Stereochemistry of Palladium-Mediated Synthesis of PAMP−BH$_3$: Retention of Configuration at P in Formation of Pd−P and P−C Bonds

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Palladium-catalyzed cross-coupling of organophosphorus compounds containing a P−H bond with aryl or vinyl halides or triflates is a useful method for P−C bond formation.[1] P-chirogenic substrates with a P=O group undergo coupling with retention of configuration at phosphorus.[2] With phosphine-boranes, however, Imamoto observed that coupling of enantiopure PH(Me)(Ph)(BH$_3$) (**1**) with *o*-AnI (*o*-An = *o*-MeOC$_6$H$_4$) to give P(*o*-An)(Me)(Ph)(BH$_3$) (PAMP−BH$_3$, **2**, a precursor to the historically and industrially important DiPAMP ligand)[3] led to retention or inversion of P stereochemistry depending on base, solvent, and temperature.[4] More recently, Livinghouse showed that adding Cu(I) to similar reactions gave tertiary phosphine-boranes in high enantiomeric excess (ee) with retention of configuration at phosphorus.[5] These stereochemical results were ascribed to the Pd−P bond formation step (transmetalation), assuming that P−C bond formation (reductive elimination) proceeds with retention of configuration at phosphorus (Scheme 1).[5,6] However, these steps could not be separated and observed directly.

Scheme 1
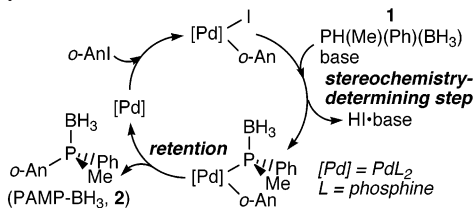
More generally, such fundamental information on the stereochemistry of organometallic reactions, while important in asymmetric catalysis, is incompletely documented.[6] For example, a standard textbook states that "A great deal of evidence suggests that the formation of C−C, C−H, and C−X bonds by reductive elimination always proceeds with retention of stereochemistry at carbon, although no case has been reported in which an isolated starting material of known stereochemistry has eliminated a product of known stereochemistry."[7] Here we show by direct observation that reductive elimination indeed proceeds with retention of configuration at phosphorus in an analogous Pd-mediated synthesis of PAMP−BH$_3$. Transmetalation also occurred with retention at low temperature, and the effect of reaction conditions on stereocontrol in this step was studied directly.

Treatment of Pd((*S*,*S*)-Chiraphos)(*o*-An)(I) (**3**) with racemic **1** and NaOSiMe$_3$ gave a mixture of the diastereomers Pd((*S*,*S*)-Chiraphos)(*o*-An)(P(Me)(Ph)(BH$_3$)) (**4a**, **4b**, Scheme 2; the product

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Scheme 2
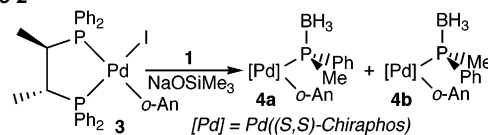
ratio depends on conditions, as described below).[8,9] After separation by recrystallization, X-ray crystallographic studies of both diastereomers (Figure 1) established the absolute configuration of the phosphido-borane P centers.[10]
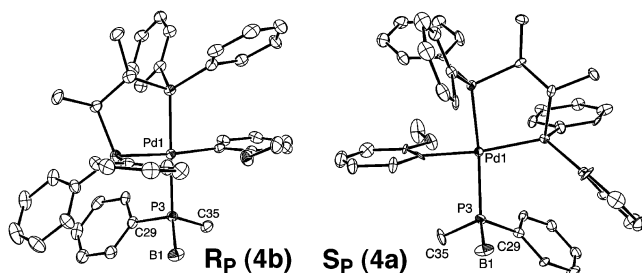
Figure 1. ORTEP diagrams of (*R*$_P$)-Pd((*S*,*S*)-Chiraphos)(*o*-An)(P(Me)(Ph)-(BH$_3$)) (**4b**) and (*S*$_P$)-Pd((*S*,*S*)-Chiraphos)(*o*-An)(P(Me)(Ph)(BH$_3$)) (**4a**).

Treatment of **3** with highly enantioenriched (*S*$_P$)- or (*R*$_P$)-**1**[11] and NaOSiMe$_3$ in THF-d_8 at −78 °C gave (*R*$_P$)-**4b** or (*S*$_P$)-**4a**, respectively, in high de, with *retention* of configuration at phosphorus (Table 1, entries 1−2).[12]

Table 1. Stereochemistry of Pd−P Bond Formation (Transmetalation) in the Reaction of **3** with **1** and NaOSiMe$_3$ in THF-d_8

entry	temperature (°C)	ee of 1[a] (%)	de of 4[b] (%)
1	−78	95 (*R*)	94 (*S*, **4a**)[c]
2	−78	99 (*S*)	94 (*R*, **4b**)
3	21	95 (*R*)	86 (*S*, **4a**)[d]
4	21	97 (*S*)	63 (*R*, **4b**)
5	21	0	23 (*S*, **4a**)[d]

[a] From chiral HPLC (Chiralcel OJ-H). [b] From integration of the ^{1}H NMR spectrum; the ee and de values obtained at −78 °C (entries 1−2) are the same, within experimental error. [c] Average of two runs. [d] Average of three runs.

The erosion of stereochemistry in room-temperature transmetalation (entries 3−4) is presumably due to inversion of the phosphido-borane anion before reaction with the Pd complex occurs.[13] With racemic **1**, dynamic kinetic resolution was observed (entry 5); one enantiomer of the anion [P(Me)(Ph)(BH$_3$)]$^−$ appears to react more quickly with chiral **3** than the other ($k_R > k_S$), and

anion interconversion (k_{inv}) can occur before transmetalation (Scheme 3). This is consistent with the greater loss of stereochem-

Scheme 3
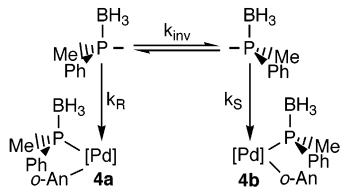
ical information in entry 4 versus entry 3 and suggests that transmetalation occurs somewhat more quickly than P inversion under these conditions, but the rates of these processes are competitive.[14]

Knowledge of the absolute configurations of **4a** and **4b** and of the enantiomers of PAMP–BH$_3$ (**2**) allowed for direct observation of the stereochemistry of reductive elimination.[3,5] Heating either diastereomer of **4** to 50 °C in the presence of 4 equiv of diphenylacetylene gave **2** and Pd((*S,S*)-Chiraphos)(PhC≡CPh) (**5**) as the major products, along with anisole and other unidentified MeO-containing byproducts.[15] The phosphine-borane, isolated by preparative TLC, was formed in high ee, with *retention* of configuration at phosphorus (Scheme 4, Table 2). Diastereomers

Scheme 4 *a*
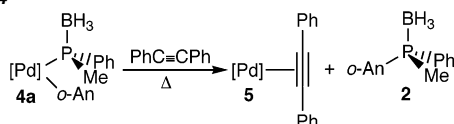
a [Pd] = Pd((*S,S*)-Chiraphos). Results with diastereomer **4b** were similar; **2** was formed with retention.

Table 2. Stereochemistry of P–C Bond Formation (Reductive Elimination) in Reaction of **4** with 4 equiv of Diphenylacetylene in THF-d_8 at 50 °C

entry	time (h)	conversion (%)^a	yield (%)^{a,b}	isomer de (%)^a	ee (**2**)^c (%)
1	72	84	51(21)	**4a** (94, *S*)	91(93) (*S*)
2	96	87	73(20)	**4a** (94, *S*)	87(93) (*S*)
3	37	96	54(20)	**4b** (100, *R*)	98 (*R*)
4	48	91	70(21)	**4b** (88, *R*)	93(92) (*R*)

a Conversions, NMR yields, and de values for **4** were determined by integration of the ^{1}H NMR spectrum versus a ferrocene internal standard. *b* Format: NMR yield (isolated yield of pure material after preparative TLC on silica). Yields are not corrected for conversion. *c* Format: ee (theoretical maximum ee corrected for conversion) (configuration); ee values from chiral HPLC (Chiralpak AD). Because **4a** and **4b** undergo reductive elimination at different rates, at incomplete conversion, unreacted **4** becomes enriched in the "slow" diastereomer **4a**, while **2** becomes enriched in the product formed from the "fast" diastereomer **4b**. Therefore, at incomplete conversion, the maximum ee of **2** may be higher than the de of precursor **4**.

4a and **4b** undergo reductive elimination at different rates; approximate half-lives under these conditions are 30 and 10 h, respectively.

In summary, direct observation showed that both Pd–P bond formation (transmetalation) and P–C bond formation (reductive elimination) proceeded with retention of configuration at phosphorus in this system. In addition to providing detailed mechanistic information on this useful class of Pd-mediated reactions, this work has more general significance in confirming long-held assumptions about the stereochemistry of these fundamental processes and suggests that the reactions of M–P and M–C bonds are similar in stereochemistry.

Supporting Information Available: Experimental procedures and characterization data (PDF) and details of the X-ray crystallographic studies (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) (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; p 333. (b) C–N bond formation at a Ni center led to inversion at carbon, but in this oxidatively induced reductive elimination, the nature of the Ni(III) intermediate could not be determined (Lin, B. L.; Clough, C. R.; Hillhouse, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 2890–2891).

(8) For related Pd phosphido-borane complexes, see: Gaumont, A.-C.; Hursthouse, M. B.; Coles, S. J.; Brown, J. M. *Chem. Commun.* **1999**, 63–64.

(9) Complex **3** exists as a 6:1 mixture of atropisomers due to restricted rotation about the Pd–C bond (Brown, J. M.; Perez-Torrente, J. J.; Alcock, N. W. *Organometallics* **1995**, *14*, 1195–1203). Likewise, atropisomers of both diastereomers **4a** and **4b** were observed.

(10) The ^{1}H NMR spectrum of the single crystal of **4b** used for the structure determination matched that of bulk **4b**, confirming the stereochemical assignment.

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(12) The apparent inversion (for example, (*S*$_P$)-**1** yields (*R*$_P$)-**4b**) is due to the convention for assigning absolute configuration.

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(14) (a) Similar dynamic kinetic resolution (26% de) was observed in toluene on a larger scale. Because of the limited solubility of **3** in toluene, NMR-scale experiments such as those in Table 1 were not possible in this solvent. (b) These observations suggest that, if reductive elimination from **4** were faster, catalytic synthesis of enantioenriched PAMP–BH$_3$ from racemic **1** would be possible. We are currently investigating this possibility with related Pd catalysts.

(15) In analogous C–X (X = N, S, O) reductive eliminations from Pd(II), adding a trap for Pd(0) improved yield and/or selectivity of the reaction: (a) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 8232–8245. (b) Mann, G.; Baranano, D.; Hartwig, J. F.; Rheingold, A. L.; Guzei, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 9205–9219. (c) Widenhoefer, R. A.; Zhong, H. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6787–6795. Similarly, after screening other trapping agents (none, *o*-AnI, (*S,S*)-Chiraphos) and temperatures, these conditions were found to give the cleanest reaction. The origin of anisole and the other unidentified byproducts remains unclear; likewise, the mechanism of formation of the arene byproduct in Pd-catalyzed aryl amination could not be elucidated (Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 3694–3703).