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Pd(OAc)$_2$-Catalyzed Domino Reactions of 1-Chloro-2-Haloarenes and 2-Haloaryl Tosylates with Hindered Grignard Reagents via Palladium Associated Arynes

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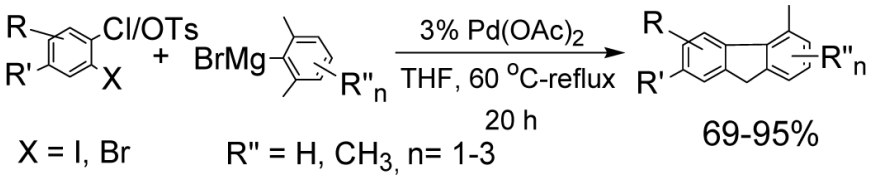
Abstract



The palladium associated aryne generation strategy and Pd(OAc)$_2$-catalyzed annulative Domino reactions of 1-chloro-2-halobenzenes and *2*-haloaryl tosylates with hindered Grignard reagents via palladium associated arynes are described. The palladium associated aryne generation strategy described here not only allows the high yield, one-step access to potentially useful substituted fluorenes from readily available 1-chloro-2-halobenzenes and *2*-haloaryl tosylates, but may also lead to the development of other tandem reactions based on these readily available *o*-leaving group bearing haloarenes

Arynes are very reactive and have recently been demonstrated as useful substrates for palladium-catalyzed carbon-carbon bond forming reactions.[1,2,3,4] However, the aryne generation strategy in reported reactions, in which arynes were generated *in situ* from expensive *o*-trimethylsilylaryl triflates, does not work well with the use of catalytic amounts of palladium because short-lived arynes are needed to search for inherently unstable palladium intermediates for reactions to occur. Consequently, a large excess of *o*-trimethylsilylaryl triflates was often required to achieve good yields. It would thus be synthetically advantageous to generate arynes with palladium species inherently associating with them, especially from readily available, cost-effective starting materials.

We have recently reported Pd(0)/*t*-Bu$_3$P-catalyzed annulative tandem reacion of 1,2-dibromobenzenes and 1-bromo-2-iodobenzene with hindered Grignard reagents.[5,6] However, readily available, less expensive 1-chloro-2-halobenzenes were found to be unsuitable substrates for such type of tandem reaction because of the reluctancy of the first-step cross-coupling product, 2-chlorobiphenyls (**I**), to undergo oxidative addition with Pd(0) species.[5] During our study, we reasoned that the initial oxidative addition adduct *o*-chloroarylpalladium (II) halides (**II**), in addition to undergo transmetalation with organometallic reagents to form **I** (Scheme 1, Path B), might undergo β-chloro group elimination to form Pd(II)ClX associated arynes (Scheme 1, Path A).[7,8] The generated Pd(II)ClX associated arynes could then undergo

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Supporting Information Available: General experimental procedures and characterization of products.

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transmetalation followed by carbopalladation to form intermediate **III,** which could further undergo other transformations (Scheme 1, Path A). Thus, the sequence of oxidative addition of Pd(0) with 1,2-dihalobenzenes followed by β-halo elimination (Path A) could be an interesting strategy for the generation of palladium assoicated arynes. Such aryne generation strategy would employ widely available 1,2-dihalobenzenes as substrates with the assurance that every generated aryne would be associated with a palladium, and thus would have advantages over the reported aryne generation strategy from *o*-trimethylsilylaryl triflates. Importantly, in this oxidative addition followed by β-halo elimination aryne generation strategy, because the formation of **III** does not involve the oxidative addition of the C-Cl bond of **I** with Pd(0) species, the overall reactivity of *o*-chlorohalobenzenes would be governed by the reactivity of C-halo bonds that undergo the initial oxidative addition with Pd(0) catalysts. Thus, 1-chloro-2-halobenzenes that were previously unsuitable for tandem reactions[5] would now be suitable ones. In addition, this aryne generation strategy might also allow other types of *o*-halo(leaving group)arenes, e. g., 2-haloaryl tosylates, to be employed as substrates for tandem/domino reactions. Herein, we report our preliminary study on such palladium associated aryne generation strategy, specifically, on Pd-catalyzed domino reactions of 1-chloro-2-halobenzenes and 2-haloaryl tosylates with hindered Grignard reagents to access substituted fluorenes.[9,10]

As depicted in Scheme 1, the direct transmetalation of *o*-chloroarylpalladium(II) halides (**II**) to form cross-coupling product **I** (Scheme 2, Path B) would compete with the formation of Pd (II)XCl associated benzynes (Path A). Therefore, factors that could influence the transmetalation and/or the β-LG 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 regent 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, we thus first examined the ligand influence. The reaction of 1-bromo-2-chlorobenzene with bulky 2-mesitylmagnesium bromide was employed as the model reaction.[11] As the initial oxidative addition was believed to occur at the C-Br bond[12] and 2-chloro-2′,4′,6′-trimethylbiphenyl (**I**) was found to be inert under $Pd(OAc)_2$/Grignard reagent condition (see Supporting Information), we exepcted that the reaction product would be 2,4-dimethylfluorene if the reaction proceeded via benzyne intermediate (Path A).[13] The reaction product would be 2-chloro-2′,4′,6′-trimethylbiphenyl if the reaction occurred via transmetalation followed by reductive elimination (Path B). Our results are listed in Table 1. We found that, with monodentate PPh_3, PCy_3, *t*-Bu_3P, an *N*-heterocyclic carbene (NHC), or bidentate DPPE, DPPB and BINAP as ligands, 2-chlorobiaryl was obtained as the major product (Table 1, entries 1−6), suggesting the reactions proceeded predominately through Path B. However, 2,4-dimethylfluorene was observed as the major product with $Pd_2(dba)_3$, Pd $(OAc)_2$ or $Pd(PhCN)_2Cl_2$ as catalysts (Table 1, entry 7), implying that Pd-associated benzynes were involved. A similar trend was also observed with sterically less hindered *p*-tolylmagnesium bromide, in which 4,4″-dimethyl-(1, 1′, 2′, 1″)-terphenyl would be the tandem reaction product (Table 1, entries 9−10). These results suggested that the absence of phosphines or NHCs favored the reaction to occur via palladium associated intermediates.

With $Pd(OAc)_2$ and $Pd_2(dba)_3$ as catalysts, we next examined other 1-chloro-2-halobenzenes and hindered Grignard reagents. Our results, which are listed in Table 2, showed that all tested 1-chloro-2-halobenzenes, including 1,2-dichlorobenzene, gave good to excellent yields of domino reaction products. Since the transmetalation rate for Pd-Cl bond has been previously established to be different from that of Pd-Br or C-I bonds,[14] our Pd(II)ClX associated aryne generation strategy (Scheme 1) suggested transmetalation of aryne coordinated Pd(II)ClX

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complexes (X = Br, I) would form more aryne coordinated ArPd(II)Cl species than aryne coordinated ArPd(II)X species (X = Br, I). In accord with this hypothesis, we expected that with substrates such as 3-bromo-4-chlorotoluene and 3-chloro-4-iodotoluene that would produce unsymmetrical arynes, two isomeric fluorenes would be obtained in unequal amounts.[15] Indeed that is what was observed (Table 2, entries 6−9). The observation of the formation of two isomeric fluorenes in a similar ratio (4~5 : 1) for these substrates (Table 2, entries 6−9) suggested that the transmetalation rates for Pd-Br and Pd-I bonds with hindered Grignard reagents were comparable to each other.

Our hypothesis also suggested that other types of *o*-halo(LG)arenes, such as 2-haloaryl tosylates which contain very inert Ar-OTs bonds, should also be suitable substrates for the domino reaction because the oxidative addition of Pd(0) with the very inert Ar-OTs bond would not be involved and the OTs group would only serve as a leaving group. We thus tested 2-haloaryl tosylates, which are readily available from 2-halophenols, as substrates for domino reactions (Table 3). We were pleased to find that with $Pd(OAc)_2$ as catalyst, high yields of domino reaction products were obtained for 2-bromophenyl tosylates, 2-iodoaryl tosylates and 1-bromo-2-naphthyltosylate (Table 3, entries 1−9).[16] However, 2-chloro-4-methylphenyl tosylate was found to be a poor substrate (Table 3, entry 10). These results suggested that the initial oxidative addition should occur at the C-X bond, rather than at the C-OTs bond, and 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 ratios for 2-bromophenyl tosylates, 2-iodo-4-methylphenyl tosylate and 1-bromo-2-naphthyltosylate (Table 3, entries 4−9) further suggested that the transmetalation occurred with comparable transmetalation rates for Pd-Br and Pd-I bonds.

To exclude that the cross-coupling-oxidative addition-sp^3 C-H activation mechanism was involved in $Pd(OAc)_2$-catalyzed domino reactions of 2-haloaryl toyslates with hindered Grignard reagents, we have carried out reaction of phenyl tosylate with 2-mesitylmagnesium bromide in the presence of 5% $Pd(OAc)_2$ at 60 °C for 20 h.[16] We found less than 5% cross-coupling product was observed, suggesting $Pd(OAc)_2$ cannot catalyze the cross-coupling of aryl tosylates with hindered Grignard reagents efficiently. 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 2). 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 3). These results suggested that $Pd(OAc)_2$-catalyzed domino reactions of 2-haloaryl toyslates with hindered Grignard reagents did not proceed through the cross-coupling-oxidative addition-sp^3 C-H activation mechanism.

In summary, based on the hypothesis that arynes could be generated with palladium species associated with them from *ortho*-leaving group bearing halobenzenes, we explored the ligand effect on such aryne generation strategy in Pd-catalyzed reactions of *o*-halo(LG)arenes with Grignard reagents. We found the reaction pathway involving palladium associated arynes as intermediates would be favored in the absence of phosphines and NHCs. Our hypothesis also gave us the opportunity to employ substrates previously unsuitable for tandem reaction, e. g., 1-chloro-2-halobenzenes and readily available 2-haloaryl tosylates, for Pd-catalyzed domino reactions with hindered Grignard reagents, which provides an efficient access to substituted fluorenes. The palladium associated aryne generation strategy described here may have potential applications for the development of other tandem reactions from readily available *ortho*-leaving group-bearing haloarenes. Our future work will thus focus on determining the

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scope and limitation of this aryne generation strategy as well as elucidating more detailed reaction mechanism.

Supplementary Material

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Acknowledgment

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11. The direct formation of benzyne from 1-bromo-2-chlorobenzene and 2-mesitylmagnesium bromide has been ruled out. See Ref. 5.
12. The initial oxidative addition occurring at the C-Cl bond in $Pd(OAc)_2$-catalyzed reaction of 1-chloro-2-bromobenzene with 2-mesitylmagniseium bromide was ruled out based on the following experiments: $Pd(OAc)_2$-catalyzed reaction of 1,2-dichlorobenzene with 2-mesitylmagnesium bromide in THF at 60 °C gave low yield of 2,4-dimethylfluorene (24%, much lower than the 95% yield observed for 1-bromo-2-chlorobenzene under the same reaction condition), indicating the initial oxidative addition at the C-Cl bond occurred very slowly. This observation suggested with 1-bromo-2-chlorobenzene as substrate, the initial oxidative addition should take place at the C-Br bond. See Supporting Information.
13. Pd-catalyzed cyclizations via sp^3 C-H activation are rare: Ref. 5. Also see: a Baudoin O, Herrbach A, Gueritte F. Angew. Chem 2003;115:5914–5918.; Angew. Chem. Int. Ed. Eng 2003;42:5736–5740.; b Suau R, Lopez-Romero JM, Rico RD. Tetrahedron Lett 1996;37:9357–9360.; c Dyker G. J. Org. Chem 1993;58:6426–6428.; d Dyker G. Angew. Chem 1994;106:117–119.; Angew. Chem. Int. Ed. Eng 1994;33:103–105.; e Dyker G. Angew. Chem 1992;104:1079–1081.; Angew. Chem. Int. Ed. Eng 1992;31:1023–1025.
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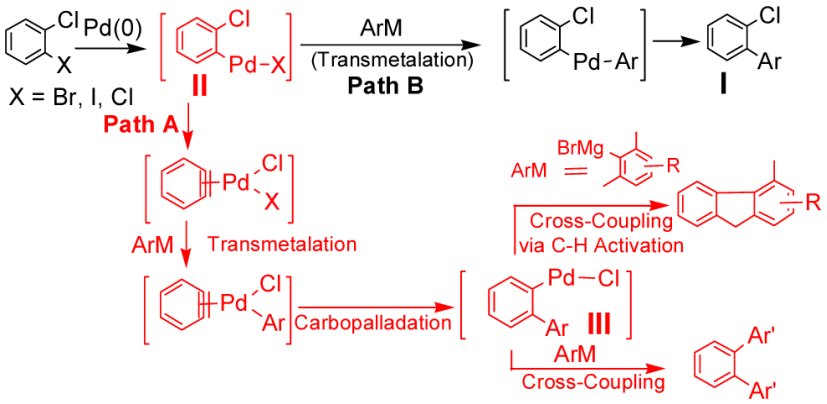
15. Two isomeric products in close to 1 : 1 ratio were always observed with unsymmetrical arynes in the reported aryne generation strategy from *o*-trimethylsilylaryl triflates, see Ref. 2.
16. Aryl tosylates have been demonstrated to undergo cross-couplings with *para*-substituted phenylmagnesium bromides and *ortho*-tolymagnesium bromide catalyzed by Pd(0)/Josiphos ligand:a Limmert ME, Roy AH, Hartwig JF. J. Org. Chem 2005;70:9364–9370. [PubMed: 16268609] b Roy AH, Hartwig JF. J. Am. Chem. Soc 2003;125:8704–8705. [PubMed: 12862447]



Scheme 1.

Outline for 1-Chloro-2-halobenzenes for Domino Reactions via Palladium(II)ClX Associated Aryne Intermediates

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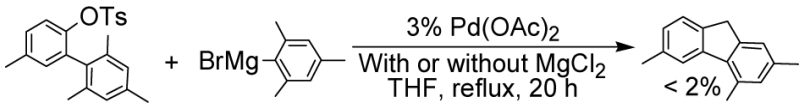

Scheme 2.

Pd-Catalyzed Reaction of 2-(2', 4', 6'-trimethyl)-4-methylphenyl tosylate with 2-Mesitylmagnesium Bromide

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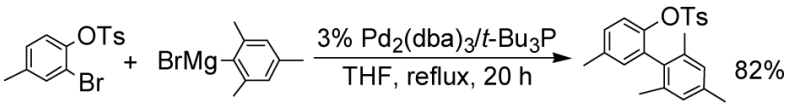

Scheme 3.
Pd(0)/*t*-Bu_3P-Catalyzed Reaction of 2-bromo-4-methylphenyl tosylate with 2-Mesitylmagnesium Bromide

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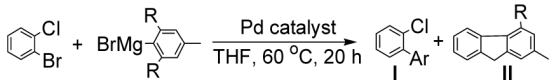
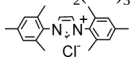
Table 1

Ligand Effect on Pd(0)-Catalyzed Cross-Couplings of 1-Bromo-2-chlorobenzene with Grignard Reagents[a]



entry	R	catalyst	conversion (%)	ratio (%)[b]	
				I	II
1	CH_3	1.5% $Pd_2(dba)_3$ + 6% Ph_3P	99	69	31
2	CH_3	1.5% $Pd_2(dba)_3$ + 6% Cy_3P	99	91	9
3	CH_3	1.5% $Pd_2(dba)_3$ + 6% *t*-Bu_3P	99	90	10
4	CH_3	3% $Pd(PPh_3)_4$	99	88	12
5	CH_3	1.5% $Pd_2(dba)_3$ + 6% 	22	99	<1
6	CH_3	1.5% $Pd_2(dba)_3$ + 3% DPPE, DPPB or BINAP	5−27	99	<1
7	CH_3	1.5% $Pd_2(dba)_3$ or 3% $Pd(PhCN)_2Cl_2$ or 3% $Pd(OAc)_2$	99	<3	>97
8	CH_3	None	0	-	-
9	H	1.5% $Pd_2(dba)_3$ + 6% *t*-Bu_3P	99	93	7[c]
10	H	3% $Pd(OAc)_2$	99	48	52[c]

[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.

[c]4,4″-dimethyl-(1,1′,2′,1″)-terphenyl was the product.

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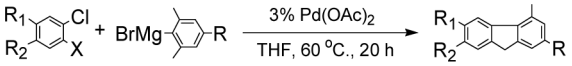
Table 2

$Pd(OAc)_2$-Catalyzed Cross-couplings of 1-Chloro-2-halobenzenes with Hindered Grignard Reagents[a]



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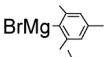
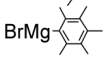
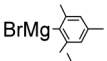
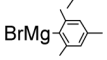
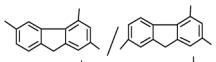
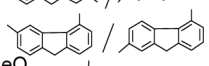
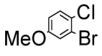
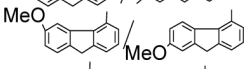
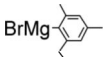
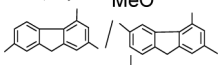
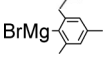
1				95
2				86
3				89
4				93
5				92
6				(77:23) 84[ed]
7				(80:20) 89[ed]
8				(78:22) 86[e]
9				(85:15) 82[e]
10				61[f]

[a]Reaction conditions (not optimized): dihalide (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, 40 h, 16% 2-chloro-2′,4′,6′-trimethylbiphenyl was observed.

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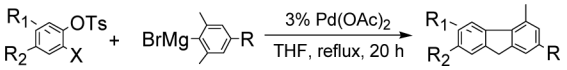
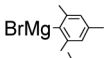
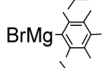
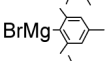
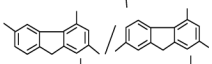
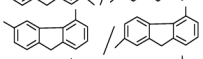
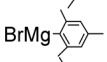
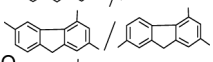
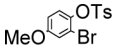
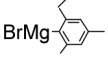
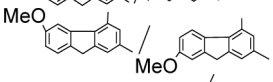
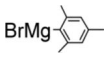
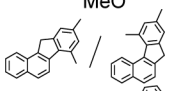
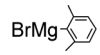
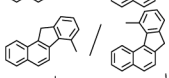
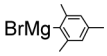
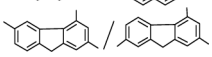
Table 3

$Pd(OAc)_2$-Catalyzed Cross-Couplings of 2-Haloaryl Tosylates with Hindered Grignard Reagents[a]



entry	tosylate	ArMgBr	product	yield(%)[b]
1				92
2				87
3				83
4				(58:42) 82[c]
5				(63:37) 74[c]
6				(62:38) 92[c]
7				(58:42) 69[c]
8				(65:35) 79[c]
9				(68: 32) 71[c]
10				< 2[c]

[a]Reaction conditions (not optimized): 2-haloaryl tosylate (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.