# Stereogenic P-Trisubstituted Phosphorus by Crystallization-Induced Asymmetric Transformation: A Practical Synthesis of Phenyl(*o*-anisyl)methylphosphine Borane

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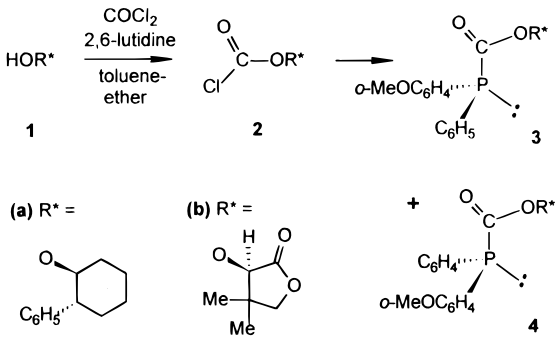
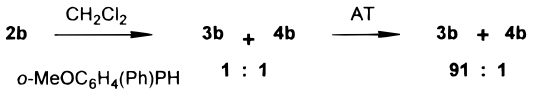
Chiral phosphines have been prepared by a variety of methods, most of which involve the displacement of a chiral leaving group from stereogenic phosphorus by an alkylmetal reagent.[1,2] Control of phosphorus configuration has also been achieved using a non-covalently bound chiral auxiliary.[3] We report an alternative approach based on the first examples of crystallization-induced asymmetric transformation (AT) at stereogenic phosphorus having three carbon substituents.[4,5] The potential of this method is illustrated in a practical synthesis of phenyl(*o*-anisyl)methylphosphine (PAMP).[6]

In principle, the AT phenomenon can be used to convert an equilibrating mixture of chiral phosphine diastereomers R*PPhAr (R*= chiral alkyl) into a single isomer if pyramidal inversion is faster than crystallization.[4] However, the melting point of the product phosphine would have to be higher than the inversion temperature (>100 °C for typical tertiary phosphines; activation energy >30 kcal/mol)[7] to achieve AT. More convenient inversion barriers of 20−25 kcal/mol are expected for alkoxycarbonylphosphines.[8] Thus, chiral derivatives R*$O_2$-CPPhAr should undergo AT near room temperature if the auxiliary R* favors a single phosphorus configuration in the crystal lattice. The alkoxycarbonyl group also provides a built-in means to modify one of the phosphorus substituents and to remove and recycle the chiral auxiliary, as described below. This is accomplished via P-alkylation followed by hydrolytic cleavage of an intermediate alkoxycarbonylphosphonium salt,[9] resulting in the formation of a tertiary phosphine with excellent enantiomeric purity.

Several chiral alcohols R*OH were surveyed for crystallinity in the corresponding P-alkoxycarbonylphosphine **3** or **4** and crystalline derivatives were obtained starting from the Whitesell auxiliary **1a**,[10] or from *(R)*-pantolactone (**1b**). For **1a**, conversion to the chloroformate **2a** with $COCl_2$/toluene + 2,6-lutidine followed by lithium *o*-anisylphenylphosphide[11,12] produced the alkoxycarbonylphosphines **3a** and **4a** (ca. 1:1 diastereomer mixture). A similar procedure from pantolactone **1b** afforded the chloroformate **2b**, but the phosphide coupling step gave undesired byproducts. On the other hand, *o*-anisylphenylphosphine reacted cleanly with **2b** in the absence of any base to produce **3b** and **4b** (1:1 ratio).[13]




Crystallization of the mixtures of **3a**,**4a** or of **3b**,**4b** afforded crystals consisting of a single dominant diastereomer in each case according to $^{31}P$ and $^{1}H$ NMR assay at −20 °C, below the threshold for pyramidal inversion. The structure of **3a** was proven by X-ray crystallography, while the assignment of **3b** was based on its eventual transformation to ($R_P$)-PAMP as described later. The pantolactone series was selected for detailed optimization in subsequent steps (see below) because **1b** is inexpensive compared to **1a**. However, analogous transformations in the Whitesell auxiliary-derived series via **3a** are facile and provide an excellent route to ($R_P$)-PAMP (see the Supporting Information for details). This series has the advantage that both enantiomers of the starting **1a** are equally available.[10,14]

Crystallization of the 1:1 mixture of **3b** and **4b** from ethanol at room temperature resulted in a dramatic change in the diastereomer ratio. On a multigram scale, the isolated product contained **3b** and **4b** in a ratio of 25−32:1 according to $^{31}P$ NMR assay (85% overall from pantolactone; direct crystallization from ethanol, two crops). Since the recovery of **3b** exceeded the amount originally present in the oil, equilibration of the phosphorus diastereomers must have occurred during the crystallization. This confirms that an AT process was involved in the product isolation step as expected. However, AT also occurred in a more surprising way. Thus, a sample containing **3b** and **4b** in a 25:1 diastereomer ratio was found to improve over time! This required nothing more than storing the solid material at room temperature (**3b**:**4b** = 48:1 after 2 weeks; 91:1

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(6) PAMP is the precursor to the renowned diPAMP ligand: Knowles, W. S. *J. Chem. Educ.* **1986**, *63*, 222. Knowles, W. S. *Acc. Chem. Res.* **1983**, *16*, 106.

(7) Baechler, R. D.; Mislow, K. *J. Am. Chem. Soc.* **1970**, *92*, 3090. Mislow, K. *Trans. NY Acad. Sci., Ser. II* **1973**, *35*, 227.

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(11) Prepared from $PhPCl_2$ by sequential treatment with *o*-anisylmagnesium bromide and $LiAlH_4$ by analogy to ref 2b (see the Supporting Information).

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(13) A similar sequence from bornyl chloroformate produced a ca. 1:1 diastereomer mixture of alkoxycarbonylphosphines analogous to **3** and **4**, but crystallization gave a quasiracemate (both diastereomers in the unit cell, 1.0:1.0 ratio).

(14) King, S. B.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 5611.

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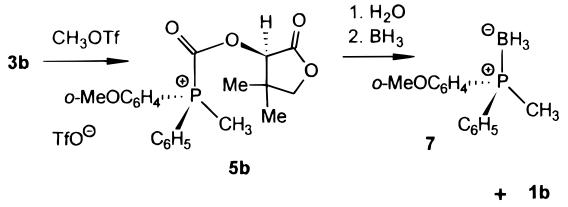
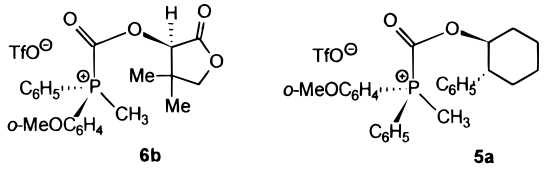
after 6 weeks), but the process could be performed more conveniently by warming the solid sample. When a 32:1 mixture was kept at 50 °C for 22 h, the sample was found to consist of a 99:1 ratio of **3b**:**4b**. No further improvement was detected after an additional 22 h. The diastereomer upgrade occurs without any cost in terms of yield (100% recovery) and must take place via the AT phenomenon. We do not know whether the upgrade involves conversion from one crystalline phase to another. A more likely scenario is that amorphous **4b** precipitates as a contaminant (3−5%) during the initial crystallization of finely divided **3b** and that the amorphous material is slowly converted to **4b** by AT.

In solution, purified **3b** is configurationally stable at −20 °C, but it readily re-equilibrates with **4b** at room temperature ($t_{1/2}$ ca. 30 min). The crude **3b**/**4b** mixture is air- and water-stable on the time scale of routine aqueous workup and it also survives brief exposure to silica gel. However, the material slowly decomposes by air oxidation and the key crystallization procedure was therefore carried out under nitrogen using deoxygenated solvents as a precaution to avoid potential complications that might interfere with efficient crystallization.

Cleavage of the P-acyl group in **3b** and conversion to PAMP was performed by P-alkylation ($CH_3OTf$, $CH_2Cl_2$ −78 to −20°C) to the acyl phosphonium salt **5b**, followed by hydrolysis. The alkylation step is crucial because pyramidal inversion




at phosphorus could re-equilibrate the diastereomers, resulting in lower diastereomeric excess (de) at the stage of **5b** and lower enantiomeric excess (ee) after hydrolysis. A highly sensitive assay for the diastereomer ratio was therefore desired, and the necessary precision was achieved using a phosphorus variant of the $^{13}C$ satellite technique that is reported for the accurate determination of large product ratios based on $^{1}H$ NMR spectra.[15] Thus, the natural abundance $^{13}C$ satellites of the proton-decoupled $^{31}P$ NMR signal of **5b** (dominant diastereomer) were compared with the $^{31}P$ signal of the minor diastereomer **6b**. This method gave reproducible ratios of **5b:**




**6b** ranging from 50:1 to 100:1, depending on the history (the extent of "aging") of the starting sample of **3b**. This was the only technique found to give acceptable accuracy, and it was used to deduce the diastereomer ratios of **3b**:**4b** mentioned earlier. The results were confirmed by ee assay after hydrolysis and conversion to PAMP borane complex as follows.

The crude acylphosphonium salt was treated with $H_2O$/THF at room temperature (3.5 h) to give recovered (*R*)-pantolactone (96% yield; >99 ee by HPLC assay) and ($R_P$)-PAMP, isolated as the borane complex in >98% yield. Starting from **3b** that had been "aged" for 2 weeks (48:1 ratio of **5b**:**6b**) the ($R_P$)-PAMP borane **7** was obtained with 94−95% ee (HPLC assay on chiral stationary phase). The enantiomeric purity of **7** was easily upgraded from 95% ee to >99.5% ee after conventional recrystallization from hexane (84% recovery based on **3b**). In another experiment, **5b** was hydrolyzed in the presence of pyridine. This produced a faster reaction (minutes at rt), and the PAMP was obtained with 97% ee starting from **3b** having 98% de.[16] This evidence confirms that the P-alkylation and hydrolysis sequence occurs with <1% equilibration of phosphorus configuration. Prior studies by Imamoto *et al.* have established efficient procedures for the conversion of **7** to diPAMP.[2b]

The overall conversion from pantolactone to recrystallized (>99.5% ee) (*R*)-PAMP borane **7** was achieved in 74% yield. A similar sequence was performed using the Whitesell auxiliary via **3a** and **5a**. This series was not optimized in detail, but the results were comparable: 80% yield of (*R*)-PAMP borane **7** (98% ee, not recrystallized) from **1b**. These findings establish the AT-based synthesis as a practical route to PAMP on a multigram scale. The corresponding borane complex **7** can also serve as the starting point for synthesis of other phosphines having stereogenic phosphorus, according to preliminary results.[17] Further examples and applications are under investigation.

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**Supporting Information Available:** Complete experimental procedures, characterization, and X-ray structure data for **3a** (37 pages). See any current masthead page for ordering and Internet access instructions.

JA970369X

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(16) A small amount of a symmetrical carbonate byproduct (<5%) was also formed.

(17) Decomplexation of **7** with $Et_2NH$ (4 h, 55 °C), P-alkylation with $Br(CH_2)_3OTBS$ and reductive cleavage of the resulting phosphonium salt gave a 10:1 ratio of $Ph(Me)P(CH_2)_3OTBS$ and *o*-$MeOC_6H_4(Me)P(CH_2)_3$-OTBS (68%). The major product was purified as the borane complex and was deprotected with $Bu_4NF$ to give $Ph(Me)P(BH_3)(CH_2)_3OH$, 77% yield, 99% ee by HPLC assay. This sequence demonstrates that **7** is useful as a precursor of other chiral phosphines.