ORGANIC LETTERS

2013
Vol. 15, No. 5
1132–1135

Hydrophosphination of Propargylic Alcohols and Amines with Phosphine Boranes

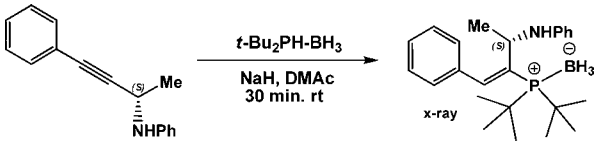
Carl A. Busacca,* Bo Qu, Elisa Farber,[†] Nizar Haddad, Nicole Grět, Anjan K. Saha, Magnus C. Eriksson, Jiang-Ping Wu, Keith R. Fandrick, Steve Han, Nelu Grinberg, Shengli Ma, Heewon Lee, Zhibin Li, Michael Spinelli, Austin Gold, Guijun Wang,[‡] Peter Wipf,[†] and Chris H. Senanayake

Chemical Development, Boehringer-Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, Ridgefield, Connecticut 06877, United States, Department of Chemistry, Center for Chemical Methodologies and Library Development, University of Pittsburgh, 219 Parkman Avenue, Pittsburgh, Pennsylvania 15260, United States, and Department of Chemistry and Biochemistry, Old Dominion University, 4541 Hampton Boulevard, Norfolk, Virginia 23529, United States

carl.busacca@boehringer-ingelheim.com

Received February 4, 2013

ABSTRACT



The first uncatalyzed hydrophosphinations of propargylic amines and alcohols with phosphine−borane complexes are described. The reactions proceed at ambient temperature or below without the use of protecting groups or the need to handle pyrophoric secondary phosphines, furnishing air-stable phosphineborane−amines and alcohols in good yields. Utilization of chiral propargylic substrates and unsymmetrical secondary phosphineboranes leads to diastereomeric *P*-chiral products that can be separated by fractional crystallization or chromatography. Initial applications of these new P−X species to asymmetric catalysis are detailed.

Phosphines are the pre-eminent class of ligands to transition metals, and broad applications of phosphines in asymmetric catalysis have been realized in the past 30 years.[1] We have recently described the facile uncatalyzed hydrophosphination of unactivated alkynes with the anions of phosphineboranes.[2] This methodology also conveniently avoids the use of pyrophoric free phosphines. The analogous hydrophosphination of propargylic substrates, if realized, would provide access to functionalized allylic systems bearing a heteroatom and substituted by a phosphine.

Direct treatment of phenylpropynol **1** with dicyclohexylphosphine borane **2** in DMF at ambient temperature with 60% NaH (2 equiv) was found to generate the desired phosphineborane−allylic alcohol **3** in 90% yield as a single stereoisomer after 18 h reaction time at 20 °C and recrystallization (Scheme 1). It is significant to note that no protection of the alcohol was required. Chiral ynol (*S*)-(−)-**4** reacted similarly, with formation of enantiomerically pure, crystalline vinylphosphine borane (*S*)-**5** in 83% yield after 3 h reaction time. In all of the cases described herein, the *Z* hydrophosphination product was the major or exclusive isomer formed. This result differs from those results obtained with alkynes lacking the alcohol functionality, all of which gave predominately *E* isomers.[2] (*S*)-**4** also

[†] University of Pittsburgh.
[‡] Old Dominion University.

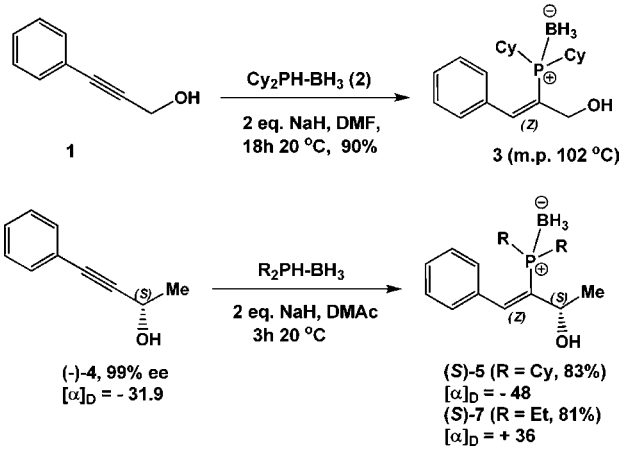
(1) For reviews, see: (a) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987; pp 21−56. (b) Busacca, C. A.; Senanayake, C. H. The Use of New Phosphines as Powerful Tools in Asymmetric Synthesis of Biologically Active Compounds. In *Comprehensive Chirality*; Carreira, E. M., Yamamoto, H., Eds.; Elsevier: Amsterdam, 2012; Vol. I, pp 167−216. (c) Lühr, S.; Holz, J.; Börner, A. *ChemCatChem* **2011**, *3*, 1708–1730. (d) van Leeuwen, P. W. N. M.; Freixa, Z.; Zuidema, E. Properties of Phosphorus Ligands. In *Phosphorus Ligands in Asymmetric Catalysis*; Börner, A., Ed.; Wiley-VCH: Weinheim, 2008; pp 1433−1454. (e) Stelzer, O.; Rossenbach, S.; Hoff, D.; Schreuder-Goedheijt, M.; Kamer, P. C. J.; Reek, J. N. H.; van Leeuwen, P. W. N. M. Ligands: Phosphorus-Containing Ligands. In *Multiphase Homogeneous Catalysis*; Börner, A., Ed.; Wiley-VCH: Weinheim, 2005; pp 66−82.

(2) Busacca, C. A.; Farber, E.; DeYoung, J.; Campbell, S.; Gonnella, N. C.; Grinberg, N.; Haddad, N.; Lee, H.; Ma, S.; Reeves, D.; Shen, S.; Senanayake, C. H. *Org. Lett.* **2009**, *11*, 5594–5597.

10.1021/ol400309y
Published on Web 02/21/2013

reacted smoothly with dicyclohexylphosphine borane **2**, giving adduct (*S*)-**5** in 83% yield after 3 h at ambient temperature (Scheme 1). The less sterically demanding diethylphosphine borane gave (*S*)-**7** as a 2:1 *Z*/*E* mixture. Mechanistically, these results imply that the regio- and stereoselectivity of the hydrophosphination is likely mainly a consequence of the attractive electrostatic interactions, first between alkoxide and phosphine borane, and followed by coordination between the alkoxide sodium cation and the vinyl anion intermediate.

Scheme 1. Hydrophosphination of Propargylic Alcohols



The reaction of a nonsymmetric phosphine borane, cyclohexylphenylphosphine borane **8**, with (*S*)-(−)-**4** was examined next, and the diastereomeric products **9c** and **9d** were produced in 78% yield after 2 h at rt (Scheme 2). The diastereomers were readily separated by fractional crystallization to give *P*-chiral-(−)-**9c** and (+)-**9d** as white solids. The relative configuration at the phosphorus center for these two products was first assigned by VCD,[3] and the stereochemistry then confirmed by a crystal structure of (−)-**9c** (Figure 1). Compound **9c**, with the R_P stereochemistry, was the less soluble and higher melting isomer. Propargylamines[4] were found to be even more reactive. Addition of phosphine borane **2** to (*S*)-**10** gave the P−N adduct in good yield after just 15 min at 0 °C (Scheme 3), again without the use of protecting groups. The stereochemistries of **10** and **11** were each determined through

(3) See the Supporting Information.

(4) For reviews on chiral propargylamines, see: (a) Zani, L.; Bolm, C. *Chem. Commun.* **2006**, 4263–4275. (b) Blay, G.; Monleon, A.; Pedro, J. R. *Curr. Org. Chem.* **2009**, *13*, 1498–1539. See also: (c) Marshall, J. A.; Wolf, M. A. *J. Org. Chem.* **1996**, *61*, 3238–2339. (d) Ding, C.-H.; Chen, D.-D.; Luo, Z.-B.; Dai, L. X.; Hou, X.-L. *Synlett* **2006**, *8*, 1272–1274. (e) Aschwanden, P.; Stephenson, C. R. J.; Carreira, E. M. *Org. Lett.* **2006**, *8*, 2437–2440. (f) Wei, C. J. *J. Am. Chem. Soc.* **2002**, *124*, 5638–5639. (g) Bisai, A.; Singh, V. K. *Org. Lett.* **2006**, *8*, 2405–2408. (h) Lo, V. K.; Kung, K. K.; Wong, M.; Che, C. *J. Organomet. Chem.* **2009**, *694*, 583–591. (i) Koradin, C.; Gommermann, N.; Polborn, K.; Knochel, P. *Chem.—Eur. J.* **2003**, *9*, 2797–2811. (j) Hattori, G.; Sakata, K.; Matsuzawa, H.; Tanabe, Y.; Miyake, Y.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2010**, *132*, 10592–10608. (k) Chen, B.-L.; Wang, B.; Lin, G.-Q. *J. Org. Chem.* **2010**, *75*, 941–944. (l) Colombo, F.; Benaglia, M.; Orlandi, S.; Usuelli, F.; Celentano, G. *J. Org. Chem.* **2006**, *71*, 2064–2070. (m) Josephson, N. S.; Carswell, E. L.; Snapper, M. L.; Hoveyda, A. H. *Org. Lett.* **2005**, *7*, 2711–2713.

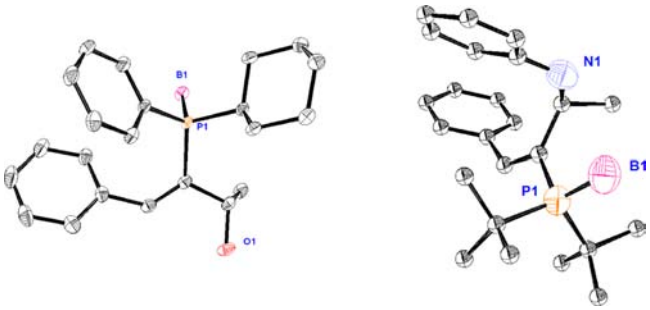
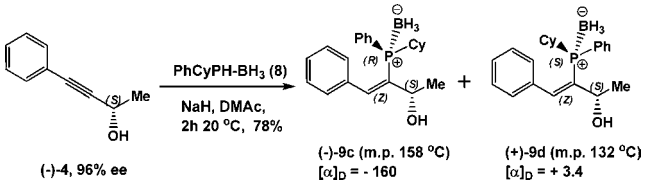


Figure 1. Crystal Structures of (−)-**9c** (left) and **12** (right).

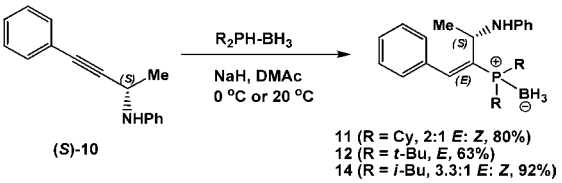
Scheme 2. Hydrophosphination with PhCyPH−BH_3



X-ray crystal structures.[3] It should be noted that no borane transfer to the amine center occurred.

The olefin geometry was assigned by ^{31}P HOESY experiments.[5] Reaction of bis-*t*-Bu phosphine borane **6** furnished a 63% yield of adduct **12**, as a crystalline solid and as a single isomer (*E*), after only 30 min at rt. The structure of **12** is shown in Figure 1. Phosphine borane **13** gave adduct **14** in high yield as a 3.3: 1 *E*: *Z*-mixture, after the same reaction time. The isomers proved to be readily separable, and both were crystalline as well.

Scheme 3. Hydrophosphinations of Propargylamine **10**



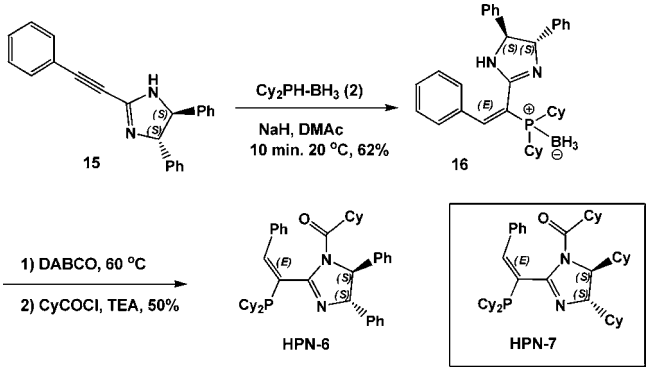
The nitrogen atom of the propargylamine can also be part of a heterocycle. Alkynylimidazoline **15** underwent hydrophosphination, as shown in Scheme 4. Reaction with dicyclohexylphosphine borane **2** gave chiral phosphinoimidazoline[6] species **16**, formed with high *E* selectivity.

(5) For a review, see: (a) Pregosin, P. S.; Kumar, P. G. A.; Fernandez, I. *Chem. Rev.* **2005**, *105*, 2977. See also: (b) Bauer, W. *Magn. Reson. Chem.* **1996**, *34*, 532–537. (c) Pregosin, P. S.; Fernandez, I. *Magn. Reson. Chem.* **2006**, *44*, 76. (d) Hughes, R. P.; Zhang, D.; Ward, A. J.; Zakharov, L. N.; Rheingold, A. L. *J. Am. Chem. Soc.* **2004**, *126*, 6169–6178.

(6) First phosphinoimidazoline ligands: Busacca, C. A. Electronically-tuned ligands. U.S. Pat. 6,316,620, 2001.

Deboronation and acylation (no glovebox needed) then provided the first member of a new class of ligands, HPN-6. Ligand HPN-7 was prepared analogously.

Scheme 4. Hydrophosphinations of Alkynylimidazolines



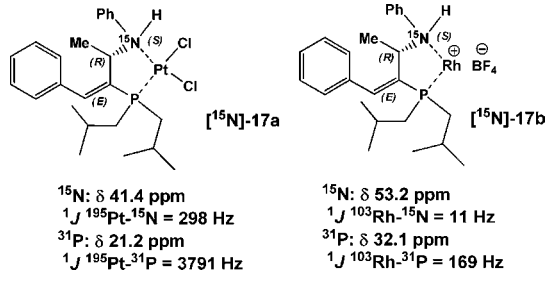


Figure 2. [^{15}N]-Labeled metal complexes.

For applications of the new P−N species to catalysis, it was necessary to establish whether they could achieve a bidentate chelation mode to transition metals. The synthesis of aminophosphine borane *E*-**14** was thus repeated (Scheme 3) with [^{15}N]-aniline to give the isotopically labeled species [^{15}N]-*E*-**14**. This compound was then deboronated and the free aminophosphine exposed to 1 equiv of ^{195}Pt, a spin 1/2 nucleus, to give the metal complex [^{15}N]-**17a** (Figure 2). The complex was analyzed by ^{15}N and ^{31}P NMR. The coordination chemical shifts (CCS: $\delta_{\text{complex}} - \delta_{\text{free ligand}}$) of ^{15}N and ^{31}P were −41 and +74 ppm, respectively. The shielding of ^{15}N and deshielding of ^{31}P are well-precedented phenomena in metal complexes.[7] Both ^{15}N and ^{31}P of complex **17a** showed coupling to platinum, with ^{1}J values of 298 and 3791 Hz, respectively. These values are

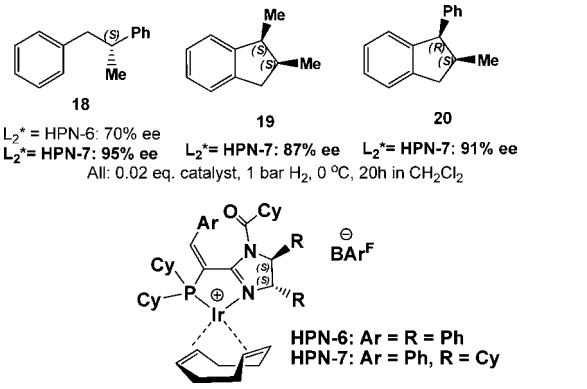


Figure 3. Asymmetric hydrogenations.

in good agreement with related platinum complexes.[7a,c,8] Reaction of the same intermediate with the spin 1/2 nucleus ^{103}Rh gave complex [^{15}N]-**17b**. The CCS values for this complex were −30 and +85 ppm (^{15}N, ^{31}P). Both nuclei again showed coupling to the metal, with ^{1}J values of 11 and 169 Hz for ^{15}N and ^{31}P, consistent with known rhodium complexes.[9] The combination of pronounced CCS values and significant scalar couplings establishes a bidentate chelation mode of these new P−N ligands.

HPN-6 and HPN-7 bear a resemblance to BIPI ligands which have been used for highly enantioselective hydrogenations,[10] with the important exception of their central alkene moiety. It was unclear whether the presence of the olefin would prove detrimental to catalysis. The cationic iridium BArF complexes of each ligand were prepared, in concert with the pioneering work of Pfaltz et al. on iridium complexes.[11] Asymmetric hydrogenations (AH) of several different olefin substrates demonstrated the competency of these ligands in catalytic transformations. Reduction of α-methylstilbene with the Ir complex of HPN-6 under just 1 bar of H_2 gave adduct **18** in a promising 70% ee, while the HPN-7 Ir complex furnished the target (100%) with a high selectivity of 95% ee under the same conditions (Figure 3).

(7) Nitrogen: (a) Pazderski, L.; Szyłk, E.; Sitkowski, J.; Kamienski, B.; Kozerski, L.; Toušek, J.; Marek, R. *Magn. Reson. Chem.* **2006**, *44*, 163–170. (b) Pazderski, L.; Toušek, J.; Sitkowski, J.; Kozerski, L.; Szłyk, E. *Magn. Reson. Chem.* **2007**, *45*, 1059–1071. (c) Busacca, C. A.; Grossbach, D.; Campbell, S. J.; Dong, Y.; Eriksson, M. C.; Harris, R. E..; et al. *J. Org. Chem.* **2004**, *69*, 5187–5195. (d) Schenetti, L.; Mucci, A.; Longato, B. *J. Chem. Soc., Dalton Trans.* **1996**, *3*, 299–303. (e) Schenetti, L.; Bandoli, G.; Dolmella, A.; Trovo, G.; Longato, B. *Inorg. Chem.* **1994**, *33*, 3169–3176. Phosphorus: (f) *^{31}P and ^{13}C NMR of Transition Metal Phosphine Complexes*; Pregosin, P. S., Kunz, R. W., Eds.; Springer-Verlag: Berlin, 1979. (g) Power, W. P.; Wasylishen, R. E. *Inorg. Chem.* **1992**, *31*, 2176–2183.

(8) (a) Pazderski, L.; Toušek, J.; Sitkowski, J.; Kozerski, L.; Szłyk, E. *Magn. Reson. Chem.* **2007**, *45*, 1059–1071. (b) Schenetti, L.; Mucci, A.; Longato, B. *J. Chem. Soc., Dalton Trans.* **1996**, *3*, 299–303. (c) Schenetti, L.; Bandoli, G.; Dolmella, A.; Trovo, G.; Longato, B. *Inorg. Chem.* **1994**, *33*, 3169–3176.

(9) Pazderski, L.; Toušek, J.; Sitkowski, J.; Kozerski, L.; Marek, R.; Szłyk, E. *Magn. Reson. Chem.* **2007**, *45*, 24–36.

(10) (a) Busacca, C. A.; Qu. B.; Grět, N.; Fandrick, K. R.; Saha, A. K.; Marsini, M.; Reeves, D.; Haddad, N.; Eriksson, M.; Wu, J.-P.; Grinberg, N.; Lee, H.; Li, Z.; Lu, B.; Chen, D.; Hong, Y.; Senanayake, C. H. *Adv. Syn. Catal.* 2013, *355*, in press. (b) Busacca, C. A.; Lorenz, J. C.; Saha, A. K.; Cheekoori, S.; Haddad, N.; Reeves, D.; Lee, H.; Li, Z.; Rodriguez, S.; Senanayake, C. H. *Cat. Sci. Technol.* **2012**, *2*, 2083–2089. (c) Busacca, C. A.; Lorenz, J. C. Electronically tuned ligands for asymmetric hydrogenation. U.S. Pat. 7,994,335, 2011. (d) Lorenz, J. C.; Busacca, C. A.; Feng, X.; Grinberg, N.; Haddad, N.; Johnson, J.; Kapadia, S.; Lee, H.; Saha, A.; Sarvestani, M.; Spinelli, E. M.; Varsolona, R.; Wei, X.; Zeng, X.; Senanayake, C. H. *J. Org. Chem.* **2010**, *75*, 1155–1161. (e) Busacca, C. A.; Lorenz, J. C.; Grinberg, N.; Haddad, N.; Lee, H.; Li, Z.; Liang, M.; Reeves, D.; Saha, A.; Varsolona, R.; Senanayake, C. H. *Org. Lett.* **2008**, *10*, 341–344.

(11) For a review, see: Pfaltz, A.; Blankenstein, J.; Hilgraf, R.; Hormann, E.; McIntyre, S.; Menges, F.; Schlonleber, M.; Smidt, S. P.; Wustenberg, B.; Zimmermann, N. *Adv. Syn. Catal.* **2003**, *345*, 33–44.

Tetrasubstituted olefins were also hydrogenated with these new catalysts. Reduction of dimethylindene under 1 bar of H_2 with the more electron-rich iridium complex HPN-7 gave product **19** with 87% ee. Hydrogenation of phenylmethylindene with the same catalyst gave the reduced product **20** in 91% ee. The highest selectivity reported to date for this challenging substrate is 96% ee (with incomplete conversion).[12] This new hydrophosphination chemistry can thus clearly be used to access novel and valuable chiral ligands for asymmetric catalysis.

In summary, the first uncatalyzed hydrophosphinations of propargylic alcohols and amines with phosphine boranes have been explored. The reactions proceed under mild conditions in a transformation with good scope with respect to both coupling partners. Preliminary applications of two of these synthetically easily accessible catalysts, HPN-6 and HPN-7, in asymmetric hydrogenation have been successfully demonstrated, and further exploration of these new P-X systems in catalytic asymmetric methodologies is now in progress.

Supporting Information Available. Experimental procedures, compound characterization, and chiral HPLC analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) Schrems, M. G.; Neumann, E.; Pfaltz, A. *Angew. Chem.* **2007**, *119*, 8422–8424. *Angew. Chem., Int. Ed. Engl.* **2007**, *46*, 8274–8276.

The authors declare no competing financial interest.