

# Transmetalation of Alkylboranes to Palladium in the Suzuki Coupling Reaction Proceeds with Retention of Stereochemistry

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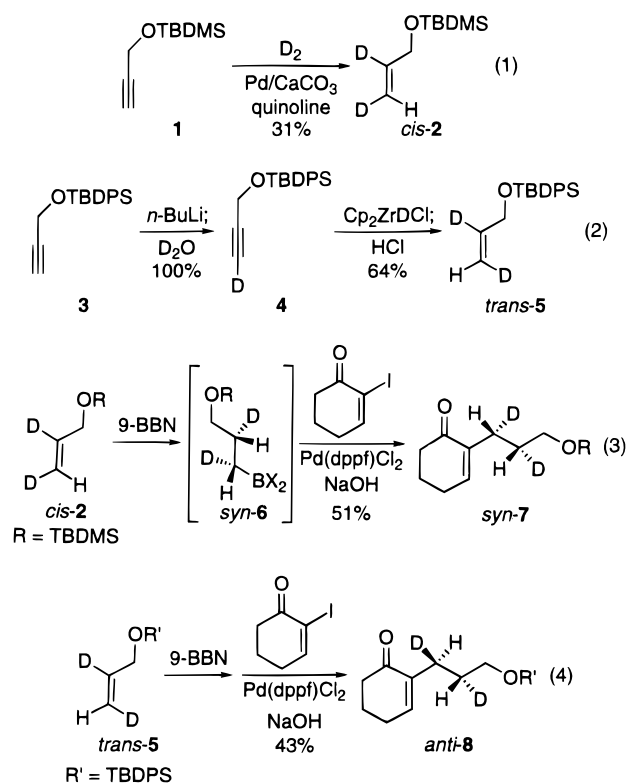
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Deuterium-labeling experiments demonstrate that the transmetalation step of the Suzuki coupling reaction of alkylboranes and  $\alpha$ -iodoenones proceeds with retention of stereochemistry.

The palladium-catalyzed cross-coupling of organoboranes and alkenyl or aryl halides (the Suzuki reaction) has achieved prominence as one of the most important metal-catalyzed carbon–carbon bond-forming reactions in organic synthesis.<sup>1</sup> The mechanism of this transformation is believed to involve oxidative addition of the electrophilic halide to a Pd(0) intermediate followed by transmetalation of the carbon substituent from boron to the resulting Pd(II) complex and finally reductive elimination to provide the coupled product.<sup>1</sup> The Suzuki reaction is a particularly powerful transformation because it permits the coupling of primary alkylboranes and alkenyl or aryl halides, a process that can be used to great synthetic advantage.<sup>2</sup> In contrast to stereochemical investigations of the related cross-couplings involving silanes<sup>3</sup> and stannanes,<sup>4–6</sup> the stereochemistry of the transmetalation of alkylboranes to palladium (either retention or inversion of configuration) has received little attention.<sup>7,8</sup> We provide evidence that primary alkylboranes undergo transmetalation to palladium with retention of configuration.<sup>9</sup>

The stereochemistry of the coupling reaction was determined by hydroboration of diastereomeric dideuteroalkenes *cis*-**2** and *trans*-**5** followed by coupling of the diastereomeric boranes to  $\alpha$ -iodocyclohexenone and examination of the spectral properties of the resulting cyclohexenones (eqs 3 and 4). These particular derivatives were chosen because they displayed well-resolved

signals in their <sup>1</sup>H NMR spectra at the stereocenter of interest, permitting facile determination of coupling constants between the protons of the CHD units.<sup>10</sup> The deuterated alkenes were prepared as shown in eqs 1 and 2. Because of the volatility of the *tert*-butyldimethylsilyl



ethers **1** and *cis*-**2**, the *tert*-butyldiphenylsilyl ether was chosen for the longer sequence leading to *trans*-**5**. The enones *syn*-**7** and *anti*-**8** were obtained by hydroboration of the respective alkenes with 9-BBN followed by addition of 2-iodocyclohexenone,<sup>11</sup> palladium catalyst, and aqueous sodium hydroxide (eqs 3 and 4, the reaction conditions were not optimized).<sup>1</sup>

The stereochemistries of the enones *syn*-**7** and *anti*-**8** were assigned by analysis of their <sup>1</sup>H NMR spectra.

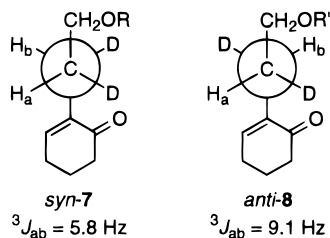
(10) Whitesides pioneered the use of similarly deuterated substrates to evaluate the stereochemical course of reactions involving alkylmetal compounds: Bock, P. L.; Boschetto, D. M.; Rasmussen, J. R.; Demers, J. P.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 2814–2825.

(11) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W.; Wovkulich, P. M.; Uskakovic, M. R. *Tetrahedron Lett.* **1992**, *33*, 917–918.

- (1) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.  
 (2) See, for example: Johnson, C. R.; Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11014–11015.  
 (3) Hatanaka, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1990**, *112*, 7793–7794.  
 (4) Labadie, J. W.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 6129–6137.  
 (5) Ye, J.; Bhatt, R. K.; Falck, J. R. *J. Am. Chem. Soc.* **1994**, *116*, 1–5.  
 (6) Falck, J. R.; Bhatt, R. K.; Ye, J. *J. Am. Chem. Soc.* **1995**, *117*, 5973–5982.  
 (7) Cyclopropylboranes with alkyl substituents trans to the boron undergo coupling to provide trans products. This observation indicates that transmetalation may occur with retention of configuration, although coupling with *cis*-substituted cyclopropylboranes was not investigated: (a) Wang, X.-Z.; Deng, M.-Z. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2663–2664. (b) Hildebrand, J. P.; Marsden, S. P. *Synlett* **1996**, 893–894. (c) Charette, A. B.; De Freitas-Gil, R. P. *Tetrahedron Lett.* **1997**, *38*, 2809–2812.

(8) Knochel has recently demonstrated that transmetalation of a secondary alkyl group from boron to zinc occurs with retention of configuration: Micouin, L.; Oestreich, M.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 245–246.

(9) Soderquist has recently presented a similar strategy to the one reported here and has arrived at the same conclusion: Soderquist, J. A.; Rane, A.; Matos, K. Presented at the 213th National Meeting of the American Chemical Society, San Francisco, CA, April 1997; paper ORGN 582. Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1997**, *63*, 461–470.



Because the dominant conformational isomer in solution should be the anti conformers depicted, the two stereoisomers should display significantly different coupling constants between the protons  $H_a$  and  $H_b$ .<sup>10</sup> The isomer derived from *cis*-2 possesses a 5.8 Hz coupling constant, whereas the isomer from *trans*-5 has a 9.1 Hz coupling constant.<sup>12,13</sup> Consequently, the palladium-catalyzed coupling occurred to give the products *syn*-7 and *anti*-8 from eqs 3 and 4, respectively. Because hydroboration is a syn addition process,<sup>14</sup> and reductive elimination from palladium proceeds with retention of configuration,<sup>15</sup> transmetalation from boron to palladium must therefore occur with retention of configuration.

In conclusion, these experiments indicate that the Suzuki coupling of primary alkylboranes to iodoalkenes proceeds with retention of configuration at the carbon atom. The results are in accord with a frontside  $S_E2$  (cyclic) mechanism for transmetalation, similar to what has been suggested for alkylsilanes.<sup>3</sup>

### Experimental Section

**General Methods.** General experimental details are provided as Supporting Information. All coupling constants are reported in Hz. Decoupling experiments were performed to confirm structural assignments. Microanalyses were performed by Atlantic Microlab, Atlanta, GA. All reactions were carried out under an atmosphere of nitrogen in glassware that had been flame-dried under a stream of nitrogen.

**1-(*tert*-Butyldimethylsiloxy)-2,3-*cis*-dideuterio-2-propene (*cis*-2).** 1-(*tert*-Butyldimethylsiloxy)-2-propyne (**1**)<sup>16</sup> (844 mg, 4.96 mmol) was dissolved in pentane (12 mL). Quinoline (640 mg, 4.96 mmol) and Pd on  $\text{CaCO}_3$  (100 mg, 5% Pd) were added, and the reaction flask was flushed with nitrogen. A balloon containing  $\text{D}_2$  was affixed, and the reaction flask was purged to ensure a  $\text{D}_2$  atmosphere. After being stirred for 45 min, the heterogeneous reaction mixture was filtered through Celite and purified by flash chromatography (10:90  $\text{CH}_2\text{Cl}_2$ :pentane), yielding a volatile, clear oil (270 mg, 31%): IR (thin film) 2957, 2351, 1472, 1071  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.24 (m, 1H), 4.17 (s, 2H), 0.92 (s, 9H), 0.07 (s, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  137.1 (t,  $^1J_{\text{CD}} = 24.2$ ), 113.5 (t,  $^1J_{\text{CD}} = 24.2$ ), 64.0, 25.9, 18.4, -5.3; HRMS (EI)  $m/z$  calcd for  $\text{C}_9\text{H}_{18}\text{D}_2$ -

(12) The  $^1\text{H}\{^2\text{H}\}$  NMR spectra showed coupling constants similar to these values (6.1 and 9.2 Hz, for *syn*-7 and *anti*-8, respectively). Variable-temperature NMR experiments also indicated only minor changes in the spectral data. At  $-50^\circ\text{C}$ , the coupling constant for *syn*-7 decreased; this resonance became a broad singlet. At this temperature, the coupling constant for *anti*-8 increased slightly to 9.3 Hz.

(13) A similar analysis has been used to determine the stereochemistry of polydeuterated alkanes: Gilchrist, J. H.; Bercaw, J. E. *J. Am. Chem. Soc.* **1996**, *118*, 12021–12028.

(14) Kabalka, G. W.; Bowman, N. S. *J. Org. Chem.* **1973**, *38*, 1607–1608.

(15) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4981–4991.

(16) The details of the preparation and characterization of this compound are provided as Supporting Information.

(17) The combustion analysis data did not differentiate deuterium and hydrogen in the evolved water. Therefore, the calculated hydrogen analyses were determined by dividing the combined masses of the hydrogen atoms (as if they were all protons) by the formula weight of the deuterated compound.

OSi ( $M^+$ ) 174.1409, found 174.1409. Anal. Calcd for  $\text{C}_9\text{H}_{20}\text{OSi}$ : C, 62.00; H, 11.56. Found: C, 62.26; H, 11.48.<sup>17</sup>

**1-(*tert*-Butyldiphenylsiloxy)-3-deuterio-2-propyne (**4**).** 1-(*tert*-Butyldiphenylsiloxy)-2-propyne (**3**)<sup>16</sup> (2.0 g, 6.8 mmol) was dissolved in THF (14 mL). *n*-Butyllithium (9.3 mL, 1.1 M in hexane) was added dropwise at  $-78^\circ\text{C}$ . The mixture was stirred at  $-78^\circ\text{C}$  for 1 h.  $\text{D}_2\text{O}$  (20.4 mL, 10.2 mmol) was added, and the mixture was stirred for 4 h. The reaction mixture was partitioned between 50 mL of  $\text{NH}_4\text{Cl}$  (saturated aqueous) and 50 mL of  $\text{Et}_2\text{O}$  and separated. The aqueous layer was washed with  $2 \times 50$  mL of  $\text{Et}_2\text{O}$ , and the organic layers were combined, dried over  $\text{Na}_2\text{SO}_4$ , and reduced in vacuo. The product was purified by flash chromatography, yielding a white solid (100% by NMR): IR (KBr) 3070, 2598, 1998, 1071  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.92 (m, 4H), 7.56 (m, 6H), 4.49 (s, 2H), 1.27 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  135.5, 132.8, 129.8, 127.7, 81.4 (t,  $^2J_{\text{CD}} = 6.8$ ), 72.9 (t,  $^1J_{\text{CD}} = 37.8$ ), 52.4, 26.6, 19.1; HRMS (EI)  $m/z$  calcd for  $\text{C}_{19}\text{H}_{21}\text{DOSi}$  ( $M^+$ ) 295.1503, found 295.1512. Anal. Calcd for  $\text{C}_{19}\text{H}_{22}\text{OSi}$ : C, 77.23; H, 7.50. Found: C, 77.29; H, 7.52.<sup>17</sup>

**1-(*tert*-butyldiphenylsiloxy)-2,3-*trans*-dideuterio-2-propene (*trans*-5).** Zirconocene chloride deuteride (130 mg, 0.5 mmol, prepared from lithium aluminum deuteride and zirconocene dichloride<sup>18,19</sup>) and benzene (3 mL) were mixed in a round-bottom flask. 1-(*tert*-Butyldiphenylsiloxy)-3-deuterio-2-propyne (**4**, 135 mg, 0.46 mmol in 1 mL of benzene) was added. The heterogeneous mixture was stirred for 10 h in the absence of light, becoming red and homogeneous. HCl was added (2 mL, 1 M, aqueous), and after 20 min,  $\text{NaHCO}_3$  was added (35 mL, saturated aqueous) followed by  $\text{NH}_4\text{Cl}$  (15 mL, saturated aqueous) and  $\text{Et}_2\text{O}$  (50 mL). The aqueous layer was separated and washed with  $2 \times 50$  mL of  $\text{Et}_2\text{O}$ . The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and reduced in vacuo. Flash chromatography (10:90  $\text{CH}_2\text{Cl}_2$ :hexane) yielded the product as a clear oil (87 mg, 64%): IR (thin film) 3071, 1590, 1112  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.69 (m, 4H), 7.38 (m, 6H), 5.10 (d,  $J = 1.6$ , 1H), 4.21 (d,  $J = 1.6$ , 2H), 1.07 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  136.6 (t,  $^1J_{\text{CD}} = 24.2$ ), 135.5, 135.3, 133.7, 127.6, 113.5 (t,  $^1J_{\text{CD}} = 23.4$ ), 64.5, 26.8, 19.3; HRMS (EI)  $m/z$  calcd for  $\text{C}_{19}\text{H}_{22}\text{D}_2\text{OSi}$  ( $M^+$ ) 298.1722, found 298.1719. Anal. Calcd for  $\text{C}_{19}\text{H}_{24}\text{OSi}$ : C, 76.45; H, 8.10. Found: C, 76.52; H, 8.16.<sup>17</sup>

**2-[3-(*tert*-Butyldimethylsiloxy)-1,2-*syn*-dideuteriopropyl]-2-cyclohexen-1-one (*syn*-7).** Propene *cis*-2 (150 mg, 0.86 mmol) was added to a solution of 9-BBN (126 mg, 1.03 mmol) in THF (15 mL) at  $0^\circ\text{C}$ . The reaction mixture was heated to reflux for 12 h. The mixture was cooled to  $25^\circ\text{C}$ , and 2-iodo-2-cyclohexene-1-one<sup>11</sup> (229 mg, 1.03 mmol), Pd-(dppf) $\text{Cl}_2$  (14 mg, 0.017 mmol), and NaOH (0.6 mL, 3 M, aqueous) were added sequentially. The mixture was again brought to reflux where it remained for 2 h. The reaction mixture was partitioned between NaCl (75 mL, saturated aqueous) and  $\text{Et}_2\text{O}$  (50 mL). The aqueous phase was separated and washed with  $2 \times 25$  mL of  $\text{Et}_2\text{O}$ . The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and reduced in vacuo. Purification by flash chromatography (10:90  $\text{EtOAc}$ :hexane) yielded pure product as a colorless oil (119 mg, 51%): IR (thin film) 2953, 2168, 1677, 1471, 1097  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.70 (t,  $J = 4.2$ , 1H), 3.56 (d,  $J = 6.5$ , 2H), 2.39 (t,  $J = 6.8$ , 2H), 2.31 (m, 2H), 2.16 (d,  $J = 5.8$ , 1H), 1.94 (quintet,  $J = 6.4$ , 2H), 1.56 (m, 1H), 0.86 (s, 9H), 0.01 (s, 6H);  $^2\text{H}\{^1\text{H}\}$  NMR (77 MHz,  $\text{CDCl}_3$ )  $\delta$  1.58, 2.20;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  199.4, 145.1, 139.3, 62.5, 38.5, 31.1 (t,  $^1J_{\text{CD}} = 19.4$ ), 26.0, 25.9, 25.4 (t,  $^1J_{\text{CD}} = 19.4$ ), 23.1, 18.2, -5.4; HRMS (EI)  $m/z$  calcd for  $\text{C}_{14}\text{H}_{23}\text{D}_2\text{O}_2\text{Si}$  ( $M^+ - \text{CH}_3$ ) 255.1749, found 255.1745. Anal. Calcd for  $\text{C}_{15}\text{H}_{28}\text{O}_2\text{Si}$ : C, 66.61; H, 10.43. Found: C, 66.76; H, 10.42.<sup>17</sup>

**2-[3-(*tert*-Butyldiphenylsiloxy)-1,2-*anti*-dideuteriopropyl]-2-cyclohexen-1-one (*anti*-8).** The procedure is identical

(18) Kautzner, B.; Wailes, P. C.; Weigold, H. *J. Chem. Soc., Chem. Commun.* **1969**, 1105.

(19) For a recent example of reactions of Schwartz's reagent with alkynes, see: Lipshutz, B. H.; Keil, R.; Ellsworth, E. L. *Tetrahedron Lett.* **1990**, *31*, 7257–7260.

with that employed to prepare *syn-7* (vide supra) to provide the product in 43% yield: IR (thin film) 3071, 2168, 1673, 1110  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.66 (m, 4H), 7.39 (m, 6H), 6.65 (t,  $J = 4.2$ , 1H), 3.64 (d,  $J = 6.3$ , 2H), 2.39 (t,  $J = 6.7$ , 2H), 2.29 (m,  $J = 5.8$ , 2H), 2.24 (d,  $J = 9.1$ , 1H), 1.93 (quintet,  $J = 6.4$ , 2H), 1.64 (m, 1H), 1.05 (s, 9H);  $^2\text{H}\{^1\text{H}\}$  NMR (77 MHz,  $\text{CDCl}_3$ )  $\delta$  1.67, 2.28;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  199.4, 145.3, 139.2, 135.5, 134.0, 129.5, 127.6, 63.2, 38.5, 30.8 (t,  $^1J_{\text{CD}} = 19.4$ ), 26.8, 26.0, 25.5 (t,  $^1J_{\text{CD}} = 19.4$ ), 23.1, 19.2; HRMS (EI)  $m/z$  calcd for  $\text{C}_{21}\text{H}_{21}\text{D}_2\text{O}_2\text{Si}$  ( $\text{M}^+ - \text{C}(\text{CH}_3)_3$ ) 337.1593, found 337.1601.

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**Supporting Information Available:** Experimental details for the preparation of **1** and **3** as well as  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for *cis-2*, **4**, *trans-5*, *syn-7*, and *anti-8* (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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