Metal-Catalyzed Hydroboration and Diboration of Thiocarbonyls and Vinyl Sulfides

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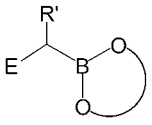
Summary: α-*Thioboronate esters are obtained directly in high yield and selectivity from metal-catalyzed additions of B−X bonds (X = H, B) to thiocarbonyl compounds and vinyl sulfides.*

Compounds containing boronic acids [$RB(OH)_2$] or boronate esters [$RB(OR')_2$] have received considerable attention as synthons for catalyzed carbon−carbon bond formation,[1] in solid-phase synthesis,[2] macrocyclic chemistry,[3] and organometallic[4] and organic synthesis,[5] and as glucose sensors for diabetes therapy.[6] Interest in these compounds also arises from their potent biological activities.[7] For instance, α-aminoboronic acids are effective and reversible inhibitors of serine proteases.[8] Recent work has also shown that the bioisosteric α-phosphonoboronate esters show biological activity in noninvasive cancer therapy.[9] As part of our ongoing investigation into generating biologically active boron compounds,[10] and considering the biological importance of organosulfur compounds,[11] we decided to examine novel metal-catalyzed boration reactions as direct routes to α-thioboronate derivatives (Figure 1). Initial results are presented herein.



E = NR_2, α-aminoboronate ester
E = $P(O)(OR)_2$, α-phosphonoboronate ester
E = SR, α-thioboronate ester

Figure 1. α-Heteroatom-substituted boronate esters.

Although the hydroboration of C−C multiple bonds is an extremely important reaction in organic synthesis, relatively little is known about the reduction of carbon−sulfur double bonds with boron hydride reagents.[12] We found that addition of 9-H-BBN (BBN = borabicyclo-[3.3.1]nonane) to thiocarbonyl compounds **1a**−**d** proceeds smoothly to give the expected borylsulfide products **2a**−**d** (Figure 2). Reactions were monitored by ^1H, ^{11}B, and ^{13}C NMR spectroscopy.[13] In contrast to diaryl ketones, however, no reaction of **1a** was observed with either catecholborane (HBcat, cat = $O_2C_6H_4$) or pinacolborane (HBpin, pin = $O_2C_2Me_4$) at room temperature. In the presence of 5 mol % $RhCl(PPh_3)_3$, the same reaction proceeded to give borylsulfides RR′CHSBcat along with varying amounts of the corresponding thiols RR′CHSH (up to 50% for **1d**), the latter products arising from degradation of the borane.[14] Analogous catalyzed hydroborations of **1a**−**d** using less reactive HBpin[15] in

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(1) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Trost, B. M.; Spagnol, M. D. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2083. (c) Chan, D. M. T.; Monaco, K. L.; Wang, R. P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933.

(2) Carboni, B.; Pourbaix, C.; Carreaux, F.; Deleuze, H.; Maillard, B. *Tetrahedron Lett.* **1999**, *40*, 7979.

(3) Farfan, N.; Hopfl, H.; Barba, V.; Ochoa, M. E.; Santillan, R.; Gomez, E.; Gutierrez, A. *J. Organomet. Chem.* **1999**, *581*, 70.

(4) Minutolo, F.; Katzenellenbogen, J. A. *Organometallics* **1999**, *18*, 2519.

(5) (a) Matteson, D. S. *Tetrahedron* **1989**, *45*, 1859. (b) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798. (c) Batey, R. A.; MacKay, D. B.; Santhakumar, V. *J. Am. Chem. Soc.* **1999**, *121*, 5075.

(6) (a) Yamamoto, M.; Takeuchi, M.; Shinkai, S. *Tetrahedron* **1998**, *54*, 3125. (b) Eggert, H.; Frederiksen, J.; Morin, C.; Chr. Norrild, J. *J. Org. Chem.* **1999**, *64*, 3846.

(7) Morin, C. *Tetrahedron* **1994**, *50*, 12521.

(8) (a) Weston, G. S.; Blázquez, J.; Baquero, F.; Shoichet, B. K. *J. Med. Chem.* **1998**, *41*, 4577. (b) Stoll, V. S.; Eger, B. T.; Hynes, R. C.; Martichonok, V.; Jones, J. B.; Pai, E. F. *Biochemistry* **1998**, *37*, 451. (c) Adams, J.; Behnke, M.; Chen, S.; Cruickshank, A. A.; Dick, L. R.; Grenier, L.; Klunder, J. M.; Ma, Y.; Plamondon, L.; Stein, R. L. *Bioinorg. Med. Chem. Lett.* **1998**, *8*, 333. (d) Gao, C.; Lavey, B. J.; Lo, C. L.; Datta, A.; Wentworth, P., Jr.; Janda, K. D. *J. Am. Chem. Soc.* **1998**, *120*, 2211. (e) Han, W.; Pelletier, J. C.; Mersinger, L. J.; Kettner, C. A.; Hodge, C. N. *Org. Lett.* **1999**, *1*, 1875. (f) Bao, D.; Huskey, W. P.; Kettner, C. A.; Jordan, F. *J. Am. Chem. Soc.* **1999**, *121*, 4684. (g) Cox, J. D.; Kim, N. N.; Traish, A. M.; Christianson, D. W. *Nat. Struct. Biol.* **1999**, *6*, 1043.

(9) (a) Pergament, I.; Srebnik, M. *Tetrahedron Lett.* **1999**, *40*, 3895. (b) Srebnik, M.; Pergament, I.; Al Aziz Quntar, A. *Abstracts of Papers*, 218th National Meeting of the American Chemical Society, New Orleans, LA; American Chemical Society: Washington, DC, 1999; INORG 287. (c) Pergament, I.; Srebnik, M. *Org. Lett.* **2001**, *3*, 217.

(10) (a) Baker, R. T.; Cameron, T. M.; Westcott, S. A. *Chem. Commun.* **1998**, 2395. (b) Vogels, C. M.; Wellwood, H. L.; Hennigar, T. L.; Biradha, K.; Zaworotko, M. J.; Westcott, S. A. *Can. J. Chem.* **1999**, *77*, 1196. (c) Mann, G.; John, K. D.; Baker, R. T. *Org. Lett.* **2000**, *2*, 2105.

(11) Cremlyn, R. J. In *An Introduction to Organosulfur Chemistry*; Wiley: Chichester, U.K., 1996.

(12) (a) Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061 and references therein. (b) Pelter, A.; Smith, K.; Brown, H. C. *Borane Reagents*; Academic Press: New York, 1988.

(13) In a typical experiment, 9-H-BBN dimer (61 mg, 0.25 mmol) in 0.5 mL of C_6D_6 was added dropwise to a blue solution of $Ph_2C{=}S$ (99 mg, 0.50 mmol) in 0.5 mL of C_6D_6. The mixture was heated to 60 °C for 1 h, whereupon the solution turned colorless. Selected NMR spectroscopic data for **2a** are as follows. ^1H NMR: δ 7.45 (d, J = 7 Hz, 4H, Ar), 7.15 (t, J = 7 Hz, 4H, Ar), 7.06 (d, J = 7 Hz, 2H, Ar), 5.76 (s, 1H, −SCH), 1.98−1.31 (ov m, 14H, BBN); ^{11}B NMR: δ 77.4 (br s). ^{13}C NMR: δ 143.9, 128.7, 128.6, 127.0, 51.9, 33.3, 30.1 (br), 24.3, 23.0, 20 (br).

(14) Westcott, S. A.; Blom, H. P.; Marder, T. B.; Baker, R. T. *Inorg. Chem.* **1993**, *32*, 2175.

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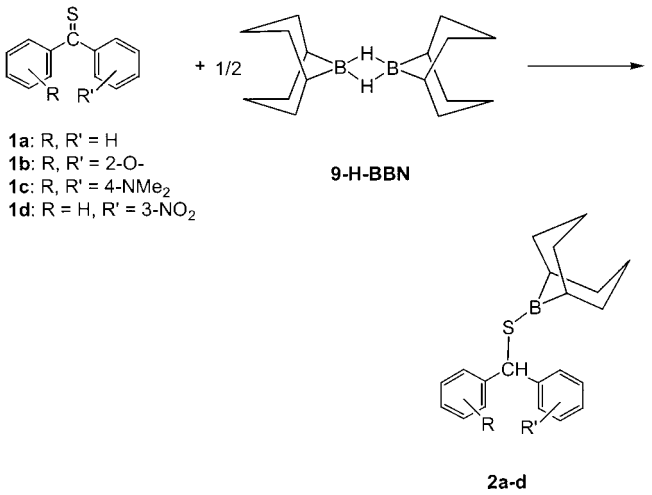

Figure 2. Hydroboration of thiocarbonyls **1a**−**d** with 9-H-BBN.

C_6D_6 at 60 °C gave the borylsulfides **3a**−**d** in higher yields (by NMR).[16] Reactions carried out in THF gave significantly more of the thiol. In contrast, catalyzed hydroborations of aliphatic (1*R*)-(−)-thiocamphor (**4**) with HBcat at room temperature or HBpin at elevated temperature gave a single isomer of the corresponding boryl sulfide **5** accompanied by minor amounts of boronate ester degradation products $B_2(cat)_3$ and $B_2(pin)_3$, respectively.[14,17]

While hydroborations of thiocarbonyl compounds give boryl sulfides, which can be hydrolyzed to the corresponding thiols, diboration reactions are unique in delivering a boryl fragment (BR_2) to the α-carbon as well. Aqueous workup of the diborated products should then provide a direct route to α-thioboronic acids. Although attempts to diborate thiocarbonyl compounds **1a**−**d** proved unsuccessful using a number of different metal catalysts, we have found that $B_2(cat)_2$ adds to (1*R*)-(−)-thiocamphor (**4**) in high yields using a catalytic amount of $RhCl(PPh_3)_3$ to give a single isomer of the diborated product **6**.[18] Aqueous workup provided the corresponding thiol **7**, but we have not yet been able to deprotect the carbon-bound boryl group to the corresponding boronic acid (Figure 3). The reactions described here are the first examples of metal-catalyzed boration reactions of a thiocarbonyl group.

A second potential route to thioboronate esters involves the hydroboration of organosulfur-substituted alkenes. Recent reports on hydroborations of related enamines using 9-H-BBN generated α-boronated amine intermediates.[19] Hydroboration of phenyl vinyl sulfide **8** with HBcat at elevated temperatures gave the expected anti-Markovnikov organoboronate ester **9** along with products arising from Lewis base-mediated degradation of the borane reagent. In the presence of a rhodium catalyst, typically 2 mol % $RhCl(PPh_3)_3$, **8** reacts with HBcat to give selective formation of the desired α-thioboronate ester **10** resulting from *an exclusive Markovnikov addition* (Figure 4; as ascertained by multinuclear NMR spectroscopy).[20] Preliminary results show that similar selectivities are observed in reactions with $PhCH_2SCH{=}CH_2$. These results are particularly intriguing, as Markovnikov additions have only been observed in appreciable amounts in catalyzed reactions of styrenes,[21] fluoroalkenes,[22] and allyl sulfones.[23] A η^3-benzyl intermediate has been invoked to rationalize the styrene selectivity, and that for the sulfones has been attributed to a directing effect of the sulfone oxygens.

Organosulfur compounds with boryl groups on both the α- and β-carbons were obtained by catalyzed diborations of phenyl vinyl sulfide. While Wilkinson's cata-

(15) (a) Pereira, S.; Srebnik, M. *Tetrahedron Lett.* **1996**, *37*, 3283. (b) Murata, M.; Watanabe, S.; Masuda, Y. *Tetrahedron Lett.* **1999**, *40*, 2585. (c) Ramachandran, P. V.; Jennings, M. P.; Brown, H. C. *Org. Lett.* **1999**, *1*, 1399. (d) Crudden, C. M. Personal communication. (e) Vogels, C. M.; Hayes, P. G.; Shaver, M. P.; Westcott, S. A. *Chem. Commun.* **2000**, 51.

(16) In a typical experiment, HBpin (61 mg, 0.51 mmol) in 0.5 mL of C_6D_6 was added dropwise to a solution of the diarylthiocarbonyl (0.50 mmol) and 5 mol % $RhCl(PPh_3)_3$ in 0.5 mL of C_6D_6. The mixture was heated to 60 °C for 2 h and then analyzed by high-field NMR spectroscopy. Selected NMR spectroscopic data of the hydroborated product are as follows. **3a**: ^{1}H NMR δ 7.56 (d, J = 7 Hz, 4H, Ar), 7.16 (t, J = 7 Hz, 4H, Ar), 7.08 (d, J = 7 Hz, 2H, Ar), 5.99 (s, 1H, SCH), 1.02 (s, 12H, pin); ^{11}B NMR δ 34.0 (br). **3b**: ^{1}H NMR δ 7.69 (d, J = 5 Hz, 2H, Ar), 7.18−7.03 (ov m, 6H, Ar), 6.05 (s, 1H, SCH), 1.13 (s, 12H, pin); ^{11}B NMR δ 33.1 (br). **3c**: ^{1}H NMR δ 7.63 (mult, 4H, Ar), 6.66 (mult, 4H, Ar), 6.16 (s, 1H, SCH), 2.56 (s, 12H, NMe), 1.05 (s, 12H, pin); ^{11}B NMR δ 33.4 (br). **3d**: ^{1}H NMR δ 8.50 (s, 1H, Ar), 7.75 (d, J = 7 Hz, 1H, Ar), 7.42 (d, J = 7 Hz, 1H, Ar), 7.35 (d, J = 7 Hz, 2H, Ar), 7.09 (ov m, 3H, Ar), 6.72 (t, J = 7 Hz, 1H, Ar), 5.80 (s, 1H, SCH), 0.97 (s, 12H, pin); ^{11}B NMR δ 33.7 (br). Boryl sulfide products decomposed in solution over time to give the corresponding thiols and $B_2(pin)_3$.

(17) In a typical experiment, HBcat (66 mg, 0.55 mmol) in 0.5 mL of C_6D_6 was added dropwise to a solution of (1*R*)-(−)-thiocamphor (84 mg, 0.50 mmol) and 2 mol % $RhCl(PPh_3)_3$ in 0.5 mL of C_6D_6. Selected NMR spectroscopic data are as follows. **5**: ^{1}H NMR δ 7.01 (m, 2H, cat), 6.79 (m, 2H, cat), 3.68 (t, J = 8 Hz, 1H), 2.05 (app d, J = 8 Hz, 3H), 1.62 (br ov m, 4H), 1.05 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 0.76 (s, 3H, CH_3); ^{11}B NMR δ 35.6 (br s); ^{13}C NMR δ 149.6 (C cat), 123.1 (CH cat), 112.7 (CH cat), 49.9, 49.5, 48.2, 46.8, 42.5, 38.7, 27.8, 20.9, 20.8, 14.5.

(18) To a benzene solution of (1*R*)−(−)-thiocamphor (79 mg, 0.47 mmol) was added $B_2(cat)_2$ (112 mg, 0.47 mmol) and 5 mol % $RhCl(PPh_3)_3$. The reaction mixture was stirred at room temperature for 16 h. Removal of the solvent yielded an amber-colored residue. A concentrated ether solution of this residue was cooled (−35 °C) to afford off-white needles (160 mg, 85%). NMR (C_6D_6) of **6**: ^{1}H δ 7.05 (2nd order m, 2H, cat), 6.74 (2nd order m, 2H, cat), 6.65 (2nd order m, 2H, cat), 6.52 (2nd order m, 2H, cat), 3.11 (d, J = 14 Hz, 1H), 2.45 (ddd, J = 14, 4, 3 Hz, 1H), 1.72 (app t, J = 4 Hz, 1H), 1.49 (m, 3H), 1.40 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.04 (m, 1H), 0.73 (s, 3H, CH_3); ^{11}B{^{1}H} δ 31.7 (br); ^{13}C{^{1}H} δ 148.8 (C cat), 148.76 (C cat), 122.9 (CH cat), 122.7 (CH cat), 112.8 (CH cat), 112 (CH cat), 52.5, 50.5, 47.2 (CH), 46.1, 43.6 (br, C-B), 37.3, 26.9, 21.6 (CH_3), 20.7 (CH_3), 14.0 (CH_3). To an ether solution of **6** (97 mg, 0.24 mmol) was added water (10 μL, 0.48 mmol). The mixture was stirred at room temperature for 0.5 h and then dried over anhydrous $MgSO_4$, which was removed by filtration. The filtrate was concentrated and cooled (−35 °C) to yield off-white needles of the corresponding thiol **7** (20 mg, 80%). NMR (C_6D_6): ^{1}H δ 7.00 (2nd order m, 2H, cat), 6.77 (2nd order m, 2H, cat), 2.57 (d, J = 13 Hz, 1H), 2.10 (ddd, J = 13, 6, 4 Hz, 1H), 2.03 (s, 1H, SH), 1.62 (t, J = 4 Hz, 1H), 1.31 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.10 (m, 4H), 0.72 (s, 3H, CH_3); ^{11}B{^{1}H} δ 32.7 (br); ^{13}C{^{1}H} δ 148.7 (C cat), 122.9 (CH cat), 112.7 (CH cat), 50.3, 50.0, 46.3 (CH), 43.6 (br, C-B), 42.3, 36.8, 27.1, 21.1 (CH_3), 20.9 (CH_3), 13.6 (CH_3).

(19) (a) Singaram, B.; Goralski, C. T.; Fisher, G. B. *J. Org. Chem.* **1991**, *56*, 5691. (b) Fisher, G. B.; Goralski, C. T.; Nicholson, L. W.; Singaram, B. *Tetrahedron Lett.* **1993**, *34*, 7693.

(20) In a typical experiment, HBcat (40 mg, 0.34 mmol) in 0.5 mL of C_6D_6 was added to a solution of phenyl vinyl sulfide (41 mg, 0.30 mmol) in 0.5 mL of C_6D_6 and heated at 80 °C for 8 h to afford **9**. NMR: ^{1}H δ 7.45−6.6 (ov m, 9H, Ph and cat), 2.96 (t, J = 8 Hz, 2H, CH_2), 1.42 (t, J = 8 Hz, 2H, CH_2); ^{11}B{^{1}H} δ 34.3 ppm (br); ^{13}C{^{1}H} δ 148.9 (C cat), 134.3, 129.3, 129.1, 122.9 (CH cat), 112.4 (CH cat), 28.7 (CH_2), 27.2 (br, C−B). For the catalyzed reaction the above mixture was stirred with 2 mol % $RhCl(PPh_3)_3$ at 20 °C for 8 h to give **10** in 95% NMR yield. NMR: ^{1}H δ 7.25−6.6 (ov m, 9H, Ph and cat), 3.02 (q, J = 8 Hz, 1H, CH), 1.48 (d, J = 8 Hz, 3H, CH_3); ^{11}B{^{1}H} δ 33.4 (br); ^{13}C{^{1}H} δ 148.4 (C cat), 131.7, 129.1, 127.0, 123.0 (CH cat), 112.7 (CH cat), 24.0 (br, C−B), 16.7 (CH_3).

(21) Beletskaya, I.; Pelter, A. *Tetrahedron* **2000**, *53*, 4957.

(22) Brown, H. C.; Chen, G.-M.; Jennings, M. P.; Ramachandran, P. V. *Angew. Chem., Int. Ed.* **1999**, *38*, 2052.

(23) Hou, X.; Hong, D.; Rong, G.; Guo, Y.; Dai, L. *Tetrahedron Lett.* **1993**, *34*, 8513.

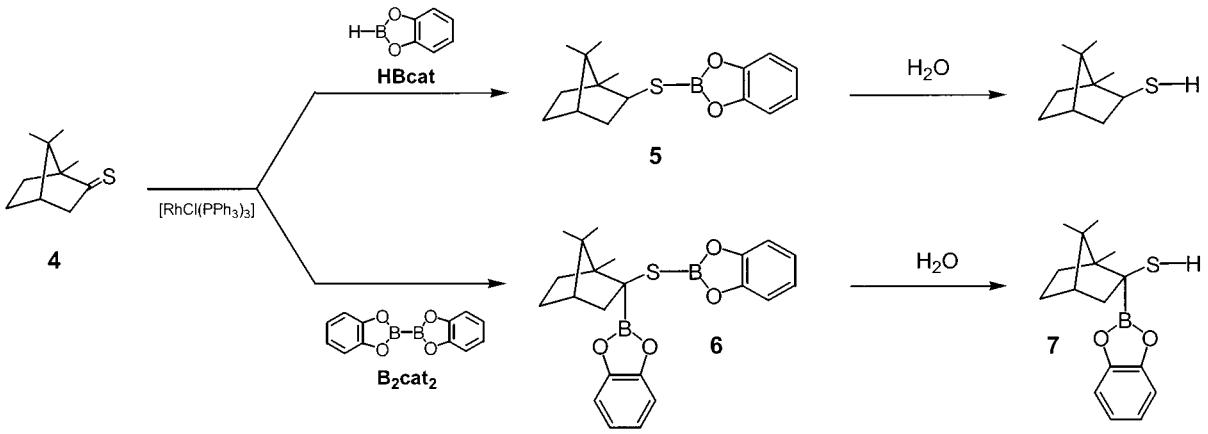

Figure 3. Hydroboration and diboration of (1*R*)-(−)-thiocamphor (**4**).

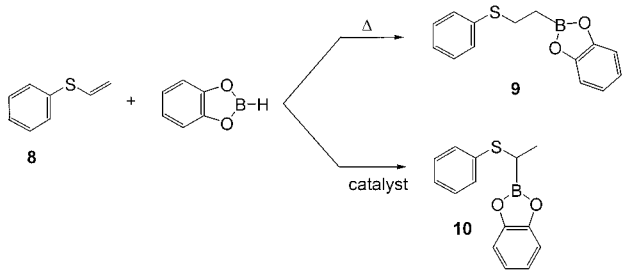

Figure 4. Hydroboration of phenyl vinyl sulfide (**8**) with catecholborane.

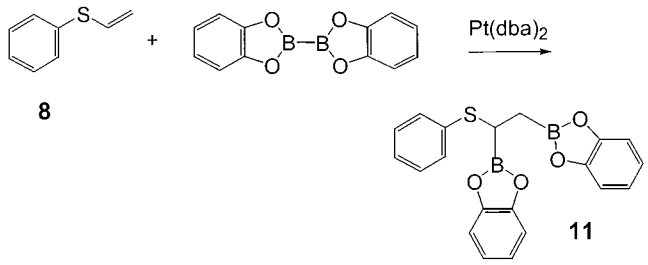

Figure 5. Diboration of **8** with $B_2(cat)_2$.

lyst and $Rh(acac)(L_2)$[24] (L_2 = 1,4-bis(diphenylphosphino)-butane and 1,1-bis(diphenylphosphino)methane) both gave significant amounts of hydroboration and borylation products, the $Pt(dba)_2$ (dba = dibenzylideneacetone)[25] catalyst afforded diboron addition product **11** in high yield (Figure 5).[26]

In summary, we have found three direct metal-catalyzed routes to alpha-thioboronate esters. We are currently exploring the scope of the substrate, the asymmetric hydroboration of alkenyl sulfides, and biological testing of these new compounds and will report our findings in due course.

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Supporting Information Available: Figures giving spectroscopic data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) (a) Westcott, S. A.; Blom, H. P.; Marder, T. B.; Baker, R. T. *J. Am. Chem. Soc.* **1992**, *114*, 8863. (b) Dai, C.; Robins, E. G.; Scott, A. J.; Clegg, W.; Yufit, D. S.; Howard, J. A. K.; Marder, T. B. *Chem. Commun.* **1998**, 1983.

(25) Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Commun.* **1997**, 689.

(26) In a typical experiment, a mixture of $B_2(cat)_2$ (52 mg, 0.22 mmol), phenyl vinyl sulfide (27 mg, 0.20 mmol), and $Pt(dba)_2$ (7 mg, 0.01 mmol) was dissolved in 0.5 mL of C_6D_6 and stirred for 2 days to afford **11** (93%) and **10** (6%), along with minor amounts of $B_2(cat)_3$. Reactions were monitored by multinuclear NMR spectroscopy. NMR for **11**: ^1H δ 7.4−6.6 (ov m, 13H, Ph and cat), 3.45 (dd, J = 9, 7 Hz, 1H, CH), 1.99 (dd, J = 17, 9 Hz, 2H, CH_2), 1.91 (dd, J = 17, 7 Hz, 2H, CH_2); $^{11}B\{^1H\}$ δ 35.1 (br); $^{13}C\{^1H\}$ NMR: δ 148.5 (C cat), 135.1 (ipso of Ph), 132.8 (Ph), 129.1 (Ph), 127.5 (Ph), 123.0, 122.8 (CH cat), 112.8, 112.6 (CH cat), 25.9 (br, CH−B), 14.2 ppm (br, CH_2−B).