Gram-Scale Preparation of VAPOL Hydrogenphosphate: A Structurally Distinct Chiral Brønsted Acid

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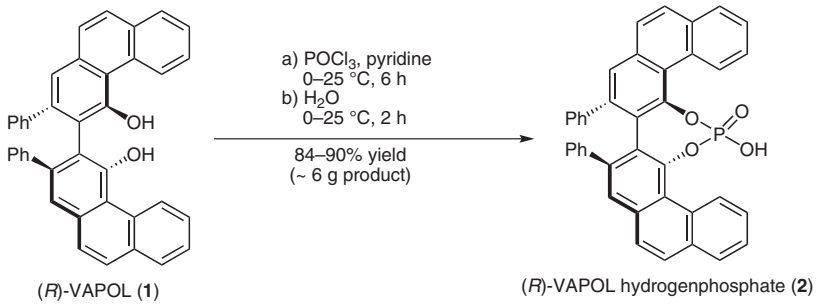
Abstract: A detailed gram-scale synthesis of VAPOL hydrogenphosphate, a structurally distinct chiral Brønsted acid, is presented. The reaction utilizes commercially available starting materials, proceeds with high yields and has been reproduced numerous times at scale.

Key words: VAPOL, asymmetric catalysis, Brønsted acid, ligands, phosphoric acid



Scheme 1 Gram-scale synthesis of (*R*)-VAPOL hydrogenphosphate

Since their discovery in 1993,[1] the biaryl diol ligands VAPOL and VANOL have carved a special niche for themselves in asymmetric catalysis, by the virtue of their unique vaulted structure (Figure 1). Be it as catalysts derived from VAPOL or VANOL and various boron compounds,[2] or those containing aluminum and zirconium,[1,3] or as stand alone catalysts,[4] these vaulted ligands have helped establish efficient systems for a variety of asymmetric reactions. This utility is poised to increase as both optical antipodes of these ligands are now commercially available.[5,6]

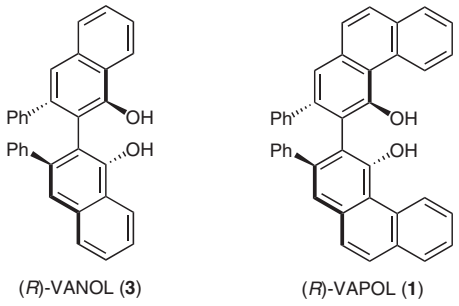


Figure 1 Structurally unique biaryl diol ligands

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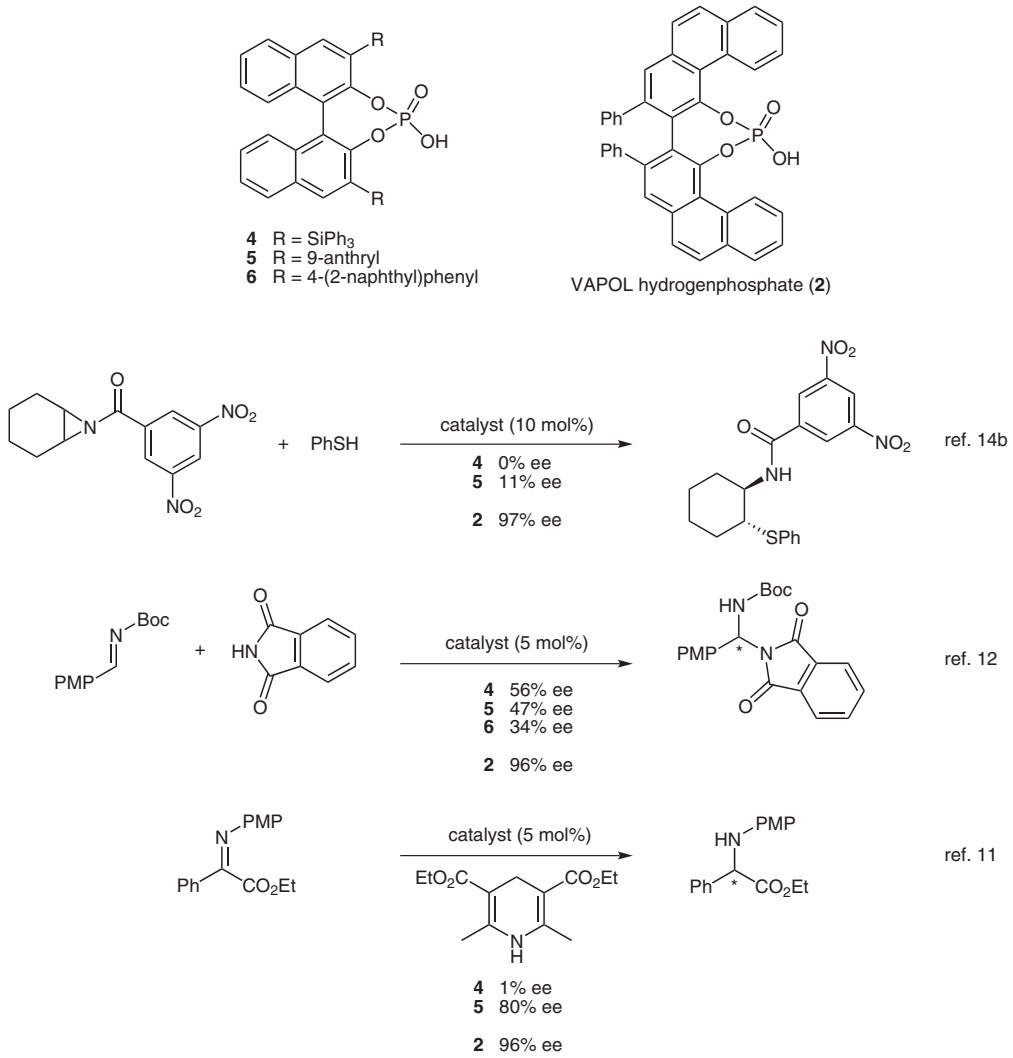
The field of chiral phosphoric acid catalysis began in 2004, with independent reports from Akiyama[7] and Terada.[8] In the short period of time since then, these Brønsted acid catalysts have made an enormous impact in the field of asymmetric organocatalysis.[9] Although most of the reports utilize chiral phosphoric acid catalysts prepared from the 3,3′-disubstituted BINOL scaffold, an increasing number of systems have recently showcased the use of the chiral phosphoric acid catalyst **2** derived from the VAPOL ligand **1** (Scheme 1). Imine amidations,[10] imino ester reductions,[11] imine imidations,[12] as well as desymmetrization of *meso*-aziridines to afford vicinal diamines[13] and vicinal amidophenylthioethers[14] have been all shown to proceed with excellent levels of asymmetric induction under catalysis by VAPOL hydrogenphosphate (**2**).

VAPOL hydrogenphosphate, by virtue of its vaulted nature, is structurally distinct from the BINOL hydrogenphosphate catalysts. The chiral environment, which is formed by the docking of a substrate to it, is sterically and electronically different from those formed with the BINOL hydrogenphosphate catalysts, resulting in a profile for reactivity and asymmetric induction that is quite singular. Several studies have already taken advantage of this difference,[10–14] and some particularly striking examples from these reports are presented in Scheme 2. In the examples shown, VAPOL hydrogenphosphate is compared with some of the most commonly used BINOL hy-



Scheme 2 Greatly improved asymmetric inductions by VAPOL hydrogenphosphate (**2**)

drogenphosphate catalysts, and affords greatly improved asymmetric inductions (Scheme 2). While there are also examples where BINOL hydrogenphosphate derivatives are superior to VAPOL hydrogenphosphate,[15] the examples presented in Scheme 2 clearly validate the inclusion of VAPOL hydrogenphosphate in any screen comprised of chiral Brønsted acids. The purpose of the work described in this report is to develop a procedure for the gram scale synthesis of VAPOL hydrogenphosphate that allows for easy access to this chiral Brønsted acid catalyst and in turn increased use in asymmetric catalysis.

Despite the significant developments reported for this catalyst, the synthesis of optically pure VAPOL hydrogenphosphate (**2**) has not been detailed anywhere in the literature. A synthesis for racemic VAPOL hydrogenphosphate has been previously reported,[6] entailing harsh (refluxing) reaction conditions. While we have not observed racemization with these conditions, we have in some cases (especially with VANOL) observed the formation of undesired side-products, which were tentatively identified as isomers or derivatives of isomers of the desired hydrogenphosphate esters, which can be reduced with Red-Al back to the free ligand without loss of optical purity. In this report, we thus describe a detailed gram-scale synthesis of the Brønsted acid catalyst **2** that involves relatively mild conditions (Scheme 1). Commercially available VAPOL (**1**) is allowed to react with $POCl_3$ in pyridine at room temperature, and is followed by the addition of water, which upon workup and purification affords VAPOL hydrogenphosphate (**2**). This reaction has been carried out at gram scale (~6 g of product) about 12 times; it is highly reproducible and consistently provides the pure product in 84–90% isolated yields. The purification procedures were developed specifically to provide material that can be reproducibly employed in all of the catalytic asymmetric reactions that have been developed for VAPOL hydrogenphosphate.

The chiral vaulted biaryl VAPOL is commercially available in both enantiomeric forms.[5] Alternately, it can be prepared according to a procedure described in the literature.[6] $POCl_3$ was purchased from Aldrich, and pyridine from Jade Scientific, and both were used as obtained. The silica gel for column chromatography was purchased from Sorbent Technologies with the following specifications: standard grade, 60 Å porosity, 230 × 400 mesh particle size, 500–600

m^2/g surface area and 0.4 g/mL bulk density. Melting points were determined on a Thomas Hoover capillary melting point apparatus. IR spectra were taken on a Nicolet IR/42 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a VXR-500 MHz instrument in DMSO-d_6 unless otherwise noted. DMSO-d_5 was used as the internal standard for both ^{1}H NMR (δ = 2.49) and ^{13}C NMR (δ = 39.5). Low-resolution mass spectral analysis was performed at the Department of Chemistry at Michigan State University, using a Hewlett Packard 5890 Series II Gas Chromatograph/Trio-I mass spectrometer. High-resolution mass spectral analysis was performed at the Department of Biochemistry at Michigan State University, using a Waters QTof Ultima with electrospray ionization (ESI). Analytical TLC was performed on Silicycle silica gel plates with F-254 indicator. Visualization was by short-wave (254 nm) and long-wave (365 nm) ultraviolet light.

(*R*)-VAPOL Hydrogenphosphate

Procedure for the Reaction

A one-neck 100 mL round-bottomed flask, fitted with a magnetic stirrer (2.50 × 1.30 × 1.10 cm), was flame-dried and cooled to r.t. under argon. (*R*)-VAPOL (**1**; 6.00 g, 11.15 mmol) was added to this flask followed by the addition of pyridine (24.50 g, 25.00 mL, 0.31 mol). The flask was then fitted with a rubber septum and an argon balloon. The mixture was stirred to completely dissolve the (*R*)-VAPOL, and a clear intense yellow solution was obtained. The flask was then placed in an ice-bath and the solution stirred at 0 °C for 20 min. $POCl_3$ (3.42 g, 2.08 mL, 22.30 mmol) was added slowly via a plastic syringe over a period of 10 min at 0 °C. The ice-bath was removed and the flask was allowed to warm up to r.t. The reaction mixture was then stirred at r.t. for another 6 h. Over this period, the color of the solution changed from intense clear yellow to a cloudy pale yellow, and solid salts started precipitating out. The flask was then placed in an ice-bath again, and stirred for 10 min at 0 °C. H_2O (25.00 mL, 1.39 mol) was added slowly via a plastic syringe into the flask over 5 min at 0 °C. The ice-bath was removed, the flask warmed to r.t. and the reaction mixture was stirred at r.t. for 2 h.

Procedure for Workup

The reaction mixture was transferred to a 2 L separatory funnel. The round-bottom flask was rinsed with CH_2Cl_2 (2 × 15 mL) and H_2O (15 mL), and the rinse was transferred to the separatory funnel each time. CH_2Cl_2 (750 mL) was added to the separatory funnel, followed by the addition of aq 1 M HCl (1000 mL). The mixture was vigorously shaken for 3 min, and the organic layer collected. This organic layer was washed again, vigorously each time, with aq 1 M HCl (6 × 1000 mL). Towards the end of this process, the organic layer changed from a clear pale yellow to a white cloudy composition. Thereafter, the organic layer was washed with brine (2 × 900 mL), towards the end of which the organic layer regained its clear pale yellow composition. This was then dried (Na_2SO_4, 80 g), filtered through a sintered glass frit covered with a layer of Celite, washed with CH_2Cl_2 (150 mL) and all volatiles were then removed via rotary evaporation. The resulting light brown solid was subjected to high vacuum (0.1 mmHg) overnight to afford the crude product in 94% yield (6.30 g, 10.50 mmol).

Procedure for Column Chromatography

A 3″ diameter column was packed to a depth of 17″ with silica gel (1700 mL), in the form of a slurry with MeOH–$CHCl_3$ (1:14).[16] The crude product was dissolved in MeOH–$CHCl_3$ (1:1, 35 mL)[17] to obtain a cloudy yellow solution, and added to the top of the silica gel layer via a pipette. The round-bottomed flask, which previously contained the crude product, was rinsed twice with MeOH–$CHCl_3$ (1:1, 2 × 3 mL) and the rinse was added to the top of the silica gel layer each time. The top of the product solution layer was brought to the top of the silica gel layer, and then a layer of sand (0.5″ × 3″) was added on the top of the silica gel layer. The top of the column was then rinsed with MeOH–$CHCl_3$ (1:14, 2 × 10 mL) and the solution let run into the sand layer each time. The column was run under gravity with a mixture of MeOH–$CHCl_3$ (1:14) as eluent. During this time, two bands could be observed travelling down the column, visible under long-wave UV (365 nm), and these bands appeared to be bright purple in color under the long-wave UV. The first band, the smaller band, is a side-product formed during the reaction,[18] and the second band, a much broader band, is the product of the reaction. After the elution started, ca. 900 mL of a void volume was collected under gravity as the first fraction. Thereafter, a second fraction was collected under gravity, ca. 350 mL (1:14 MeOH–$CHCl_3$), which was the side-product. After the side-product completely eluted (confirmed by the disappearance of the purple band on the column under long-wave UV), a void volume of ca. 200 mL (1:14 MeOH–$CHCl_3$) was collected under gravity before the product began to elute. Once the product started eluting, the eluent system was changed to 1:3 MeOH–$CHCl_3$, and N_2 pressure was applied and the column was flushed. The product continued to elute for ca. 3600 mL of the eluent (1:3 MeOH–$CHCl_3$). At that point, the product stopped eluting, as observed by the disappearance of an intense purple spot on TLC, observed under short-wave UV (254 nm).[19] All product fractions were then collected, the volatiles removed by rotary evaporation and subjected to high vacuum (0.1 mmHg) overnight, to afford the product as a light brown solid in 109% yield (7.30 g, 12.17 mmol). ^{1}H NMR analysis of this product revealed substantial amounts of residual MeOH and $CHCl_3$ solvents, which explained the >100% yield.

Procedure for Removal of Residual Solvents

The product, in a one-necked 500 mL round-bottomed flask, was dissolved in a minimum amount of CH_2Cl_2 to get a clear yellow solution.[20] Then the flask was filled almost completely with pentanes while swirling by hand, during which time the product VAPOL hydrogenphosphate started precipitating out. The resulting solution was swirled by hand for a few minutes. This was then filtered with a Büchner funnel, the solid product dried under a stream of N_2 on the Büchner funnel, collected and subjected to high vacuum (0.1 mmHg) for at least 3–4 h. This precipitation cycle was repeated (usually 6–7 times) until ^{1}H NMR analysis of the product showed complete (or almost complete) removal of the residual solvent peaks.

Procedure for Drying of the Product[21]

The VAPOL hydrogenphosphate obtained from the above procedure was placed on an aluminum foil boat into an Abderhalden drying gun. It was then dried under high vacuum (0.1 mmHg) over refluxing benzene for 48 h. The above procedure affords the product (*R*)-VAPOL hydrogenphosphate as a white solid in 84–90% isolated yield (for 87% yield: 5.83 g, 9.72 mmol); mp >300 °C; $[\alpha]_D^{23}$ –146.5 (*c* 1.0, CH_2Cl_2).

IR (film): 3854s, 1653s, 1558 cm^{-1} s.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 6.44 (d, *J* = 8.2 Hz, 4 H), 6.96 (t, *J* = 7.6 Hz, 4 H), 7.11 (t, *J* = 7.4 Hz, 2 H), 7.64 (s, 2 H), 7.70–7.76 (m, 4 H), 7.89 (d, *J* = 8.8 Hz, 2 H), 7.94 (d, *J* = 8.8 Hz, 2 H), 8.05 (d, *J* = 7.8 Hz, 2 H), 9.75 (d, *J* = 8.1 Hz, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 121.23, 125.98, 126.46, 126.58, 126.79, 126.92, 127.51, 128.03, 128.48, 128.58, 128.88, 129.13, 132.81, 133.91, 139.34, 140.55, 149.2 (d, *J* = 9.3 Hz, 1 C) (1 carbon not located).

^{31}P NMR (121 MHz, DMSO-d_6): δ = 1.05 (s).

MS: *m*/*z* (%) = 600 (43, M^+), 520 (21), 221 (64), 44 (100).

HRMS: *m*/*z* calcd for $C_{40}H_{24}O_4P$ (M – H): 599.1412; found: 599.1434.

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(16) Commercial $CHCl_3$ stabilized with amylene was used; and NOT the $CHCl_3$ stabilized with EtOH. It was found that if the latter is used, it becomes extremely difficult to remove the residual EtOH from the product.
(17) Sometimes it is difficult to dissolve the crude product in 35 mL of 1:1 MeOH–$CHCl_3$. In such cases, a little pure MeOH could be added to help the dissolution. Alternately, the mixture could be heated at ca. 30 °C to aid the dissolution.
(18) The side-product was collected, subjected by rotary evaporation to dryness and high vacuum (0.1 mmHg) for 2 h. Its weight was 21 mg, and ^1H NMR analysis showed a mixture of unidentified products.
(19) The product, when spotted on a TLC and observed under short-wave UV (254 nm), is an intense purple spot.
(20) Sometimes, the VAPOL hydrogenphosphate obtained after column chromatography did not dissolve in CH_2Cl_2 to give a clear solution. In such cases, the crude product should be left on high vacuum (0.1 mmHg) overnight again, which might solve the problem. If not, then the precipitation should be carried out with the emulsion obtained on the addition of CH_2Cl_2 to the crude product – it was found that it proceeded just fine even if a clear solution was not obtained.
(21) It has been observed in some reactions[10] that lower asymmetric inductions are obtained if the VAPOL hydrogenphosphate is not properly dried.