Exploration of Methods for the Synthetic Pathway of Chiral Organophosphonates

Jackson Shuman and Jeremy M. Erb*

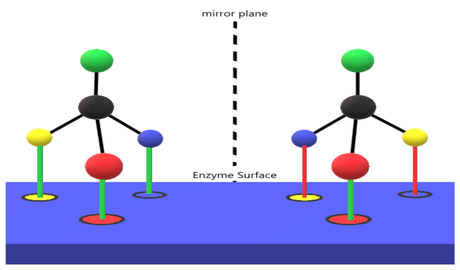
Department of Chemistry, University of Dayton, 300 College Park Dayton, OH 45469
jerb01@udayton.edu

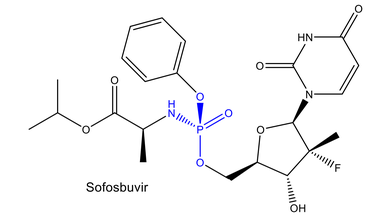
Abstract

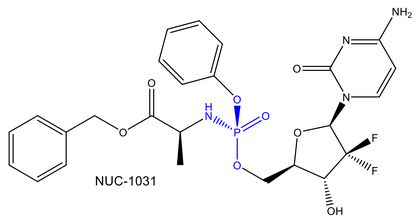
Numan and Brichacek developed a new method for the synthesis of chiral organophoshinates in 2021 with moderate yields and mediocre stereoselectivity. In their publication, they first generated isopropyl phenyl-H-phosphinate (i-Pr PhPHO) as a starting material by reaction of phenylphosphinic acid and liquid 2-propanol at high temperatures in a tightly sealed reaction vial. They reported yields of around 70-75%. However, when done in our lab, the yield was only 11% or less. Several attempts at improving yield centered around increases in temperature, but this ultimately made no changes in yield. Further research uncovered a different method for the synthesis of *i*-Pr PhPHO proposed by Afarinkia and Yu which utilizes alkyl chloroformates and phenylphosphinic acid. This new reaction yielded upwards of 90% product in our lab. It also takes far less time, requiring only 15 minutes to reflux compared to the 18 hours of the old method. The new method also has the benefit of being safer since it does not require heating a sealed-volume apparatus. We tested a new catalyst, HyperBTM, for its ability to create chiral organophosphinates using Numan's protocol. Although very similar in structure to Numan's catalyst (BTM), HyperBTM has an increased amount of steric bulk and slightly larger ring size that we envisioned would be more selective in the reaction. We found that the use of HyperBTM results in trace yields of the desired product. Enantiomeric excess was undetermined due to the low yield. An alternative strategy is currently underway that combines BTM with various transition metals to form a cooperative bifunctional catalytic approach that we envision will have greater success.

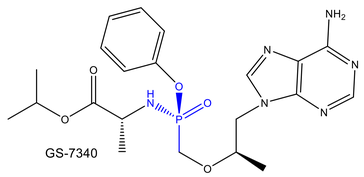
Background on Chiral Organophosphates

Chiral organophosphorus compounds have an increasing importance in drug design. When attached to various drug molecules, they can improve their enzymatic inhibitory capabilities. One such application is Sofosbuvir, which plays an important antiviral role in treatment of hepatitis-C. There exist similar molecules with anti-HIV and anti-cancer promises which similarly utilize the function of a chiral organophosphorus group to increase their effectiveness as a drug, such as NUC-1031 and GS-7340. Studies of these drugs had also revealed that one enantiomer was dramatically and significantly more effective than the other. In the agricultural industry, pesticides are heavily used that rely on chiral phosphorus-containing groups for their effectiveness. The wide range of organophosphorus compounds in several fields speaks to the importance of control of chirality during synthesis, as biological systems are highly selective concerning chirality. To date, only a limited number of studies have focused on their stereoselective synthesis.

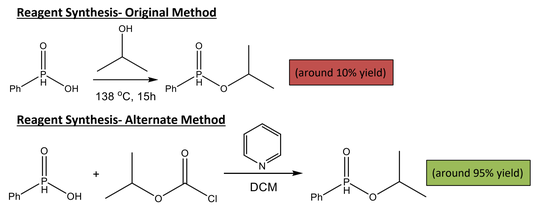




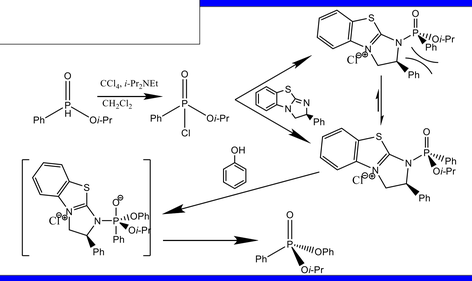




Our Strategy



Mechanism Proposed by Numan and Brichacek

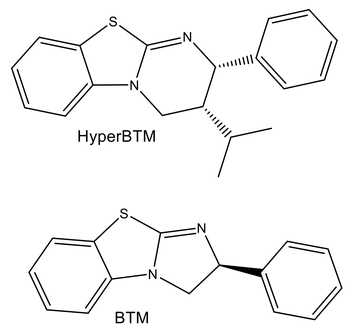


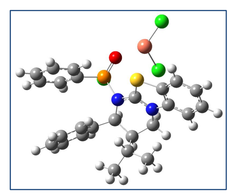
Our Results

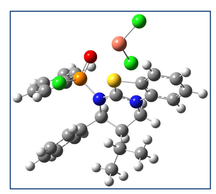
Entry	Reagent Synthesis Method	Time	Temperature	Percent Yield
1	Original	≈18 hours	138 ºC	9%
2	Original	≈18 hours	145 ºC	10%
3	Original	≈18 hours	150 ºC	11%
4	Alternate	Refluxed for 15-30 minutes	40 ºC	96%

Entry	Catalyst	Alcohol	Percent Yield	HPLC Results
1	HyperBTM	Methanol	0%	Not Available
2	HyperBTM	Methanol	Trace Amounts (<1%)	Not Available
3	BTM	Methanol	Yield not calculated (estimated to be <15%)	No separation with Whelk-01 and RegisPack chiral columns

Catalysts Used



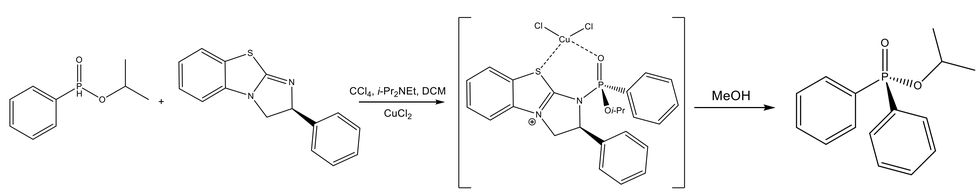




Optimization calculations suggest that when (*R*)-HyperBTM attacks Isopropyl phenylphosphonochloridate two diastereomeric intermediates can form (shown above) that have an energy difference of 2.14 kcal/mol. When copper (II) chloride is added, the difference in energy increased to be 2.49 kcal/mol. These results show that the reaction's stereoselectivity can be increased by the addition of copper (II) chloride, giving us motivation to improve upon the poor to moderate stereoselectivities reported by Numan and Brichacek, which typically were no higher than 60% ee. These DFT calculations were done using Gaussian 16 with a B3LYP/6-31+g(d) level of theory for optimizations on all atoms except for copper which used the SDD basis set.

Future Work

- Verify enantiomeric excess from Numan and Brichacek's work using a new chiral column (Reflect I-Cellulose Z)
- Run experiments with the addition of a transition metal to explore its effect on the stereoselectivity of the reaction.
- Test different combinations of groups attached to phosphorus in place of isopropyl and methyl groups to explore the scope of the reaction with the metal.



Acknowledgments and References

I would like to acknowledge the University of Dayton for providing resources for our research, the College of Arts and Sciences for providing funding through the Dean's Summer Fellowship Program, and Jeremy Erb for guidance throughout the project. We also gratefully acknowledge the NSF (CHE-2018678) and the Ohio Action Fund for a MRI award in support of a 400 MHz NMR spectrometer at the University of Dayton that was used on this project.

References

- Numan, A.; Brichacek, M. Asymmetric Synthesis of Stereogenic Phosphorus P(V) Centers Using Chiral Nucleophilic Catalysis. Molecules 2021, 26 (12), 3661. https://doi.org/10.3390/molecules26123661.
- Afarinkia, Kamyar, and Hiu-wan Yu. "Hewitt reaction revisited." Tetrahedron letters 44, no. 4 (2003): 781-783. https://doi.org/10.1016/S0040-4039(02)02647-3.
- Pertusati F.; McGuigan C. Diastereoselective Synthesis of P-Chirogenic Phosphoramidate Prodrugs of Nucleoside Analogues (ProTides) via Copper Catalysed Reaction. Chemical Communications, 51, 2015, 8070–8073. https://doi.org/10.1039/C5CC00448A.
- Rios Morales E. H.; Balzarini J.; Meier C. Stereoselective Synthesis and Antiviral Activity of Methyl-Substituted Cyclo Sal-Pronucleotides. Journal of Medicinal Chemistry, 55, 2012, 7245–7252. https://doi.org/10.1021/jm3008085.
- Zhang L.; Miao Y.; Lin C. Enantiomeric Separation of Six Chiral Pesticides That Contain Chiral Sulfur/Phosphorus Atoms by Supercritical Fluid Chromatography. Journal of Separation Science, 41, 2018, 1460–1470. https://doi.org/10.1002/jssc.201701039.