reactions of 1,2-dibromobenzenes with limited amount of 2-mesitylmagnesium bromide[a]

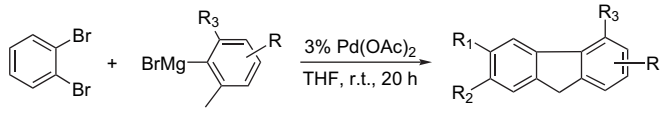


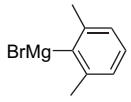
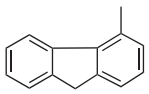
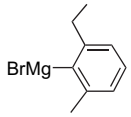
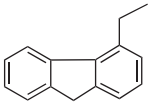
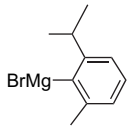
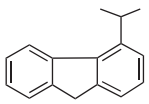
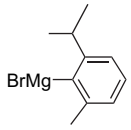
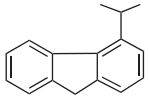
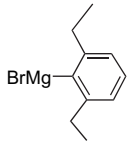
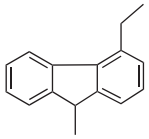
Entry	X	R	Pd catalyst	Conversion (%)	Ratio (%)	
					I	**III**
1	Br	H	3% $Pd(OAc)_2$	46	0	100
2	Br	H	1.5% $Pd_2(dba)_3$/*t*-Bu_3P	48	7	93
3	Br	CH_3	3% $Pd(OAc)_2$	49	0	100
4	Br	CH_3	1.5% $Pd_2(dba)_3$/*t*-Bu_3P	45	12	88

[a] Reaction conditions: 1,2-dibromobenzene (1.0 equiv), Grignard reagent (0.5 equiv), 3% Pd catalyst, THF (2 ml), rt, 20 h. Ratios of **I** to **III** were based on GC–MS data.

2-bromoaryl tosylates/benzenesulfonates (Table 7, entries 1–13). However, 2-chloro-4-methylphenyl tosylate was found to be a poor substrate (Table 7, entry 14). Comparing the reaction results with 2-halo-4-methylphenyl tosylates as substrates (Table 7, entries 6, 7, and 14) revealed that 2-iodo-4-methylphenyl tosylate was a better substrate than 2-bromo-4-methylphenyl tosylate and 2-chloro-4-methylphenyl tosylate was virtually inactive. As these substrates only differ in their halo groups and chloro group was more electron-withdrawing than Br or I group, our results suggested that the initial oxidative addition should occur at the C–X bond, rather than at the C–OTs bond. Otherwise, 2-chloro-4-methylphenyl tosylate would be the better substrate than 2-bromo-4-methylphenyl tosylate and 2-iodo-4-methylphenyl tosylate. This thinking was further confirmed by the fact that no reaction was observed for pyrocatechol ditosylate (Table 7, entry 15). Thus, the reluctance of the C–Cl bond in 2-chloro-4-methylphenyl tosylate to undergo the initial oxidative addition with Pd(0) species excluded it as a suitable substrate for the domino reaction. The observation of two isomers, rather than only one, in similar ratio for 2-bromophenyl tosylates/benzenesulfonates, 2-iodo-4-methylphenyl tosylate, and 1-bromo-2-naphthyl tosylate/benzenesulfonate (Table 7, entries 6–13) further suggested that the transmetalation occurred with comparable transmetalation rates for Pd–Br and Pd–I bonds.

Table 6
Pd-catalyzed cross-couplings of 1,2-dibromobenzene with hindered Grignard reagents[a]

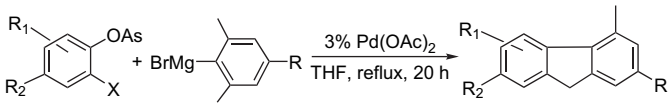


Entry	R BrMg	Substituted fluorene	Yield[b] (%)
1			99
2			68
3			29
4			72[c]
5			<1

[a] Reaction conditions (not optimized): dihalide (1.0 equiv), Grignard reagent (2.5 equiv), 3% $Pd(OAc)_2$, THF (2 ml), rt.
[b] Isolated yields.
[c] Reaction temperature: 60 °C.

Aryl tosylates have been demonstrated to undergo cross-couplings with *para*-substituted phenylmagnesium bromides and *ortho*-tolymagnesium bromide when catalyzed by Pd(0)/Josiphos ligand.[24] We have carried out the reaction of phenyl tosylate with 2-mesitylmagnesium bromide in the presence of 5% $Pd(OAc)_2$ at 60 °C for 20 h. We found that the cross-coupling product was formed in less than 5% yield, suggesting that $Pd(OAc)_2$ cannot catalyze the cross-coupling of aryl tosylates with hindered Grignard reagents efficiently (Scheme 9). We also found that 2-(2′,4′,6′-trimethyl)-4-methylphenyl tosylate, intermediate that would be formed if the domino reaction proceeded via cross-coupling-oxidative addition-sp^3 C–H activation mechanism, was unable to be converted to 2,4,6-trimethylfluorene under $Pd(OAc)_2$/Grignard reagent or $Pd(OAc)_2$/$MgCl_2$/Grignard reagent condition (Scheme 10). We have further carried out the $Pd_2(dba)_3$/*t*-Bu_3P-catalyzed reaction of 2-bromo-4-methylphenyl tosylate with 2-mesitylmagnesium bromide and 2-(2′,4′,6′-trimethyl)-4-methylphenyl tosylate was isolated in 82% yield with no cyclized fluorene being observed (Scheme 11). These results strongly suggested that

Table 7
$Pd(OAc)_2$-catalyzed reactions of 2-haloaryl arenesulfonates with hindered Grignard reagents[a]



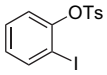
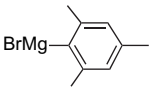
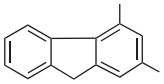
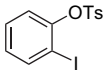
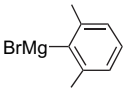
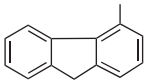
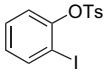
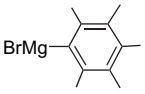
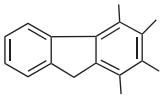
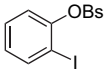
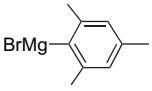
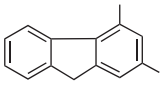
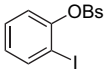
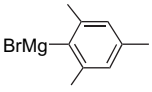
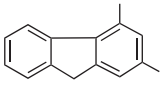
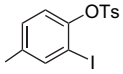
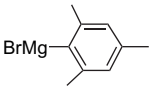
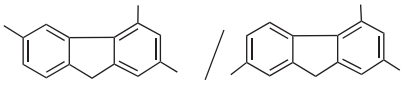
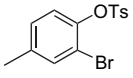
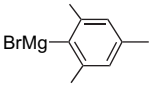
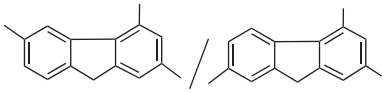
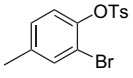
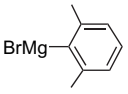
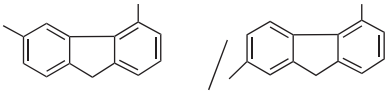
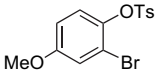
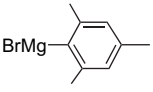
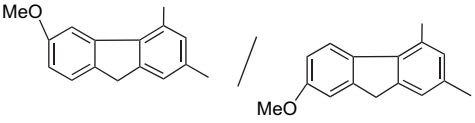
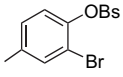
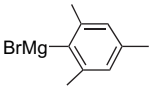
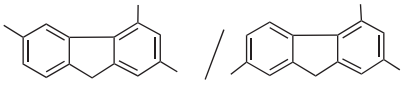
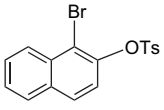
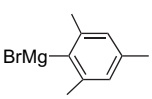
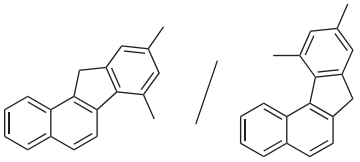
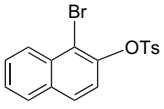
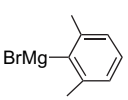
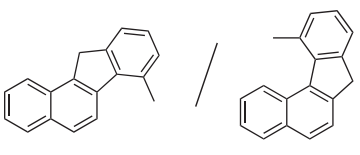
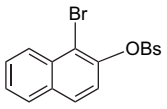
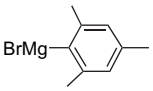
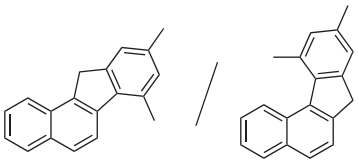
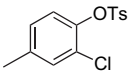
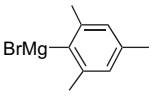
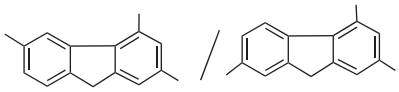
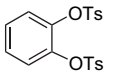
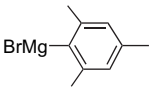
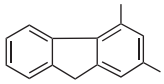
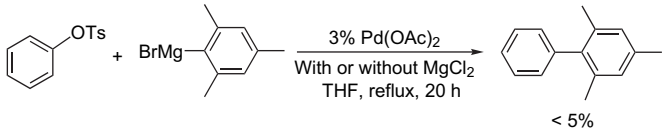
Entry	Tosylate	ArMgBr	Product		Yield[b] (%)
1					92
2					87
3					83
4					95
5					86
6				(62:38)[c]	92
7				(58:42)[c]	82
8				(63:37)[c]	74
9				(58:42)[c]	69
10				(71:29)[c]	49
11				(65:35)[c]	79
12				(68:32)[c]	71

Table 7 (*continued*)

Entry	Tosylate	ArMgBr	Product		Yield[b] (%)
13				(55:45)[c]	47
14					<2
15					<2

[a] Reaction conditions (not optimized): 2-haloaryl arenesulfonate (1.0 equiv), Grignard reagent (2.5 equiv), $Pd(OAc)_2$ (3%), THF (2 ml), reflux.
[b] Isolated yields.
[c] Ratio based on ^1H NMR.

$Pd(OAc)_2$-catalyzed domino reactions of 2-haloaryl arenesulfonates with hindered Grignard reagents did not proceed through the cross-coupling-oxidative addition-sp^3 C–H activation mechanism.

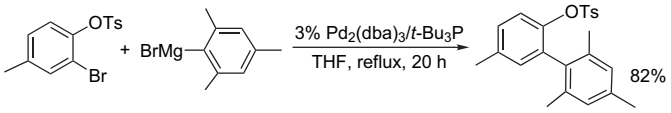


Scheme 9. $Pd(OAc)_2$-catalyzed reaction of phenyl tosylate with 2-mesitylmagnesium bromide.

As our results supported that the initial oxidative addition should not occur at the C–OTs bond, the similar ratio of the substituted fluorenes observed for unsymmetrical 2-bromoaryl tosylates/benzenesulfonates, 2-iodo-4-methylphenyl tosylate, and 1-bromo-2-naphthyl tosylate/benzenesulfonate excluded the pathway that the transmetalation occurs first followed by aryne formation, in which only one isomer of substituted fluorenes would be expected. Our study further suggested that the pathway to form Pd(LG)X associated arynes first followed by transmetalation should be predominant, if not the only one.[25]

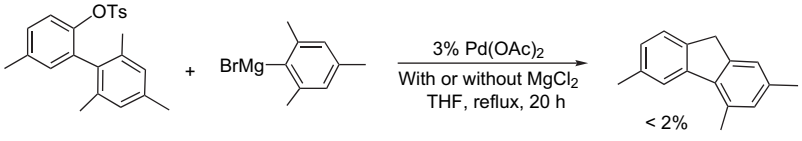
3. Summary

We demonstrated that simple palladium complexes such as $Pd(OAc)_2$ were excellent catalysts for 1,2-dihalobenzenes and 2-haloaryl arenesulfonates to undergo annulative reactions with hindered Grignard reagents to form substituted fluorenes.



Scheme 11. Pd(0)/*t*-Bu_3P-catalyzed reaction of 2-bromo-4-methylphenyl tosylate with 2-mesitylmagnesium bromide.

Our study was based on the hypothesis that two mechanistic pathways might be possible for the reaction of 1,2-dihalobenzenes with Grignard reagents, namely (a) the pathway that involves the cross-coupling of 1,2-dihalobenzenes with Grignard reagents to form 2-halobiphenyls followed by oxidative addition and sp^3 C–H activation, and (b) the pathway that involves the oxidative addition of 1,2-dihalobenzenes to form 2-haloarylPd(II)X complexes followed by β-halo elimination to form palladium associated arynes, transmetalation, carbopalladation, and sp^3 C–H activation. We explored the ligand effect and leaving group effect on these two pathways. We found that these two pathways were highly ligand dependent and the reaction pathway involving palladium associated arynes as intermediates could be controlled by omitting the use of phosphine and NHC ligands for palladium catalysts. We also found that a better leaving halo group favored the benzyne forming pathway and the sp^3 C–H activation preferentially occurred at benzylic C–(1°)H bonds over nonbenzylic C–(1°)H bonds (nonbenzylic methyl group), benzylic C–(2°)H bonds, and benzylic C–(3°)H bonds. Our palladium associated aryne hypothesis allowed us to identify simple palladium complexes, e.g., $Pd(OAc)_2$, as the catalyst and a broad range of 1,2-dihalobenzenes including previously unsuitable 1-chloro-2-halobenzenes and 2-haloaryl arenesulfonates as



Scheme 10. $Pd(OAc)_2$-catalyzed reaction of 2-(2′,4′,6′-trimethyl)-4-methylphenyl tosylate with 2-mesitylmagnesium bromide.

substrates for high yield synthesis of substituted fluorenes. Our study also suggested that 2-(leaving group)arylPd(II) complexes most likely formed Pd(leaving group)X associated arynes first followed by transmetalation with Grignard reagents and carbopalladation, rather than undergo transmetalation with Grignard reagent first following by aryne formation and carbopalladation. The work described here provides a high yield, one-step access to substituted fluorenes from readily available 1,2-dihalobenzenes and 2-haloaryl arenesulfonates and hindered Grignard reagents, and our method may find applications in the preparation of substituted fluorene-containing molecules including polymers.

4. Experimental section

4.1. General

NMR spectra were recorded on Varian 200 MHz or 600 MHz spectrometers. GC–MS experiments were carried out using an Agilent GC/MS instrument consisting of a 6890N series GC and a 5973 Mass Selective Detector System. All yields reported refer to isolated yields (average of two runs) unless otherwise indicated, and the product purity was estimated to be greater than 95% as determined by ^{1}H NMR. Compounds described in the literature were characterized by comparison of their melting points, ^{1}H NMR, and ^{13}C NMR spectra to reported data. Some of the new compounds were also characterized by elemental analysis.

THF was dried with sodium/benzophenone. 2,6-Dimethylphenylmagnesium bromide, 2-mesitylmagnesium bromide, and *p*-tolylmagnesium bromide were purchased from Aldrich Chemical Co. and used directly. $Pd_2(dba)_3$ and *t*-Bu_3P were purchased from Strem and used as received. $Pd(OAc)_2$ was obtained as a gift from Frontier Scientific, Inc. 3-Bromo-4-chlorotoluene,[26] 3-chloro-4-iodotoluene,[27] and 2-iodo-4-methylphenol[28] were prepared according to literature procedures. Aryl tosylates and benzenesulfonates were prepared by treating the corresponding phenols with *p*-toluenesulfonyl chloride or benzenesulfonyl chloride in dichloromethane containing excess of triethylamine at room temperature overnight. Bromopentamethylbenzene and pentamethyl phenylmagnesium bromide were prepared according to literature.[29,30] Other chemical reagents were purchased from Alfa Aesar and used directly.

4.2. General procedure of the ligand effect on domino reactions of 1-bromo-2-chlorobenzene with Grignard reagents

In a glove box with N_2-atmosphere, to a mixture of 1-bromo-2-chlorobenzene (1.0 mmol) and 2.0 ml THF (in a Schlenk flask) were added palladium source (0.015 mmol) and phosphine ligands (0.06 mmol). After stirred for 5–10 min, Grignard reagent (2.5 ml, 1 M in THF, 2.5 mmol) was added. The mixture was allowed to stir under 60 °C for 20 h. After quenched with water, the reaction mixture was extracted with ethyl acetate twice. The organic layer was washed with brine and the solvent was evaporated under vacuum. ^{1}H NMR analysis of the reaction mixture gave the conversion of the reaction, and the ratio of the products.

4.3. General procedure of the leaving group effect on domino reactions of 1,2-dihalobenzenes with Grignard reagents

In a glove box with N_2-atmosphere, to a mixture of 1,2-halobenzene (1.0 mmol) and 2.0 ml THF (in a Schlenk flask) was added $Pd(OAc)_2$ (0.015 mmol). After stirred for 5–10 min, 2-mesitylmagnesium bromide (2.5 ml, 1 M in THF, 2.5 mmol) was added. The mixture was allowed to stir at 60 °C or at room temperature for 20 h. After quenched with water, the reaction mixture was extracted with ethyl acetate twice. The organic layer was washed with brine and the solvent was evaporated under vacuum. ^{1}H NMR analysis of the reaction mixture gave the conversion of the reaction, and the ratio of the products.

4.4. General procedure for Pd-catalyzed domino reactions of 1,2-dihalobenzenes with hindered Grignard reagents

In a glove box with N_2-atmosphere, to a mixture of 1,2-dihalobenzenes (1.0 mmol) and 1.0 ml THF (in a Schlenk flask) was added palladium acetate (0.03 mmol) or $Pd_2(dba)_3$ (0.015 mmol). After stirred for 5–10 min, Grignard reagent (2.5 ml, 1 M in THF, 2.5 mmol) was added. The mixture was allowed to stir at room temperature or 60 °C for 20 h. After being quenched with water, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine and the solvent was evaporated under vacuum. Flash chromatography on silica gel (hexane/ethyl acetate=100:0–90:10) gave the products.

4.5. General procedure for $Pd(OAc)_2$-catalyzed domino reaction of 2-haloaryl tosylates with hindered Grignard reagents

In a glove box with N_2-atmosphere, to a mixture of 2-haloaryl tosylate (1.0 mmol) and 1.0 ml THF (in a Schlenk flask) was added palladium acetate (6.7 mg, 0.03 mmol). After stirred for 5–10 min, Grignard reagent (2.5 ml, 1 M in THF, 2.5 mmol) was added. The mixture was allowed to stir under refluxing for 20 h. After quenched with water, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine and the solvent was evaporated under vacuum. Flash chromatography on silica gel (hexane/ethyl acetate=100:0–90:10) gave the products.

4.5.1. 2,4-Dimethylfluorene[31]

White solid. Mp: 66.5–67.5 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.87 (d, J=7.2 Hz, 1H), 7.53 (d, J=7.2 Hz, 1H), 7.36 (t, J=7.8 Hz, 1H), 7.27 (t, J=7.2 Hz, 1H), 7.21 (s, 1H), 6.97 (s, 1H), 3.86 (s, 2H), 2.69 (s, 3H), 2.39 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): δ 143.9, 143.5, 142.7, 137.16, 136.2, 132.7, 129.9, 126.5, 125.6, 124.8, 123.1, 122.6, 36.9, 21.3, 20.9 ppm.

4.5.2. 4-Methylfluorene[32]

White solid. Mp: 69–71 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.93 (d, J=7.8 Hz, 1H), 7.56 (d, J=7.2 Hz, 1H), 7.39 (t, J=7.2 Hz, 1H), 7.38 (d, J=7.8 Hz, 1H), 7.30 (t, J=7.2 Hz, 1H), 7.22 (t, J=7.8 Hz, 1H), 7.15 (d, J=7.8 Hz, 1H), 3.91 (s, 2H), 2.73 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): δ 143.7, 143.6, 142.7, 139.8, 133.0, 129.0, 126.6, 126.4, 126.0, 124.9, 123.1, 122.4, 37.1, 21.1 ppm.

4.5.3. 1,2,3,4-Tetramethylfluorene[33]

White solid. Mp: 121.5–122.5 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.97 (d, J=8.4 Hz, 1H), 7.53 (d, J=7.8 Hz, 1H), 7.34 (dd, J=8.4, 0.6 Hz, 1H), 7.25 (dd, J=8.4, 0.6 Hz, 1H), 3.76 (s, 2H), 2.66 (s, 3H), 2.32 (s, 6H), 2.29 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): δ 143.7, 143.6, 139.9, 137.0, 133.7, 133.5, 129.4, 129.1, 126.4, 125.3, 124.7, 123.1, 36.6, 16.8, 16.5, 16.5, 16.2 ppm. Anal. Calcd for $C_{17}H_{18}$: C, 91.84%; H, 8.16%. Found: C, 91.58%; H, 8.19%.

4.5.4. 2,4,6-Trimethylfluorene/2,4,7-trimethylfluorene

Off-white solid. Mp: 43–57 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.74 (d, J=7.8 Hz, 1H), 7.68 (s, 1H), 7.40 (d, J=7.8 Hz, 1H), 7.34 (s, 1H), 7.19 (s, 1H), 7.18 (s, 1H), 7.18–7.16 (m, 2H), 7.08 (d, J=7.2 Hz, 1H), 6.95 (s, 1H), 3.81 (s, 4H), 2.69 (s, 4H), 2.66 (s, 2H), 2.46 (s, 4H), 2.42 (s, 2H), 2.38 (s, 6H) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): δ 144.4, 143.8, 143.7, 142.9, 140.6, 140.1, 137.2, 137.2, 136.0, 136.0, 135.7, 135.3, 132.6, 132.2, 129.8, 129.8, 127.3, 126.4, 125.6, 124.4, 123.4, 123.1, 123.1, 122.3, 36.7, 36.5, 21.8, 21.4, 21.3, 21.3, 21.0, 20.8 ppm. Anal. Calcd for $C_{16}H_{16}$: C, 92.26%; H, 7.74%. Found: C, 91.93%; H, 7.78%.

4.5.5. The structure of 2,4,6-trimethylfluorene was established by NOE effect

Recrystallization on the mixture of 2,4,7-trimethylfluorene/2,4,6-trimethylfluorene by hexanes gave >90% pure 2,4,6-trimethylfluorene. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.68 (s, 1H), 7.40 (d, J=7.8 Hz, 1H), 7.19 (s, 1H), 7.08 (d, J=7.8 Hz, 1H), 6.95 (s, 1H), 3.80 (s, 2H), 2.68 (s, 3H), 2.46 (s, 3H), 2.38 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): δ 144.4, 142.9, 140.6, 137.2, 136.1, 136.0, 132.6, 129.8, 126.4, 124.4, 123.4, 123.1, 36.5, 21.8, 21.3, 21.0 ppm. NOE effect observed when the peak at 3.80 ppm was irradiated: 3.5% for the peak with chemical shift of 7.40 ppm and 3.4% for the peak with chemical shift of 7.19 ppm.

4.5.6. 3,5-Dimethylfluorene/2,5-dimethylfluorene

Off-white solid. Mp: 43–62 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.78 (d, J=7.8 Hz, 1H), 7.72 (s, 1H), 7.42 (d, J=7.8 Hz, 1H), 7.36–7.36 (m, 1H), 7.21–7.15 (m, 1H), 7.13–7.11 (m, 1H), 3.84 (s, 2H), 2.72 (s, 3H), 2.70 (s, 3H), 2.46 (s, 3H), 2.42 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): δ 144.0, 143.9, 143.4, 142.9, 140.7, 140.0, 139.8, 139.8, 136.04, 135.8, 133.0, 132.6, 128.9, 128.8, 127.4, 126.9, 126.2, 125.9, 125.6, 124.5, 123.8, 122.8, 122.4, 122.3, 36.9, 36.7, 21.8, 21.4, 21.2, 21.0 ppm.

4.5.7. The structure of 3,5-dimethylfluorene was established by NOE effect

Recrystallization of the mixture of 2,5-dimethylfluorene/3,5-dimethylfluorene by hexanes gave >95% pure 3,5-dimethylfluorene. Mp: 77–78.5 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.73 (s, 1H), 7.43 (d, J=8.4 Hz, 1H), 7.38 (d, J=7.8 Hz, 1H), 7.19 (t, J=8.4 Hz, 1H), 7.13 (m, 2H), 3.85 (s, 2H), 2.73 (s, 3H), 2.47 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 150.855 MHz): δ 144.0, 142.9, 140.7, 139.8, 136.1, 133.0, 128.9, 126.9, 126.2, 124.5, 123.8, 122.4, 36.7, 21.8, 21.2 ppm. NOE effect observed when the peak at 3.85 (s) ppm was irradiated: 2.9% for the peak with chemical shift of 7.43 ppm and 2.5% for the peak with chemical shift of 7.38 ppm.

4.5.8. 3-Methoxy-5-methylfluorene/2-methoxy-5-methylfluorene

Compound was obtained as a mixture with a ratio of 78:22. The structure of 3-methoxy-5-methylfluorene was established by NOE effect. Recrystallization from the mixture of 3-methoxy-5-methylfluorene and 2-methoxy-5-methylfluorene in hexanes gave 3-methoxy-5-methylfluorene as a white solid. Mp: 70–71 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.49 (d, J=2.4 Hz, 1H), 7.45 (d, J=8.4 Hz, 1H), 7.38 (d, J=7.2 Hz, 1H), 7.20 (t, J=7.2 Hz, 1H), 7.14 (d, J=7.8 Hz, 1H), 7.87 (dd, J_1=8.4, 2.4 Hz, 1H), 3.89 (s, 3H), 3.84 (s, 2H), 2.72 (s, 3H). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 158.8, 144.7, 143.9, 139.6, 135.8, 133.0, 128.9, 126.5, 125.1, 122.5, 111.3, 109.4, 55.6, 36.3, 21.0 ppm. NOE effect observed when the peak at δ 3.84 ppm was irradiated: 7.45 (d, 0.3%), 7.38 (d, 0.3%).

4.5.9. 2,3,5,7-Tetramethylfluorene

White solid. Mp: 104–105 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.64 (s, 1H), 7.31 (s, 1H), 7.18 (s, 1H), 6.94 (s, 1H), 3.79 (s, 2H), 2.68 (s, 3H), 2.38 (s, 3H), 2.37 (s, 3H), 2.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 150.871 MHz): δ 144.0, 141.2, 140.6, 137.4, 135.6, 134.5, 134.0, 132.2, 129.7, 126.0, 123.8, 123.1, 36.5, 21.3, 20.9, 20.3, 20.0 ppm.

4.5.10. 2,3,5-Trimethylfluorene

White solid. Mp: 86.5–87.5 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.68 (s, 1H), 7.36 (d, J=7.2 Hz, 1H), 7.32 (s, 1H), 7.16 (t, J=7.2 Hz, 1H), 7.11 (d, J=7.2 Hz, 1H), 3.82 (s, 2H), 2.71 (s, 3H), 2.37 (s, 3H), 2.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 150.871 MHz): δ 143.6, 141.4, 140.6, 140.0, 134.6, 134.5, 132.5, 128.8, 126.0, 125.8, 124.2, 122.3, 36.6, 21.1, 20.3, 20.0 ppm.

4.5.11. 4-Ethylfluorene[34]

White solid. Mp: 35–36 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.92 (d, J=7.8 Hz, 1H), 7.57 (d, J=7.2 Hz, 1H), 7.41 (t, J=7.2 Hz, 1H), 7.39 (d, J=7.8 Hz, 1H), 7.31 (t, J=7.2 Hz, 1H), 7.27–7.24 (m, 1H), 7.19 (d, J=7.2 Hz, 1H), 3.92 (s, 2H), 3.12 (q, J=7.2 Hz, 2H), 1.39 (t, J=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 143.9, 143.7, 142.1, 139.4, 139.0, 127.1, 126.7, 126.6, 126.0, 124.9, 123.2, 122.5, 37.1, 27.2, 14.3 ppm.

4.5.12. 4-Isopropylfluorene[34]

Colorless liquid. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.97 (d, J=7.8 Hz, 1H), 7.55 (d, J=7.2 Hz, 1H), 7.39 (d, J=6.0 Hz, 1H), 7.38 (t, J=7.8 Hz, 1H), 7.33 (d, J=7.8 Hz, 1H), 7.30 (t, J=6.0 Hz, 2H), 3.90 (s, 2H), 3.84 (m, 1H), 1.41 (d, J=6.6 Hz, 6H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 144.3, 143.9, 143.8, 142.0, 138.5, 126.7, 126.6, 125.9, 124.9, 123.6, 123.0, 122.4, 37.1, 29.5, 22.8 ppm.

4.5.13. 7,9-Dimethyl-11H-benzo[a]fluorene and 9,11-dimethyl-7H-benzo[c]fluorene

Anal. Calcd for $C_{19}H_{16}$: C, 93.40%; H, 6.60%. Found: C, 93.60%; H, 6.54%. The structure of 7,9-dimethyl-11*H*-benzo[*a*]fluorene was established by NOE effect. Recrystallization from the mixture of 7,9-dimethyl-11*H*-benzo[*a*]fluorene and 9,11-dimethyl-7*H*-benzo[*c*]fluorene by using hexanes as solvent gave 7,9-dimethyl-11*H*-benzo[*a*]fluorene as a white solid. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.07 (d, J=8.4 Hz, 1H), 8.00 (d, J=8.4 Hz, 1H), 7.90 (d, J=7.8 Hz, 1H), 7.85 (d, J=8.4 Hz, 1H), 7.53 (t, J=7.8 Hz, 1H), 7.45 (t, J=7.8 Hz, 1H), 7.29 (s, 1H), 7.00 (s, 1H), 4.14 (s, 2H), 2.77 (s, 3H), 2.42 (s, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 144.0, 140.1, 139.9, 138.1, 135.9, 132.1, 131.9, 130.5, 130.1, 128.6, 127.3, 126.2, 125.1, 124.0, 123.2, 121.6, 35.6, 21.3, 20.8 ppm. NOE effect was observed when irradiated at the peak at δ 4.14 ppm: 8.00 (d, 0.5%), 7.29 (s, 0.3%). NOE effect observed when the peak at δ 2.77 ppm was irradiated: 8.07 (d, 0.5%), 7.00 (s, 0.29%). NOE effect observed when the peak at δ 2.42 ppm was irradiated: 7.29 (d, 0.22%), 7.00 (s, 0.19%).

4.5.14. 9,11-Dimethyl-7H-benzo[c]fluorene

Off-white solid. Obtained from the mother liquid of the recrystallization of the mixture of 7,9-dimethyl-11*H*-benzo[*a*]-fluorene and 9,11-dimethyl-7*H*-benzo[*c*]fluorene with >90% purity. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.51 (d, J=8.4 Hz, 1H), 7.88 (d, J=8.4 Hz, 1H), 7.76 (d, J=7.8 Hz, 1H), 7.58 (d, J=7.8 Hz, 1H), 7.48 (t, J=7.8 Hz, 1H), 7.43 (t, J= 7.8 Hz, 1H), 7.21 (s, 1H), 7.07 (s, 1H), 3.90 (s, 2H), 2.82 (s, 3H), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 145.1, 142.3, 139.0, 138.4, 135.7, 133.7, 131.6, 131.4, 128.7, 128.6, 127.4, 126.8, 124.5, 124.5, 123.0, 122.9, 38.0, 25.1, 21.0 ppm. NOE effect observed when the peak at δ 3.90 ppm was irradiated: 7.58 (d, 0.5%), 7.21 (s, 0.3%).

4.5.15. 7-Methyl-11H-benzo[a]fluorene and 11-methyl-7H-benzo[c]fluorene

Anal. Calcd for $C_{18}H_{14}$: C, 93.87%; H, 6.13%. Found: C, 93.69%; H, 6.01%. The structure of 7-methyl-11*H*-benzo[*a*]-fluorene was established by NOE effect. Recrystallization from the mixture of 7-methyl-11*H*-benzo[*a*]fluorene and 11-methyl-7*H*-benzo[*c*]fluorene by using hexanes as solvent gave 7-methyl-11*H*-benzo[*a*]fluorene as a white solid. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.10 (d, J=8.4 Hz, 1H), 8.01 (d, J=8.4 Hz, 1H), 7.90 (d, J=8.4 Hz, 1H), 7.86 (d, J=8.4 Hz, 1H), 7.53 (t, J=7.8 Hz, 1H), 7.47 (d, J=7.2 Hz, 1H), 7.47 (t, J=7.2 Hz, 1H), 7.22 (t, J=7.8 Hz, 1H), 7.17 (d, J=7.8 Hz, 1H), 4.17 (s, 2H), 2.80 (s, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 143.6, 140.7, 140.3, 140.0, 132.5, 132.0, 130.4, 129.2, 128.6, 127.4, 126.3, 126.0, 125.3, 124.1, 122.4, 121.8, 35.7, 21.0 ppm. NOE effect observed when the peak at δ 4.17 ppm was irradiated: 8.10 (d, 0.9%), 7.47 (s, 0.3%).

4.5.16. 11-Methyl-7H-benzo[a]fluorene

Off-white solid. Obtained from the mother liquid of the mixture of 11-methyl-7*H*-benzo[*c*]fluorene and 7-methyl-11*H*-benzo[*a*]fluorene by using hexanes as solvent with >85% purity. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.51 (d, J=8.4 Hz, 1H), 7.91 (d, J=8.4 Hz, 1H), 7.80 (d, J=8.4 Hz, 1H), 7.62 (d, J=8.4 Hz, 1H), 7.51 (t, J=7.2 Hz, 1H), 7.46 (t, J=7.2 Hz, 1H), 7.42 (d, J=7.2 Hz, 1H), 7.26 (t, J=8.4 Hz, 1H), 7.25 (d, J=7.2 Hz, 1H), 3.97 (s, 2H), 2.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 144.7, 142.7, 141.6, 138.3, 133.7, 132.0, 130.6, 128.8, 128.6, 128.6, 127.9, 126.8, 125.9, 124.6, 123.0, 122.0, 38.2, 25.1 ppm. NOE effect was observed when the peak at δ 3.97 ppm was irradiated: 7.62 (d, 0.3%), 7.42 (s, 0.2%).

4.6. Pd(OAc)$_2$-catalyzed reaction of 2-halo-2′,4′,6′-trimethylbiphenyl with 2-mesitylmagnesium bromide

In a glove box with nitrogen atmosphere, to a mixture of 2-chloro-2′,4′,6′-trimethylbiphenyl or 2-fluoro-2′,4′,6′-trimethylbiphenyl (0.1 mmol) and 0.5 ml THF (in a Schlenk flask) was added $Pd(OAc)_2$ (0.7 mg, 0.003 mmol). After stirred for 5–10 min, Grignard reagent THF solution (0.25 ml, 1 M in THF, 0.25 mmol) was added. The mixture was allowed to stir under 60 °C for 20 h. After quenched with water, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine and the solvent was evaporated under vacuum. No reaction was observed by ^{1}H NMR.

4.7. Pd(OAc)$_2$-catalyzed reaction of phenyl tosylate with 2-mesitylmagnesium bromide

In a glove box with nitrogen atmosphere, to a mixture of phenyl tosylate (62 mg, 0.25 mmol) and 0.5 ml THF (in a Schlenk flask) was added palladium acetate (1.7 mg, 0.007 mmol). After stirred for 5–10 min, 2-mesitylmagnesium bromide THF solution (0.6 ml, 1 M in THF, 0.6 mmol) was added. The mixture was allowed to stir under 60 °C for 20 h. After quenched with water, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine and the solvent was evaporated under vacuum. ^{1}H NMR showed that the yield of the cross-coupling product was less than 5%.

4.8. Pd(OAc)$_2$-catalyzed reaction of 2-chloro-5-methylphenyl tosylate with 2-mesitylmagnesium bromide

In a glove box with nitrogen atmosphere, to a mixture of 2-chloro-5-methylphenyl tosylate (0.25 mmol) and 0.5 ml THF (in a Schlenk flask) was added $Pd(OAc)_2$ (1.7 mg, 0.0075 mmol). After stirred for 5–10 min, Grignard reagent

(0.65 ml, 1 M in THF, 0.65 mmol) was added. The mixture was allowed to stir under refluxing for 20 h. After quenched with water, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine and the solvent was evaporated under vacuum. No reaction was observed by ^{1}H NMR.

4.9. $Pd_2(dba)_3$/t-Bu_3P-catalyzed reaction of 2-bromo-4-methylphenyl tosylate with 2-mesitylmagnesium bromide

In a glove box with N_2-atmosphere, to a mixture of 2-bromo-4-methylphenyl tosylate (170.5 mg, 0.5 mmol) and 1.0 ml THF (in a Schlenk flask) were added $Pd_2(dba)_3$ (6.9 mg, 0.0075 mmol) and *t*-Bu_3P (6.1 mg, 0.03 mmol). After stirred for 5–10 min, 2-mesitylmagnesium bromide (1.25 ml, 1 M in THF, 1.25 mmol) was added. The mixture was allowed to stir under refluxing for 20 h. After quenched with water, the reaction mixture was extracted with ethyl acetate twice. The organic layer was washed with brine and the solvent was evaporated under vacuum. Flash chromatography on silica gel (hexane/ethyl acetate=100:0–90:15) gave the cross-coupling product 2-(2′,4′,6′-trimethylphenyl)-4-methylphenyl tosylate in 82% yield. White solid. Mp: 75–76 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.31 (d, J=7.8 Hz, 1H), 7.25 (d, J=8.4 Hz, 2H), 7.15 (dd, J=7.8, 1.8 Hz, 1H), 7.07 (d, J=8.4 Hz, 2H), 6.94 (d, J=1.8 Hz, 1H), 6.80 (s, 2H), 2.40 (s, 3H), 2.35 (s, 3H), 2.32 (s, 3H), 1.86 (s, 6H) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): δ 144.8, 144.3, 136.9, 136.6, 136.6, 133.7, 133.6, 133.1, 132.3, 129.2, 129.0, 127.9, 127.7, 122.6, 21.6, 21.0, 20.9, 20.3 ppm.

4.10. Palladium-catalyzed reaction of 2-(2′,4′,6′-trimethyl)-4-methylphenyl tosylate with 2-mesitylmagnesium bromide

In a glove box with N_2-atmosphere, to a mixture of 2-(2′,4′,6′-trimethyl)-4-methylphenyl tosylate (95 mg, 0.25 mmol) and 0.5 ml THF (in a Schlenk flask) was added $Pd(OAc)_2$ (1.7 mg, 0.0075 mmol). After stirred for 5–10 min, 2-mesitylmagnesium bromide (0.65 ml, 1 M in THF, 0.65 mmol) was added. The mixture was allowed to stir under refluxing for 20 h. After quenched with water, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine and the solvent was evaporated under vacuum. No 2,4,6-trimethylfluorene was observed by ^{1}H NMR.

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Supplementary data

NMR spectra of the products of palladium-catalyzed annulative reactions. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.01.020.

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