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

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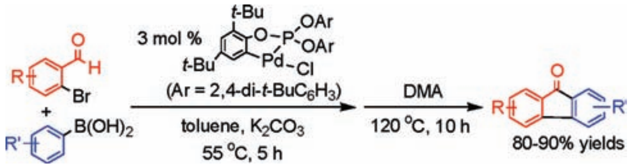
ABSTRACT



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.[5–8] 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

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[1] Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2006.

[2] For recent reviews on sequential reactions, see: (a) Nicolaou, K. C.; Chen, J. S. *Chem. Soc. Rev.* **2009**, *38*, 2993–3009. (b) Kirsch, S. F. *Synthesis* **2008**, 3183–3204. (c) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134–7186. (d) Wasilke, J.-C.; Obrey, S. J.; Baker, T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001–1020. (e) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136.

[3] For recent reviews, see: (a) Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev.* **2005**, *105*, 2527–2572. (b) Beletskaya, I. P.; Cheprakov, A. V. *J. Organomet. Chem.* **2004**, *689*, 4055–4082. (c) Bedford, R. B. *Chem. Commun.* **2003**, 1787–1796. (d) Newkome, G. R.; Puckett, W. E.; Gupta, V. K.; Kiefer, G. E. *Chem. Rev.* **1986**, *86*, 451–489.

[4] Most type I palladacycles are known to exist as bridged dimers and to dissociate into monomeric forms during reactions. Type I palladacycles in this paper were drawn in monomeric forms.

[5] For recent reviews on transition metal-catalyzed addition reactions of organoborons with carbonyl-containing compounds, see: (a) Miyaura, N. *Synlett* **2009**, 2039–2050. (b) Gutnov, A. *Eur. J. Org. Chem.* **2008**, 4547–4554. (c) Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 3364–3366. (d) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829–2844. (e) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169–196 and references cited therein.

[6] (a) Xing, C.-H.; Liao, Y.-X.; He, P.; Hu, Q.-S. *Chem. Commun.* **2010**, 3010–3012. (b) He, P.; Lu, Y.; Dong, C.-G.; Hu, Q.-S. *Org. Lett.* **2007**, *9*, 343–346. (c) He, P.; Lu, Y.; Hu, Q.-S. *Tetrahedron Lett.* **2007**, *48*, 5283–5288.

[7] (a) Liao, Y.-X.; Xing, C.-H.; He, P.; Hu, Q.-S. *Org. Lett.* **2008**, *10*, 2509–2512. (b) Liao, Y.-X.; Hu, Q.-S. *J. Org. Chem.* **2010**, *75*, 6986–6989.

[8] Also see: (a) Suzuma, Y.; Hayashi, S.; Yamamoto, T.; Oe, Y.; Ohta, T.; Ito, Y. *Tetrahedron: Asymmetry* **2009**, *20*, 2751–2758. (b) Bedford, R. B.; Dumycz, H.; Haddow, M. F.; Pilarski, L. T.; Orpen, A. G.; Pringle, P. G.; Wingad, R. L. *Dalton Trans.* **2009**, 7796–7804. (c) Yu, A.; Cheng, B.; Wu, Y.; Li, J.; Wei, K. *Tetrahedron Lett.* **2008**, *49*, 5405–5407. (d) Bedford, R. B.; Pilarski, L. T. *Tetrahedron Lett.* **2008**, *49*, 4216–4219. (e) Lu, X.; Lin, S. *J. Org. Chem.* **2005**, *70*, 9651–9653. (f) Bedford, R. B.; Betham, M.; Charmant, J. P. H.; Haddow, M. F. A.; Orpen, G.; Pilarski, L. T.; Coles, S. J.; Hursthouse, M. B. *Organometallics* **2007**, *26*, 6346–6353. (g) Gibson, S.; Foster, D. F.; Eastham, G. R.; Tooze, R. P.; Cole-Hamilton, D. J. *Chem. Commun.* **2001**, 779–780.

10.1021/ol200693d

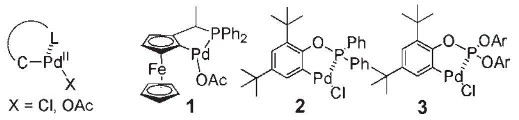
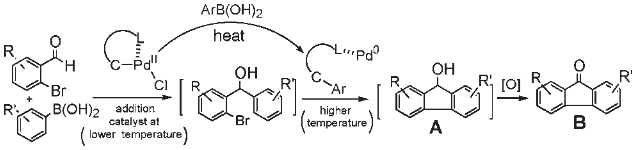


Figure 1. Type I palladacycles.

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 activation[10] 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.

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



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 K_3PO_4, K_2CO_3, 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*-methylphenylboronic 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

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(9) Also see: Bedford, R. B.; Hazelwood, S. L.; Limmert, M. E.; Albisson, D. A.; Draper, S. M.; Scully, P. N.; Coles, S. J.; Hursthouse, M. B. *Chem.—Eur. J.* **2003**, *9*, 3216–3227.

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(11) For recent examples of Pd(II)-catalyzed oxidation of alcohols, see: (a) R., J.; Goddard, W. A., III *J. Am. Chem. Soc.* **2006**, *128*, 9651–9660. (b) Schultz, M. J.; Adler, R. S.; Zierkiewicz, W.; Privalov, T.; Sigman, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 8499–8507. (c) Steinhoff, B. A.; Guzei, I. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2004**, *126*, 11268–11278. (d) Mori, K.; Hara, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2004**, *126*, 10657–10666. (e) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2001**, *123*, 7725–7726.

(12) For examples, see: (a) Poriel, C.; Ferrand, Y.; Juillard, S.; Le Maux, P.; Simonneaux, G. *Tetrahedron* **2004**, *60*, 145–158. (b) Thiemann, F.; Piehler, T.; Haase, D.; Saak, W.; Luetzen, A. *Eur. J. Org. Chem.* **2005**, 1991–2001. (c) Cheng, X.; Hou, G.-H.; Xie, J.-H.; Zhou, Q.-L. *Org. Lett.* **2004**, *6*, 2381–2383. (d) Collins, C. S.; Sun, D.; Liu, W.; Zuo, J.-L.; Zhou, H.-C. *J. Mol. Struct.* **2008**, *890*, 163–169. (e) Tierney, M. T.; Grinstaff, M. W. *J. Org. Chem.* **2000**, *65*, 5355–5359. (f) Han, Y.; Bisello, A.; Nakamoto, C.; Rosenblatt, M.; Chorev, M. *J. Pept. Res.* **2000**, *55*, 230–239. (g) Greenlee, M. L.; Laub, J. B.; Rouen, G. P.; DiNinno, F.; Hammond, M. L.; Huber, J. L.; Sundelof, J. G.; Hammond, G. G. *Biorg. Med. Chem. Lett.* **1999**, *9*, 3225–3230. (h) Perry, P. J.; Read, M. A.; Davies, R. T.; Gowan, S. M.; Reszka, A. P.; Wood, A. A.; Kelland, L. R.; Neidle, S. *J. Med. Chem.* **1999**, *42*, 2679–2684. (i) Koyama, H.; Kamikawa, T. *Tetrahedron Lett.* **1997**, *38*, 3973–3976. (j) Carney, J. R. *J. Org. Chem.* **1997**, *62*, 320–324.

(13) For recent examples of other tandem, domino, sequential, or one-pot reaction approach to fluorenones, see: (a) Sun, C.-L.; Liu, N.; Li, B.-J.; Yu, D.-G.; Wang, Y.; Shi, Z.-J. *Org. Lett.* **2010**, *12*, 184–187. (b) Zhao, Y.-B.; Mariampillai, B.; Candito, D. A.; Laleu, B.; Li, M.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 1849–1852. (c) Thirunavukkarasu, V. S.; Parthasarathy, K.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2008**, *47*, 9462–9465. (d) Waldo, J. P.; Zhang, X.; Shi, F.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 6679–6685. (e) Zhang, X.; Larock, R. C. *Org. Lett.* **2005**, *7*, 3973–3976. (f) Campo, M. A.; Larock, R. C. *Org. Lett.* **2000**, *2*, 3675–3677.

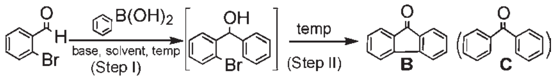
(14) The use of 6 equiv of base was necessary for the first step addition reaction to complete without the occurrence of the cross-coupling reaction.

(15) (a) Ackermann, L.; Mulzer, M. *Org. Lett.* **2008**, *10*, 5043–5045. (b) Imoto, S.; Uemura, T.; Kakiuchi, F.; Chatani, N. *Synlett* **2007**, 170–172. (c) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496–16497. (d) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754–8756.

(16) (a) Huestis, M. P.; Fagnou, K. *Org. Lett.* **2009**, *11*, 1357–1360. (b) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, *10*, 1759–1762. (c) Liegault, B.; Fagnou, K. *Organometallics* **2008**, *27*, 4841–4843. (d) Caron, L.; Campeau, L.-C.; Fagnou, K. *Org. Lett.* **2008**, *10*, 4533–4536. (e) Liegault, B.; Lee, D.; Huestis, M. P.; Stuart, D. R.; Fagnou, K. *J. Org. Chem.* **2008**, *73*, 5022–5028.

(17) Fluorenol was observed as the intermediate (GC-MS analysis) when the reaction was stopped after 2 h.

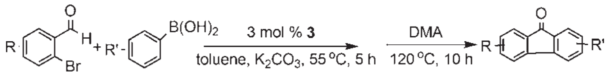
Table 1. Palladacycle **3**-Catalyzed Sequential Reactions of Phenylboronic Acid with 2-Bormobenzaldehyde[a]

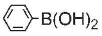
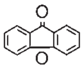
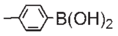
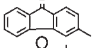
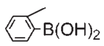
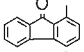
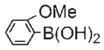
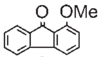
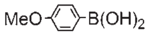
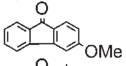
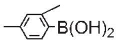
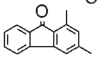
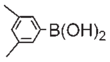
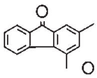
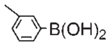
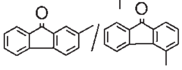
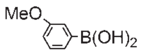
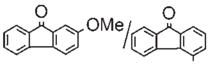
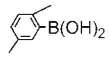
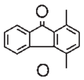
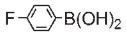
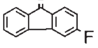
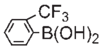
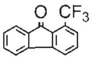
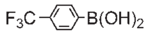
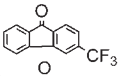
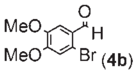
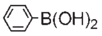
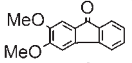
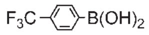
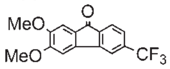
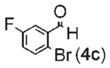
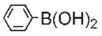
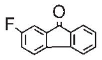
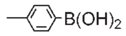
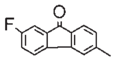
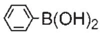
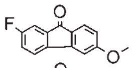
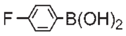
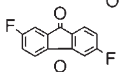
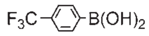
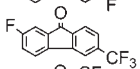
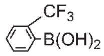
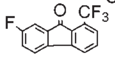


					conv (%)[b]		
entry	base	solvent	additive	temp for step I/ step II	step I	step II	ratio[c] of **B**:**C**
1	K_3PO_4	toluene		55/120	100	100	1:99
2	K_2CO_3	toluene		55/120	100	100	1:99
3	KF	toluene		55/120	94	14	
4	K_3PO_4	DMA		55/120	100[d]		
5	K_2CO_3	DMA		55/120	100[d]		
6	K_2CO_3	toluene/ DMA		55/120	100	54	8:92
7	K_2CO_3	toluene/ DMA	t-$BuCO_2H$	55/120	100	16	29:71
8	K_2CO_3	toluene/ DMA	t-$BuCO_2H$	55/140	100	61	44:56
9	K_2CO_3	toluene/ DMA	t-$BuCO_2H$	55/120 [e]	100	83	42:58
10	K_3PO_4	toluene/ DMA	t-$BuCO_2H$	55/120	100	100	57:33[f,g]
11	K_2CO_3	toluene/ DMA	t-$BuCO_2H$	55/120[e,f]	100	100	92:8

[a] Reaction 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. [b] Conversion based on ^1H NMR. [c] Conversion based on GC-MS analysis. [d] Biphenyl-2-carbonylaldehyde as the only product. [e] Reaction time: 10 h. [f] Reaction carried out under air. [g] 10% 2-phenylbenzophenone was observed.

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



entry	R	ArB(OH)$_2$	fluorenone	yield (%) [b]
1	H (**4a**)			87
2	**4a**			83
3	**4a**			85
4	**4a**			89
5	**4a**			83
6	**4a**			89
7	**4a**			86
8	**4a**		 (9:1) [c]	82
9	**4a**		 (30:1) [c]	81
10	**4a**			83
11	**4a**			86
12	**4a**			81
13	**4a**			88
14	 (**4b**)			86 [d]
15	**4b**			90 [d]
16	 (**4c**)			82
17	**4c**			81
18	**4c**			83
19	**4c**			84
20	**4c**			87
21	**4c**			80

[a] Reaction conditions: aldehyde (1.0 equiv), arylboronic acid (1.1 equiv), toluene (1.5 mL), K_2CO_3 (6 equiv), 55 °C for 5 h, and then DMA (1.5 mL), 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 with a 5 mol % catalyst loading.

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 (Scheme 2). Substituted indenofluorenediones are useful building blocks for materials synthesis[18] 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

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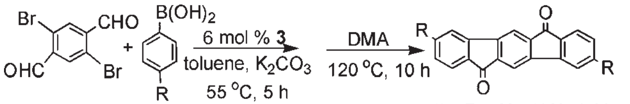
(18) For recent examples, see: (a) Park, Y.; Lee, J.-H.; Jung, D. H.; Liu, S.-H.; Lin, Y.-H.; Chen, L.-Y.; Wu, C.-C.; Park, J. *J. Mater. Chem.* **2010**, *20*, 5930–5936. (b) Yen, W.-C.; Pal, B.; Yang, J.-S.; Hung, Y.-C.; Lin, S.-T.; Chao, C.-Y.; Su, W.-F. *J. Polym. Sci., Part A: Polym. Chem.* **2009**, *47*, 5044–5056. (c) Lin, T.-C.; Hsu, C.-S.; Hu, C.-L.; Chen, Y.-F.; Huang, W.-J. *Tetrahedron Lett.* **2009**, *50*, 182–185. (d) Poriel, C.; Liang, J.-J.; Rault-Berthelot, J.; Barriere, F.; Cocherel, N.; Slawin, A. M. Z.; Horhant, D.; Virboul, M.; Alcaraz, G.; Audebrand, N.; Vignau, L.; Huby, N.; Wantz, G.; Hirsch, L. *Chem.—Eur. J.* **2007**, *13*, 10055–10069. (e) Reisch, H.; Wiesler, U.; Scherf, U.; Tuytuylkov, N. *Macromolecules* **1996**, *29*, 8204–8210.

(19) For examples, see: (a) Usta, H.; Risko, C.; Wang, Z.; Huang, H.; Deliomeroglu, M. K.; Zhukhovitskiy, A.; Facchetti, A.; Marks, T. J. *J. Am. Chem. Soc.* **2009**, *131*, 5586–5608. (b) Usta, H.; Facchetti, A.; Marks, T. J. *J. Am. Chem. Soc.* **2008**, *130*, 8580–8581. (c) Usta, H.; Facchetti, A.; Marks, T. J. *Org. Lett.* **2008**, *10*, 1385–1388. (d) Nakagawa, T.; Kumaki, D.; Nishida, J.-i.; Tokito, S.; Yamashita, Y. *Chem. Mater.* **2008**, *20*, 2615–2617.

Scheme 2. Type I Palladacycle-Catalyzed Indenofluorenedione Preparation by the New Sequential Reaction



5a: R = H , 49% yield
5b: R = *t*-Bu , 58% yield

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.

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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.