

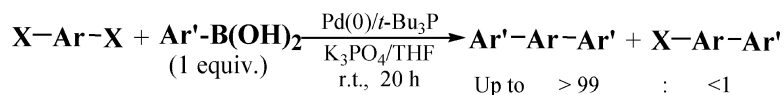
Communication

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Preferential Oxidative Addition in Palladium(0)-Catalyzed Suzuki Cross-Coupling Reactions of Dihaloarenes with Arylboronic Acids

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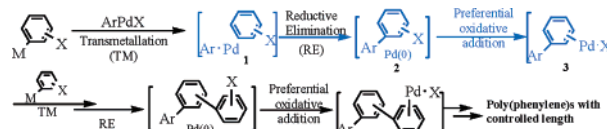
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Although Pd(0)-catalyzed cross-coupling polymerizations have become extremely powerful tools for the synthesis of an array of polydisperse conjugated polymers,^{1,2} controlled Pd(0)-catalyzed cross-coupling polymerizations for the synthesis of conjugated polymers with desired length remain elusive.³ Scrutiny of the cross-coupling polymerization mechanism suggests that such controlled polymerizations would be possible if the fate of the regenerated Pd(0) catalyst could be controlled. For example, the polymerization of AB-type monomers would be controllable if the regenerated Pd(0) catalyst could be oriented to undergo oxidative addition preferentially with its homogeneously generated coupling product (Scheme 1). Because Pd(0)-catalyzed cross-coupling polymerizations proceed via repeating the oxidative addition–transmetalation–reductive elimination catalytic cycle, we reasoned that it should be appropriate to study one particular catalytic cycle of a polymerization process to address whether and how the preferential oxidative addition could be achieved. We also reasoned that cross-coupling reactions that possess the same particular preferential oxidative addition step as that of the hypothetical polymerization processes should be appropriate model reactions. In this communication, we report our study on one type of such model reactions, the cross-coupling reactions of dihalobenzenes with 1 equiv of arylboronic acids⁴ (Scheme 2) to establish that it is possible to achieve such preferential oxidative addition when appropriate Pd(0) catalyst is employed.

As shown in Scheme 2, mechanistically, the Pd(0) catalyst regenerated from the first reductive elimination is expected to situate nearby and interact with its homogeneously formed 1-aryl-*n*-halobenzene (AHB) ($n = 2, 3, \text{ or } 4$).⁵ It could undergo oxidative addition with the AHB (Path A) or diffuse out of the vicinity of the AHB (Path B). The diffused Pd(0) catalyst is expected to undergo oxidative addition with a dihalobenzene, because the amount of dihalobenzene is in excess relative to that of AHB due to the use of a limited amount of arylboronic acid, and is more reactive than AHB due to electronic and/or steric effects (Path B). We envisioned that the key to achieve the preferential oxidative addition would lie in how to achieve faster oxidative addition of the regenerated Pd(0) with the AHB (Path A) over its diffusion process (Path B), and the efficiency of the preferential oxidative addition could be assessed by examining the ratio of the Path A product (diarylbenzene) vs the Path B product (AHB). It has been established that the nature of the ligands has great influence on the oxidative addition rate of a Pd(0) catalyst.² We thus began our study by screening different ligands by using the cross-coupling of 1,2-dibromobenzene with *p*-tolylboronic acid as the model reaction. Our results are listed in Table 1. We found that triphenylphosphine and bidentate DPPF or DPPE gave very poor results (Table 1, entries 1–2). More electron-rich monodentate phosphines including Buchwald-type monophosphines⁶ gave high conversions with significant amount of diarylbenzene formations, suggesting the preferential oxidative addition occurred to some extent (Table 1,

Scheme 1. Hypothetic Controlled Pd(0)-Catalyzed Cross-Coupling Polymerization of AB-Type Monomers



Scheme 2. Pd(0)-Catalyzed Cross-Couplings of Dihalobenzenes with 1 equiv of Arylboronic Acids

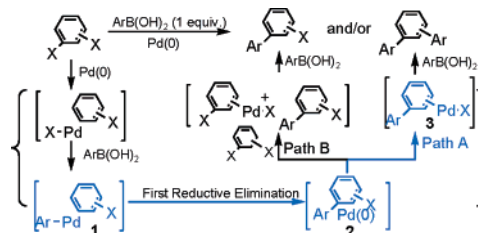


Table 1. Room-Temperature Pd(0)-Catalyzed Cross-Couplings of 1,2-Dibromobenzene with *p*-Tolylboronic Acid^a

Entry	Pd(0) + Ligand	Conversion (%) ^b	Mono: Di ^b
1	Pd ₂ (dba) ₃ + 4 PPh ₃	10	92 : 8
2	Pd ₂ (dba) ₃ + 2 DPPF or DPPE	< 2%	
3	Pd ₂ (dba) ₃ + 4 <i>o</i> -tolyl ₃ P	99	49 : 51
4	Pd ₂ (dba) ₃ + 4	97	57 : 43
5	Pd ₂ (dba) ₃ + 4	93	38.5 : 61.5
6	Pd ₂ (dba) ₃ + 4 Cy ₃ P	66	35 : 65
7	Pd ₂ (dba) ₃ + 4 <i>t</i> -Bu ₃ P	99	2 : 98 ^c

^a Reaction conditions (not optimized): 1,2-dibromobenzene (1.0 equiv), *p*-tolylboronic acid (1.0 equiv), K₃PO₄ (3 equiv), THF (2 mL), room temperature. ^b Based on ¹H NMR. ^c Based on GC–MS.

entries 3–6). Bulky, electron-rich *t*-Bu₃P⁷ was found to give a very satisfying result, with excellent conversion and excellent percentage of diarylbenzene (Table 1, entry 7).^{8,9} These results clearly showed that the preferential oxidative addition for the regenerated Pd(0) can be achieved by careful selection of the catalyst system.

With Pd(0)-*t*-Bu₃P as the catalyst system, the cross-coupling reactions of a number of 1,2-dibromobenzenes with arylboronic acids were examined, and our results are listed in Table 2. As shown in Table 2, all tested 1,2-dibromobenzenes including those with electron-withdrawing and electron-donating substituents gave high disubstituted/monosubstituted product ratio,⁸ suggesting the preferential oxidative addition occurred efficiently. As expected, the cross-coupling of 1-chloro-2-iodobenzene with *p*-tolylboronic acid, which involves the oxidative addition of an inert C–Cl bond, gave exclusively the monosubstituted product (Table 2, entry 9), suggesting the diffusion process was much faster than the oxidative

Table 2. Room-Temperature Pd(0)-Catalyzed Cross-Couplings of 1,2-Dihalobenzenes with Arylboronic Acids^a

Entry	Dihalide	Ar-B(OH) ₂	Mono : Di ^b	Yield(%) ^c
1			<1 : >99	96
2			2 : 98	98
3			<1 : >99	96.5
4			4 : 96	90
5			<1 : >99	94
6			<1 : >99	92
7			<1 : >99	78
8			<1 : >99	82
9			>99 : <1	99 ^d
10			21 : 79	72

^a Reaction conditions (not optimized): dibromide (1.0 equiv), arylboronic acids (1.0 equiv), K₃PO₄ (3 equiv), Pd₂(dba)₃ (2.5%), *t*-Bu₃P (10%), THF (2 mL), room temperature. ^b Ratio based on GC-MS. ^c Isolated yields of diarylbenzenes. ^d Conversion of *p*-tolylboronic acid based on ¹H NMR.

Table 3. Room-Temperature Pd(0)-Catalyzed Cross-Couplings of Dihalobenzenes with Arylboronic Acids^a

Entry	Dihalide	Ar-B(OH) ₂	Mono : Di ^b	Yield(%) ^c
1			0.3 : 99.7 (1 : 332)	96
2			1.5 : 98.5	91
3			1 : 99	86
4			3 : 97	43
5			6 : 94	23
6			9 : 91	80

^a Reaction conditions (not optimized): dihalide (1.0 equiv), arylboronic acid (1.0 equiv), K₃PO₄ (3 equiv), THF (2 mL), room temperature. ^b Ratio based on GC-MS. ^c Isolated yields of diarylarenes.

addition process for the regenerated Pd(0) catalyst. Surprisingly, the coupling of 1,2-diiodobenzene with *p*-tolylboronic acid, which involves the oxidative addition with a very reactive C-I bond,^{7c} gave only a 21:79 ratio of mono:di product (Table 2, entry 10). This less efficient preferential oxidative addition might suggest that the larger size of the second iodo group destabilizes the interaction of the regenerated Pd(0) catalyst with the homogeneously generated product, leading to a formally faster diffusion process.

To address whether the preferential oxidative addition could occur for substrates with spatially separated reactive sites, we have examined the cross-couplings of 1,3- and 1,4-dihalobenzenes with 1 equiv of arylboronic acids. We found that excellent ratios of diarylbenzenes vs monoarylbenzenes were observed for both 1,3-diiodobenzene and 1,3-dibromobenzene, suggesting the preferential oxidative addition also occurred efficiently (Table 3, entries 1–3). That the preferential oxidative addition occurred more efficiently for 1,3-diiodobenzene than for 1,2-diiodobenzene and 1,3-dibromobenzene suggests that the size of the second iodo group no longer interferes with the diffusion process and is consistent with the established results of C-I bonds having a higher oxidative addition rate with Pd(0) than C-Br bonds do.^{2,7c} Such a trend was also

observed for 1,4-dihalobenzenes (Table 3, entries 4–5). Interestingly, the 1,4-dihalobenzenes underwent much slower Suzuki cross-couplings than their 1,2- and 1,3-analogues (Table 3, entries 4–5). Such unusual results suggest that the oxidative addition of the regenerated Pd(0) to C-Br or C-I bond, although faster than the diffusion process, occurs slower than the similar oxidative addition processes for the 1,2- and 1,3-analogues, and serves as the rate-limiting step.¹⁰ Finally, we have also carried out the Suzuki cross-couplings of 2,5-dibromothiophene, and efficient preferential oxidative addition was also observed (Table 3, entry 6).

In summary, we have demonstrated that the regenerated Pd(0) catalyst in the cross-coupling of dihaloarenes with arylboronic acids could undergo oxidative addition preferentially with its homogeneously formed coupling product when the appropriate Pd(0) catalyst system is employed. The Pd(0)/*t*-Bu₃P was identified as a powerful catalyst system to achieve efficient preferential oxidative addition. Our study may lead to the development of controlled Pd(0)-catalyzed cross-coupling polymerizations for the preparation of conjugated polymers with desired lengths. Future work in this direction is under active investigation.

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Supporting Information Available: The general procedure and product characterization for Pd(0)/*t*-Bu₃P-catalyzed cross-couplings of dihalobenzenes with arylboronic acids. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- Hu, Q.-S. In *Synthetic Methods for Step-Growth Polymers*; Rogers, M., Long, T., Eds.; Wiley: New York, 2003; pp 467–526.
- (a) de Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; Wiley-VCH: New York, 2004. (b) Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis*; Wiley-VCH: New York, 1998. (c) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987.
- For potential applications of conjugated molecules with desired length as molecular electronics, see: (a) Carroll, R. L.; Gorman, C. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 4378. (b) Tour, J. M. *Acc. Chem. Res.* **2000**, *33*, 791–804.
- The use of 1 equiv or less of boronic acids is important for differentiating products of the preferential oxidative addition pathway from the nonpreferential oxidative addition pathway. For cross-couplings of dihalobenzenes with 2 equiv (or more) of arylboronic acids: (a) Berthiol, F.; Kondolff, I.; Doucet H.; Santelli, M. *J. Organomet. Chem.* **2004**, *689*, 2786–2798. (b) Simoni, D. et al., *Tetrahedron Lett.* **2003**, *44*, 3005–3008. (c) Basu, B.; Das, P.; Bhuiyan, M. M. H.; Jha, S. *Tetrahedron Lett.* **2003**, *44*, 3817–3820. (d) van der Vlugt, J. I.; Bonet, J. M.; Mills, A. M.; Spek, A. L.; Vogt, D. *Tetrahedron Lett.* **2003**, *44*, 4389–4392. (e) Paul, S.; Clark, J. H. *Green Chem.* **2003**, *5*, 635–638. (f) Oh, C. H.; Lim, Y. M. *Bull. Korean Chem. Soc.* **2002**, *23*, 663–664. (g) Eastmond, G. C.; Paprotny, J.; Steiner, A.; Swanson, L. *New J. Chem.* **2001**, 379–384.
- Recent examples: (a) Yin, J.; Rainka, M. P.; Zhang, X.-X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162–1163. (b) Kocovsky, P.; Vyskocil, S.; Cisarova, I.; Sejbal, J.; Tislerova, I.; Smrcina, M.; Lloyd-Jones, G. C.; Stephen, S. C.; Butts, C. P.; Murray, M.; Langer, V. *J. Am. Chem. Soc.* **1999**, *121*, 7714–7715.
- Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550–9561.
- Pd(0)/*t*-Bu₃P for cross-coupling reactions: for a review: (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176–4211. Selected recent examples: (b) Stambuli, J. P.; Kuwano, R.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 4746–4748. (c) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028.
- Self-coupling products of boronic acids were observed in low yields (0–3%). See Supporting Information.
- 1,2-Dibromobenzene exhibited higher reactivity than 2-bromobiphenyl in Pd(0)/*t*-Bu₃P-catalyzed Suzuki cross-coupling reaction. See Supporting Information.
- Completed conversion was observed when the reaction was carried out at 60 °C for 20 h, with 79% isolated yield and 9:91 of mono:di product ratio.

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