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Fluorenone Synthesis by Palladacycle-Catalyzed Sequential Reactions of 2-Bromobenzaldehydes with Arylboronic Acids

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Abstract

A new, anionic four-electron donor-based (Type I) palladacycle-catalyzed sequential reaction of 2-bromobenzaldehydes with arylboronic acids based on the addition reaction, cyclization via C-H activation-oxidation sequence is described. Our study provided an efficient access to a variety of substituted fluorenones/indenofluorenediones from readily available arylboronic acids and 2-bromobenzaldehydes.

One-pot, multistep reactions such as sequential, tandem, domino or cascade reactions combine two or more bond-forming reactions into one synthetic process and can lead to rapid increase of molecular complexity with minimized isolation/purification efforts.^{1,2} The development of new one-pot, multistep reactions represents one of the most active frontiers in synthetic organic chemistry. In our laboratory, we were interested in exploring anionic four-electron donor-based (Type I) palladacycles, which constitute a large family of readily available and air-stable cyclic palladium(II) complexes (Figure 1),^{3,4} as catalysts for addition reactions of arylboronic acids with carbonyl-containing compounds.^{5, 6,7,8} We have demonstrated that Type I palladacycles such as **1–3** (Figure 1) efficiently catalyzed addition reactions of arylboronic acids with carbonyl-containing compounds.⁶ Studies from other groups as well as our group also showed that Type I palladacycles could generate Pd(0) species upon treatment with arylboronic acids at elevated temperature.^{3,9} Such generated Pd(0) species could undergo oxidative addition with aryl halides to form arylPd(II)X species,³ which could undergo other transformations including cross-coupling reactions via C-H activation. These studies suggested to us that Type I palladacycles could function as two kinds of palladium catalysts [Pd(II) and Pd(0) catalysts] under different reaction temperature. We thus envisioned that a new sequential reaction could be developed by taking advantage of this double catalyst nature of Type I palladacycles: addition reactions of arylboronic acids with halo-bearing aromatic aldehydes at lower temperature followed by cyclization via C-H activation¹⁰ at elevated temperature to form fluorenols (**A**), which could be further oxidized to fluorenones (**B**) (Scheme 1).¹¹ This new type of sequential reaction could thus lead to rapid access to substituted fluorenones, which are useful starting materials for organic synthesis,^{12,13} from readily available 2-bromobenzaldehydes and arylboronic acids. In this communication, we reported our results on such a new sequential reaction.

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Supporting Information Available: General procedures and product characterization for Type I palladacycle-catalyzed sequential reactions of 2-bromobenzaldehydes with arylboronic acids. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Our study began with the reaction condition screening by examining the reaction of 2-bromobenzaldehyde and phenylboronic acid with palladacycle **3** as the catalyst. Our results are summarized in Table 1. We found that by using toluene as solvent, the addition reaction step (Step I) occurred smoothly with K₃PO₄, K₂CO₃ or KF as bases,¹⁴ but the cyclization via C-H activation/oxidation (Step II) did not go well (Table 1, entries 1–3). Rather benzophenone (**C**) was obtained. DMA was then examined as the solvent for the reaction because it has been used as solvent for cross-coupling reactions via C-H activation.¹⁵ We found when DMA was used, Step I could not occur, rather cross-coupling reaction was observed (Table 1, entries 4 and 5). We then carried out the addition reaction in toluene first and then the cyclization/oxidation in DMA. We found by using trimethylacetic acid as an additive,¹⁶ very encouraging results were observed (Table 1, entries 6–10). Gratifyingly, we found that by carrying out the reaction in air, the desired fluorenone was obtained in an excellent yield (Table 1, entry 11).¹⁷

After establishing the reaction conditions, the scope of the reaction was examined. We found that high yields of an array of structurally diversified substituted fluorenones were obtained with arylboronic acids including sterically hindered, electron-rich and electron-poor ones (Table 2, entries 1–13). When *m*-substituted phenylboronic acids such as *m*-methyl phenylboronic acid and *m*-methoxyphenylboronic acid were used, two isomeric products were obtained, and the ratio of 2-substituted fluorenones to 4-substituted fluorenones was observed to be 30 : 1 and 9 : 1, respectively (Table 2, entries 8 and 9). Other 2-bromobenzaldehydes were also found to be suitable substrates, and high yields of a variety of substituted fluorenones were obtained (Table 2, entries 14–21).

We have further tested the sequential reaction of 2,5-dibromoterephthalaldehyde with phenylboronic acid and 4-*tert*-butylphenylboronic acid. We found the sequential reaction occurred smoothly, and indenofluorenediones **5a** and **5b** were obtained in 49% and 58% yields, respectively. Substituted indenofluorenediones are useful building blocks for materials synthesis¹⁸ and are recently of interest as *n*-type semiconductors/field-effect transistors.¹⁹

In summary, we have demonstrated that Type I palladacycles can function as both Pd(II) and Pd(0) catalysts for a new sequential reaction of 2-bromobenzaldehydes with arylboronic acids based on the addition reaction, cyclization via C-H activation and oxidation sequence. Our study provided an efficient access to a variety of substituted fluorenones/indenofluorenediones from readily available arylboronic acids and 2-bromobenzaldehydes. Our study may also lead to the development of other one-pot, multistep reactions with the transition metal-catalyzed addition reaction as a key reaction component.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Type I Palladacycles

Scheme 1.

Type I Palladacycles as Double Catalysts for a New Sequential Reaction Based on the Addition Reaction, Cyclization via C-H Activation, and Oxidation Sequence

Scheme 2.

Type I Palladacycle-Catalyzed Indenofluorenedione preparation by the New Sequential Reaction

Table 1

Palladacycle **3**-Catalyzed Sequential Reactions of Phenylboronic Acid with 2-Bromobenzaldehyde ^a

entry	Base	solvent	additive	temperature		conv (%) ^b		ratio ^c
				Step I/Step II		Step I		
				Step I	Step II	Step I	Step II	B:C
1	K ₃ PO ₄	Toluene	-	55/120	100	100	100	1:99
2	K ₂ CO ₃	Toluene	-	55/120	100	100	100	1:99
3	KF	Toluene	-	55/120	94	14	-	-
4	K ₃ PO ₄	DMA	-	55/120	100 ^d	-	-	-
5	K ₂ CO ₃	DMA	-	55/120	100 ^d	-	-	-
6	K ₂ CO ₃	Tol./DMA	-	55/120	100	54	8:92	
7	K ₂ CO ₃	Tol./DMA	<i>t</i> -BuCO ₂ H	55/120	100	16	29:71	
8	K ₂ CO ₃	Tol./DMA	<i>t</i> -BuCO ₂ H	55/120	100	61	44:56	
9	K ₂ CO ₃	Tol./DMA	<i>t</i> -BuCO ₂ H	55/120 ^e	100	83	42:58	
10	K ₃ PO ₄	Tol./DMA	<i>t</i> -BuCO ₂ H	55/120	100	100	57:33, ^{f,g}	
11	K ₂ CO ₃	Tol./DMA	<i>t</i> -BuCO ₂ H	55/120 ^{e,f}	100	100	92:8	

^aReaction conditions: aldehyde (1.0 equiv), phenylboronic acid (1.1 equiv), toluene (1.5 mL), base (6 equiv), 55 °C for 5 h, and then DMA (5 mL), 120 °C for another 5 h.

^bConversion based on ¹H NMR.

^cConversion based on GC-MS analysis.

^dBiphenyl-2-carbonylaldehyde as the only product.

^eReaction time: 10 h.

^fReaction carried out under air.

^g10% 2-phenylbenzophenone was observed.

Table 2Type I Palladacycle **3**-Catalyzed Sequential Reactions of Arylboronic Acids with 2-Bromobenzaldehydes ^a

entry	R	ArB(OH) ₂	
1	H (4a)
2	4a
3	4a
4	4a
5	4a
6	4a
7	4a
8	4a

entry	R	ArB(OH) ₂	
9	4a		
10	4a		
11	4a		
12	4a		
13	4a		
14

entry	R	ArB(OH) ₂
15	4b	
16		
17	4c	
18	4c	
19	4c	
20	4c

entry	R	ArB(OH) ₂
21	4c	

^a Reaction conditions: aldehyde (1.0 equiv), arylboronic acid (1.1 equiv), toluene (1.5 mL), K₂CO₃ (6 equiv), 55 °C for 5 h, and then 120 °C for another 10 h.

^b Isolated yields.

^c Based on GC-MS analysis.

^d Reaction was carried out at 80 °C for 25 h and then 120 °C for another 10 h.