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Facile Synthesis of Highly Congested 1,2-Diphosphinobenzenes from Bis(phosphine)boronium Salts

Yoshikazu Yamamoto,[†] Toru Koizumi,[†,‡] Kosuke Katagiri,[†,‡] Yui Furuya,[†] Hiroshi Danjo,*[,†] Tsuneo Imamoto,[‡] and Kentaro Yamaguchi*[,†]

Department of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences at Kagawa Campus, Tokushima Bunri University, and CREST, Japan Science and Technology Agency (JST), 1314-1 Shido, Sanuki, Kagawa 769-2193, Japan, and Department of Chemistry, Faculty of Science, Chiba University, 1-33 Yayoi-cho, Inage-ku, Chiba 263-8522, Japan

danjo@kph.bunri-u.ac.jp

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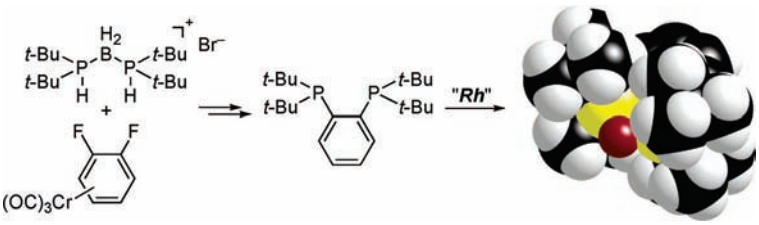
ABSTRACT



Bis(phosphine)boronium salts 3a–c were designed and prepared as key building blocks for the synthesis of highly congested diphosphinobenzenes. The preparation of sterically hindered *ortho*-phenylene-bridged diphosphines 1a–c was achieved by the reaction of the bis(phosphine)boronium salts 3a–c with difluorobenzenechromium complex 2 and subsequent removal of the BH_2 group. The steric nature of diphosphine 1a was revealed in single-crystal X-ray analysis of its Rh complex.

The design and synthesis of new phosphine ligands is one of the most important research subjects in the field of transition-metal catalyses.[1] Recently, bulky monophosphines such as tri-*tert*-butylphosphine and biaryldicyclohexylphosphines were proven to be effective for Pd-catalyzed amination of aryl halides,[2] α-arylation of carbonyls,[3,4a] and cross-coupling of arylboronic acids with aryl chlorides[4] or alkyl bromides.[5] The utility of bulky diphosphine ligands represented by 1,3-bis(di-*tert*-butylphosphino)propane (dtbpp) or 1,2-bis(di-*tert*-butylphosphinomethyl)benzene (dtbpmb) was also demonstrated mainly in Pd-catalyzed alkoxycarbonylation of olefins[6] or aryl halides,[7] in which high TON and

[†] Tokushima Bunri University and CREST.
[‡] Chiba University.

(1) For representative reviews of chiral phosphine ligands, see the following: (a) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029−3069. (b) Ohkuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 1−110. (c) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994. (d) Pietrusiewicz, K. M.; Zabrocka, M. *Chem. Rev.* **1994**, *94*, 1375−1411.

(2) For reviews, see: (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131−209. (b) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; p 1051.

(3) (a) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108−11109. (b) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382−12383. (c) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473−1478.

(4) For reviews, see: (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211. (b) Miura, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2201−2203.

(5) Netherton, M. R.; Dai, C.; Neuschütz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099−10100.

(6) (a) Koide, Y.; Bott, S. G.; Barron, A. R. *Organometallics* **1996**, *15*, 2213−2226. (b) Clegg, W.; Eastham, G. R.; Elsegood, M. R. J.; Tooze, R. P.; Wang, X. L.; Whiston, K. *Chem. Commun.* **1999**, 1877−1878. (c) Pugh, R. I.; Drent, E. *Adv. Synth. Catal.* **2002**, *344*, 837−840. (d) Rucklidge, A. J.; Morris, G. E.; Cole-Hamilton, D. J. *Chem. Commun.* **2005**, 1176−1178.

(7) Jimenez-Rodriguez, C.; Eastham, G. R.; Cole-Hamilton, D. J. *Dalton Trans.* **2005**, 1826−1830.

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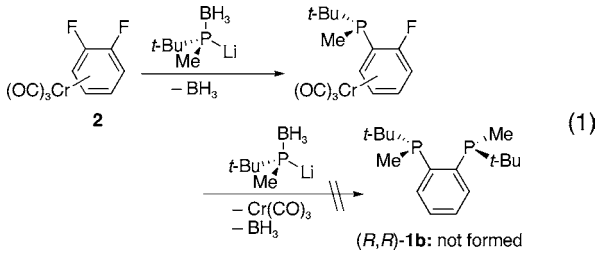
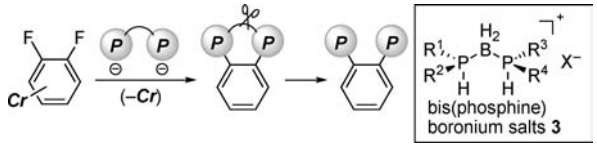
regioselectivity were observed. However, despite their high utility, the synthesis of such phosphines is quite difficult because of their own steric hindrance, and only a limited number of bulky phosphines have been prepared so far. As part of our continuing research toward the development of efficient transition-metal catalyses, we report here a new approach to a class of sterically hindered diphosphines that shows promise in various catalytic processes. We focused on 1,2-diphosphinobenzenes **1** with bulky alkyl substituents on phosphorus atoms.[8] The *ortho*-phenylene backbone is rigid and is expected to form a highly regulated reaction environment. Previously, we tried to prepare a P-chiral diphosphine, (*R*,*R*)-1,2-bis(*tert*-butylmethylphosphino)benzene ((*R*,*R*)-**1b**), according to the S_NAr approach in which 1,2-difluorobenzenetricarbonylchromium (**2**) and (*S*)-*tert*-butylmethylphosphine−borane were employed as coupling components.[9] Despite numerous attempts to use any order of events, sequential substitution of the two halogens with two phosphino groups did not proceed at all (eq 1). The



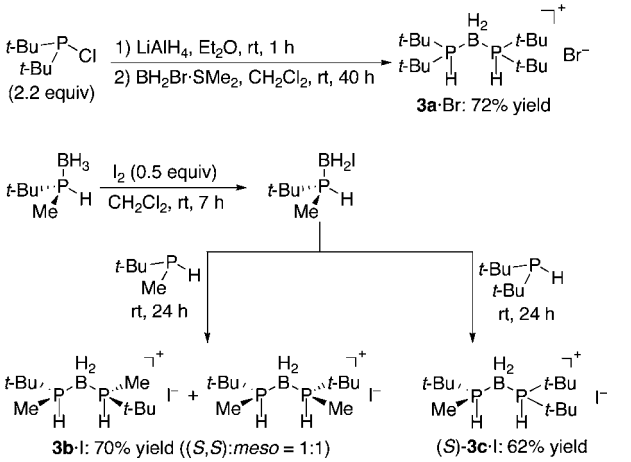
boranato(dialkyl)phosphino group was too bulky to be introduced at the ortho position of the phosphinobenzenes. To avoid steric repulsion between two phosphorus nucleophiles, we used bis(phosphine)boronium salts **3**, in which two secondary phosphine compounds are coupled through the BH_2 linkage (Scheme 1).[10]

Scheme 1. Design of Bis(phosphine)boronium Salts **3**



The preparation of **3** was easily achieved by reacting secondary phosphine with monobromoborane (Scheme 2).[11]

Scheme 2. Preparation of Bis(phosphine)boronium Salts **3**



Di-*tert*-butylphosphine, generated in situ from di-*tert*-butylchlorophosphine and lithium aluminum hydride, was treated with 0.5 equiv of a monobromoborane dimethylsulfide complex. The reaction proceeded in dichloromethane at room temperature to afford bis(di-*tert*-butylphosphine)boronium bromide (**3a**·Br) in 72% yield. Optically active bis(phosphine)boronium salts were also prepared from optically pure secondary phosphine−boranes. Thus, (*S*)-*tert*-butylmethylphosphine−borane was converted into the corresponding phosphine−iodoborane by treatment with 0.5 equiv of iodine,[12] which was then coupled with racemic *tert*-butylmethylphosphine to afford bis(*tert*-butylmethylphosphine)boronium iodide (**3b**·I) in 70% yield as a mixture of diastereomers. Diastereomerically enriched (*S*,*S*)-**3b**·I could be obtained by recrystallization from THF (96% de). Boronium salt (*S*)-**3c**·I was also prepared from (*S*)-*tert*-butylmethylphosphine−borane (99% ee) and di-*tert*-butylphosphine in the same manner.

Synthesis of diphosphines **1** was then carried out with the boronium salts **3a**−**c** as starting materials (Scheme 3). At first, **3a** was subjected to the coupling reaction with 1,2-difluorobenzenetricarbonylchromium (**2**) after deprotonation with 2.0 equiv of *n*-BuLi at ambient temperature. The reaction took place in the presence of 5 equiv of HMPA at 65 °C, and diphosphinobenzeneboronium salt **4a**·Br was obtained in 62% yield.[13] As the second step, the removal of the bridging boronium group of the diphosphineboronium compound was attempted under various reaction conditions. Boronium salt **4a**·Br was stable against strong acids such as trifluoromethanesulfonic acid or tetrafluoroboric acid, which are effective reagents for the deboranation of phosphine−boranes.[14] The boronium group was also intact in 1-methylpyrrolidine at 60 °C.[15] After screening various reaction

(8) For examples, see: (a) Kyba, E. P.; Liu, S.-T.; Harris, R. L. *Organometallics* **1983**, *2*, 1877−1879. (b) Kyba, E. P.; Kerby, M. C.; Rines, S. P. *Organometallics* **1986**, *5*, 1189−1194. (c) Burk, M. *J. Am. Chem. Soc.* **1991**, *113*, 8518−8519. (d) Gray, M.; Chapell, B. J.; Felding, J.; Taylor, N. J.; Snieckus, V. *Synlett* **1998**, 422−423. (e) Miura, T.; Imamoto, T. *Tetrahedron Lett.* **1999**, *40*, 4833−4836. (f) Imamoto, T.; Sugita, K.; Yoshida, K. *J. Am. Chem. Soc.* **2005**, *127*, 11934−11935.

(9) Katagiri, K.; Danjo, H.; Yamaguchi, K.; Imamoto, T. *Tetrahedron* **2005**, *61*, 4701−4707.

(10) (a) Schmidtbaur, H. *J. Organomet. Chem.* **1980**, *200*, 287−306. (b) Westcott, S. A.; Blom, H. P.; Marder, T. B. *Inorg. Chem.* **1993**, *32*, 2175−2182.

(11) Martin, D. R.; Merkel, C. M.; Ruiz, J. P. *Inorg. Chim. Acta* **1985**, *100*, 293−297.

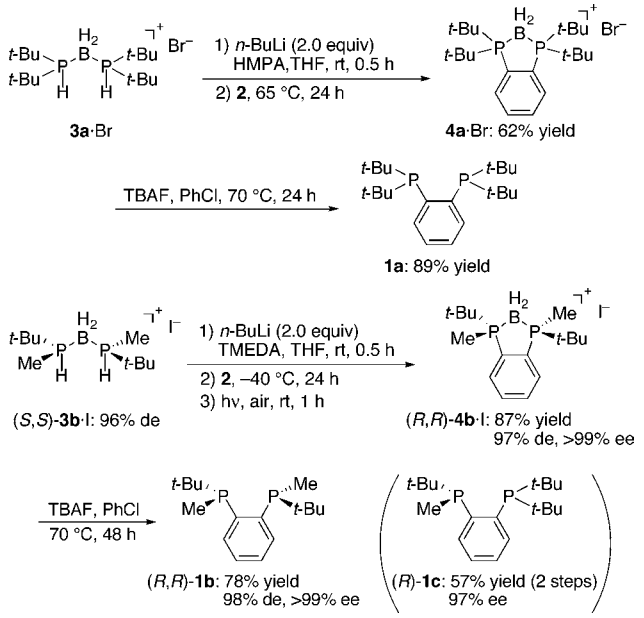
(12) Imamoto, T.; Hikosaka, T. *J. Org. Chem.* **1994**, *59*, 6753−6759.

(13) $Cr(CO)_3$ was removed under these reaction conditions without irradiation of sunlight.

(14) (a) Mckinstry, L.; Livinghouse, T. *Tetrahedron Lett.* **1994**, *35*, 9319−9322. (b) Mckinstry, L.; Livinghouse, T. *Tetrahedron* **1995**, *51*, 7655−7666.

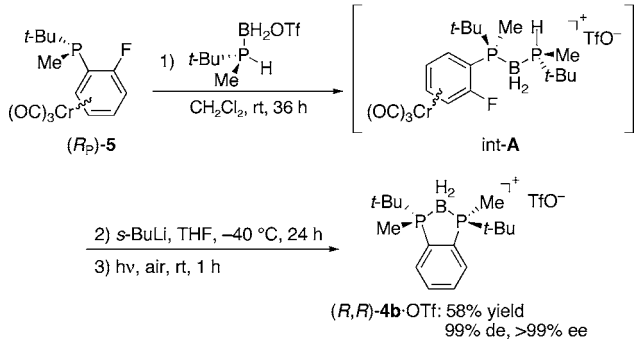
(15) Imamoto, T.; Kusumoto, T.; Suzuki, N.; Sato, K. *J. Am. Chem. Soc.* **1985**, *107*, 5301−5303.

Scheme 3. Preparation of Diphosphinobenzenes **1**



conditions, tetra-*n*-butylammonium fluoride (TBAF) was found to be effective for this transformation. Thus, the reaction took place in the presence of 3.0 equiv of TBAF in chlorobenzene at 70 °C, and **1a** was formed in 89% yield within 24 h. Optically active P-chiral diphosphines were also prepared from boronium salts (*S*,*S*)-**3b**·I and (*S*)-**3c**·I. The coupling reaction of (*S*,*S*)-**3b** with **2** (1:1 molar ratio) proceeded at −40 °C, and (*R*,*R*)-**4b**·I with 97% de was obtained in 87% yield. The optical purity of (*R*,*R*)-**4b**·I was determined to be >99% ee by reverse-phase chiral HPLC analysis.[16] The reaction of (*R*,*R*)-**4b**·I with TBAF was also successful, and free P-chiral diphosphine (*R*,*R*)-**1b** was obtained in 78% yield. The enantiomeric excess of (*R*,*R*)-**1b** was determined to be >99% (98% de) in its phosphine sulfide form, indicating that almost no racemization occurred during the diphosphine synthesis. Unsymmetric P-chiral diphosphine (*R*)-**1c** was prepared in the same manner (57% yield, 97% ee in two steps). Optically active diphosphine-boronium salt **4b** could also be obtained according to the stepwise protocol shown in Scheme 4. Phosphine (R_P)-**5** was coupled with (*S*)-*tert*-butylmethylphosphine−trifluoromethanesulfonyloxyborane to form int-**A** (not isolated). Intramolecular S_NAr took place after deprotonation of the terminal phosphino group to give (*R*,*R*)-**4b**·OTf in 58% yield. The P-stereogenic centers were completely retained during this transformation (99% de, <99% ee).

Scheme 4. Stepwise Procedure for the Preparation of Bis(phosphine)boronium Salts **4b**



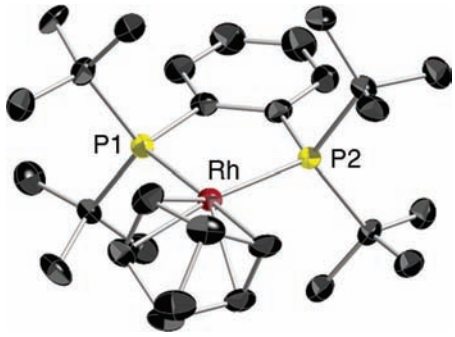
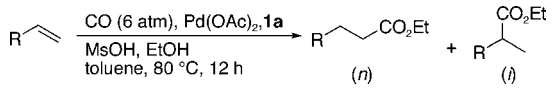


Figure 1. ORTEP drawing of [**1a**·Rh(nbd)]PF_6. Hydrogen atoms and PF_6 are omitted for clarity.

The single-crystal X-ray analysis of [**1a**·Rh(nbd)]PF_6 revealed that although the bite angle (P1−Rh−P2) of 82.5° is small in comparison to other diphosphines[6a,b] the four *tert*-butyl groups on phosphorus atoms effectively shield the coordination surface (Figure 1). It is noteworthy that the norbornadiene ligand is significantly inclined (23°) from the coordination plane due to steric hindrance of the *tert*-butyl groups.

The utility of diphosphine ligand **1a** was tested in palladium-catalyzed hydroesterification of terminal olefins (Table 1). The reaction was conducted in the presence of 0.2 mol % of $Pd(OAc)_2$, 0.25 mol % of **1a**, and 1.5 mol % of methanesulfonic acid under 6 atm of CO. In each case, the reaction proceeded smoothly and gave the corresponding hydroesterification product mainly in linear form. This regioselectivity is similar to that obtained by dtbpp rather

Table 1. Pd-Catalyzed Hydroesterification of Olefins[a]



entry	R	yield/%[b]	*n*/*i*[c]
1	Ph	92	7.7:1
2	2-MeC_6H_4	94	30:1
3	4-$MeOC_6H_4$	42[d]	7.7:1
4	4-ClC_6H_4	88	5.6:1
5	*n*-Hex	73	5.0:1

[a] Reagents and conditions: olefin (2.5 mmol), $Pd(OAc)_2$ (0.2 mol %), **1a** (0.25 mol %), MsOH (1.5 mol %), EtOH (0.4 mL), toluene (1 mL), CO (6 atm), 80 °C, 12 h. [b] Isolated yield. [c] Determined by ^1H NMR. [d] 4-(1-Ethoxyethyl)anisole was formed in 37% yield.

than dtbpmb, probably owing to the small bite angle of **1a**.[17] The hydroesterification did not proceed in the presence of **1c** instead of **1a**.

In conclusion, bis(phosphine)boronium salts **3a**−**c** were prepared as key building blocks for highly advantageous diphosphine synthesis. The preparation of sterically hindered *ortho*-phenylene-bridged diphosphines **1a**−**c** was achieved by the reaction of the bis(phosphine)boronium salts **3a**−**c** with the difluorobenzenechromium complex **2** and subsequent removal of the BH_2 group. The performance of **1a** was demonstrated in Pd-catalyzed hydroesterification of olefins.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds and X-ray diffraction data for [**1a**·Rh(nbd)]PF_6 in the form of a CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Decreased enantiomeric excess (97% de, 83% ee) was observed when the coupling reaction was carried out at room temperature.

(17) Ooka, H.; Inoue, T.; Itsuno, S.; Tanaka, M. *Chem. Commun.* **2005**, 1173−1175.