Catalysis for Catalysis: Synthesis of Mixed Phosphine−Phosphine Oxide Ligands via Highly Selective, Pd-Catalyzed Monooxidation of Bidentate Phosphines
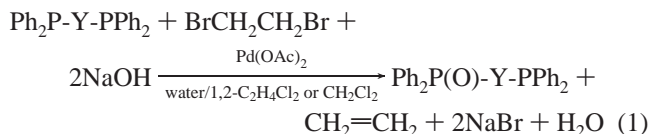
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In this paper, we report the first metal-catalyzed, highly selective, and efficient mono-oxidation of bidentate phosphines to bis-phosphine monoxides (BPMOs) of the general formula R_2P-(O)-Y-PR_2, where Y is a divalent bridging group. A number of BPMOs have proven to be valuable soft/hard ligands for inorganic/organometallic synthesis[1] and especially catalysis with transition metals.[2−5] The use of BPMOs for the hydroformylation[2] and hydroxycarbonylation[5] of olefins resulted in one of the highest linear-to-branched product ratios ever observed for such reactions. The temperature (200 °C) and pressure (500 psi) normally required to run the Monsanto process (MeOH + CO to AcOH)[6] can be brought down to as low as 80 °C and 50 psi, with no loss in catalytic turnover frequency, by simply activating the conventional Rh catalyst with $Ph_2P(O)(CH_2)_2PPh_2$.[3a,d] Despite its great potential and anticipated diversity, the coordination and catalytic chemistry of BPMOs still remains in its infancy due to the lack of a convenient, general method to synthesize these ligands.[7]

A selective mono-oxidation reaction of readily available bidentate phosphines would apparently be the simplest and most attractive strategy for the preparation of BPMOs. However, the direct oxidation of $Ph_2P(CH_2)_nPPh_2$ with conventional oxidants (e.g., O_2, H_2O_2, Br_2/H_2O) is nonselective, always leading to mixtures of the unreacted diphosphine, its monoxide, and its dioxide.[9−11] Tedious column separations of such mixtures and poor isolated yields are inevitable when preparing BPMOs via the conventional diphosphine oxidations.[10] In sharp contrast with this, our anaerobic Pd-catalyzed biphasic oxidation with 1,2-dibromoethane/alkali is remarkably selective, giving rise to the desired mono-oxidized product (eq 1).

$$Ph_2P\text{-}Y\text{-}PPh_2 + BrCH_2CH_2Br +$$
$$2NaOH \xrightarrow[\text{water/1,2-C}_2\text{H}_4\text{Cl}_2 \text{ or CH}_2\text{Cl}_2]{\text{Pd(OAc)}_2} Ph_2P(O)\text{-}Y\text{-}PPh_2 +$$
$$CH_2{=}CH_2 + 2NaBr + H_2O \quad (1)$$

Reaction 1 occurs under mild conditions, affording various BPMOs in up to 90% isolated yield (Table 1). Our research was focused on aromatic substrates containing PPh_2 moieties, which cannot be mono-oxidized selectively, using the "protonation followed by oxidation" technique developed by Mäding and Scheller.[11] All reactions were run on a 0.1−100 g scale, with the substrate-to-catalyst ratio being in the range of 1000−100.[12]

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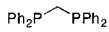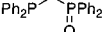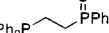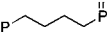
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(10) (a) Despite very poor yields, e.g., 13%,[10b] and the tediuos isolation procedure, the direct nonselective oxidation is sometimes preferred over other literature methods.[7] (b) Brock, S. L.; Mayer, J. M. *Inorg. Chem.* **1991**, *30*, 2138.

(11) (a) Protonated forms of much more basic Alk$_2$P(CH$_2$)$_n$PAlk$_2$ (e.g., Alk = Me; $n = 2$)[10b] may be mono-oxidized in a *selective* manner. This technique is not applicable to less basic Ph$_2$P(CH$_2$)$_2$PPh$_2$ and other aromatic diphosphines. (b) Mäding, P.; Scheller, D. *Z. Anorg. Allg. Chem.* **1988**, *567*, 179.

(12) All reactions were run under N$_2$ and monitored by TLC and/or ^{31}P NMR. The products were isolated in air. Representative procedures for the synthesis of dppeO and dppmO follow. **dppeO:** (a) Aqueous NaOH (10%, 20 mL) was added to a solution of Pd(OAc)$_2$ (10 mg, 4.45 × 10^{-2} mmol), dppe (4.00 g, 10.05 mmol), and 1,2-dibromoethane (2.85 g, 15.2 mmol) in 1,2-dichloroethane (30 mL). The biphasic system was vigorously stirred under reflux for 7 h, until the originally yellow mixture turned pale yellow or almost colorless. The organic phase was filtered through a silica plug which was then washed with 60 mL of CH$_2$Cl$_2$/AcOEt (5:3 by volume). After the combined organic solutions were evaporated and treated with ether, white crystals of dppeO were washed with ether and dried under vacuum. The yield was 3.62 g (87%). ^{1}H NMR (CDCl$_3$, 20 °C), δ 2.3 (m, 4H, CH$_2$); 7.2−7.7 (m, 20H, Ph). (b) Under similar conditions (21.5 h), dppeO was obtained (40.75 g, 78%) from Pd(OAc)$_2$ (50 mg, 22.3 × 10^{-2} mmol), dppe (50.00 g, 125.6 mmol), 1,2-dibromoethane (36 g, 191.5 mmol) in 1,2-dichloroethane (200 mL) and 20% NaOH (125 mL). **dppmO:** 20% NaOH (6 mL) and NaI (40 mg, 0.27 mmol) were added to a solution of Pd(OAc)$_2$ (5 mg, 2.2 × 10^{-2} mmol), dppm (2.00 g, 5.21 mmol), and 1,2-dibromoethane (2.0 g, 10.64 mmol) in 1,2-d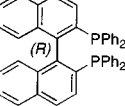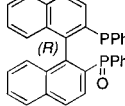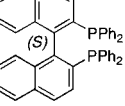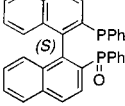ichloroethane (10 mL). After the biphasic system was vigorously stirred under reflux for 4 h, the organic phase was filtered through a silica plug which was then washed with CH$_2$Cl$_2$/AcOEt (3:1 by volume). The combined organic solutions were evaporated to dryness to produce crude solid dppmO which was redissolved in a small amount of boiling CH$_2$Cl$_2$ and precipitated with 100 mL of ether. After standing for 2 h at room temperature, fluffy needles of dppmO were filtered off, washed with ether, and dried under vacuum. The yield was 1.53 g (74%). ^{1}H NMR (CDCl$_3$, 20 °C), δ 3.1 (d, 2H, *J* = 12.7 Hz, CH$_2$); 7.1−7.9 (m, 20H, Ph).

Table 1. Pd-catalyzed Mono-Oxidation of Bidentate Phosphines

substrate	reaction conditions[a]	Pd(OAc)$_2$ catalyst, weight %	time, h	product	yield, %	^{31}P NMR, δ, ppm (J_{P-P}, Hz)
dppm Ph$_2$P⌣PPh$_2$	A, B	0.2	4	dppmO Ph$_2$P⌣PPh$_2$=O	74–85	-27.0; +29.8 (50.5)
dppe Ph$_2$P⌣⌣PPh$_2$	A	0.1–0.5	7–22	dppeO	78–90	-11.5; +32.3 (48.0)
dppp Ph$_2$P⌣⌣⌣PPh$_2$	A	0.2	6	dpppO	73–77	-17.2; +32.1
dppb Ph$_2$P⌣⌣⌣⌣PPh$_2$	C	0.25	72	dppbO	80–83	-15.5; +32.3
dppfc	B, D	0.5	24	dppfcO	50–65	-16.7; +28.5
BINAP (R)	E	0.5	72	BINAP(O) (R)	80	-15.2; +27.0
BINAP (S)	E	0.5	72	BINAP(O) (S)	80	-15.2; +27.0

^{a} A: 1,2-dichloroethane, 10−20% NaOH, 1.5−2 equiv C$_2$H$_4$Br$_2$, reflux. B: in the presence of NaI (8−10 mol equiv/Pd). C: CH$_2$Cl$_2$, 20% NaOH, 2 equiv C$_2$H$_4$Br$_2$, room temperature. D: CH$_2$Cl$_2$, 20% NaOH, 3 equiv C$_2$H$_4$Br$_2$, reflux. E: CH$_2$Cl$_2$, 4.5% NaOH, 4 equiv C$_2$H$_4$Br$_2$, room temperature for 48 h, then under reflux with 8% NaOH for 1 more day.

Although Pd(OAc)$_2$ is the most convenient catalyst to use, a wide variety of Pd and Pt compounds, e.g., PdCl$_2$, Na$_2$PdCl$_4$, K$_2$PtCl$_4$, phosphine complexes, and so forth, may be used as well. In general, Pd catalysts are more efficient than their Pt counterparts.[13] *Importantly, to obtain high yields of BPMOs, reaction conditions should be thoroughly optimized for each particular diphosphine substrate to be oxidized.* For instance, the oxidation of dppp to dpppO occurs with the highest yield when conducted at 80 °C, whereas room temperature and longer reaction times benefit the clean formation of dppbO from dppb (Table 1). In some cases (dppm, dppfc), the mono-oxidation is much more efficient when run in the presence of small quantities of iodide anion. At this point, the effect of the I$^-$ is not entirely understood.[14]

Catalytic process 1 was realized by means of an elaborate design stemming from fundamentals of organic and modern organometallic chemistry, rather than from screening techniques. The mechanism of the catalytic oxidation involves the hard base-promoted selective intramolecular redox process Pd(II)/P(III) → Pd(0)/P(V),[15] followed by reoxidation of the resulting Pd(0) species back to the catalytically active Pd(II). The latter forms via the oxidative addition of BrCH$_2$CH$_2$Br to give a bromoethyl complex, [LPd(Br)(CH$_2$CH$_2$Br)], which then loses ethylene as a result of β-halogen elimination.[16] Detailed mechanistic studies of reaction 1 will be reported separately.

Due to the presence of both the soft (P) and hard (O) nucleophilic centers within one molecule, hemilabile[17] BPMO

ligands can (i) stabilize the transition metals in both low and high oxidation states and (ii) form labile chelates which easily generate highly reactive, coordinatively unsaturated species, thus providing the metal complex with low activation energy paths to isomerisation, oxidative addition, migratory insertion, reductive elimination reactions, and so forth. It is hoped that due to the simple and efficient catalytic route to BPMOs described herein, these valuable ligands will soon enjoy many new applications in synthesis and catalysis.

(13) In the absence of a metal catalyst, a slow, nonselective oxidation occurs.

(14) It is conceivable that the iodide somehow facilitates oxidative addition of BrCH$_2$CH$_2$Br to the Pd(0) species involved in the catalytic cycle due to the formation of electron-enriched anionic Pd iodo species and/or generation of more electrophilic ICH$_2$CH$_2$Br because of the equilibrium BrCH$_2$CH$_2$Br + I$^-$ ⇌ ICH$_2$CH$_2$Br + Br$^-$.

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