



Oxidative dimerization: Pd(II) catalysis in the presence of oxygen using aqueous media

Jay P. Parrish, Young C. Jung, Ryan J. Floyd and Kyung Woon Jung*

Department of Chemistry, University of South Florida, 4202 E. Fowler Avenue, Tampa, FL 33620-5250, USA

Received 13 August 2002; accepted 5 September 2002

Abstract—Reported herein is a method for the formation of symmetric biaryls and dienes via oxidative dimerization of aryl and alkenyl boronic acids. These conditions utilized Pd(II) catalysts under an oxygen atmosphere with water as the solvent. The use of phase transfer catalysts promoted efficient and mild syntheses of a wide range of materials. © 2002 Elsevier Science Ltd. All rights reserved.

The synthesis of biaryls has been widely studied beginning with the classic Ullmann coupling.¹ Many reactions including Stille and Suzuki couplings allow for the syntheses of both symmetric and unsymmetrical biaryls in high yields.² Recent interest in oxidative dimerizations for the synthesis of symmetric biaryls has resulted in a number of studies, mostly employing organostannanes.³ Our group has reported improved conditions for the rapid synthesis of biaryls from stannanes using Cu(II) salts as Pd(II) catalyst reoxidants.⁴ However, organotin compounds and their by-products are difficult to remove and highly toxic.⁵ To alleviate the problems associated with organostannanes, alternatives employing less-toxic analogs such as boronic acids are desirable. Additionally, aryl and vinyl boronic acids are becoming more readily available from commercial sources.⁶

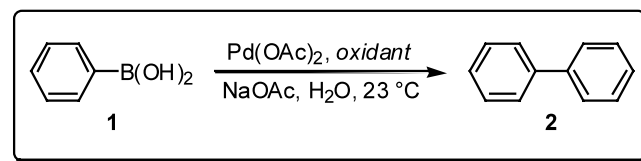
There have been several reports utilizing boronic acids in oxidative dimerizations⁷ and others using oxygen conditions.⁸ Jackson et al. reported Pd(II) catalyzed couplings of arylboronic acids using oxygen conditions.⁹ However, the reaction conditions gave side products resulting in low yields of desired products and provided limited examples. To minimize side reactions, use of phase transfer catalysts (PTC) was reported for the couplings of arylboronic acids with olefins in aqueous media.¹⁰

We report herein the palladium-catalyzed carbon–carbon bond formation via the oxidative dimerization of

boronic acids. By using oxygen as the catalyst reoxidant, rapid formation of dimerized products can be obtained in aqueous media under PTC conditions.¹¹ As a distinguishing feature, our procedure allows for the synthesis of dienes in good yields with limited side products.

The role of the catalyst reoxidant in the dimerization of phenylboronic acid **1** was critical. The reaction was run under nitrogen, air, and oxygen as oxidants, which were delivered either by bubbling or via balloon (Table 1). Very low yields (<10%) of biphenyl **2** were obtained when the reaction was run under nitrogen conditions, indicating the need for an oxygen source (entry 1). With the use of air, only 21% yield of the desired product was obtained (entry 2). With oxygen, a 95% yield of **2** was achieved in a shorter reaction time (entry 3). Surprisingly, no other side products were detected in

Table 1. Effect of oxidant choice on oxidative dimerization of phenylboronic acid



| entry | oxidant | time (h) | yield (%) |
|-------|----------------|----------|-----------|
| 1 | N ₂ | 48 | >10 |
| 2 | Air | 24 | 21 |
| 3 | O ₂ | 3 | 95 |

Keywords: biaryls; Pd(II) catalysis; dienes; homocoupling; oxygen; water.

* Corresponding author. Tel.: 1-813-974-7306; fax: 1-813-974-0640; e-mail: kjung@chuma.cas.usf.edu

the reaction mixture. From these results, we inferred that oxygen was the source of reoxidation and best applied in the pure oxygen form. We then established the optimum reaction conditions using NaOAc as the base in aqueous media. In most cases, water was a highly effective solvent either with or without PTC.

The PTC employed depended on the substrates being screened, but we found that PTCs with long chain alkyl groups were generally effective for this protocol with few exceptions (Tables 2–4). The exact mechanism of PTC in this reaction was not investigated. However, we found that it increased the compatibility of arylboronic acids with water and palladium catalysts dramatically and minimized the side reactions using catalytic amounts.

We began screening a variety of substituted phenylboronic acids as shown in Table 2.¹² Electron rich 4-methoxyphenylboronic acid (**3**) gave 4,4'-dimethoxy biphenyl in 95% yield after 3 hours without the use of a PTC (entry 1). Likewise, similar substrate 4,4'-diphenoxybiphenyl was prepared in 95% yield after 10 hours (entry 2). As stated previously, the need for PTC to facilitate dimerization is dependent on the boronic acid employed. As such, the dimerization of 3,4-(methylenedioxy)phenyl boronic acid (**5**) required cetyltrimethylammonium hydrogensulfate (10 mol%, 0.1 M solution) as a PTC. The reaction was completed after 10 hours and in 84% yield (entry 3). No de-acetalization products were detected in the reaction mixture.

The dimerization of 4-(dimethylamino)phenyl boronic acid (**6**) was smooth to provide the biphenyl in 93% yield after 10 hours (entry 4). No side products resulting from direct oxidation of the nitrogen were detected. Electron withdrawing groups did not appear to have an effect on the course of the reaction as has been seen in other cases.¹³ 3-Cyanophenylboronic acid (**7**) gave 3,3'-dicyanobiphenyl in 98% yield after 10 hours (entry 5) in the presence of PTC. 4,4'-Difluorobiphenyl was prepared in nearly quantitative yield after only 3 hours without the need for PTC (entry 6). The 4-bromo and 4-iodo congeners were also screened, but produced low yields of desired products (<30%) despite our best efforts. 3-Acetylphenylboronic acid (**9**) gave the biphenyl product in 94% yield in 3 hours (entry 7).

We then turned our focus to determining steric effects in the reaction. *o*-Tolylboronic acid (**10**) was screened and gave only 61% yield of the biphenyl product (entry 8). Likewise, 2,6-dimethylphenylboronic acid (**11**) gave a 58% yield of the corresponding biphenyl in 10 hours using sodium dodecyl sulfate (entry 9). Interestingly, this reaction was not effected using cetyltrimethylammonium hydrogensulfate. From these results, we inferred that steric effects hindered product formation of these two substrates as compared with the result of phenylboronic acid. Additionally, we attribute the lower yields of these substrates to the low solubility of the boronic acids in water, even under PTC conditions. If steric effects were a main factor, the addition of the extra methyl in entry 9 would have decreased the yield

Table 2. Formation of biphenyls from boronic acids

| $\text{Ar-B(OH)}_2 \xrightarrow[\text{PTC, H}_2\text{O, 23 }^\circ\text{C}]{\text{Pd(OAc)}_2, \text{O}_2, \text{NaOAc}} \text{Ar-Ar}$ | | | | | |
|---|--------------|------|------|-------|--|
| entry | boronic acid | PTC | time | yield | |
| 1 | (3) | None | 3 h | 95% | |
| 2 | (4) | None | 10 h | 95% | |
| 3 | (5) | A | 10 h | 84% | |
| 4 | (6) | None | 10 h | 93% | |
| 5 | (7) | B | 10 h | 98% | |
| 6 | (8) | None | 3 h | 99% | |
| 7 | (9) | None | 3 h | 94% | |
| 8 | (10) | B | 10 h | 61% | |
| 9 | (11) | C | 10 h | 58% | |

Phase transfer catalyst (PTC) employed, 10 mol%, 0.1 M H₂O solution: A = CH₃(CH₂)₁₅N(CH₃)₃HSO₄; B = CH₃(CH₂)₁₃N(CH₃)₃Br; C = CH₃(CH₂)₁₁OSO₃Na

Table 3. Formation of biaryls from boronic acids

| $\text{R-B(OH)}_2 \xrightarrow[\text{PTC, H}_2\text{O, 23 }^\circ\text{C}]{\text{Pd(OAc)}_2, \text{O}_2, \text{NaOAc}} \text{R-R}$ | | | | | |
|--|--------------|------|------|-------|--|
| entry | boronic acid | PTC | time | yield | |
| 1 | (12) | A | 10 h | 95% | |
| 2 | (13) | None | 10 h | 87% | |
| 3 | (14) | B | 10 h | 98% | |
| 4 | (15) | A | 10 h | 79% | |
| 5 | (16) | B | 10 h | 62% | |

Phase transfer catalyst (PTC) employed, 10 mol%, 0.1 M H₂O solution: A = CH₃(CH₂)₁₅N(CH₃)₃HSO₄; B = CH₃(CH₂)₁₃N(CH₃)₃Br

Table 4. Formation of dienes from boronic acids

$$\text{R}-\text{CH}=\text{CH}-\text{B}(\text{OH})_2 \xrightarrow[\text{PTC, H}_2\text{O, 23}^\circ\text{C}]{\text{Pd}(\text{OAc})_2, \text{O}_2, \text{NaOAc}} \text{R}-\text{CH}=\text{CH}-\text{CH}=\text{CH}-\text{R}$$

| entry | boronic acid | PTC | time | yield | |
|-------|--------------|------|------|-------|-----|
| 1 | | (17) | A | 12 h | 75% |
| 2 | | (18) | B | 10 h | 73% |
| 3 | | (19) | B | 10 h | 85% |
| 4 | | (20) | C | 10 h | 79% |
| 5 | | (21) | C | 10 h | 65% |

Phase transfer catalyst (PTC) employed, 10 mol%, 0.1 M H₂O solution:
 A = CH₃(CH₂)₁₃N(CH₃)₃Br; B = CH₃(CH₂)₁₅N(CH₃)₃HSO₄; C = Bu₄NOH

proportionally. As gleaned from the experimental results, the yields of entries 8 and 9 are virtually the same, implying that steric effect is not a sole governor on the reaction.

Having obtained satisfactory results in the dimerization of phenylboronic acids, we then turned our focus to the synthesis of biaryls as shown in Table 3. Thus, 2-naphthaleneboronic acid was dimerized in 10 hours and in 95% yield (entry 1). Likewise, 1-naphthaleneboronic acid (**13**) reacted to give an 87% yield, albeit without the need of PTC (entry 2). Next, 4-dibenzofuranboronic acid (**14**) reacted under PTC conditions in very high yield (entry 3). Without the use of PTC conditions, we found numerous side products occurred. Phenol formation was the major side product, resulting from the addition of water to the palladium complex. Additionally, proton exchange also occurred with the boron moiety to generate the unfunctionalized aromatic.¹⁴

We were also interested in the dimerization of heterocyclic boronic acids. The dimerization of thianaphthene-2-boronic acid (**15**) was efficient, but gave only 79% yield after 10 hours (entry 4). Furthermore, 5-formyl-2-thiopheneboronic acid (**16**) reacted to give the biaryl in only 62% yield (entry 5). In both cases, the starting material was completely consumed and only phenol and unfunctionalized aromatic products were isolated. The dimerizations of other furan and thiophene-based boronic acids were attempted, but with limited success. Thus, we concluded that most heteroatom-containing substrates were ineffective for dimerization using this protocol.

The synthesis of dienes through the oxidative dimerization of vinylboronic acids was efficient as shown in Table 4. *trans*-2-Phenylvinylboronic acid (**17**) gave good yield of the (*E,E*)-diene product under PTC conditions (entry 1). Only one isomer was isolated with no

side products detected, and the remainder of the reaction mixture was unreacted starting material. The 4-fluoro congener (**18**) reacted to give the (*E,E*)-diene exclusively in 73% yield after 10 hours (entry 2). Additionally, the 4-chloro compound (**19**) gave 85% yield of the desired diene under similar conditions (entry 3).

The synthesis of long chain dienes was also effective using our protocol. For example, the dimerization of *trans*-1-hexen-1-ylboronic acid (**20**) gave (*5E,7E*)-5,7-dodecadiene exclusively in 79% yield after 10 hours (entry 4). Additionally, *trans*-1-octen-1-ylboronic acid (**21**) gave (*7E,9E*)-7,9-hexadecadiene in 65% yield (entry 5). The remainder of the reaction mixture in entries 4 and 5 was unreacted starting material. With the long chain alkenyl boronic acids, we screened the standard PTCs that had been used with previous examples in Tables 2–4. However, these catalysts were ineffective and gave mostly unidentified side products instead of the desired dimerized materials. Fortunately, the use of tetrabutylammonium hydroxide facilitated the dimerization of long chain alkenyl boronic acids.

In conclusion, we have developed a method for the formation of symmetric biaryls and dienes via the oxidative dimerization of boronic acids. These conditions utilize Pd(II) catalysts under an oxygen environment with water as the solvent. The use of PTCs allows for the efficient and mild synthesis of a wide range of products in a rapid fashion. Our reaction allows for a more environmentally benign and cost-effective alternative to standard oxidative dimerization conditions with organostannanes. Additionally, our protocol enhances previous examples of boronic acid dimerization by increasing utility of the reaction. We have achieved this by broadening the range of substrates employed to include substituted phenyls, biaryls, heterocycles, and dienes.

Acknowledgements

We acknowledge generous financial support in part from the National Institutes of Health (RO1 GM 62767).

References

- For the reviews of the Ullmann coupling, see: (a) Lindley, J. *Tetrahedron* **1984**, *40*, 1433; (b) Kozhevnikov, I. V.; Matveev, K. I. *Russ. Chem. Rev.* **1978**, *47*, 649; (c) Fanta, P. E. *Synthesis* **1974**, 9.
- For the Stille reaction, see: (a) Mitchell, T. N. In *Metal-Catalyzed Cross Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley: New York, 1998, pp. 167–202; (b) Mitchell, T. N. *Synthesis*, **1992**, 803; (c) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. For the Suzuki reaction, see: (d) Suzuki, A. In *Metal-Catalyzed Cross Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley: New York, 1998, pp. 49–97; (e) Miyaura, N. *Chem. Rev.* **1995**, *95*, 2457; (f) Suzuki, A. *Pure Appl. Chem.* **1994**, *66*, 213.

3. For selected examples of oxidative dimerization reactions, see: (a) Kang, S.-K.; Baik, T.-G.; Jiao, X. H.; Lee, Y.-T. *Tetrahedron Lett.* **1999**, *40*, 2383; (b) Kang, S.-K.; Namkoong, E.-Y.; Yamaguchi, T. *Synth. Commun.* **1997**, *27*, 641; (c) Wright, M. E.; Porsch, M. J.; Buckley, C.; Cochran, B. B. *J. Am. Chem. Soc.* **1997**, *119*, 8393; (d) Tamao, K.; Ohno, S.; Yamaguchi, S. *J. Chem. Soc., Chem. Commun.* **1996**, 1873; (e) Boons, G.-J.; Entwistle, D. A.; Ley, S. V.; Woods, M. *Tetrahedron Lett.* **1993**, *34*, 5649; (f) Liebeskind, L. S.; Riesinger, S. W. *Tetrahedron Lett.* **1991**, *32*, 5681; (g) Tolstikov, G. A.; Miftakhov, M. S.; Danilova, N. A.; Vel'der, Y. L.; Spirikhin, L. V. *Synthesis* **1989**, 633.
4. For our studies, see: Parrish, J. P.; Flanders, V. L.; Floyd, R. J.; Jung, K. W. *Tetrahedron Lett.* **2001**, *42*, 7729.
5. For toxicology studies, see: (a) Smith, P. J. *Toxicological Data on Organotin Compounds, Publication 538*. International Tin Research Institute: London, 1978. For examples of purification techniques, see: (b) Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: Boston, 1987, pp. 36–37.
6. Aldrich Chemical Catalog 2000–2001, Aldrich Chemical Co., Milwaukee.
7. For oxidative dimerizations with boronic acids, see: (a) Wong, M. S.; Zhang, X. L. *Tetrahedron Lett.* **2001**, *42*, 4087; (b) Moreno-Manas, M.; Perez, M.; Pleixats, R. *J. Org. Chem.* **1996**, *61*, 2346; (c) Percec, V.; Bae, J.-Y.; Zhao, M.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 176.
8. For oxygen-promoted carbon–carbon bond formations, see: (a) Weissman, H.; Song, X.; Milstein, D. *J. Am. Chem. Soc.* **2001**, *123*, 337; (b) Matoba, K.; Motofusa, S.-I.; Cho, C. S.; Ohe, K.; Uemura, S. *J. Organomet. Chem.* **1999**, *574*, 3; (c) Miura, M.; Tsuda, T.; Satoh, T.; Pivsa-Art, S.; Nomura, M. *J. Org. Chem.* **1998**, *63*, 5211.
9. Smith, K. A.; Campi, E. A.; Jackson, W. R.; Marcuccio, S.; Naeslund, C. G. M.; Deacon, G. B. *Synlett* **1997**, 131.
10. For the use of PTCs, see: (a) Lautens, M.; Roy, A.; Fukuoka, K.; Martin-Matute, B. *J. Am. Chem. Soc.* **2001**, *123*, 5358; (b) Grasa, G. A.; Nolan, S. P. *Org. Lett.* **2000**, *3*, 119.
11. Jones, R. A. *Quaternary Ammonium Salts: Their Use in Phase-Transfer Catalysed Reactions*; Academic Press: New York, 2001.
12. **Representative experimental procedure:** Phenylboronic acid (122 mg, 1.0 mmol, 1 equiv.) was mixed with water in the reaction flask (10.0 mL, 0.1 M solution) and rapid stirring was begun (Note: with reactions using PTC, a stock 0.1 M aqueous solution was added here instead). Into the solution was added NaOAc (272 mg, 2.0 mmol, 2 equiv.) and Pd(OAc)₂ (11 mg, 0.05 mmol, 0.05 equiv.). A balloon of O₂ was placed over the neck of the flask and the solution was stirred at room temperature for 3 h. The mixture was then diluted with 1:1 hexanes/EtOAc (10 mL), extracted with 1:1 hexanes/EtOAc (3×20 mL), then washed with H₂O (10 mL). The organic layer was concentrated in vacuo, and subjected to flash chromatography (30 g SiO₂, eluted with 10:1 hexanes/EtOAc) to afford biphenyl (73 mg, 95%).
13. For the effects of substituents on transition-metal coupling reactions, see: (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508; (b) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379; (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457; (d) Sonogashira, K. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley: New York, 1998, pp. 203–229.
14. For mechanistic considerations of the oxidative dimerization of boronic acids and formation of side products, see: Ref. 7b.