

Abstract

Current synthetic routes of bisphosphine monoxides (BPMOs) are limited. Standard oxidizers produce a mixture of dioxide and monoxide products with remaining bisphosphine reagent. Current methods used include selective, Pd-catalyzed oxidation and mono-reduction of bisphosphine dioxides using several moisture-sensitive materials. The primary goal of this project has been the discovery of simpler methods to selectively produce BPMOs in high purity. Explored methods, described herein, include using mild, organic oxidizers and using the well-established Wittig reaction to selectively oxidize one phosphorus center. $^{31}\text{P}\{^1\text{H}\}$ NMR and MS were used to characterize the products and determine product distributions for all attempts.

Background

Bisphosphine monoxides (BPMOs) are hemi-labile ligands useful for catalyzing a variety of reactions. BPMOs contain both a Lewis acid and base in the same molecule, which makes it useful for inorganic synthesis, metal complex catalysis, cancer and AIDS research, and analytical chemistry.¹ Current synthetic routes are limited since normal oxidizers such as hydrogen peroxide produce a mixture of unoxidized, monooxidized, and bisoxidized phosphines. The current preferred methods include selective monooxidation via a Pd-catalyzed reaction (74-84% bis(diphenylphosphino)methane monoxide)¹, which is expensive and air-sensitive, and monoreduction of bisphosphine dioxides using an anhydride, a thiol, and N,N-diisopropylethylamine (52% bis(diphenylphosphino)methane monoxide).² This research aims to discover a simpler method to produce monooxidized bisphosphines in high purity. Bis(diphenylphosphino)methane (dppm) was used for these initial tests because of its readily availability and relatively low cost. Explored synthetic routes included using a milder oxidizer and using the well-established Wittig reaction to selectively oxidize one phosphorus center. $^{31}\text{P}\{^1\text{H}\}$ NMR and MS were used to characterize the products and their ratios in our attempts to identify a more efficient synthetic procedure.

References

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Results

Phosphonium salt synthesis: Phosphonium salt was successfully produced in very high purity at room temperature. Addition of excess ethyl bromoacetate to the reaction did not affect purity and may be a good way to ensure complete conversion of dppm.

$^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3) run on the 1:1 reaction product produced phosphonium salt doublet peaks at δ 23.52 ($J_{\text{PP}} = 65.82$ Hz) and δ -26.36 ($J_{\text{PP}} = 65.82$ Hz). $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3) run on the 2:1 reaction product produced phosphonium salt doublet peaks at δ 23.50 ($J_{\text{PP}} = 60.83$ Hz) and δ -26.38 ($J_{\text{PP}} = 65.82$ Hz), and also an additional doublet that we currently attribute to the bisphosphonium salt.

Figure 2: $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3) of phosphonium salt made from dppm and a 2:1 ratio of bromoethyl acetate.³

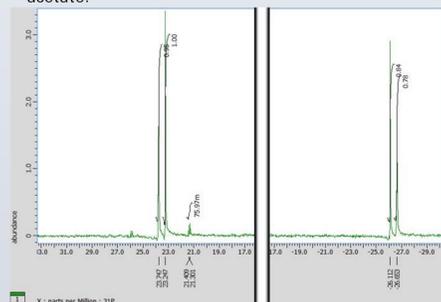


Figure 3: ^1H NMR (CDCl_3) of phosphonium salt made from dppm and 2:1 ratio of bromoethyl acetate.

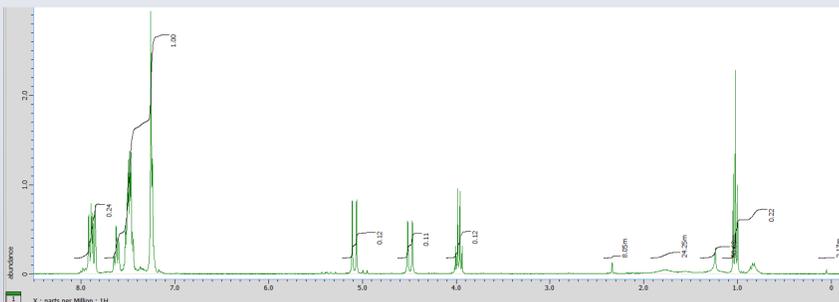


Figure 4: $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3) of Wittig on water reaction with premade phosphonium salt.^{1,4,5}

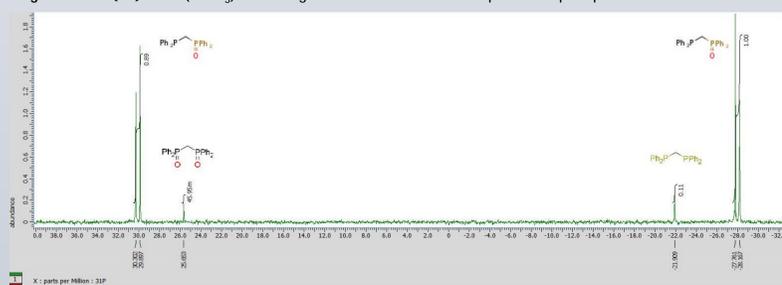
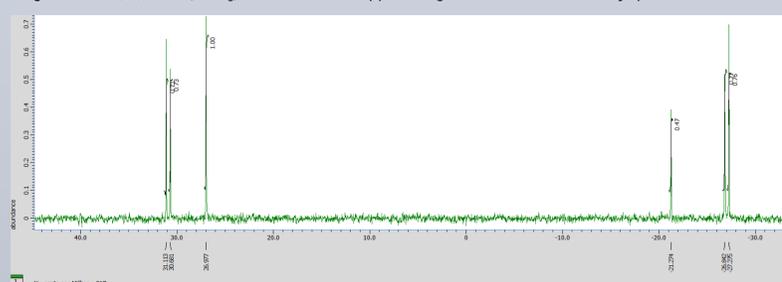


Figure 5: $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3) of oxidation of dppm using slow addition of benzoyl peroxide.^{1,4,5}

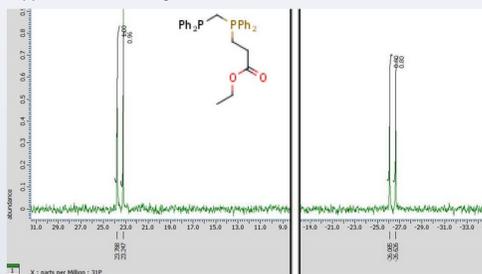


Reaction	Dppm Monoxide	Dppm	Dppm Dioxide
3% H_2O_2	37.91%	32.68%	29.41%
MW Phosphonium*	16.86%	12.30%	33.05%
aq. Wittig	45.10%	15.69%	39.22%
tBuOOH	37.63%	34.84%	27.53%
benzoyl peroxide	63.37%	6.97%	29.66%
benzoyl peroxide (slow)	66.89%	10.59%	22.52%
aq. Wittig (step-wise)	92.38%	5.38%	2.25%

Table 1: Product ratios of several attempted reactions. Ratios determined using the peak integrations on the $^{31}\text{P}\{^1\text{H}\}$ NMR. The oxidation trials using 3% H_2O_2 and tBuOOH produced products only slightly better than random distribution, which was 33.33% each of dppm monoxide, dppm dioxide, and dppm. The aqueous Wittig (step-wise) trial had a better product ratio than the published yield for the Pd-catalyzed synthesis.

* MW Phosphonium reaction also had leftover phosphonium

Figure 1: $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3) of phosphonium salt made from dppm and bromoethyl acetate.³



Wittig reaction: Separating the steps in the aqueous procedure to make the phosphonium salt first then oxidize it was much more efficient than dumping all the chemicals in at once and heated to reflux. The optimized procedure produced twice as much dppm monoxide as the original procedure. $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3) run on the reaction product of the Wittig on water done with previously made phosphonium salt produced a mixture with a majority of dppm monoxide doublets. The peaks in Figure 4 are found at δ 30.10 ($J_{\text{PP}} = 49.27$ Hz), δ 25.65, δ -21.91, and δ -27.96 ($J_{\text{PP}} = 49.39$ Hz).

Oxidation: Benzoyl peroxide appeared to be a promising oxidant for synthesis of dppm monoxide, so we attempted to optimize the oxidation by slowing down the oxidation by slowing down the addition of benzoyl peroxide and performing in an ice bath. The slowed down oxidation was only slightly more efficient than the original oxidation with benzoyl peroxide. $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3) run on the product showed a mixture of dppm monoxide, dioxide, and dppm. The peaks in Figure 5 are found at δ 30.90 ($J_{\text{PP}} = 52.56$ Hz), δ 26.98, δ -21.27, δ -27.06 ($J_{\text{PP}} = 52.68$ Hz).

Experimental

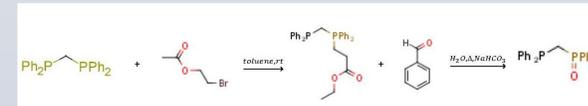
Oxidation Reactions: Initially, oxidation was attempted using several organic and inorganic oxidizers on dppm dissolved in toluene at room temperature. All oxidation reactions were allowed to sit for one day before characterizing by $^{31}\text{P}\{^1\text{H}\}$ NMR. After seeing moderate success with some of the organic oxidizers, the procedure was optimized by slowing down the reaction in an ice bath.

Wittig Reactions: Several different setups for the Wittig reaction were attempted.

Procedure 1: Phosphonium salt is prepared by microwave irradiation at 160 °C in toluene for 60 minutes. After isolation, the dppm phosphonium salt is dissolved in dichloromethane with a 1:1 addition of benzaldehyde and 50 % aqueous NaOH.

Procedure 2: Phosphonium salt is prepared by dissolving dppm in toluene and adding 1 equiv. of ethyl bromoacetate at room temperature. After isolation, the phosphonium salt was refluxed with benzaldehyde in an aqueous, saturated sodium bicarbonate solution for 30 minutes.

Scheme 1: Aqueous Wittig synthesis of dppm monoxide.



Conclusion

Diphenylphosphinomethane monoxide can be synthesized in high purity using an aqueous Wittig reaction separated into a phosphonium salt synthesis step and an oxidation step. Mild organic oxidizers show promise for producing high purity BPMOs if sufficiently slowed to limit oxidation of both phosphorus centers. Benzoyl peroxide was by far the best performing organic oxidizer - providing a 2:1 ratio of monoxide to dioxide.

Next Steps

The oxidation procedure can potentially be further optimized by adjusting the rate of oxidant addition. Further optimizations can be done for the aqueous Wittig procedure to increase yield, using and improved isolation protocol. The aqueous Wittig will also be tested using different bisphosphines to compare effectiveness.

Acknowledgements

A special thanks to the Winona State Department of Chemistry for the use of their chemicals and equipment. Also, thanks to Dr. Joseph West for his guidance throughout this project.