Tandem Reactions

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Synthesis of Fluorene and Indenofluorene Compounds: Tandem Palladium-Catalyzed Suzuki Cross-Coupling and Cyclization**

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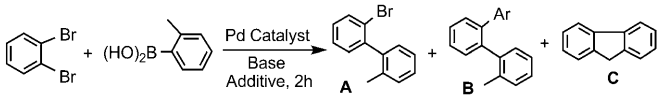
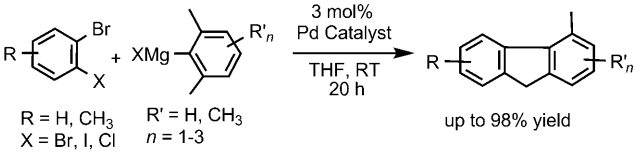
Palladium-catalyzed carbon–carbon bond-forming reactions proceeding through a C–H bond activation strategy have recently emerged as useful tools in organic synthesis.[1,2] In our laboratory, we have initiated a program to explore new tandem reactions[3] in which C–H bond activation is the key reaction component. In this context, we have recently documented palladium-catalyzed tandem reactions of 1,2-dihalobenzenes with hindered Grignard reagents to form 4-methylfluorenes (Scheme 1), in which Grignard reagents served as both cross-coupling partners and bases.[4] Although these new tandem reactions provided efficient access to substituted fluorenes, there are noticeable drawbacks associated with them; for example, Grignard reagents are air and moisture sensitive, and more importantly, the formed substituted fluorenes always bear a methyl group at the C4 position because the tandem reactions only worked well with 2,6-dimethylphenylmagnesium halides. On the basis of our understanding of the reaction mechanism depicted in Scheme 2, in which the cross-coupling of **I** with organometallic reagents (path a) competes with the cyclization proceeding through a C–H activation process (path b), we speculated that the requirement of the use of 2,6-dimethylphenylmagnesium halides might result from the fast cross-coupling of Grignard reagents with aryl halides. Therefore, we wondered whether the use of less nucleophilic coupling reagents, such as arylboronic acids, could circumvent this drawback. In addition, arylboronic acids, which have been demonstrated to be excellent cross-coupling reagents in

Table 1: Palladium-catalyzed cyclization of 1,2-dibromobenzene with 2-methylphenylboronic acid.[a]

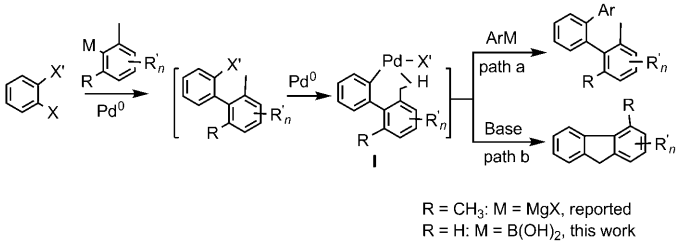


Entry	Catalyst	Base	Solvent	*T* [°C]	Conv. [%]	A/B/C[b]
1	$[Pd_2(dba)_3]/t$Bu$_3$P	K_3PO_4	THF	80	67	28:72:0
2	$[Pd_2(dba)_3]/t$Bu$_3$P	K_3PO_4	toluene	110	83	76:24:0
3	$[Pd_2(dba)_3]/t$Bu$_3$P	K_3PO_4	DMA	140	70	11:89:0
4	$[Pd_2(dba)_3]/t$Bu$_3$P	K_2CO_3	DMA	140	66	27:73:0[c]
5	$Pd(OAc)_2/t$Bu$_3$P	K_2CO_3/tBuCO$_2$H	DMA	140	<1	–
6	$Pd(OAc)_2$	K_2CO_3	DMA	140	79.5	56:44:0
7	$Pd(OAc)_2$	K_2CO_3/tBuCO$_2$H	DMA	140	55	73:27:0
8	$Pd(OAc)_2/PCy_3$	K_2CO_3	DMA	140	40	65:18:17
9	$Pd(OAc)_2/PPh_3$	KF	DMA	140	51.5	29:22:9
10	$Pd(OAc)_2/PCy_3$	K_3PO_4	DMA	140	63	42:56:2
11	**$Pd(OAc)_2/PCy_3$**	**K_2CO_3/tBuCO$_2$H**	**DMA**	**140**	**99**	**0:6:94**
12	$Pd(OAc)_2/PPh_3$	K_2CO_3/tBuCO$_2$H	DMA	140	96	74:26:0
13	$Pd(OAc)_2/PCy_3$	KF/tBuCO$_2$H	DMA	140	70	34:4:62
14	$Pd(OAc)_2/PCy_3$	CsF/tBuCO$_2$H	DMA	140	97	0:45:55
15	$Pd(OAc)_2/PCy_3$	KOAc/tBuCO$_2$H	DMA	140	14	91:9:0
16	**$Pd(OAc)_2/PCy_3$**	**K_2CO_3/tBuCO$_2$H**	**DMA**	**140**	**99**	**0:12:88**

[a] Reaction conditions: Dibromide (1.0 equiv), arylboronic acid (1.1 equiv), palladium catalyst (3 mol%), base (6 equiv), solvent (2 mL). [b] Ratio based on GC–MS analysis of the reaction mixture. [c] 1,2-Diarylbenzene was observed. DMA = dimethylacetamide, dba = dibenzylideneacetone.



Scheme 1. Palladium-catalyzed tandem reactions of hindered Grignard reagents with *o*-dihalobenzenes.



Scheme 2. Double cross-couplings versus cross-coupling and cyclization proceeding through C(sp^3)–H bond activation.

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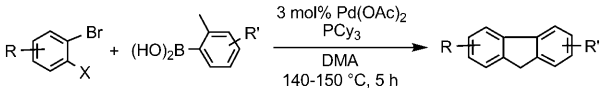
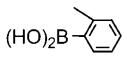
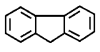
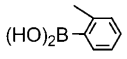
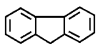
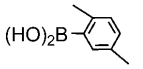
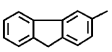
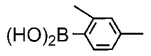
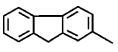
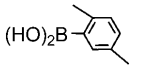
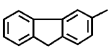
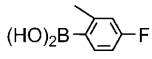
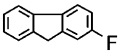
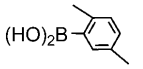
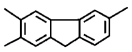
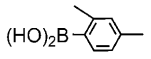
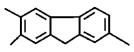
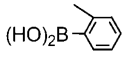
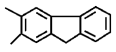
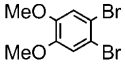
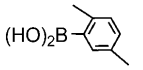
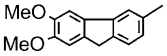
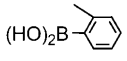
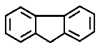
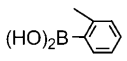
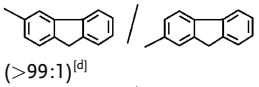
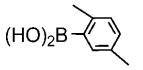
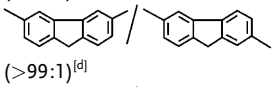
Suzuki coupling reactions,[5] are readily available, air and moisture stable, and functional-group compatible. Herein, we describe our results from our investigation into $Pd(OAc)_2/PCy_3$-catalyzed tandem reactions of 1,2-halobenzenes with 2-methylphenylboronic acids to access substituted fluorenes and indenofluorenes.[6–8]

We anticipated that the challenge to realize a tandem Suzuki cross-coupling and cyclization proceeding through C–H activation would require achieving the C–H activation (Scheme 2; path b) while minimizing double Suzuki cross-coupling reaction (Scheme 2; path a). We reasoned that factors including ligand, base, and reaction temperature would influence the interaction of the Pd^{II} center of intermediate **I** with the C–H bond and impact the cyclization proceeding through $C(sp^3)$–H bond activation. The bases used for the Suzuki cross-coupling reaction are typically inorganic bases such as K_3PO_4, KF, and K_2CO_3, which are not strong enough to remove a proton on an sp^3-hybridized carbon atom at room temperature. These bases are typically used at elevated reaction temperatures for C–H activation processes.[1,2] We began by examining the tandem reaction of 1,2-dibromobenzene with 2-methylphenylboronic acid at elevated reaction temperatures. We found that with a $[Pd_2(dba)_3]/t\mathrm{Bu}_3\mathrm{P}$ catalyst system, which has been demonstrated to be an excellent catalyst for the tandem cross-coupling and cyclization with hindered Grignard reagents as reaction partners,[4a] no cyclization product was observed, even with $K_2CO_3/t\mathrm{BuCO}_2\mathrm{H}$ as the base[9] at 140 °C (Table 1, entries 1–5). These results suggested that $t\mathrm{Bu}_3\mathrm{P}$ was not an effective ligand for the tandem Suzuki cross-coupling and cyclization reaction. Furthermore, testing revealed that by using $Pd(OAc)_2/PCy_3$ as the catalyst and $K_2CO_3/t\mathrm{BuCO}_2\mathrm{H}$ as the base, excellent yields of the desired cyclization product, fluorene, were observed (Table 1, entries 7–12). A screening of bases showed that $Cs_2CO_3/t\mathrm{BuCO}_2\mathrm{H}$ was also effective (Table 1, entries 13–16). Therefore, by using $Pd(OAc)_2/PCy_3$ as the catalyst and $M_2CO_3/t\mathrm{BuCO}_2\mathrm{H}$ (M = K, Cs) as the base, it was possible to realize the tandem Suzuki cross-coupling and cyclization proceeding through C–H activation.[10,11]

Having established the feasibility of the tandem reaction sequence, we next examined the tandem reaction using other 1,2-dihalobenzenes and other 2-methylphenylboronic acids (Table 2). We found that various 1,2-dihalobenzenes including 1-bromo-2-iodobenzene, 1,2-dibromobenzenes, 1-bromo-2-chlorobenzene, and 1,2-dichlorobenzene all afforded the cyclization products in good to high yields (Table 2, entries 1–9). Reaction of unsymmetrical 3-bromo-4-chlorotoluene and 4-chloro3-iodotoluene with 2-methyphenylboronic acids afforded predominantly 3-methylfluorene (>97%). The observation of 2-chloro-2′-methylbiphenyls as intermediates in these reactions suggested that the tandem reaction occurred through cross-coupling and subsequent cyclization as depicted in path b of Scheme 1.[12]

Table 2: Palladium-catalyzed tandem reactions of 1,2-dihalobenzenes with 2-methylphenylboronic acids.[a]



Entry	Dihalide	Boronic acid	Fluorene	Yield [%][b]
1				91
2				78
3				92
4				81.5
5				90
6				55[c]
7				85.5
8				84
9				79
10				74
11				81
12			 (>99:1)[d]	93
13			 (>99:1)[d]	96
14			(97:3)[d]	83

[a] Reaction conditions (not optimized): Dihalide (1.0 equiv), arylboronic acid (1.1 equiv), 3 mol% $Pd(OAc)_2$, 6 mol% PCy_3, $t\mathrm{BuCO}_2\mathrm{H}$ (1 equiv), K_2CO_3 (6 equiv), DMA (2 mL), 140–150 °C, 5 h. [b] Yields of isolated products. [c] 5 mol% $Pd(OAc)_2$, 10 mol% PCy_3, $t\mathrm{BuCO}_2\mathrm{H}$ (2 equiv) at 30 °C for 4 h. [d] Ratio based on ^{1}H NMR analysis.

The excellent regioselectivity observed for 3-bromo-4-chlorotoluene (Table 2, entries 10 and 11) implied that this tandem reaction protocol could be extended for the preparation of other planar fluorene-related analogues such as indenofluorenes. Therefore, when 1,4-dibromo-2,5-dichlorotoluene was used as the starting material, indenofluorenes could be obtained in good yields (Scheme 2). In addition, we also accomplished the preparation of indenofluorene **II**, using 3-bromo-4-chlorotoluene as the starting material, through an iterative tandem Suzuki cross-coupling and cyclization process (Scheme 3).

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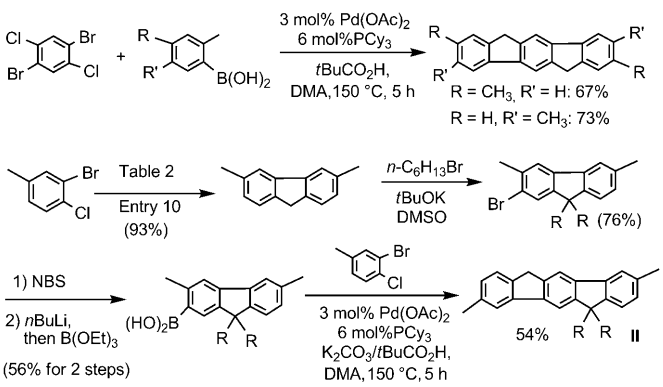

Scheme 3. Indenofluorene preparation by palladium-catalyzed tandem Suzuki coupling and cyclization.

In summary, we have demonstrated that tandem Suzuki cross-coupling and cyclization proceeding through C(sp^3)–H bond activation for 1,2-dihalobenzenes with 2-methylphenylbronic acids could be efficiently achieved by employing $Pd(OAc)_2/PCy_3$ as the catalyst system. This ring-forming reaction overcame the drawbacks associated with the use of Grignard reagents as reaction partners and allows efficient access to a broad spectrum of potentially useful substituted fluorenes and indenofluorenes. Our study has suggested that other ladder-type fluorene-based analogues could be accessed through an iterative approach, and work towards this is underway.

Experimental Section

General procedure for $Pd(OAc)_2/PCy_3$-catalyzed tandem Suzuki coupling reactions of 2-methylarylboronic acids with *o*-dihalobenzenes: DMA (2 mL) was added to a vial containing *o*-dihalobenzene (0.5 mmol), 2-methylarylboronic acid (0.55 mmol), K_2CO_3 (3 mmol), palladium(II) acetate (0.015 mmol), tricyclohexylphosphine (0.03 mmol), and trimethylacetic acid (0.5 mmol). After the reaction mixture had been stirred at 140–150 °C for 5 h, the mixture was cooled down to room temperature. The reaction mixture was quenched by adding water. The mixture was extracted with CH_2Cl_2. The organic layer was washed with brine. After removal of the solvents the crude reaction mixture was purified by column chromatography on silica gel with hexanes as the eluent to afford the desired fluorene or indenofluorene products.

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Keywords: C–H bond activation · cross-coupling · fluorenes · palladium · tandem reaction

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